**Organic chemistry / by Frank C. Whitmore.**


**Contributors**

Whitmore, Frank C. 1887-1947.

**Publication/Creation**

London : Chapman & Hall, 1937.

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# ORGANIC CHEMISTRY

*By*

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***First Published, March 1937***
*Reprinted, August 1937*

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# PREFACE

This work is a one-volume reference-text designed for practising organic chemists, for others who have to take occasional cognizance of organic compounds and their reactions, and for students who have pursued organic chemistry for at least a year with the aid of the many excellent elementary and intermediate textbooks now available. All efforts have been directed to making it a text of advanced character designed for those already possessing reasonable knowledge and experience in organic chemistry.

In the compilation of this work practically all available sources of information have been drawn upon. Special use has been made of all the existing advanced one-volume texts in German, French and Italian. In cases where English translations of such texts contain material not in the originals they also have been used.

The author's thanks are due to his many friends in industry who have helped freely with facts and comments on industrial processes to the full extent compatible with the ordinary practices of trade secrecy. During the eight years in which the book has been written Marion Mason Whitmore has helped in all stages of the work. To Ann Reimel Young and Margaret Zerbey, Librarians of the School of Chemistry and Physics, go thanks for extensive help in literature searches. Beulah Mattern Knop and Alice Long have carried on the difficult typing year after year. Hearty thanks go to the score of organic chemists in Pond Laboratory who speeded the preparation of the Index. No thanks could be adequate for the painstaking and faithful work of Delcena Crabtree and Mary Louise Shaner to whom fell the arduous task of sorting the forty-nine thousand index slips.

The author will be grateful to his colleagues in the industrial and academic fields for advice on errors both of commission and omission which they note in the work.

FRANK C. WHITMORE

STATE COLLEGE, PENNSYLVANIA,
February 1, 1937

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# INTRODUCTION

In keeping with the present trend toward aliphatic chemistry, especially in British and American industry, nearly three-fourths of the work is devoted to aliphatic and alicyclic chemistry. The section on aromatic chemistry is shorter than in most volumes of this type while that on heterocyclic compounds is relatively larger. The wide occurrence of aromatic properties is emphasized. The complex alkaloids are presented in an orderly arrangement based on an analysis and classification of possible combinations of nitrogen-ring systems.

Other works and the literature should be consulted for the application of analytical and physical principles to organic chemistry and for many details in the development of the science. Thus, the reader will fail to find in this work many of the historically interesting formulas which have been proposed for benzene.

Another type of omission is that of details about the distillation and utilization of coal tar. This is because of the lack of any uniformity at the present time in the working up of this important material. A still different type of omission is that of the details of the work on the sex hormones. In this, as in many similar cases throughout the work, references are given to sources of as detailed information as the reader can wish.

Instead of giving full references in the text or in footnotes the names of investigators are included in parentheses. These can be used as clues to further details in conjunction with the ordinary indexes of the chemical literature. No attempt has been made to recognize priority among such workers. In fact, in many cases the name cited is that of a recent worker in whose articles can be found summaries of earlier work.

General principles have been stressed throughout the work. Many of these such as the initiation of reactions by preliminary addition and the tendency for ring closure appear repeatedly.

A deliberate attempt has been made to explode what might be called the fallacy of homologous series in which it is often assumed that a knowledge of the first two or three members of a series furnishes a satisfactory knowledge of the series itself. Thus, in the alcohol series it has been necessary to go at least to the seven carbon member before distinct novelties in properties and reactions cease to appear.

The use of electronic conceptions has been definitely limited to those cases in which ordinary structural formulas fail. In most processes in organic chemistry the bond corresponds exactly to the effect of an electron pair and nothing is achieved by substituting two dots for the conventional dash.

In details of nomenclature, a lack of consistency will be noted. This can perhaps be excused on the basis of the lack of uniformity in usage among organic chemists.

British Annual Reports and Organic Syntheses are constantly referred to because they offer, respectively, excellent summaries and detailed preparative directions. Unfortunately, in neither case are the references as complete as might be possible.

The explanation of all references and abbreviations is included in the Index.

Entirely aside from its use in locating specific material, the Index will be helpful, especially to advanced students, in selecting the important compounds and processes of organic chemistry and then following them through a range of examples covering the entire science.

In treating the whole of organic chemistry in a single volume a decidedly condensed style has been necessary. Thus the two chief users of this work, the practising chemist and the advanced student, will find the use of paper and pencil helpful in expanding many of the formulas and equations.

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# PART I

## ALIPHATIC COMPOUNDS

### I. HYDROCARBONS

#### *A.* Saturated Hydrocarbons, $C_nH_{2n+2}$

**Paraffins,** alkanes, homologs of methane or marsh gas.

This simplest homologous series of organic chemistry shows the gradation in physical properties characteristic of such series. From a gas, only slightly less volatile than oxygen, the repeated increase of $CH_2$ in the compounds produces volatile liquids at $C_5$ and low-melting solids at $C_{16}$. The increase in boiling point for an increase of $CH_2$ decreases with the higher members. Of isomers, the normal (*n*-) (straight chain) member has the highest boiling point. In the series to $C_8$ the *n*-hydrocarbons boil lower than the lowest boiling isomer of the next homolog. Thus all the octanes boil higher than the *n*-heptane. At that point in the series, however, the spread between two successive *n*-hydrocarbons becomes so small and the possibility of branching, with accompanying lowering of the b.p., so great that at least two of the highly branched nonanes boil lower than *n*-octane. The densities of the *n*-alkanes increase from 0.4 to a limiting value of about 0.78. The value 0.77 is reached by the $C_{11}$ member. A further increase in the carbon chain gives little change in density (Krafft).

The index of refraction ($n_D^{20}$) for the liquid *n*-alkanes varies from 1.3577 for *n*-pentane to 1.4270 for *n*-pentadecane. A rise of 1° *decreases* the $n_D$ by 0.00055 for *n*-pentane and 0.00044 for *n*-dodecane. The use of the $\alpha$ line of the hydrogen spectrum instead of the D line *decreases* the $n^{20}$ for *n*-pentane by 0.0019 and for *n*-dodecane by 0.0022 while the use of the $\beta$ line in place of the D line gives *increases* of 0.0044 and 0.0053 respectively.

The alkanes are practically insoluble in water but soluble in most organic liquids. In aniline their solubility is limited at

ordinary temperature. The Critical Solution Temperatures (C.S.T.) in aniline and in liquid sulfur dioxide are characteristic of the individual hydrocarbons both in this and other series. The C.S.T. in aniline for some of the *normal* alkanes in °C. follows: $C_5$, 71.4; $C_6$, 69.0; $C_7$, 69.9; $C_8$, 71.8; $C_9$, 74.4; $C_{10}$, 77.5; $C_{11}$, 80.6; $C_{12}$, 83.7. The C.S.T. in liquid $SO_2$ is as follows: $C_6$, 10.2; $C_8$, 26.9; $C_{10}$, 37.3; $C_{12}$, 47.3; $C_{14}$, 55.5; $C_{32}$, 110.0°.

Because of their inability to *add* reagents the alkanes are called *saturated hydrocarbons*. Thus they can react with halogens only by *substitution*, a hydrogen atom being removed for each halogen which enters the molecule. They do not ordinarily react with hydrogen. When they do, a splitting of the carbon chain occurs. Thus ethane under extreme conditions reacts with hydrogen to give methane. A mixture of the higher members of the series, paraffin wax, received its name because of its inertness to acids and oxidizing agents (from *parum affinis*). Because methane is inert to most reagents and because the next few *normal* homologs are rather inert, the name paraffin hydrocarbons has given the impression that the entire series is very inactive chemically. This is not true. Even paraffin wax is fairly reactive with oxygen at slightly elevated temperatures (preparation of acids, E.P. 959). While reagents such as nitric acid, sulfuric acid, chromic acid mixture or potassium permanganate do not act readily with the lower *normal* members, some of them act with the higher members and with the branched members containing a *tertiary hydrogen*, $R_3CH$. This hydrogen can be replaced by $-NO_2$, $-SO_3H$ or $-OH$ with nitric acid, sulfuric acid or oxidizing agents. All of the paraffins react readily with chlorine at slightly elevated temperatures to give substitution of hydrogen by chlorine (chlorination). In much the same way vapor phase nitration (replacement of H by $NO_2$) can be successfully carried out with the paraffins (Hass 1936). An important difference is that nitration shows a greater tendency to split the carbon chain. Thus the nitration of propane gives not only 1- and 2-nitropropane but also gives nitromethane and nitroethane. If the latter two substances become industrially important, they will probably be made in this way.

In the first part of the series the increase of $CH_2$ makes a marked difference in the percentage composition. Farther up the series this addition makes less effect as the composition approaches that of $(CH_2)_n$ namely 85.7% C and 14.3% H. Thus analyses of higher members of the series will not tell them apart. An ordinarily accurate C and H determination would hardly distinguish between the $C_{20}$ and $C_{30}$ members.

**Possible and Known Isomers.** Using only the conception of the tetravalence of carbon the following numbers of *structural isomers* are predicted for the alkanes: 1 each for $C_1$, $C_2$ and $C_3$, 2 for $C_4$, 3 for $C_5$, 5 for $C_6$, 9 for $C_7$, 18 for $C_8$, 35 for $C_9$ and 75 for $C_{10}$. Methods of calculating the number of theoretically possible isomers have been developed (Henze, Blair, 1931–32; Perry 1932). The numbers obtained are over 100,000 for $C_{20}$ and over 100 million for $C_{30}$. Many of the structural isomers contain asymmetric carbon atoms and can thus give rise to stereoisomers. Thus, of the 18 structurally isomeric octanes, 3-Me-heptane (the meanings of all abbreviations are given in the index), 2,3-$Me_2$-hexane, 2,4-$Me_2$-hexane and 2,2,3-$Me_3$-pentane each contains an asymmetric carbon and could exist in *dextro* and *levo* optically active forms. A fifth octane, 3,4-$Me_2$-hexane contains two similar asymmetric carbons and could exist in *d*-, *l*- and *meso*-forms. Thus the total number of isomers of the octanes becomes 24, of which 11 are stereoisomers and 13 are non-stereoisomers. Similarly for $C_{10}$ the 75 structure isomers give rise to 101 stereoisomers and 35 non-stereoisomers. Soon the numbers predicted lose all physical significance, there being a total of 3,395,964 "possible" isomeric eicosanes ($C_{20}$).

Turning from the predicted to the known we find that all the predicted structural isomers have been prepared for the first eight members of the alkane series. Of the 35 possible structurally isomeric nonanes about half have been prepared. Many optically active hydrocarbons have also been prepared (p. 25) (Levene 1931).

The preparation of the higher alkanes involves many difficulties among which are (1) the decreased activity of the larger molecules involved, (2) the failure of many reactions when extreme branching of the carbon chain occurs (Conant, Blatt 1929), (3) re-

| C atoms | Name | m. °C. | b. °C. |
|---|---|---|---|
| 1. | Methane | −182.4 | −161.4 |
| 2. | Ethane | −183.5 | − 88.3 |
| 3. | Propane | −189.9 | − 44.1 |
| 4. | Butane | −138.9 | 0.6 |
| 5. | Pentane | −135. | 36.0 |
| 6. | Hexane | − 95.4 | 68.7 |
| 7. | Heptane | − 90.6 | 98.4 |
| 8. | Octane | − 56.9 | 125.6 |
| 9. | Nonane | − 53.7 | 150.7 |
| 10. | Decane | − 29.7 | 174.0 |
| 11. | Undecane | − 25.7 | 195.8 |
| 12. | Dodecane | − 9.7 | 216.2 |
| 13. | Tridecane | − 6.2 | 234. |
| 14. | Tetradecane | 5.5 | 252.5 |
| 15. | Pentadecane | 10. | 270.5 |
| 16. | Hexadecane | 20. | 287.5 |
| 17. | Heptadecane | 22.5 | 303. |
| 18. | Octadecane | 28. | 317. |
| 19. | Nonadecane | 32. | 330. |
| 20. | Eicosane | 36. | $205^{15}$* |
| 21. | Heneicosane | 40.5 | $215^{15}$ |
| 22. | Docosane | 44.0 | $224.5^{15}$ |
| 23. | Tricosane | 47.5 | 320.7 |
| 24. | Tetracosane | 51.0 | $243^{15}$ |
| 25. | Pentacosane | 54. | $259^{15}$ |
| 26. | Hexacosane | 57. | $268^{15}$ |
| 27. | Heptacosane | 59.5 | $270^{15}$ |
| 28. | Octacosane | 62. | $286^{15}$ |
| 29. | Nonacosane | 63.5 | $295^{15}$ |
| 30. | Triacontane | 66. | $304^{15}$ |
| 31. | Hentriacontane | 68. | $302^{15}$ |
| 32. | Dotriacontane (dicetyl) | 70.2 | $310^{15}$ |
| 33. | Tritriacontane | 72. | $328^{15}$ |
| 34. | Tetratriacontane | 73.5 | $336^{15}$ |
| 35. | Pentatriacontane | 74.0 | $341^{15}$ |
| 36. | Hexatriacontane | 76. | $265^{1.0}$ |
| 40. | Tetracontane | 81. | $241^{0.3}$ |
| 50. | Pentacontane | 92. | |
| 60. | Hexacontane | 99. | |
| 62. | Dohexacontane (dimyricyl) | 101. | |
| 64. | Tetrahexacontane (dilacceryl) | 102. | |
| 70. | Heptacontane | 105. | |

* Pressure in mm. of Hg.

arrangement due to branched chains (Whitmore 1932), and (4) the difficulty in separating and purifying the high molecular products.

The constants given are from I.C.T. and articles of later date.

The largest alkane molecule which has ever been prepared is $C_{94}H_{190}$ – 2,5,9,13,17,24,28,32,36,41,45,49,53,60,64,68,72,75-octadecamethylhexaheptacontane (Karrer, Stevens 1931).

The melting points of the *n*-alkanes beginning with $C_{18}$ form a smooth curve (Carothers 1930).

**Occurrence of the Alkanes.** The alkanes are widely distributed in nature. Methane occurs in natural gas from 75 to nearly 100%, in "fire damp" in coal mines and as "marsh gas" formed by the decay of vegetable matter. The higher homologs are found to a decreasing extent in natural gas and to an increasing extent in petroleum. A typical analysis of a natural gas from a large high pressure line supplied from many wells of various ages and from different sands gave the following percentages: methane 78, ethane 13, propane 6, butanes 1.7, pentanes .6, hexanes .3, heptanes and above .4. Gas from the Lower Oriskany Sand of Pennsylvania has 98.8% methane while a gas from Glasgow, Kentucky has been found with only 23% (EP 13).

Analysis of natural gas, EP 1092–1124.

The most important occurrence of the alkanes is in petroleum. Probably all petroleums contain at least some of this series. The proportions of hydrocarbons of other series and non-hydrocarbon constituents vary over wide ranges. Pennsylvania grade petroleum probably contains the largest amount of paraffin hydrocarbons, although there are indications that some Michigan crudes contain a still larger proportion, especially of the normal hydrocarbons.

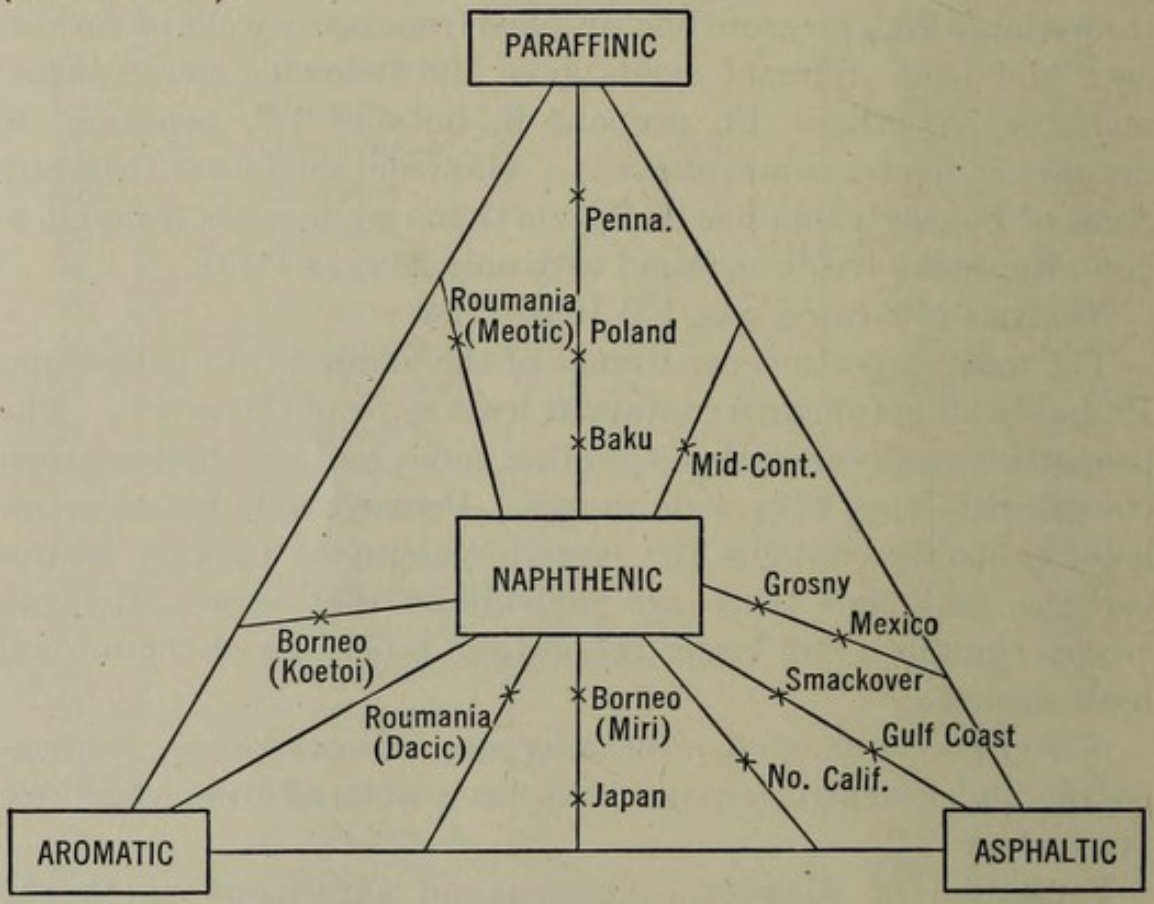
*n*-Heptane, *n*-nonane, *n*-hexadecane, *n*-heptacosane, *n*-nonacosane and *n*-hentriacontane have been isolated from vegetable products.

**Formation of Alkanes.** There is no agreement as to the probable mode of formation of natural gas and petroleum (Engler 1906, Brooks 1931, 1936, EP 35). The destructive distillation of vegetable materials, such as wood and the various forms of coal, as well as certain bituminous shales gives varying

amounts of the alkanes. "Low temperature tar" obtained by heating soft coal at about 600° contains alkanes which, at higher temperatures, are converted to aromatic substances. The cracking of cotton seed oil gives a gas containing 35% methane, 12% ethane and 5% propane and a liquid distillate containing 37% of higher alkanes.

The methods of preparation of the alkanes will be given under the individual members of the series.

**Petroleum** consists of complex mixtures of hydrocarbons concerning the nature of which there is very little information. Indications are that all these materials contain members of the methane series, the polymethylene series and the benzene series of hydrocarbons. The general composition of crude petroleums from different sources may be indicated by the following chart (Gruse 1928).




Many petroleum fractions contain hydrocarbons more deficient in hydrogen than any known series. These extend to $C_nH_{2n-20}$ (EP 28). There is no conclusive evidence that any natural petroleum contains members of the olefin series. The difference

between petroleums of various sources is in the proportions of the different types of hydrocarbons and in the nature and amounts of impurities (EP 19). Thus Pennsylvania crude oil contains a large proportion of methane hydrocarbons and practically no impurities of sulfur or nitrogen compounds. Mid-Continent (Oklahoma and Texas) crudes contain larger proportions of aromatic and polymethylene compounds (naphthenes) and larger amounts of sulfur compounds.

The present ignorance of the actual compounds in crude petroleums is nothing less than colossal. About thirty hydrocarbons have been isolated and certainly identified (EP 27). These make up less than ten per cent of a single Mid-Continent crude. No other crude has been studied even to that extent. Many hydrocarbons believed to be present in petroleums have been reported on insufficient evidence. Extreme care is necessary in purifying and identifying even relatively simple paraffin hydrocarbons (Washburn 1930). California crudes contain larger amounts of sulfur compounds, as well as some nitrogen compounds (Bailey 1930) (EP 819). Mexican, Venezuelan and Colombian crudes contain still larger amounts of sulfur compounds. The nature of the sulfur compounds in crude petroleum is little known (EP 421–463). Other important petroleum fields are those of Russia, Persia, Rumania and Borneo. Smaller fields are found in many parts of the world including even France, Germany and Italy. The United States in recent years has produced over 70% of the World's crude oil. The American Petroleum Institute, 250 Park Avenue, New York City, issues frequent bulletins covering World petroleum statistics. The extent and amount of crude petroleum deposits is now known to be many times what was suspected a few years ago.

The basis of petroleum technology was laid by a report by Benjamin Silliman, Jr., of Yale, made in 1855 (Johns 1923) on a sample of surface petroleum from Titusville, Pennsylvania. In 1859 the first oil well was sunk near Titusville by E. L. Drake. Its production was 25 barrels per day.

The refining of petroleum has grown into a most complex chemical engineering industry. Distillation is the chief method used in separating crude petroleum into useful products. At the

present time the distilled fractions from crude petroleum are casinghead gasoline, gasoline, kerosene, gas oil and, in some cases, lighter lubricating oils ("neutrals"). The residues from distillation supply most of the lubricating oils ("bright stock") petrolatum (vaseline) and either paraffin wax or petroleum pitch, depending on the nature of the crude. Fractions of the distillate boiling about 0° and about 20° have been called cymogene and rhigoline respectively. Higher boiling portions of the volatile part of petroleum are called petroleum ether and ligroin. Usually the boiling range is given with these names to avoid confusion. *Benzine* is an indefinite term roughly corresponding to a volatile gasoline. Gasoline (petrol) is any mixture of hydrocarbons which can be used in spark ignition internal combustion engines. Too much low boiling material will prevent the fuel from being sucked as liquid into the carburetor thus causing "vapor lock," while too much high boiling material results in imperfect combustion and excessive carbon deposition in the engine cylinders. Formerly the only requirements for gasoline were that it should be neither too volatile nor too non-volatile and should not contain enough sulfur compounds to cause corrosion. These simple requirements were changed by the high compression motor, introduced to increase the power of an automobile for a given weight of engine. Increased compression caused detonation or knocking of the fuel in place of its rapid smooth combustion. It was found that gasolines from different sources and different processes varied widely in knock characteristics. In general, straight chain paraffin hydrocarbons knock worse and aromatic hydrocarbons, olefins and highly branched paraffins knock less (p. 26). The discovery of negative catalysts for detonation, notably tetraethyl lead (Midgley), has revolutionized the gasoline industry. At first used only in special quality anti-knock gasoline (Ethyl Gas), it is now used in lesser amounts in almost all gasoline (U.S.A.). The amount of pure tetraethyl lead used per year is undoubtedly well in excess of 20 million pounds.

Kerosene is any mixture of hydrocarbons which is not volatile enough for use as gasoline but which can be burned in lamps and similar devices. Since gasoline is subject to tax in many cases and kerosene is not, it has become necessary to have a legal

definition of the two. In Pennsylvania the definition of kerosene in 1936 involved the following data: flash pt. above 114° F., not over 10% and 45% distillable at 347° F. and 392° F. respectively. Kerosene of this quality would contain little below the decanes.

Analysis of petroleum distillates, EP 1125–1153.

Until the end of the Nineteenth Century, the most important product from petroleum was kerosene. The lower boiling products were of little use. To prevent the inclusion of them in kerosene, stringent regulations were made as to the "flash point" and "fire point" of kerosene in order to insure its safe use. The first "cracking" or thermal decomposition of the higher fractions of petroleum was for the purpose of increasing the yield of kerosene above that obtainable by straight distillation. With the development of the internal combustion engine, gasoline has become the important product, with lubricating oil a close second. Kerosene is only a by-product. In order to increase the yield of gasoline, many different cracking processes have been perfected. These operate under a wide range of conditions of temperature and pressure and on materials such as gas oil, kerosene and even the crude petroleum itself. Yields of gasoline as high as 70% of the crude have been obtained. The cracking of kerosene or gasoline to obtain more gasoline or gasoline of higher anti-knock quality is called "re-forming." Some of the important cracking processes used in the United States are the following: Burton, Dubbs, Isom, Jenkins, Buerger, Cross, Koontz, Holmes-Manley, Tank and Tube, deFlorez and Gyro (Owen 1929) (EP 91–119). Another important cracking process involves the use of heat in the presence of anhydrous aluminum chloride, which is recovered from the reaction residue by distillation (McAfee) (EP 190).

Cracked gasolines are rich in olefins and diolefins. This has an advantage due to the anti-knock properties of these unsaturated compounds (EP 961), but the disadvantage that the unsaturated compounds, especially the diolefins, tend to polymerize and form "gums" which clog the carburetor (EP 881, 889). The tendency of higher olefins and diolefins from cracking operations to form complex products is being utilized in the manufacture of resins from petroleum (Thomas, Hochwalt).

Sulfuric acid is used in refining petroleum fractions to remove various objectionable materials including sulfur compounds. Unfortunately this treatment also removes some of the aromatic compounds and the olefins and diolefins (from cracked gasoline). This is undesirable since these materials have great anti-knock value. The present tendency is to add small amounts of stabilizers (negative catalysts) to cracked gasoline to delay polymerization. These stabilizers are usually compounds of the anti-oxidant type such as naphthylamines, *p*-aminophenol and diphenylhydrazine (EP 889–913).

The use of sulfuric acid in petroleum refining is undoubtedly decreasing.

An important development in the refining of petroleum is the hydrogenation process of Bergius originally intended for the conversion of low grade coals to a fuel oil resembling petroleum. The hydrogenation of petroleum produces types of lubricating oils and anti-knock gasolines different from those from other processes. One of the most important advantages of the hydrogenation process is that all organic sulfur compounds contained in the crudes are converted to hydrogen sulfide which is readily removed as gas without the necessity of the expensive treatment with concentrated sulfuric acid which was used for removing sulfur in other processes (Haslam 1932). The catalysts used consist of sulfides of Group V of the Periodic Table which are not poisoned by sulfur impurities. Large amounts of methane are formed during the hydrogenation. This is treated with steam catalytically to give hydrogen for the process (EP 205, 266). Thus hydrogenation may be regarded as a combination of cracking and hydrogenation. It has the advantage of not producing coke as does cracking alone.

The refining of lubricants seems likely to be revolutionized by the use of extraction by partially miscible solvents such as phenol, cresylic acid (mixture of cresols, xylenols and higher phenols), nitrobenzene, dichlorodiethyl ether ("chlorex") and furfural. These extraction processes are natural outgrowths of one long used in the industry, the extraction of petroleum fractions with liquid sulfur dioxide (Edeleanu process) for the removal of sulfur compounds.

Paraffin wax was originally obtained from tars from the distillation of wood, peat, and lignite, but is now obtained from petroleum especially from paraffin-base oils such as Pennsylvania grade crude. Little is known about the composition of paraffin wax except that it consists mainly of higher alkanes and probably contains only small amounts of the normal compounds (Henderson). Paraffin wax in lubricating oils causes the oil to partly solidify at low temperatures. This can be avoided by removing the wax. This is usually done by diluting the lubricant with a low boiling petroleum fraction, chilling by artificial refrigeration, centrifuging out the separated wax and distilling off the solvent. This process is not only costly but there is some possibility that the wax is an advantage in the lubricant except for the danger of its solidifying. Hence substances have been introduced to delay or inhibit wax crystallization (Paraflow). Such substances consist of complex mixtures of complicated molecules incapable of crystallizing. Perhaps they are adsorbed on the first microcrystals and prevent their growth and action as nuclei for the crystallization of the main mass of wax. A typical crystallization inhibitor of this kind is obtained by heavily chlorinating paraffin and treating the product with naphthalene and aluminum chloride. It is easy to see that the products are complicated.

Petrolatum (vaseline) is a buttery mixture of hydrocarbons similar to paraffin.

Liquid petrolatum (sometimes called Russian oil, white oil or "Nujol") is a high boiling petroleum distillate which has been treated with fuming sulfuric acid until no further reaction takes place. It is practically odorless and tasteless and is used as a laxative.

Heavier grades of petroleum oils which are not suitable for other purposes are now being burned in Diesel engines. This involves their being sprayed into the cylinders and ignited by compression without the use of spark plugs. The present rapid increase in the use of Diesel engines is leading to a definite effort to standardize and find the best Diesel fuels. Cetane and cetene (p. 49) and methylnaphthalene are used as low knock and high knock standard fuels for rating Diesel fuels. It is to

be noted that the knock qualities of a fuel are exactly opposite for a Diesel motor and for a spark ignition motor. Thus an aromatic hydrocarbon like methylnaphthalene is a good anti-knock material for the latter while a long straight chain compound like cetane or cetene ($n$-$C_{16}$) gives extreme knock (p. 49).

Ozokerite, earthwax, is a natural paraffin wax found in Galicia and near Baku. When bleached it is used as "ceresin." It is harder and has a higher melting point than ordinary paraffin wax.

Asphalt is found in large deposits on the island of Trinidad and in various other places. It is a complex oxidation and polymerization product of hydrocarbons, probably from crude petroleum. Large amounts of petroleum pitch are now used in place of natural asphalt. Gilsonite is a high grade asphalt found in Utah.

Carbon black is obtained by the partial combustion of natural gas (EP 234–54).

**Artificial Petroleum from Coal.** Coals, especially those of the lower ranks such as bituminous and brown coals, contain considerable amounts of hydrogen but less than that contained in the heaviest petroleums. These coals can be hydrogenated under high pressure with suitable catalysts (Bergius) to give a material essentially like petroleum. Methane which is a considerable by-product can be used with steam as the source of the hydrogen used in the process. The hydrogenation of low grade coal to give liquid fuels and lubricants is at present assuming industrial importance in countries which have coal but no petroleum. In the future it will be important for the whole world because the coal reserve is undoubtedly many times that of petroleum. It is interesting to note in passing that the first hydrogenation of coal was accomplished by Berthelot by means of hydriodic acid.

Another solution of the problem of converting coal to liquid fuels involves its conversion to water gas by steam.

$$C + H_2O \rightarrow CO + H_2$$

The gaseous mixture with suitable catalysts gives a complex liquid fuel (Synthol, Franz Fischer).

## Individual Paraffin Hydrocarbons

### Methane, $CH_4$

*Commercial Sources*:

1. Natural gas consists largely of methane (75–100%).

2. Gas formed by heating soft coal contains 30–40% methane.

3. Anaerobic bacterial decomposition of vegetable matter (mainly cellulose) gives gases rich in methane. The gas from the activated sludge process of sewage disposal contains as much as 80% methane. Recently a process has been proposed for converting farm waste, such as cornstalks, into a fuel gas containing about 50% methane (Buswell 1929, 1930, 1933).

4. The hydrogenation of coal, petroleum and similar products (Bergius 1923, 1926) forms large amounts of methane gas.

*Preparation.*

*A*. General Methods (applicable to higher hydrocarbons).

1. By the hydrolysis of a methyl Grignard compound.

$$CH_3MgX + H_2O \rightarrow CH_4 + MgX(OH)$$

Dilute acid or a solution of an ammonium salt is usually used to dissolve the basic magnesium salt formed. If only a small amount of methane is desired, methyl iodide may be used to make the Grignard complex. If a larger amount is needed methyl bromide gas may be generated from methanol, sodium bromide and sulfuric acid. If still larger amounts are needed a tank of compressed methyl chloride gas should be obtained since this substance is available as a commercial refrigerant.

2. Purified dimethylmercury or methylmercuric sulfate treated with concentrated sulfuric acid gives pure dry methane. The mercury dimethyl (very toxic) is a high boiling liquid while the methylmercuric sulfate is a slightly volatile easily crystallized solid.

3. By heating anhydrous sodium acetate with soda lime (a mixture of the hydroxides of sodium and calcium obtained by slaking quick lime in concentrated sodium hydroxide solution).

$$CH_3CO_2Na + NaOH \rightarrow CH_4 + Na_2CO_3$$

This method becomes less and less valuable with higher members of the series, especially with branched compounds.

4. By reduction of alkyl halides by metallic sodium in liquid ammonia.

$$CH_3I + 2\,Na + NH_3 \rightarrow CH_4 + NaI + NaNH_2$$

The escaping methane can be freed from ammonia by washing with acid.

*B.* Special Methods.

1. By removing the higher hydrocarbons from natural gas by activated carbon (Storch 1933).

2. By passing a mixture of carbon monoxide or dioxide with hydrogen over finely divided nickel at about 300° (Sabatier and Senderens).

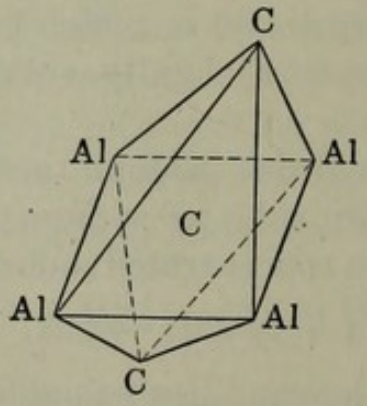
$$CO_2 + H_2 \rightarrow CO + H_2O$$
$$CO + 3\,H_2 \rightarrow CH_4 + H_2O$$

Other catalysts may be employed such as Pt, Pd and even Fe (Fischer, Tropsch 1923). Presumably hydrogen first adds to the carbon monoxide to give formaldehyde which is then further reduced to methanol. Since both of these substances are more easily reduced than carbon monoxide, they do not appear in the final products. The catalyst is obtained by soaking a porous material such as pumice or diatomite brick in a solution of a suitable nickel salt such as the nitrate or oxalate, drying and heating to form the oxide and finally reducing the oxide to the metal by hydrogen at a carefully adjusted temperature.

3. By the hydrolysis of aluminum carbide (Rep. 1913, 56).

$$Al_4C_3 + 12\,H_2O \rightarrow 3\,CH_4 + 4\,Al(OH)_3$$

Aluminum carbide probably has the molecular structure.




Impurities usually give traces of $H_2$ and $C_2H_2$.

4. By passing hydrogen at 475° through a mixture of carbon and nickel (Bone 1897).

5. By the action of hydrogen sulfide and carbon disulfide with hot copper, the first synthesis of methane (Berthelot 1856).

6. By passing CO or $CO_2$ over hot calcium hydride, $CaH_2$.

*Physical Properties.* Methane is a colorless gas with a faint odor. It is slightly soluble in water but more so in alcohol. Its critical temperature and pressure are −82.5° and 45.7 atm. Its m.p. and b.p. are −183° and −161.4°. It can be liquefied by liquid air. The best method of determining methane in the presence of other hydrocarbons is by low temperature distillation (ethane, b. −88.3°, propane, b. −44.5°) (Rosen 1931, Podbielniak 1933, Rose 1936).

*Tetrahedral Structure.* The suggestion that methane has a pyramidal structure (Henri, Rev. 1927, 189–202) rather than the usually accepted tetrahedral structure is based on an incorrect interpretation of X-ray and macrocrystalline data.

**Reactions of Methane.** The surprising inactivity of methane may be due to its having an outer shell of eight electrons as in the rare gases, the four hydrogen atoms being inside this outer shell. The ionization potential of methane is of the same order of magnitude as that of argon.

1. When heated at about 1000°, methane gives a small yield of benzene (0.2 gal. per 1000 cu. ft.) and other aromatic compounds. Careful studies of the pyrolysis of methane indicate that the first step is its conversion to hydrogen and free methylene, ($CH_2$) (Kassel 1932). The latter reacts with a molecule of methane to give ethane. Under properly controlled conditions as high as 95% yields of ethane can be obtained (Storch 1932). The ethane loses hydrogen to form ethylene and then further to form acetylene. The latter polymerizes to form benzene. Under ordinary conditions all the intermediate products are less stable and the mixture issuing from the hot zone consists of unchanged methane and a small amount of benzene and higher products (EP 37–90; Hague 1929; Rep. 1930, 82; Frolich 1931). In the absence of all possible catalysts, methane at 1000° gives only acetylene and hydrogen (Holliday 1931).

2. Oxidation (Egloff, Rev. *6*, 91, EP 846).

(*a*) With excess of oxygen at high temperatures complete combustion gives carbon dioxide and steam. One cu. ft. of methane gives 1000 B.T.U. whereas the same amounts of coal gas and ordinary water gas give only 500 and 300 B.T.U. respectively.

(*b*) With insufficient oxygen it is possible to limit the combustion and obtain carbon monoxide and water as the chief products. There has been much speculation as to the mechanism of the combustion of methane. The first product is probably methanol formed by the direct introduction of an atom of oxygen into a molecule of methane. Methanol is readily dehydrogenated or oxidized to formaldehyde and hydrogen or steam. Formaldehyde is decomposed by heat to carbon monoxide and hydrogen or is readily oxidized to formic acid which decomposes to form carbon monoxide and water. Since all of these possible intermediate products are more sensitive to heat and oxidation than are methane, carbon monoxide and water, they are not likely to survive among the reaction products.

(*c*) Nitrogen peroxide oxidizes methane to give a small yield of formaldehyde (Frolich 1928).

3. With steam. The most important practical reaction of methane next to its complete combustion for the production of heat is its reaction with steam at high temperatures (800–1000° C.) in the presence of catalysts such as nickel activated by promoters such as alumina or thoria to give carbon monoxide and hydrogen. This is the chief source of hydrogen for commercial hydrogenation of coal and petroleum and for the synthesis of ammonia (Houk 1932). The carbon monoxide formed will further react with steam at about 500° C. with an iron oxide catalyst promoted with chromium oxide to give carbon dioxide and hydrogen. Thus four molecules of hydrogen are obtained from one molecule of methane and two molecules of steam (EP 276).

4. With chlorine. The reaction of methane with chlorine is likely to be explosive. The products are hydrogen chloride, carbon, and the four possible chlorinated methanes. If the violence of the reaction is abated by bringing the gases together in a reactor filled with sand, the formation of carbon is practically eliminated. By modern methods of distillation it is possible to

separate the methyl chloride, methylene chloride, chloroform and carbon tetrachloride formed in the reaction (Rep. 1919, 69; 1923, 74; Curme 1922, EP 686). By using volume ratios of $N_2$, $CH_4$ and $Cl_2$ of 80 : 8 : 1 over a catalyst of cupric chloride on pumice at 450°, it is possible to convert 45% of the chlorine to methyl chloride.

The conversion of methane to its chlorination products is not commercially important at the present time for the following reasons, among others: (*a*) There are cheap methods for making pure methyl chloride, chloroform and carbon tetrachloride. (*b*) Most of the possible uses for methylene chloride are better served by formaldehyde. (*c*) Cheap methane in the form of natural gas and cheap chlorine from cheap hydroelectric power are usually not located near each other geographically. One or the other has to be transported.

Bromine would presumably act with methane much like chlorine. Iodine is much less reactive and, moreover, the hydrogen iodide formed would tend to reverse any substitution, thus giving the original hydrocarbon. Fluorine reacts violently with methane giving almost entirely carbon and hydrogen fluoride.

5. Methane under the influence of alpha particles or of an electrical discharge is condensed to a mixture of complex hydrocarbons (Lind 1930, EP 264).

6. Methane can be converted to HCN in 10% yield by passing it with $NH_3$ over $Al_2O_3$ at 1000°. An electric discharge through $CH_4$ and $N_2$ converts the former nearly completely to HCN.

7. Methane does *not react* with the following: (*a*) ordinary oxidizing agents, (*b*) hydrogen, (*c*) reducing agents, (*d*) acids, (*e*) bases, (*f*) metals.

Methane, Storch, U.S.B. of Mines, Information Circular 6549 (1932).

**Ethane,** $CH_3CH_3$, occurs in varying amounts in natural gas (EP 13). The statement that it forms the chief gas of a well near Pittsburgh is erroneous. It can be prepared by the general methods from sodium propionate, ethyl Grignard reagents, ethyl halides, and ethyl mercury compounds.

In common with the other homologs of methane it can be made by the Wurtz reaction from the proper alkyl halide and metallic sodium.

$$2\,CH_3I + 2\,Na \rightarrow CH_3CH_3 + 2\,NaI$$

The yield is poor. Apparently the first step is the formation of sodium iodide and free methyl radicals. These then react to give ethane and by-products as follows:

$$2\,CH_3 \rightarrow CH_3CH_3$$
$$2\,CH_3 \rightarrow CH_4 + [CH_2]$$
$$2\,[CH_2] \rightarrow CH_2{=}CH_2$$
$$n\,[CH_2] \rightarrow C_nH_{2n}$$

High boiling polymers are always formed in the Wurtz reaction.

Ethane is also obtained during the electrolysis of sodium acetate solution (Kolbe).

$$2\,CH_3CO_2Na + 2\,H_2O \rightarrow C_2H_6 + 2\,CO_2 + 2\,NaOH + H_2$$

The ethane and carbon dioxide are liberated at the positive electrode (anode).

The best way of making pure ethane is by the catalytic hydrogenation of ethylene prepared from ethanol and sold in very pure form for use in anesthesia. Ethylene is available in enormous amounts from the products of cracking processes.

*Reactions of Ethane.* Ethane is much more reactive than methane.

1. On *heating* it gives hydrogen and ethylene which then undergoes a very complex series of decompositions and polymerizations (Pease 1928).

2. When treated with insufficient *oxygen*, especially in the presence of platinum as a catalyst, ethane gives a considerable amount of formaldehyde, much more than can be obtained from methane by any oxidation method (EP 850). Presumably the process involves the intermediate formation of ethylene and ethylene glycol.

3. Chlorine and bromine react readily with ethane giving a complex mixture of halogenated products (EP 712). These reactions have never been studied thoroughly because of their

complexity, the lack of a cheap source of ethane and the fact that the desirable substitution products of ethane can be made more satisfactorily by indirect means.

4. The silent electric discharge converts ethane to hydrocarbon mixtures of M.W. 100–500 depending on conditions (Lind 1928).

5. At high temperatures and pressures ethane can be hydrogenated to methane.

6. Ethane does not react with ordinary oxidizing and reducing agents, nor with acids, bases and metals.

**Propane,** $CH_3CH_2CH_3$. While propane can be prepared by methods analogous to those for making its two lower homologs, there is no necessity for so doing because it can readily be obtained in almost any desired amount from the more volatile fractions of "natural gasoline" or "casinghead" gas. This contains about 20% propane and butanes. (EP 18.) It can be selectively adsorbed on activated charcoal, then removed by steam and finally fractionally distilled under pressure to any desired degree of purity.

Rather impure propane is sold in tanks under moderate pressure for use as a household fuel gas (Pyrofax). Propane has recently found wide use in the petroleum industry as a combined solvent and refrigerant for simultaneously extracting and dewaxing a lubricating fraction (Mueller process) (Duo-Sol process) (Wilson 1936).

Propane is more reactive than ethane. Thermal decomposition gives mainly ethylene and methane with smaller amounts of propylene and hydrogen (Pease 1928). The ethylene is used to make ethylene glycol and some fifty related products. The propylene is changed to isopropyl alcohol and acetone.

Propane with $O_2$ below the ignition point gives propylene, acetaldehyde and $CO_2$ (Pease 1929).

The vapor-phase nitration of propane gives 1- and 2-nitropropanes and smaller amounts of nitroethane and nitromethane (Hass 1936).

**Butanes,** $C_4H_{10}$. The two isomers, normal butane and isobutane are available in any desired quantity and degree of purity by separation from natural gas by means of selective adsorption or fractional distillation under pressure.

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1. *n-Butane*, $CH_3CH_2CH_2CH_3$, b. + 0.6°, shows practically the same reactions as propane or ethane but is more reactive. On pyrolysis it gives all the theoretically possible products, namely, methane, ethane, ethylene, propylene, butene-1, butene-2 and hydrogen. The predominant reaction gives methane and propylene.

An electrical discharge converts *n*-butane to a mixture of hydrocarbons of somewhat the same complexity as crude petroleum. One of the resulting fractions contains a mixture of octanes and octenes (Lind 1929).

Pure *n*-butane, mixed with a definite amount of dry air, is used as a standard fuel for the accurate heat treatment of special steels.

2. *Isobutane*, trimethylmethane, $(CH_3)_3CH$, b. −10.2°. On heating at 600° it gives more isobutylene and hydrogen than methane and propylene while at 700° the reverse is true (Hurd 1929).

In addition to the expected reactions, isobutane gives others on account of its *tertiary* hydrogen atom. Mild oxidation with oxygen or an oxidizing agent like potassium permanganate converts this hydrogen to a hydroxyl forming tertiary butyl alcohol (Meyer 1883). Concentrated sulfuric acid and fuming nitric acid replace the tertiary hydrogen by the sulfonic acid group ($SO_3H$) and the nitro group ($NO_2$) respectively. With various catalysts it adds to olefins like isobutylene to give complex mixtures containing 2,2,4-$Me_3$-pentane (Ipatieff 1935).

Mixed butanes are used for "carburetting" water gas to render its flame luminous.

**Pentanes,** $C_5H_{12}$. *Normal pentane*, $CH_3(CH_2)_3CH_3$, b. 36°, and *isopentane*, dimethylethylmethane, 2-Me-butane, $(CH_3)_2CHCH_2CH_3$, b. 28°, are readily obtained from natural gas. The casinghead or natural gasoline made from natural gas by compression or adsorption methods contains 15–35% of a pentane mixture boiling 27–40° (EP 18). The reactions of normal and isopentane are like those of the butanes. Less usual reactions are the following: *n*-Pentane with acetyl chloride and $AlCl_3$ gives 2-acetylpentane and with CO, HCl, and $AlCl_3$ gives ethyl isopropyl ketone (Hopff 1931). Isopentane with CO and HCl in the

presence of $AlBr_3$ and $Cu_2Cl_2$ gives, among other products, 2,2-dimethylbutanol. Isopentane in vapor phase oxidation gives isovaleraldehyde, then isobutyraldehyde and finally acetone at which point the oxidation becomes slower (Edgar 1929). Isopentane with dil. nitric acid gives 2-nitro-2-Me-butane. With more concentrated acid it gives di- and trinitro compounds (EP 1042).

The chlorination of mixed *n*- and *iso*-pentane has been developed commercially (Ayres 1929, Clark 1930, EP 721, 726). A mixture of chlorine with a large excess of hydrocarbon is passed very rapidly through iron tubes at about 300°. The chlorine reacts completely with the formation of all the theoretically possible monochlorides and smaller amounts of higher chlorides. These chlorides are used as such or are converted to alcohols, olefins and acetates (Pentasol, Pentacetate, Sharples).

Pentane is used in thermometers for low temperatures.

*Neopentane* (the prefix *neo*- indicates the presence of a C attached by all four valences to other C atoms), tetramethyl methane, $(CH_3)_4C$, b. 9.5°, is obtained by the action of dimethylzinc on acetone dichloride, 2,2-dichloropropane, prepared from acetone, and phosphorus pentachloride, or on a tertiary butyl halide. The best preparation is from *ter*-butyl chloride and methylmagnesium chloride (Whitmore 1933).

Neopentane, on pyrolysis, gives methane and isobutylene (Frey 1933). On chlorination it gives neopentyl chloride, $(CH_3)_3CCH_2Cl$, without any rearrangement (Whitmore 1933). This chloride cannot be made from the corresponding alcohol (pp. 73, 128).

*The normal hydrocarbons from* $C_5$ *to* $C_{12}$ have been obtained in high purity from suitable petroleum fractions by distillation, exhaustive treatment with chlorosulfonic acid ($ClSO_3H$) to remove all more active material and final careful distillation (Shepard, Henne, Midgley 1931).

The following physical constants have been determined for the pure hydrocarbons: boiling point, melting point, density, ($d_4^{20}$ and $d_4^{25}$), index of refraction ($n$) at 20°, 25° and 45.3° for the $\alpha$, D, and $\beta$ lines, molecular refraction and dispersion, critical solution

temperature with aniline, viscosity, specific heat, heat of fusion, dielectric constant, fluidity, heat of combustion, vapor pressure, Raman spectra and Nekrasov Constant, $T\sqrt{\frac{MR}{M - MR}}$, in which $T$ is the absolute b.p., $M$ the mol. wt. and $MR$ the Molecular Refractivity calculated by the Lorentz-Lorenz formula, $\frac{n^2 - 1}{(n^2 + 2)d}$. Pure normal alkanes have a faint but decidedly pleasant odor entirely different from that of the impure materials which resemble the characteristic odor of petroleum fractions.

The sizes and shapes of the molecules of *n*-heptane, *n*-octane, and *n*-nonane in the gaseous state have been determined (Mack 1932). They exist as loose helixes.

*n*-Hexane, *n*-octane, *n*-decane and *n*-tetradecane can be prepared by the Wurtz reaction by the action of Na on the normal halides containing 3, 4, 5 and 7 carbon atoms which are readily available. A trace of acetonitrile acts catalytically. It must be remembered that numerous by-products are formed and must be removed from the product. This is easy because of wide differences in the boiling points (The Wurtz Reaction, Wooster, Rev. 1932, 79).

The preparation of a normal hydrocarbon from a mixture of two alkyl halides of nearly the same carbon content with sodium is seldom practical. There are *three* main products with boiling points rather close together and a correspondingly large number of by-products.

The normal paraffins from $C_5$ to $C_{12}$ have been synthesized and their physical constants have been determined (Mair 1932).

**Hexanes** (Maman 1934). Four of the hexanes, *n*-hexane, 2-methylpentane (at Geneva in 1892 a Congress of organic chemists adopted and greatly expanded the system of nomenclature for complex organic compounds devised by Hofmann in 1865—Am. *15*, 50; Ber., *26*, 1595) (isohexane) (the prefix *iso*- applies correctly only to compounds containing $Me_2CH-$ attached to a normal chain), 3-Me-pentane, and 2,3-$Me_2$-butane have been isolated from Oklahoma petroleum (Bruun 1930). All five of the hexanes have been repeatedly synthesized.

2,3-$Me_2$-butane, diisopropyl, in common with all paraffins having tertiary H atoms, reacts readily with dilute nitric acid to give a tertiary nitro compound. More vigorous treatment also replaces the other tertiary H (EP 1043).

2,2-$Me_2$-butane, trimethylethylmethane, neohexane, although it contains no *ter*-H, reacts readily with nitric acid to give a 3-nitro compound. (Markownikoff 1900.) The structure is proved by reduction with alkaline stannite solution to give the oxime of methyl *ter*-butyl ketone.

**Heptanes.** Normal heptane is obtained by distillation and chemical treatment of the oil obtained from the resin of the Jeffrey pine (Kremers). In common with other normal paraffins it exhibits a bad "knock" in an internal combustion engine. *n*-Heptane is used as a standard in knock rating (Edgar 1927). For this purpose it was originally made from the Jeffrey pine but is now prepared synthetically. Several processes are available.

*n*-Butyraldehyde condenses readily with acetone. The following steps are then easy.

$$\mathrm{PrCHO} + \mathrm{CH_3COCH_3} \rightarrow \mathrm{PrCHOHCH_2COCH_3}$$
$$\rightarrow \mathrm{PrCH{=}CHCOCH_3} \rightarrow \mathrm{PrCH_2CH_2COCH_3} \rightarrow \mathrm{CH_3(CH_2)_5CH_3}$$

Another possible process would be the catalytic reduction of di-*n*-propyl ketone obtained from *n*-butyric acid. The following process might be better although it involves more steps. *n*-Butyraldehyde is subjected to the aldol condensation, the aldol is dehydrated and hydrogenated to the acid. This gives *n*-heptane on decarboxylation. Each of the steps from butanol-1 to *n*-heptane can be done catalytically.

$$2\ \mathrm{EtCH_2CHO} \rightarrow \mathrm{EtCH_2CHOHCH(Et)CHO} \rightarrow \mathrm{PrCH{=}C(Et)CHO}$$
$$\rightarrow \mathrm{BuCH(Et)CHO} \rightarrow \mathrm{BuCH(Et)CO_2H} \rightarrow \mathrm{BuCH_2Et}$$

The same result is achieved by oxidation and decarboxylation starting with 2-ethylhexanol-1, a commercial product (C and C). *n*-Heptane, can also be made by the reduction of heptaldehyde (oenanthol) obtained in the destructive distillation of castor oil (mainly glyceryl ricinoleate).

*n*-Heptane, 2,2-$Me_2$-pentane and 2- and 3-Me-hexane have been found in petroleum (EP 27).

All nine of the possible isomers, $C_7H_{16}$, have been prepared in a high state of purity (Edgar 1929). A variety of physical properties such as b.p., index of refraction, density, f.p., C.S.T. in aniline, molecular refractivity and dispersion, molecular volume, compressibility, coefficient of expansion, surface tension, viscosity and dielectric properties have been measured for these pure materials.

Six of the isomeric heptanes were made by the following steps:

1. Grignard reagent + ketone → tertiary alcohol.
2. Alcohol → olefin mixture.
3. Olefin mixture → heptane.

Thus 2-methyl hexane was made as follows:

1. *n*-Butyl magnesium bromide in anhydrous ether with acetone followed by treatment with acid gave 2-methylhexanol-2 (dimethyl-*n*-butylcarbinol).

2. Dehydration of the alcohol by refluxing with a trace of iodine (applicable to higher tertiary alcohols only, Hibbert) gave mainly 2-methyl-hexene-2 with a small amount of the isomeric 2-methyl-hexene-1.

3. Passage of the mixed olefins with purified hydrogen over hot finely divided nickel gave 2-methylhexane, isohexane.

Similar methods gave 3-methylhexane, 3-ethylpentane, 2,3-dimethylpentane, 2,4-dimethylpentane and 2,2,3-trimethylbutane.

2,2-Dimethylpentane and 3,3-dimethylpentane could not be prepared by this series of reactions because the corresponding alcohols, 2,2-dimethylpentanol-3 and 3,3-dimethylpentanol-2 contain the "neopentyl alcohol" system (p. 136) and undergo *rearrangements* on dehydration, giving chiefly 2,3-dimethylpentene-2. These two heptanes were made by a modified Wurtz reaction involving the reaction of a suitable Grignard reagent with an alkyl halide in the presence of dry ether and mercuric chloride. The yield was poor but better than that obtainable by any other known method.

One of the simplest optically active hydrocarbons *l*-2,3-dimethylpentane (methylethylisopropylmethane), has been made in the following steps (Levene).

Optically active material is obtained by resolving *dl*-butanol-2 into its *d*- and *l*- forms (Pickard, Kenyon 1911). The alcohol is heated with phthalic anhydride to give hydrogen *sec*-butyl phthalate. This is then combined with the optically active base, brucine, to give brucine *dextro-sec*-butyl and brucine *levo-sec*-butyl phthalates. Recrystallization separates these, the former being less soluble. Acidification precipitates the optically active hydrogen *sec*-butyl phthalate which is then saponified to give the optically active butanol-2.

The conversion of dextrorotatory butanol-2 involves the steps: Conversion to the levorotatory bromide by hydrogen bromide, reaction of the latter with the sodium derivative of ethyl methylmalonate, followed by saponification and acidification to give the methyl *sec*-butyl malonic acid which loses carbon dioxide at 190° to give dextrorotatory methyl-*sec*-butyl-acetic acid (2,3-dimethyl-*n*-valeric acid). This is converted to the dextrorotatory ethyl ester which is reduced by sodium and absolute alcohol to the primary alcohol, levorotatory 2,3-dimethylpentanol-1. This is converted to the dextrorotatory bromide by $PBr_3$. Conversion of the bromide to the Grignard reagent and treatment of the latter with acid gives levorotatory 2,3-dimethylpentane. The specific rotations $[\alpha]_D^{25}$ (p. 121) of the optically active substances involved in this series of changes are approximately as follows: Butanol-2, +8.4; 2-Bromobutane, −13.8; 2,3-Dimethyl-valeric acid, +1.3; Ethyl ester, +1.9; 2,3-Dimethylpentanol-1, −0.9; 1-bromo-2,3-dimethylpentane, +2.9; 2,3-Dimethylpentane, −9.4 (Levene, Marker 1931).

**Octanes.** The eighteen possible octanes have been prepared by methods similar to those described for the heptanes (Noller 1929, Edgar 1929, Whitmore 1933).

The Wurtz reaction was first used (1855) in the action of isobutyl iodide and sodium to give 2,5-$Me_2$-hexane. *n*-Octane is obtained by the Wurtz reaction in 65% yield (Lewis 1928). As always the reaction gives considerable amounts of by-products

(p. 18) *n*-Octane can also be obtained readily by chilling the proper fraction from petroleum with liquid air.

*n*-Octane with anhydrous $AlCl_3$ at 120–150° gives butane and polymeric olefins (Grignard 1924).

The preparation of hexamethylethane, 2,2,3,3-$Me_4$-butane, requires special processes. Of those, perhaps the best is the peculiar reaction of silver bromide with *ter*-butylmagnesium chloride to form the hydrocarbon, $MgX_2$ and metallic Ag.

2,2,4-Trimethylpentane is made by the catalytic hydrogenation of the diisobutylenes obtained from *ter*-butyl alcohol or isobutylene and sulfuric acid. This substance, incorrectly called "iso-octane," is used as a standard in determining detonation properties, "knock rating" or "octane number" of gasoline (Edgar 1927). The "octane number" is the per cent of 2,2,4-$Me_3$-pentane in a mixture of that substance and *n*-heptane which has the same "knock" as the gasoline being tested. An isomer, 2,2,3-$Me_3$-pentane has an even lower knock rating but there is no feasible way to prepare it. The limiting compression ratios for those two octanes are 7 to 1 and 12 to 1 for the 2,2,4- and the 2,2,3-isomers respectively.

The vapor phase oxidation of *n*-octane has been carefully studied (Edgar 1929). The first product is octanal. This then goes to heptanal and CO and $CO_2$. The change continues step by step through the lower aldehydes. This process apparently involves "chain reactions" which give detonation or "knock." These processes are inhibited by tetraethyl lead, a good "anti-knock." When branched chain octanes are used the aldehyde formation and degradation take place until a branch in the chain is reached, when the reaction is distinctly retarded. This is related to the low knock properties of highly branched hydrocarbons such as 2,2,4-$Me_3$-pentane (EP 9, 61).

**Higher Alkanes.** Many of these have been made by methods analogous to those already described. As usual the hydrocarbons with highly branched chains offer the greatest difficulties. Thus the highly branched nonane, 2,2,4,4-$Me_4$-pentane has only been obtained by the action of dimethyl zinc on the product of HBr addition to the diisobutylenes, 2,2,4-$Me_3$-4-bromopentane. The boiling point is 122°, thus lower than that of *n*-octane, b. 125°.

*n*-Decane is readily separated from petroleum by careful distillation and freezing (Bruun 1932).

*n*-Undecane has been made from undecoic acid and HI (Krafft 1882) and from *n*-butyl toluene sulfonate and *n*-heptylmagnesium bromide (14% yield) (Gilman 1925).

2,11-$Me_2$-dodecane is obtained by hydrogenating the olefins from the di-tertiary glycol made from ethyl sebacate and excess methylmagnesium bromide.

The normal $C_{20}$, $C_{30}$, $C_{40}$, $C_{50}$, $C_{60}$, $C_{70}$ and about 25% of higher unidentified hydrocarbons, $C_{10n}$, have been obtained by the Wurtz reaction with sodium and decamethylene bromide, $Br(CH_2)_{10}Br$, in absolute ether (Carothers 1930). The separation was accomplished by a molecular still (Washburn 1929). The reduction involved in the process is explained as follows: (Q = an organic group.)

$$QBr + 2\,Na \rightarrow QNa + NaBr$$
$$QNa + Et_2O \rightarrow QH + EtONa + C_2H_4$$

Perhydrolycopene, $C_{40}H_{82}$, 2,6,10,14,19,23,27,31-$Me_8$-dotriacontane, is obtained by catalytic hydrogenation of lycopene.

The most important chemical reaction of higher hydrocarbons is their instability to heat, their ability to be "cracked" at about 500° into smaller more volatile molecules suitable for gasoline (EP 91–119). The detailed chemistry of this important industrial process is little known. All cracking processes applied to all petroleums give in varying amounts alkanes, alkenes, naphthenes and aromatic compounds. The last two are probably formed from the alkanes. The initial step in the pyrolysis of an alkane may be

$$RCH_2CH_2CH_2R' \rightarrow RCH{=}CH_2 + CH_3R'$$

This is probably preceded by the formation of free radicals (Rice 1933). The conversion of a naphthene to an aromatic compound involves the removal of hydrogen. This may react with olefins or be evolved. Some hydrogen is practically always found in cracked gases. The lower olefins formed tend less to polymerize and thus survive to a larger extent in the gases which are always by-products of cracked gasoline. These form the basis for the

important industrial processes involving ethylene, propylene and the butylenes. Another constant by-product of cracking is petroleum coke (EP 225). This is the ultimate result of continued polymerization and removal of hydrogen.

The chlorination of paraffin wax has recently become important because of the use of the highly chlorinated products in making wax crystallization inhibitors (Paraflow) and probably in extreme pressure lubricants.

A reaction of the higher alkanes which will undoubtedly be of the greatest practical importance in the future is their oxidation by means of air or oxygen to form long chain acids similar to those characteristic of the animal and vegetable fats and oils.

## *B.* Unsaturated Hydrocarbons, $C_nH_{2n}$

### Olefins, Alkylenes or Alkenes, Ethylene and its Homologs

An olefin contains two less H atoms than the corresponding paraffin and is characterized by an unsaturation which makes possible the *addition* of two univalent groups to two adjacent carbon atoms. This condition of unsaturation is indicated by a *double bond*, C=C. Such a double bond is merely an empirical indication of a point of unsaturation and activity in the molecule. Even less is known about its true nature than about that of the single bond between two carbon atoms. Electronically a double bond is represented by a "sharing" of two *electron pairs* by two adjacent atoms, $R_2C :: CR_2$ or $R_2C \vdots CR_2$ in which R is H or an organic group. Addition to the double bond may be due to an "activation" or polarization (complete or partial).

$$H : \underset{\cdot\cdot}{\overset{H}{C}} :: \underset{\cdot\cdot}{\overset{H}{C}} : H \rightleftarrows H : \underset{\cdot\cdot}{\overset{H}{C}} : \underset{\cdot\cdot}{\overset{H}{C}} : H$$

(Lewis 1916, Lowry 1923, Carothers 1924, Francis 1925, Kharasch 1928, Prevost 1931). In most cases this picture adds nothing to the ordinary conception that the double bond "opens" and adds a univalent group at each end. The olefinic bond has been subjected to a quantum mechanics analysis (Mulliken 1932).

In the olefins there is possible not only isomerism due to different carbon skeletons but also due to differences in the position of the double bond. Thus the possible numbers of structural isomers are: $C_4$, 3; $C_5$, 5; $C_6$, 13; $C_7$, 27; $C_8$, 68. All of these have been made through the heptylenes (Boord 1933).

*Occurrence and Formation.* Because of their great reactivity, olefins are not found in natural products. They are formed in the thermal decomposition of almost all carbon compounds. Thus the cracking of cottonseed oil gives about 30% unsaturated compounds (Egloff 1932). The total amount of olefins obtained as by-products in cracking processes for making gasoline is enormous. In 1936 the amount of the first three olefins formed in this way was about $5 \times 10^{10}$ cu. ft.

Pintsch gas obtained by cracking the gas oil fraction of petroleum contains 35–40% olefins.

The *physical properties* of the alkenes closely resemble those of the alkanes. Ethylene boils some 15° below ethane but the corresponding higher members in the two series boil at nearly the same points. In general the 1-olefin is lower boiling than the isomers with the double bond farther from the end of the chain. Thus the boiling points of *n*-heptane, heptene-1, and heptene-2 are 98.4°, 93.5°, and 98.3° respectively. The melting points of the olefins are somewhat lower than those of the corresponding paraffins. The presence of a double bond increases the density about 0.015 for straight chain compounds. For branched chain compounds the increase varies widely. Thus the values of $d_4^{20}$ for 2-Me-pentane, 2-Me-pentene-1 and 2-Me-pentene-4 are 0.652, 0.682 and 0.665. In the 1-olefin the branching of the chain and the double bond each strengthens the effect of the other while in the 4-olefin they are apparently independent. The density of pentene-1 is 0.641 while that of nonene-1 is 0.731. The double bond increases the index of refraction ($n_D^{20}$) about 0.011 for l-olefins. The increase is greater when the double bond is nearer the middle of the molecule and also in branched molecules.

The *chemical properties* of the alkenes are in strong contrast to those of the alkanes. Not only do they *add* a great variety of reagents with the greatest ease but they also react with themselves to form *polymers*.

ALPHA OLEFINS

| | m. °C. | b. °C. |
|---|---|---|
| Ethylene | −169 | −104 |
| Propylene | | − 48.2 |
| Butene-1 | | − 6.7 |
| Pentene-1 | | + 30.1 |
| Hexene-1 | | 63.5 |
| Heptene-1 | | 93.5 |
| Octene-1 | | 122. |
| Nonene-1 | | 145.3 |
| Decene-1 | | 172. |
| Undecene-1 | | 84/18 mm. |
| Dodecene-1 | − 31. | 96/15 |
| Tridecene-1 | | 233 |
| Tetradecene-1 | − 12. | 127/15 |
| Pentadecene-1 | | 247 |
| Hexadecene-1 (cetene) | + 4. | 155/15 |
| Octadecene-1 | + 18. | 179/15 |
| Hexacosene-1 (cerotene) | 58. | |
| Triacontene-1 | 62. | |

**Methylene,** $[CH_2]$, has never been prepared pure. (Nef.) All attempts to make it, yield ethylene, $C_2H_4$, and higher polymers, $(CH_2)_n$, (Butlerow 1861). The free methylene radical has been obtained by heating iodomethylmagnesium iodide in nitrogen (Muskat). It reacts with $O_2$ to give formaldehyde and with CO to give ketene. The pyrolysis of diazomethane, $CH_2N_2$, gives the methylene radical (Rice 1933).

**Ethylene,** ethene, $CH_2=CH_2$, was discovered in 1795 by the four Dutch chemists Deimann, Van Troostwick, Bondt, and Louwrenburgh. It occurs in the gases obtained by *cracking* almost any organic material. It is thus found in illuminating gas and in the gases from the manufacture of cracked gasoline. Its older name "olefiant gas" comes from its action with chlorine to form an oil (ethylene dichloride).

*Ethylene may be prepared* by a number of methods which are also general for its homologs.

1. By dehydration of ethanol above 150° by means of sulfuric acid, phosphoric acid, benzene sulfonic acid, etc.; by catalytic

action of heated aluminum oxide, etc. This last method, using a mixture of superheated steam and ethanol passed over kaolin was employed for making ethylene for the preparation of "mustard gas" ($\beta\beta'$-dichlorodiethylsulfide) during the World War.

2. By removal of halogen acid from an ethyl halide by means of an alcoholic solution of a base, usually potassium hydroxide. The yield of olefin is lessened by the simultaneous formation of an *ether* corresponding to the alkyl halide and the alcohol used. At least two explanations have been proposed for this side reaction. One involves the following equilibrium

$$EtOH + KOH \rightleftharpoons EtOK + H_2O$$

The *potassium* ethylate can then react with the ethyl halide to give diethyl ether (Williamson reaction). Another explanation assumes the dissociation of the ethyl halide into a free radical containing *bivalent carbon*, ethylidene, $CH_3CH=$ (Nef). This is so reactive that it is incapable of independent existence. Part of its rearranges to $H_2C=CH_2$ and part of it adds ethyl alcohol to form diethyl ether. The complexity of the process can be seen from the fact that neopentyl iodide with alcoholic KOH gives mainly neopentane (p. 73).

3. By removal of two halogen atoms from an ethylene halide, $XCH_2CH_2X$ by means of zinc or magnesium. A modification of this method depends on the fact that ethylene iodide loses its iodine on heating and forms ethylene. Thus if ethylene bromide is heated with an alcoholic solution of potassium iodide the products are potassium bromide, iodine and ethylene.

4. By electrolysis of sodium succinate solution (Kolbe).

5. The large amount of ethylene used for making ethylene glycol and the many related commercial products (some 50 in 1936) has been prepared by cracking fairly pure propane from natural gas (Cameron 1932). The accompanying methane is used to supply part of the heat for the cracking process. The present tendency is to locate plants using ethylene near the large petroleum refineries where enormous amounts of this gas are available in the "cracked gases" (EP 120).

*The reactions of ethylene* are characteristic of compounds containing a double bond between carbon atoms.

1. Hydrogen adds under the influence of catalysts such as platinum black or colloidal palladium in water or alcohol suspension or, best, finely divided nickel at temperatures around 300° (Sabatier, Senderens 1905). The discovery of this process laid the basis for the countless hydrogenations of theoretical and practical importance which are now conducted in nearly every field of organic chemistry. A copper catalyst can be used in place of nickel. The combination of ethylene and hydrogen is a homogeneous second-order reaction (Pease 1932). Ethylene may be activated by the action of alpha particles (Lind 1926) and by excited Hg atoms (Taylor 1929).

A mechanism has been suggested for the hydrogenation involving the steps: (1) Addition of a proton to an activated ethylene molecule, (2) addition of two electrons (from the metal catalyst), and (3) addition of a second proton (Ingold 1929).

Hydrogenation of ethylene with a Pt catalyst is used as an accurate method of determination in presence of ethane and methane (Meulen 1931). The volume of hydrogen consumed equals the volume of ethylene present.

2. Halogens add to ethylene, chlorine most readily and iodine least. Besides ethylene dichloride, chlorine gives higher chlorides such as 1,1,2-trichloroethane (Stewart 1929). This is ascribed to activation of the molecules during the reaction. This activation may well take the form of the addition of a positive Cl and the loss of a proton followed by the further addition of $Cl_2$. Similar changes are common with olefins having the grouping $RR'C=C$ (p. 41).

Ethylene with a mixture of chlorine and bromine (bromine chloride) gives ethylene chlorobromide (1-chloro-2-bromoethane). No ethylene chloride is obtained.

The reaction of ethylene with bromine has been studied extensively (Ingold 1932). In the gaseous state there is no reaction (Stewart 1923). Glass, moisture and light favor the reaction. A lining of paraffin in the reaction vessel practically stops the reaction between ethylene and gaseous bromine while a lining of stearic acid catalyzes it better than glass. (Norrish 1923). Ethylene acts very slowly in the dark with a solution of bromine in dry $CCl_4$. Strangely it acts more rapidly at 0° than at 25°.

The reaction is accelerated by traces of moisture or by illumination (Davis 1928).

The reaction of ethylene with iodine is incomplete and reversible by heat (Mooney 1931). Iodine chloride and iodine bromide also add to ethylene.

3. Halogens in presence of reactive solvents or ionized salts give products containing halogen and a radical from the salt or solvent.

(*a*) Water. Chlorine or bromine in water with ethylene give the halohydrins, $XCH_2CH_2OH$, which are important in commercial syntheses (Curme 1921). Their formation is usually ascribed to the addition of hypochlorous or hypobromous acid formed from the halogen and water. Only small amounts of ethylene dihalides are formed.

(*b*) Aqueous salt solutions. Bromine and NaCl solution convert ethylene to the chlorobromide. With sodium nitrate solution the product is the nitrate of ethylene bromohydrin, $BrCH_2CH_2ONO_2$.

(*c*) Alcohols. Ethers of the halohydrins are obtained. Thus a methanol solution of bromine with ethylene gives $\beta$-bromoethyl methyl ether.

These reactions seem to favor the conception that the initial step is the addition of a positive halogen. This is followed by the addition of a negative ion, either halide or from the solution or solvent. The great tendency for hydroxyl and alkoxyl ions to add is noteworthy.

4. Halide acids add, HI most readily and HCl least. Traces of ether assist the addition, probably through the formation of oxonium salts (Rep. 1920, 55). The addition is also catalyzed by carbon and silica. The technique of the addition of HX to ethylenic linkages has been improved (Kharasch 1933). Pure ethylene and hydrogen chloride do not react in the absence of the liquid phase (Maas 1933). The presence of $AlCl_3$ catalyzes the addition effectively (Waterman 1934).

5. Sulfuric acid adds H to one carbon and $-OSO_3H$ to the other. Accompanying this addition reaction, is a small amount of polymerization in which two or more molecules of ethylene add to each other (Brooks 1918). The absorption of ethylene by

sulfuric acid is much slower than that of the higher olefins. Large quantities of acid are required, nearly 30 parts of concentrated acid for 1 part of ethylene. This method is used, however, for the commercial production of ethyl alcohol (EP 300). Sulfuric acid saturated with salts such as silver and nickel sulfates absorbs ethylene more rapidly than the pure acid. Ethylene is absorbed by silver nitrate solution (Morris 1929). Oleum $H_2S_2O_7$, forms ethionic acid, $HO_3SCH_2CH_2OSO_3H$, the acid sulfate of isethionic acid, $\beta$-hydroxyethyl sulfonic acid, $HOCH_2CH_2SO_3H$. Sulfur trioxide gives carbyl sulfate, the anhydride of ethionic acid.

$$\begin{matrix} CH_2 \\ \| \\ CH_2 \end{matrix} + 2\,SO_3 \rightarrow \begin{matrix} CH_2 - SO_2 - O \\ | \qquad\quad / \\ CH_2 - O - SO_2 \end{matrix}$$

Chlorosulfonic acid, $ClSO_3H$, absorbs ethylene much more rapidly than does sulfuric acid.

6. Nitric acid gives $\beta$-nitroethyl nitrate, $O_2NCH_2CH_2ONO_2$.

7. The chlorides of sulfur add to ethylene. This method is the best preparation for mustard gas, the most important poison gas of the World War. The reaction was first noted by the Scotchman, Guthrie (1860).

$$2\,C_2H_4 + S_2Cl_2 \rightarrow S + (ClCH_2CH_2)_2S$$

Similarly, selenium monochloride adds but the latter also acts as a chlorinating agent on the selenide formed.

$$2\,C_2H_4 + 2\,Se_2Cl_2 \rightarrow 3\,Se + (ClCH_2CH_2)_2SeCl_2$$

Selenium oxychloride, $SeOCl_2$, gives the same compound and $SeO_2$ (EP 577).

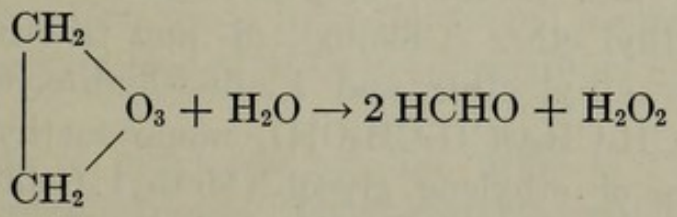
8. Mercuric salts which hydrolyze, such as the sulfate, nitrate and acetate, add to ethylene in alkaline water or alcohol solution to give compounds of the types $Y-HgCH_2CH_2OH$, $(Y-HgCH_2CH_2)_2O$, and $Y-HgCH_2CH_2OR$ in which Y is an acid radical (Hofmann 1900). The halides are less soluble than the other salts and are obtained by simply adding the calculated amount of NaX to the reaction mixture. These Hg compounds react with iodine to give ethylene iodohydrin, diiodo ethyl ether, and iodoethyl alkyl ethers thus proving the position of the C—Hg

linkage. With acids they would be expected to give the corresponding hydrogen substitution products but, instead, all three types of compounds give quantitative yields of ethylene. Because of this peculiar reaction these compounds have been formulated as merely molecular compounds, $C_2H_4.Hg(OH)Y$, $2\,C_2H_4.Hg_2OY_2$ and $C_2H_4.Hg(OR)Y$ (Manchot). The question has been settled in favor of the *structural* formulas by the preparation in optically active form of such a compound with an asymmetric carbon (Marvel).

9. Ethylene adds benzene and other aromatic compounds under the influence of anhydrous aluminum chloride (Friedel-Crafts) (EP 559). Thus benzene and ethylene give all the possible ethyl substituted benzenes.

10. Dilute solutions of oxidizing agents such as potassium permanganate or barium chlorate add two hydroxyl groups to the adjacent carbons to form glycol, $HOCH_2CH_2OH$. With more drastic conditions, the glycol first formed is further oxidized with the separation of the two carbons.

11. Incomplete oxidation of ethylene with air gives formaldehyde (EP 874). Ethylene with ozone gives an ozonide which is hydrolyzed to formaldehyde.



$$CH_2\text{(}O_3\text{)}CH_2 + H_2O \rightarrow 2\,HCHO + H_2O_2$$

12. Ethylene, in common with other olefins, burns with a luminous flame. This property is utilized in making carburetted water gas by adding the cracked products from gas oil and similar materials.

Ethylene is used with oxygen for welding and cutting metals (Calorene). While its flame is not as hot as that obtained with acetylene, it has the advantage of being stable under high pressures in ordinary steel cylinders.

13. Ethylene can be polymerized difficultly by heat alone or catalytically by means of complex silicates such as floridin (Lebedef 1910, EP 588), but only with difficulty by acids (Brooks 1918). When ethylene is thus polymerized the products are

extremely complex (Montmollin 1916). Polymerization by the silent electric discharge yields butene-1 and hexene-1 (Mignonac 1929).

14. The pyrolytic reactions of ethylene are most complex giving among other products, carbon, hydrogen, methane, ethane, propylene, butylene, butadiene and aromatic products (Egloff 1931, 1935).

15. Ethylene reacts with aqueous alkalies at 400° and 50 atm. pressure to give acetates and hydrogen. Similarly propylene gives propionic acid.

16. With $CO_2$ at high temperature and pressure in the presence of catalysts and ultraviolet light, acrylic acid, $CH_2=CHCO_2H$, and its polymers are obtained in low yields (EP 586).

## Summary

The chemical versatility of ethylene is evidenced by the fifty commercial products available from it in 1936. These include ethylene chlorohydrin, ($ClCH_2CH_2OH$), ethylene glycol, ($HOCH_2CH_2OH$), and its nitrates and acetates, ethylene dichloride, ethylene oxide, ethanol, ethyl ether, vinyl chloride, ($CH_2=CHCl$) and acetate, ethylene diamine, ethyl sulfate, $\beta\beta'$-dichloro ethyl ether (Chlorex), di- and tri-ethylene glycols ($\beta\beta'$-dihydroxy ethyl ether and 1,2-di-$\beta$-hydroxyethoxyethane, $HOCH_2CH_2OCH_2CH_2OCH_2CH_2OH$), mono methyl, ethyl and $n$-butyl ethers of ethylene glycol (Methyl Cellosolve, Cellosolve, $EtOCH_2CH_2OH$, and Butyl Cellosolve respectively; $\beta$-hydroxyethyl alkyl ethers), diethyl ether of ethylene glycol (1,2-diethoxyethane), mono methyl, ethyl and $n$-butyl ethers of diethylene glycol (Methyl Carbitol, Carbitol, $EtOCH_2CH_2OCH_2CH_2OH$, and Butyl Carbitol respectively; $\beta$-hydroxyethyl-$\beta'$-alkoxyethyl ethers), mono-, di- and tri-ethanol amines, $HOCH_2CH_2NH_2$, $(HOCH_2CH_2)_2NH$ and $(HOCH_2CH_2)_3N$, triethylene tetramine, $NH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$, morpholine, $O(CH_2CH_2)_2NH$, morpholine ethanol (N-hydroxyethyl morpholine), $O(CH_2CH_2)_2NCH_2CH_2OH$, acetates of the cellosolves and of carbitol, phthalates of the cellosolves, and 1,4-dioxan (diethylene oxide), $O(CH_2CH_2)_2O$.

Ethylene finds two important *biological uses*, namely, as a general anesthetic for surgery and as an agent to hasten the ripening of bananas, citrous fruits, bulbs and potatoes. It is especially valuable in ripening fruit which is picked green for transportation. Treatment with ethylene stimulates the proteolytic enzymes of pineapples (Harvey 1927). Many other chemicals have similar effects (Denny 1924, 1933). Among them are ethylene chlorohydrin, sodium thiocyanate, thiourea, ethylene dichloride, furfural, ethyl bromide and vinyl chloride.

In addition to its ordinary industrial significance the military importance of a well-developed ethylene industry cannot be overemphasized.

**Propylene,** propene, methylethylene, $CH_3CH=CH_2$, can be made by the standard methods from *n*-propyl alcohol, isopropyl alcohol, *n*-propyl halides, isopropyl halides and from propylene dihalides. It can also be made by heating glycerol (1,2,3-trihydroxypropane) with zinc dust.

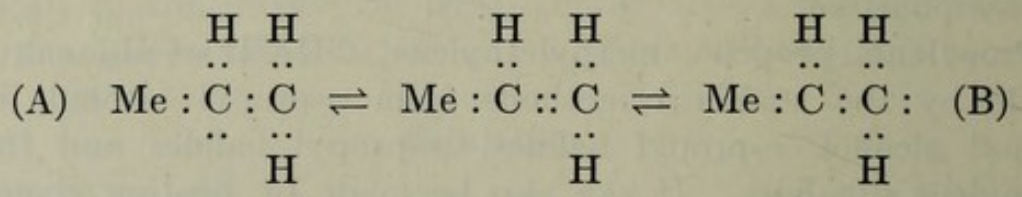
The propylene used commercially for the preparation of isopropyl alcohol (Petrohol), propylene glycol and acetone is obtained as a by-product in the cracking of petroleum fractions to make gasoline and of propane to make ethylene (EP 127). Pure propylene is best made from the propyl alcohols passed in the vapor phase over heated $Al_2O_3$ in copper tubes (Ipatieff 1903, 1934).

The reactions of propylene are like those of ethylene with certain added complications. Thus propylene with pure bromine gives a 90% yield of propylene dibromide and 4% of 1,2,3-tribromopropane. With bromine and iron it gives 40% of the 1,2,3- and 17% of the 1,1,2-tribromo compound. With ferric bromide or aluminum as catalyst the yields of the tribromides are 8% and 33% respectively (Rep. 1923, 74).

When the addend has two unlike parts, two different addition products are possible since the double bond is not symmetrically placed. Both possible products are formed but one usually predominates to the extent of 90% or more. This chief product is the one in which the hydrogen or the "positive" part adds to the end carbon, Markownikoff's Rule (1870). Thus propylene gives mainly isopropyl compounds with halide acids and sulfuric

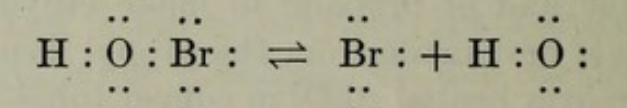
acid (EP 320). With hypochlorous acid it gives mainly 1-chloropropanol-2 (EP 499). The direction of addition depends on the polarity of the parts of the addend. With hypohalous acids the OH is "negative" and the halogen "positive" although the ionization of these substances gives $H^+$ and $XO^-$ ions. The phenomena expressed in Markownikoff's Rule may be pictured as follows:

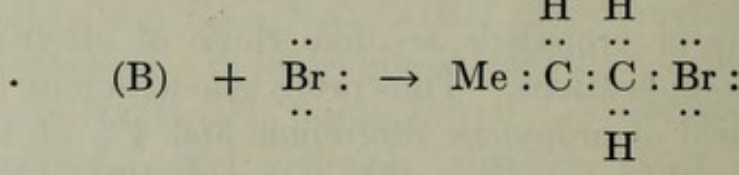
1. The inactive double bond is activated in some way. The extra electron pair instead of being shared by the two olefinic carbons becomes more closely associated with one of them. In an unsymmetrical olefin this can take place in two ways:



2. The addition to the activated molecule may be regarded as taking place through the addition of ions or through the preliminary formation of molecular compounds.

(*a*) Ionic mechanism.





The hydroxyl ion would then add to the middle carbon and thus complete the latter's octet of electrons. If (A) reacts, the positive bromine attaches itself to the electron pair on the middle carbon leaving the hydroxyl to unite with the end carbon.

(*b*) Molecular mechanism. A loose molecular compound is first formed. Because of the greater stability of the C—Br linkage as compared with the Br—O linkage this compound would liberate the hydroxyl with its complete octet. This could then combine with the middle carbon. The whole subject of the addition of an unsymmetrical molecule XY to an unsymmetrical

olefin is still unsettled. (Rep. 1919, 89, 1923, 105; Rev. *5*, 57–602 (1928); Ingold 1931.) The influence of the solvent used is important. Thus glacial acetic acid favors the addition of HBr to an alpha olefin to give mainly the primary bromide (Ipatiew 1904, Delacre 1906). Neopentylethylene (Whitmore 1933), pentene-1 and heptene-1 (Sherrill 1934) have been found to add HBr gas to give *only* the *primary* bromides. A most profound effect is exerted by the presence of peroxides (Kharasch 1933). Thus propylene in the presence of peroxides adds HBr to give *n*-propyl bromide.

While olefins do not add iodine readily they add iodine monochloride, ICl. In the case of unsymmetrical olefins both possible addition products are obtained but the predominant one has the I on the carbon with the most H atoms (cf. Markownikoff's Rule). Iodine in presence of silver salts causes the addition of I and the radical of the salt to the double bond. Thus the nitrite and acetate with iodine add a nitro and an acetate group respectively.

Propylene is much more reactive than ethylene. For instance, propylene is absorbed completely by 85% sulfuric acid whereas ethylene is absorbed rapidly only by fuming sulfuric acid. Propylene is also oxidized more rapidly than ethylene. With oxygen at 500°, propylene gives acetaldehyde, formaldehyde, oxides of carbon, butylenes, amylenes, and hexylenes (Lenker 1932).

The pyrolysis of propylene at 600° gives a complex mixture including $H_2$, methane, ethylene, acetylene, ethane and about 25% of aromatic hydrocarbons (Hurd 1930).

Propylene is polymerized more readily by acids than ethylene. It is rapidly polymerized at 250° by various silicates such as floridin and "catasil" ($Al_2O_3$ adsorbed on silica gel) (Gayer 1933). The volatile products contain 6,7,5,9 and 8 carbon atoms in decreasing abundance. Obviously the reactions involved are complex.

The following products are commercially available from propylene as a raw material: isopropyl alcohol, isopropyl acetate, isopropyl ether, acetone, methylisobutylcarbinol, propylene chlorohydrin, propylene glycol, propylene oxide, propylene dichloride, $\beta\beta'$-dichloro isopropyl ether, and methyl isobutyl ketone.

**Butylenes,** $C_4H_8$. The isomers are:

1. Butene-1, alpha butylene, ethylethylene, $CH_3CH_2CH=CH_2$, b. $-6.7°$.

2. Butene-2, beta butylene, symmetrical dimethylethylene, pseudo butylene, $CH_3CH=CHCH_3$, *cis* form, b. $+3.7°$, *trans* form, b. $+1.0°$.

3. Isobutylene, gamma butylene, methylpropene, unsymmetrical dimethylethylene, $(CH_3)_2C=CH_2$, b. $-6.6°$.

With increasing complexity, new complications appear.

*Preparation.* 1. The dehydration of *n*-butyl alcohol (butanol-1) by acids, instead of giving butene-1 alone, gives a mixture of this with butene-2. If either of these is desired pure, it is necessary to convert the mixture to dibromides, separate these by careful distillation and then treat each pure dibromide with zinc to regenerate the corresponding olefin (Lucas 1930). The dehydration of butanol-1 by hot $Al_2O_3$ usually gives the same mixture of butenes but if the catalyst is *free from all acid impurities* only butene-1 is obtained (Pines 1933).

2. Pure butene-1 may be made from a methyl Grignard reagent and allyl bromide (Lucas 1928). This is a good general method for making 1-olefins free from the 2-isomers (Brooks 1918). Butene-1 has also been obtained from vinyl bromide and diethyl zinc (Wurtz 1869).

3. Butene-1, made by cracking hydrocarbons, contains much butene-2. Practically, this does no harm because both butenes give the same secondary alcohol(butanol-2), when sulfuric acid is added to them and the resulting alkyl hydrogen sulfate is hydrolyzed. In the cracking process some isobutylene is also obtained. In commercial practice the isobutylene is removed by more dilute sulfuric acid than will dissolve the *n*-butenes and is converted into tertiary butyl alcohol (trimethylcarbinol). The *n*-butenes are then absorbed in more concentrated sulfuric acid to make secondary butyl alcohol.

4. Strangest of all, the ordinary dehydration of isobutyl alcohol (2-methylpropanol-1) at high temperatures instead of giving only isobutylene as would be expected gives also butene-1 and butene-2, by the rearrangement of a methyl group. The course of such

rearrangements may be explained by a simple application of electronic conceptions (Whitmore 1932). The use of $Al_2O_3$ free from all acid impurities gives pure isobutylene (Ipatiev 1903, Pines 1933).

5. Butene-2 exists in stereoisomeric forms indicating that the double bond limits the free rotation of the doubly linked carbon atoms. Thus two forms are possible, *cis* butene-2 $\begin{matrix} Me-C-H \\ \| \\ Me-C-H \end{matrix}$ b. 3.7° and *trans* butene-2 $\begin{matrix} Me-C-H \\ \| \\ H-C-Me \end{matrix}$ b. 1.0°. These have been prepared from angelic and tiglic acids, stereoisomeric alpha methylcrotonic acids, $MeCH=CMeCO_2H$, respectively (Lucas 1929).

*Reactions.* The butylenes resemble propylene in their reactions. Thus butene-1 and isobutylene add HBr to give 2-bromobutane and *ter*-butyl bromide according to Markownikoff's Rule. This mode of addition can be reversed in the presence of *added* peroxides to give at least 80% of isobutyl bromide (Kharasch 1934). Isobutylene does not oxidize in air to give enough peroxides to reverse the addition.

Isobutylene is much more stable to heat than isobutane. (Hurd 1929). At 700° it gives methane, hydrogen, propylene and a complex mixture of aromatic hydrocarbons including benzene and toluene and probably xylenes, naphthalene, phenanthrene and anthracene.

The reaction of isobutylene and $Cl_2$ results in substitution products instead of the expected dichloride. Probably the addition of a halogen molecule to a double bond takes place in two steps, (1) the addition of a "positive" halogen atom and (2) the addition of a negative halide ion (Francis 1925, Terry 1925). With isobutylene, the second step does not take place. Instead a proton is lost by the initial addition product to give HCl. The net changes may be summarized:

$$2\,(CH_3)_2C=CH_2 + Cl_2 \rightarrow CH_2=C(CH_3)CH_2Cl + (CH_3)_3CCl$$

Some HCl gas is evolved. The beta methallyl chloride is avail-

able from the action of chlorine with the isobutylene of cracked gases (Shell). An isomer, isocrotyl chloride, $Me_2C=CHCl$, is also obtained. This behavior of certain olefins with halogens has long been known. Olefins which add HX with great ease react with chlorine and bromine to give unsaturated halides instead of the expected dihalides (Kondakoff 1891).

Isobutylene with bromine gives 75% isobutylene dibromide, 17% 1,2,3-tribromo-2-Me-propane and 7% *ter*-butyl bromide. This is the same type of change observed in the action of chlorine by Kondakoff on isobutylene and by Stewart on ethylene. The unsaturated bromide, perhaps in the nascent state, adds another molecule of bromine.

Isobutylene with aqueous $KI_3$ solution gives *ter*-butyl alcohol and isobutylene oxide, $Me_2C-CH_2$ (O). This is probably due to

(*a*) the instability of a 1,2-diiodide, (*b*) the ease of addition of HI and HIO to isobutylene, (*c*) the ease of hydrolysis of a tertiary iodide, (*d*) the reducing action of HI on an iodide, (*e*) the ready loss of HI by an iodohydrin.

Isobutylene with acetyl chloride and $AlCl_3$ gives the HCl addition product of mesityl oxide, $Me_2CClCH_2COMe$.

Isobutylene adds nitrogen trichloride according to Markownikoff's Rule (positive chlorine as in HOCl) to give the remarkable compound, 2-dichloroamino-2-chloromethylpropane (Coleman 1928). This is stable and forms a hydrochloride with HCl whereas most N—Cl compounds react with HCl to give chlorine.

The butylenes polymerize much more readily than the lower olefins. Isobutylene polymerizes most readily. This is characteristic of olefins containing the grouping, $RR'C=C$, related to tertiary alcohols.

Various acid and silicate catalysts (Butlerow *1876*, Lebedef 1930) convert isobutylene to polymers containing two to seven and even more isobutylene units. The structures of the di-isobutylenes and the tri-isobutylenes have been definitely established as follows: Di-isobutylenes (Whitmore 1932): 2,4,4-trimethylpentene-1, b. 101.2°; 2,4,4-trimethylpentene-2, b. 104.5°. These are formed in the ratio 4 : 1. Tri-isobutylenes: 2,2,4,6,6-

$Me_5$-heptene-3, 2-neopentyl-4,4-$Me_2$-pentene-1 (*unsym*-di-neopentyl-ethylene), 2,4,4,6,6-$Me_5$-heptene-2 and -1. The formation of the di- and tri-isobutylenes may be formulated on the basis of the addition of a proton from the catalyst, the addition of the resulting "positive" *ter*-butyl group to isobutylene, followed by the loss of a proton, etc. (Whitmore 1934.)

In common with all olefins isobutylene is polymerized by $AlCl_3$. A coordination of the latter with the extra electron pair has been suggested as a step in the polymerization (Hunter 1933). The well-known polymerizing effect of $BF_3$ can be explained in the same way.

"Tertiary-base" olefins, i.e., olefins related to tertiary alcohols and corresponding to formulas $R_2C=CH_2$, $R_2C=CHR$, and $R_2C=CR_2$ (R groups alike or different) react with primary and secondary alcohols in presence of catalysts (usually acidic) to form mixed ethers (Edlund 1934). This method is useful in removing isobutylene from the *n*-butylenes.

Paraffins will add to olefins in the presence of various catalysts such as a combination of $BF_3$, HF and Ni (Ipatiev 1935). The catalyst also causes rearrangement. Thus isobutane and isobutylene give 2,2,4-$Me_3$-pentane ("iso-octane") and isomeric octanes. This reaction is important in making gasoline because the by-product gases from a petroleum refinery are rich in paraffins and olefins and the products from this reaction are highly branched and thus give good anti-knock value.

The gases from low-pressure vapor-phase cracking of petroleum (Gyro Process) contain about 50% of $C_2$ to $C_4$ olefins. These can be polymerized to gasoline by heat and pressure (Wagner 1935).

**Amylenes,** $C_5H_{10}$. All the possible structural isomers have been prepared.

1. Pentene-1, *n*-propylethylene, $CH_3CH_2CH_2CH=CH_2$, b. 30°.
2. Pentene-2, *sym*-methylethylethylene, $CH_3CH_2CH=CHCH_3$, b. 36.4°.
3. 2-Me-butene-1, *unsym*-methylethylethylene, $CH_3CH_2C(CH_3)=CH_2$, b. 32°.
4. 2-Me-butene-2, trimethylethylene, $(CH_3)_2C=CHCH_3$, b. 38.4°.

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5. 3-Me-butene-1, isopropylethylene, $(CH_3)_2CHCH=CH_2$, b. 20.1°.

These can be prepared like the butylenes but with correspondingly greater complications due to rearrangements. The dehydration of amyl alcohols gives the following mixtures: pentanol-1, pentene-1 and -2; pentanol-2, pentene-2 and -1; *sec*-butyl-carbinol, 2-methylbutene-2 and -1 and pentene-2; isoamyl alcohol, 2-methylbutene-2 and a little isopropylethylene; *ter*-amyl alcohol, 2-methylbutene-2 and -1.

Commercial "amylene" was formerly made by dehydrating commercial amyl alcohol, itself a mixture. Now pentene-2 and trimethylethylene are available (Sharples). 2-chloro-2-methylbutane and 3-chloro-2-methylbutane formed during the chlorination of isopentane lose HCl during the subsequent treatment with alkali, giving mainly trimethylethylene.

The reactions of the amylenes present few peculiarities. At high temperatures and in the presence of catalysts, methylbutenes suffer shifts of the double bond (Ipatieff 1903). Isopropylethylene and *unsym*-methylethylethylene are converted mainly to trimethylethylene. The change may be regarded as the addition of $H^+$ to one carbon and a loss of $H^+$ from a different carbon. This is the equivalent of the older conception that water was added one way and split off in a different way.

Pentene-1 in solution in hexane, glacial acetic acid or $CCl_4$ adds HBr contrary to Markownikoff's Rule to give only *n*-amyl bromide (Sherrill 1934).

Pentene-2 has been reported as obtainable in two isomeric forms (electromers?) one of which gives 3-bromopentane and the other 2-bromopentane with HBr (Kharasch 1928, Sherrill 1929). The existence of such electromeric 2-pentenes is probably impossible (Lucas 1935).

Apparently the addition of HBr to an unsymmetrical olefin compound of the type $RCH=CHR'$ is not influenced by peroxides (J. C. Smith 1935).

The amylenes give complex addition products with $N_2O_3$, $N_2O_4$ and NOCl (Schmidt, 1902, 1903; Wallach 1915). These types of addition products are most important in the terpene series. The complexity of these substances is due to the tendency

of the secondary nitroso group CHNO to isomerize to an isonitroso or hydroximino group C=NOH and also to change to a dimer, perhaps containing the grouping $=CH-\underset{\downarrow}{\overset{}{N}}=\underset{\downarrow}{\overset{}{N}}-CH=$ (O O) or some tautomeric form. The true nitroso compounds are blue whereas the other compounds are colorless.

Trimethylethylene with nitrosyl chloride, gives the blue nitrosochloride, $Me_2CClCH(NO)Me$. On standing or on heating this changes to the oxime, $Me_2CClC(=NOH)Me$. The bimolecular nitrosochloride is obtained directly from trimethylethylene, an alkyl nitrite and fuming hydrochloric acid.

Nitrous anhydride and nitrogen tetroxide give a nitrosite and a nitrosate respectively of which the blue nitroso forms are as follows:

$Me_2C(ONO)CH(NO)Me$ and $Me_2C(ONO_2)CH(NO)Me$

These are convertible to the hydroximino and bis- forms.

The rate of hydrogenation of the isomeric pentenes has been studied (Davis 1932).

The amylenes differ widely in their activity with acids. Thus isopropylethylene does not act with 5N HCl in months whereas trimethylethylene acts in 5 hrs. 2-Methylbutene-1 acts even more rapidly.

The amylenes related to *ter*-amyl alcohol react with phenols in the presence of acid catalysts to give phenol ethers and, on rearrangement, tertiary amyl phenols (Niederl 1931). This reaction is general for olefins, $R_2C=C$.

The amylenes polymerize with different degrees of ease, trimethylethylene forming "di-isoamylenes" and higher polymers most readily (Brooks 1918, Norris 1927). The "diamylene" available from pentane chlorination and presumably consisting mainly of dimers of trimethylethylene has been shown to contain 2,3,4,4-$Me_4$-hexene-2 and 2,2,3,4-$Me_4$-hexene-4 (Drake 1935). The formation of the latter represents a new reaction in polymerization.

Trimethylethylene with acetyl chloride and $AlCl_3$ gives the unsaturated ketone, 2,3-$Me_2$-pentene-2-one-4, $Me_2C=CMeCOMe$.

**Hexylenes,** $C_6H_{12}$. All thirteen possible structural isomers have been prepared. Most of these offer no peculiarities not observed with the amylenes.

In the case of 3-Me-hexene-2, the *cis* and *trans* stereomers boil far enough apart (5°) so that they can be separated by careful fractional distillation (van Risseghem 1922).

**Tetramethylethylene,** 2,3-$Me_2$-butene-2, $(CH_3)_2C=C(CH_3)_2$ b. 72°.

*Preparation.* 1. By removal of $Br_2$ from its dibromide obtained by the action of HBr on pinacol (tetramethylethylene glycol) prepared by the reduction of acetone with amalgamated magnesium.

2. By dehydration of dimethylisopropylcarbinol made from isopropyl Grignard reagent and acetone or from MeMgX and an isobutyric ester or methyl isopropyl ketone.

3. By dehydration of pinacolyl alcohol, $Me_3CCHOHMe$. Surprisingly, this is the best method of preparation giving the following products: Tetramethylethylene, b. 72°, 61% yield; *unsym*-methylisopropylethylene, b. 54°, 31%; *ter*-butylethylene, b.p. 41°, 3%. Thus the "normal" dehydration involving the methyl group becomes only a side reaction and rearrangement is the principal process (Whitmore 1933).

The reactions of tetramethyl-ethylene are typical olefin reactions. In many ways they are simplified by the symmetry of the molecule and the absence of H from the ethylene carbons. Thus it gives with NOCl, $N_2O_3$ and $N_2O_4$ simple addition compounds of the blue true nitroso type without any complication of tautomerism or dimerization,

$Me_2CClC(NO)Me_2$, Nitrosochloride $\qquad$ $Me_2C(ONO)C(NO)Me_2$, Nitrosite

$Me_2C(ONO_2)C(NO)Me_2$
Nitrosate

In the presence of acid catalysts $Me_4$-ethylene gives an equilibrium mixture of the three olefins listed above. (Whitmore 1934.) Thus the common shift of a double bond involving only the rearrangement of H atoms (Ipatieff 1903) has been expanded to include shifts of a double bond which involve the rearrange-

ment of alkyl groups as well. This phenomenon is undoubtedly of the greatest importance in determining the final olefin mixture obtained from an alcohol by dehydration with rearrangement.

$Me_4$-ethylene is polymerized by acid catalysts. This includes a rearrangement of a methyl group.

Tertiarybutylethylene, 3,3-$Me_2$-butene-1, $(CH_3)_3CCH=CH_2$, b. 41°. As has been seen, its preparation by dehydration of the corresponding secondary alcohol is not possible. Its preparation is made possible by a reaction discovered by Tschugaeff (1899) which gives the normal dehydration products even when all other processes give rearrangement products. It consists in decomposing the methyl xanthate of the alcohol related to the desired olefin. Pinacolyl alcohol is converted to the sodium alcoholate and treated with carbon disulfide to give the sodium xanthate. This is converted to the methyl compound by MeI or $Me_2SO_4$. This is decomposed by heat to give the desired olefin, carbon oxysulfide and methyl mercaptan (Fomin 1899, Schurman 1933).

$$Me_3CCH(ONa)Me \xrightarrow{CS_2} Me_3CCH(Me)OCS_2Na \rightarrow Me_3CCH(Me)OCS_2Me \rightarrow Me_3CCH=CH_2 + COS + MeSH$$

A better preparation is by the pyrolysis of pinacolyl acetate (Whitmore 1933, Dolliver 1937).

Tertiary butylethylene when impure (peroxides?) adds HBr to give the primary bromide. With acid catalysts it is converted almost completely to a 2 : 1 mixture of $Me_4$-ethylene and 2,3-$Me_2$-butene-1.

**Heptylenes,** $C_7H_{14}$. All twenty-seven possible structural isomers have been prepared, largely by the new methods devised by Boord (1930–33). The dehydration of heptyl alcohols prepared in making the isomeric heptanes gives mixtures which cannot be separated by distillation. The methods of Boord lead to pure individual olefins. They depend on the following reactions:

*a.* An aldehyde with an alcohol and HCl to give an alpha chloroether.

$$RCH_2CHO + HCl + EtOH \rightarrow RCH_2CHCl-OEt$$

R may be H or an organic group.

*b*. The action of the chloroether with bromine to give an alpha beta dibromoether, RCHBrCHBr—OEt.

*c*. The action of a Grignard reagent to replace the alpha bromine by an alkyl group, RCHBrCHR′—OEt.

*d*. The resulting beta bromo-ether reacts with zinc with removal of the bromine and the alkoxyl group. This is like the action of Zn with a 1,2-dibromide. It leaves an olefin, determined by the aldehyde and Grignard reagent used, RCH=CHR′.

Examples of four of the five possible types (Boord) of olefins as selected from the heptylenes (Soday 1933) and the reagents for their preparation by the "beta bromoether synthesis" follow:

| | Aldehyde | Grignard reagent |
|---|---|---|
| I. $AmCH=CH_2$, b. 94.9° | MeCHO | Am |

$Me_2EtCCH=CH_2$, b. 76.9°, cannot be made by this method but has been made by Tschugaeff's xanthate method from 3,3-$Me_2$-pentanol-2 (Schurman 1933).

| | | |
|---|---|---|
| II. BuCH=CHMe, b. 98.3° | EtCHO | Bu |
| | AmCHO | Me |

$Me_3CCH=CHMe$, b. 76°, is made from 2,2-$Me_2$-pentanol-3 through the xanthate (Schurman 1933).

| | | |
|---|---|---|
| III. $MeBuC=CH_2$, b. 91.3° | MeCHO | Me and Bu |

With this type of olefin the beta bromoether in the above process (*c*) is treated with KOH to give an alpha alkyl-vinyl ether, $CH_2=C(R)OEt$. This is treated with bromine to give $BrCH_2CBr(R)-OEt$, and then with the second Grignard reagent to introduce the other alkyl group to give $BrCH_2CR'(R)-OEt$, after which the beta bromine and ethoxyl groups are removed by zinc as usual to give $CH_2=CRR'$. $(Me_3C)MeC=CH_2$, b. 80°, is readily obtained by dehydrating $Me_5$-ethanol. No rearrangement is possible.

| | | |
|---|---|---|
| IV. $Me_2C=CHPr$, b. 94.5° | AmCHO | Me |

The higher beta bromoether, obtained in step (*c*), is converted to the $\alpha\beta$-unsaturated ether. A small by-product of $\beta\gamma$-unsaturated ether can be removed by distillation. The $\alpha\beta$-product

is then converted to the dibromide which is treated with a second mol of Grignard reagent. Zinc then gives the olefin.

V. $MeEtC=CMe_2$, b. 91° has been made from the tertiary alcohol.

**Octylenes,** $C_8H_{16}$. Only about one third of the 66 possible structural isomers have been prepared.

The two diisobutylenes, b. 101.2° and 104.5° (p. 42), are the best known octylenes. Their hydrogenation gives 2,2,4-$Me_3$-pentane ("iso-octane"), the anti-knock standard used with *n*-heptane in rating gasolines (p. 26). HCl and HBr add readily to give 2,2,4-$Me_3$-4-halogen-pentanes. Chlorine and bromine give unsaturated halides instead of the dihalides. Oxidation of mixed diisobutylenes with dichromate and acid gives a fair yield of methyl neopentyl ketone, $MeCOCH_2CMe_3$.

Two of the more difficultly obtainable octylenes, 3,3-$Me_2$-hexene-4, b. 106°, and 2,2-$Me_2$-hexene-3, b. 100.1°, have been made by the xanthate reaction (Schurman 1933).

The highly branched octylenes, *unsym.*-diisopropylethylene, b. 103°; 2,3,4-$Me_3$-pentene-2, b. 115°; 2,2,3-$Me_3$-pentene-3, b. 112°; and 2,3,3-$Me_3$-pentene-1, b. 108° have been made by dehydration of the corresponding tertiary alcohols (Whitmore 1932).

Higher olefins can be made by heating the palmitic or stearic esters of the higher alcohols under suitably diminished pressure (Krafft 1883).

Higher normal olefins, cetene ($C_{16}$), cerotene ($C_{26}$) and melene ($C_{30}$) have been made from cetyl alcohol, chinese wax and beeswax respectively. Cetene has been used as a standard for Diesel fuel. In this type of engine it gives no "knock" (p. 12). It has now been replaced by the more stable cetane.

Mixed higher alkenes obtained by cracking a petroleum rich in alkanes have been polymerized to give an artificial lubricating oil (Syntholube).

Olefin mixtures obtained by cracking processes can be converted to special resins.

**Determination of the Structure of Olefins.** This is best done by the action of ozone to give ozonides. This process is little understood. The decomposition of the ozonides (often danger-

ously explosive) gives carbonyl compounds (ketones, aldehydes, acids) related to the two parts of the molecule held together by the double bond (Harries 1904, Church 1934). The difficult part of the process is the isolation and identification of these products especially with lower aliphatic compounds.

The auto-oxidation of olefins is of great practical importance because of gum formation from olefins in cracked gasolines (Egloff) (Milas, Rev. 1932, I, 295–364).

## *C.* Unsaturated Hydrocarbons, $C_nH_{2n-2}$

### 1. Diolefins, Dienes

These may be classified according to the relative position of the two olefinic linkages: (*a*) Allene, $CH_2=C=CH_2$, and its homologs, (*b*) Butadiene-1,3, $CH_2=CH-CH=CH_2$, in which the double bonds are conjugated and its homologs (Rep. 1916, 79; 1917, 130; 1922, 102), and (*c*) compounds in which the double bonds are separated by at least two single linkages as in pentadiene-1,4, $CH_2=CHCH_2CH=CH_2$ (EP 631–61).

**Allene,** propadiene, dimethylenemethane, $CH_2=C=CH_2$, b. $-32°$, is best made by the action of zinc dust on 2,3-dibromopropene, obtained by the action of alcoholic KOH on 1,2,3-tribromopropane from the addition of bromine to allyl bromide. It is also among the products of the electrolysis of salts of itaconic acid. Allene polymerizes readily at 400–600° to give complex liquid mixtures containing aromatic compounds (Hurd). Sulfuric acid converts allene to acetone, the addition of a molecule of water producing the enol form of acetone, $CH_2=C(OH)CH_3$. Allene, with excess bromine gives $BrCH_2CBr_2CH_2Br$, a liquid of camphor odor. Hypochlorous acid gives $ClCH_2COCH_2Cl$, $ClCH_2COCH_2OH$, and $CH_2=CClCH_2OH$. Alcoholic KOH gives $CH_2=C(CH_3)OC_2H_5$, ethyl isopropenyl ether. Such an addition does not ordinarily take place with a C=C bond unless it is alpha-beta to a C=O bond. Thus the grouping C=C−C=O bears a certain resemblance to the C=C=C grouping. Allene reacts with Na in ether to give sodium methylacetylide, $CH_3C\equiv CNa$.

A consideration of the spatial relations of an allene of the type,

$RR'C=C=CRR'$, will show that it could exist in enantiomorphic and, therefore, optically active forms.

Homologs of allene of the type, $RCH=C=CH_2$, are prepared as follows (Bouis 1928): acrolein, $CH_2=CHCHO$, is treated with RMgX to give the substituted allyl alcohol, $RCHOHCH=CH_2$, with $PBr_3$ this largely undergoes an allylic rearrangement to give $RCH=CH-CH_2Br$; addition of bromine followed by fusion with 75% aqueous KOH gives $RCHBrCBr=CH_2$ which reacts with zinc dust to give the allene. The simpler homologs boil as follows: Me (butadiene-1,2), 19°; Et, 45°; *n*-Pr, 78°; iso-Pr (4-methylpentadiene-1,2), 70°; n-Bu, 106°; *iso*Bu, 96°. Addition of bromine (1 mol) takes place mainly in the 2,3 position. Cold sulfuric acid gives a methyl ketone. Heating with sodamide isomerizes the allene to an acetylene, giving the sodium derivative.

Allene homologs of the type, $RR'C=C=CH_2$, can be made from ketones, RR'CHCOMe, by treatment with $PCl_5$ and then with alcoholic KOH.

All the allenes, even the 1,3-dialkylated ones, react with Na to give sodium acetylides, $RC\equiv CNa$ (Favorsky 1888).

$Me_4$-allene, b. 70°.

**Butadiene**-1, 3, erythrene, divinyl, vinylethylene, crotonylene, pyrrolylene, $CH_2=CH-CH=CH_2$, b. +1°, is best made by the action of zinc on 1,2,3,4-$Br_4$ butane, m. 117°, purified by crystallization from alcohol. The bromide can be made from crude butadiene obtained by heating with soda lime (*a*) 2,3-$Br_2$-butane, (*b*) chlorinated butyl chloride or, best, (*c*) crotyl chloride, $CH_3CH=CH-CH_2Cl$ (Jacobson 1932). The last involves an allylic rearrangement. (EP 155) Probably the best preparation of crude butadiene is by passing the vapors of cyclohexene over a red-hot Pt wire. Another good method is from *n*-BuOH by treatment with HCl and then with chlorine to give 1,2-, 1,3- and 1,4-dichlorides which react with soda lime at 700° to give butadiene (Muskat 1930).

The diene can also be made by exhaustive methylation (p. 195) from pyrrolidine and from tetramethylene diamine obtainable by the Hofmann rearrangement of the diamide of adipic acid.

$$NH_2CO(CH_2)_4CONH_2 + Br_2 + KOH \rightarrow NH_2(CH_2)_4NH_2$$

Chlorine adds to butadiene to give a 1,2- and a 1,4-dichloride and the two stereoisomeric tetrachlorides. The boiling points at 40 mm. are 45°, 76°, 111° and 132° (m. 72°) respectively. The 1,2-dichloride does not rearrange to the 1,4-dichloride as is possible with the dibromides. Thus the formation of the 1,4- cpd. does not take place by rearrangement of the 1,2- cpd. but is due to an allylic shift of the double bond during the reaction (Muskat 1930).

$$CH_2=CHCH=CH_2 \rightarrow$$

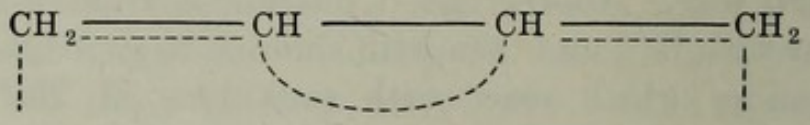
$$ClCH_2-\overset{*}{C}HCH=CH_2 \rightarrow ClCH_2CH=CH-CH_2^*$$

$$\downarrow \qquad\qquad\qquad\qquad \downarrow$$

$$ClCH_2-CHClCH=CH_2 \quad ClCH_2CH=CHCH_2Cl$$

The carbon marked * is one left with only six electrons by the addition of the positive Cl to the extra electron pair of the double bond. The presence and nature of substituents change the ease of the rearrangement step and consequently of the relative amounts of 1,2- and 1,4-product (Gillet 1922, Muskat 1930–).

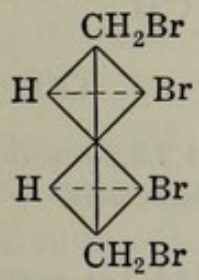
Butadiene gives a 1,2-dibromide, $CH_2=CHCHBrCH_2Br$, b. 52° (10 mm.) and two isomeric 1,4-dibromides, $BrCH_2CH=CHCH_2Br$, one m. 54° and the other a liquid b. 59° (13 mm.). The solid is the *trans* form since it gives racemic erythritol (EP 649). This 1,4 addition was explained by (Thiele 1899) on the basis of his famous theory of *partial valences*. This assumed the unsaturation of the olefinic linkage to be made up of partial valences. With double bonds in the 1,3 position the neighboring partial valences could satisfy each other, thus leaving the partial valences in the 1,4 positions as the most unsaturated points in the molecule. A closer study of this type of reaction throws doubt



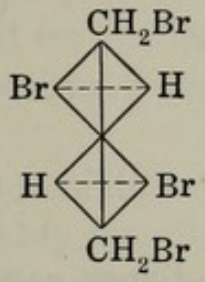

on the validity of this mechanism. In addition to the solid 1,4 product, a liquid 1,2 addition product is formed. Thus the addition of bromine also gives 1,2-dibromobutene-3. At present there is a tendency to explain the reactions of conjugated diolefins on the basis of the initial addition of the positive part of the

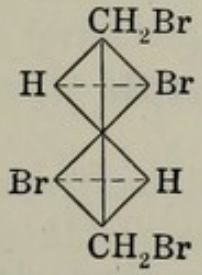
addend followed by an allylic rearrangement of the resulting fragment and the final addition of the negative portion of the addend.

Butadiene-1,3 with excess bromine gives two tetrabromides, one difficultly soluble in petroleum ether and melting at 119° and the other more soluble, m. 39°. These are stereoisomers of the same type as the tartaric acids, one being meso and the other racemic. In this case it is not possible to resolve the latter into optically active forms because of the lack of a suitable group for compound formation with an optically active reagent.




meso



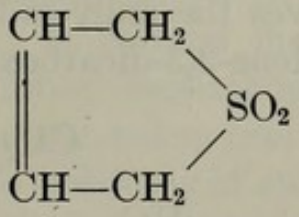




racemic

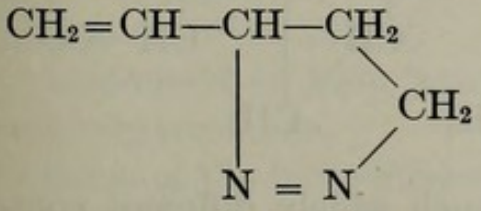
It adds ICl in $CH_2Cl_2$ at −35° to give the 1,4- and 1,2-products in the ratio 4 : 1 (Ingold 1931). It adds ammonia, 1 : 4, to give tributenyl amine,

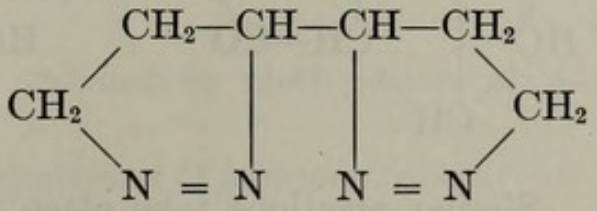
$$(MeCH{=}CHCH_2)_3N \text{ (EP 656)}.$$

Like other conjugated dienes it reacts with sulfur dioxide to give a cylic sulfone,




It adds one or two mols of diazomethane, $CH_2N_2$, to give 5-vinylpyrazoline and 5,5′-dipyrazoline.

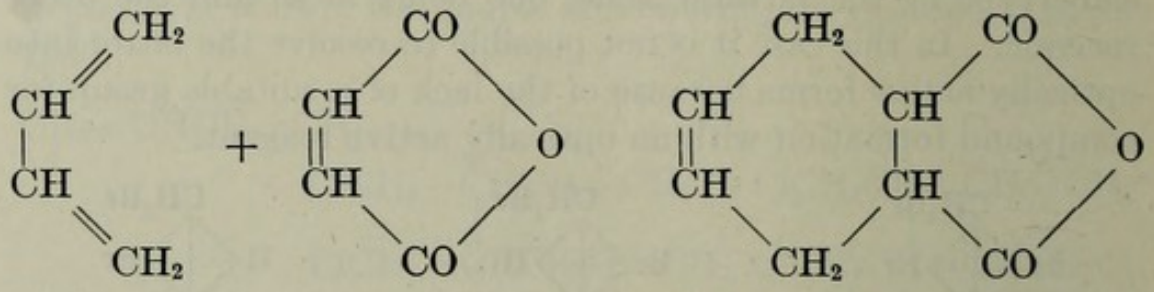



In this case 1,2-addition gives 5-membered rings whereas the more usual 1,4-addition would give a 7-membered ring.

1-Bromobutadiene adds $Br_2$, HBr, and HOBr in the 1,4-position (Muskat 1933).

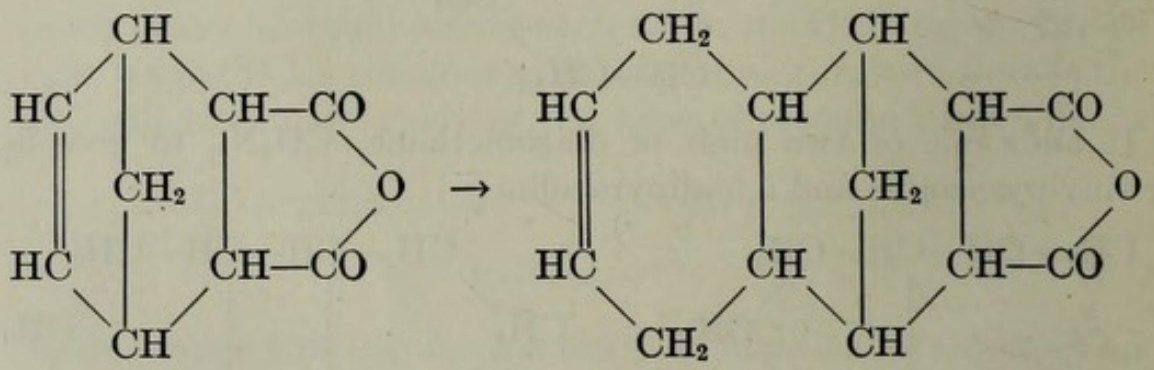
Perhaps the most interesting 1,4- addition of butadiene-1,3 and other conjugated diolefins is the Diels-Alder reaction (1928–) with maleic anhydride and similar conjugated ($\alpha\beta$) unsaturated carbonyl compounds.



Anhydride of 1,2,3,6-tetrahydrophthalic acid

The three simplest butadienes can be identified by reaction with maleic anhydride to give anhydrides of tetrahydrophthalic acid and its homologs (Birch 1932). The mps. of the anhydrides from butadiene, isoprene, and piperylene are respectively 104°, 64°, 62°.

Butadiene can also add to certain cyclic olefinic bonds which are not $\alpha\beta$ to carbonyl groups. Thus, with 3,6-endomethylene-1,2,3,6-tetrahydrophthalic anhydride obtained from cyclopentadiene and maleic anhydride, it gives the anhydride of 1,4-endomethylene-$\Delta$6,7-octahydronaphthalene-2,3-dicarboxylic acid.



Similar reactions take place with such widely different compounds as acrolein and benzoquinone giving tetrahydrobenzaldehyde, tetrahydro-$\alpha$-naphthoquinone and octahydroanthraquinone

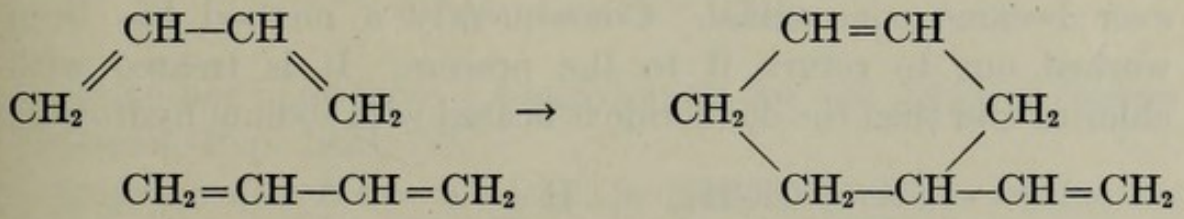
depending on whether one or two mols of the diene react with the quinone (EP 650) (Rep. 1930, 88) (Allen, Ed. 1933).

"Die Methoden der Dien-Synthese," Alder, Berlin, 1933.

The Diels-Alder reaction gives a good method for separating dienes from other materials and identifying them since the compounds with maleic anhydride are well crystallized and have characteristic melting points (EP 660).

Butadiene-1,3 polymerizes to a rubber-like material. The small amount of it in the butylene fraction of cracked gases from gasoline manufacture offers a possible source for a rubber substitute (Brooks). Because of its tendency to gum formation, the determination of butadiene in petroleum gases is important (Tropsch 1934).

One type of polymerization of dienes results in the formation of cyclic compounds and probably resembles the Diels-Alder reaction in being a 1,4-addition of the diene to a double bond in another molecule (Vaughan 1932).




**Isoprene,** 2-Methylbutadiene-1,3, b. 37°, is the most important diolefin (EP 153, 635). It can be made by the destructive distillation of natural rubber (caoutchouc). Because it can be polymerized readily to rubber, many processes have been evolved for its preparation. The synthesis of rubber by these processes has not become commercial partly because their threat to the natural rubber industry has stimulated the improvement in the growing of plantation rubber to the point where it has sold as low as five cents per pound.

Isoprene has been made by exhaustive methylation of β-methylpyrrolidine.

Some of the more interesting syntheses of isoprene follow:

1. Trimethylethylene, converted to the dichloride and then treated with alkali to remove 2 HCl. A difficulty here is the formation of 2-Me-3-chlorobutene-2 instead of the dichloride.

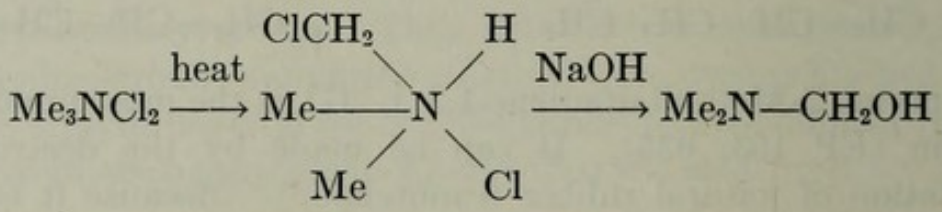
This could be converted to *unsym*-$Me_2$-allene. Addition of HCl to this would give 2-Me-2,4-dichlorobutane which could be converted to isoprene. (Frdl. *11*, 804).

2. Chlorination of isoamyl chloride under suitable conditions will attack the tertiary H giving 2-Me-2,4-dichlorobutane which with bases will give isoprene.

3. Many methods involving exhaustive methylation have been proposed. One of these involves the following steps starting with methyl ethyl ketone:

$$MeCOCH_2Me + Me_2NH + HCHO \rightarrow MeCOCH(Me)CH_2NMe_2$$

This ketone can be reduced to the alcohol electrolytically and the latter dehydrated. Methyl chloride can be added to give the quarternary ammonium chloride, which on distillation with NaOH should give isoprene. There are many obviously troublesome points in such a synthesis. The trimethyl amine formed in the exhaustive methylation would form a problem if the process ever became commercial. Consequently a method has been worked out to return it to the process. It is treated with chlorine and then the dichloride is heated with sodium hydroxide.




The rearrangement of the chlorine from N to C is the same as that involved in the probable mechanism of the halogenation of aniline and similar substances.

Isoprene adds bromine to give a 1,4-dibromide and a tetrabromide. With 2 HBr it gives 2-Me-2,4-dibromobutane (EP 647). The addition of 1 HBr gives an unstable tertiary bromide (1,2-addition) which changes on standing to a primary bromide (the 1,4-product), 2-Me-4-bromobutene-2. On hydrolysis, this undergoes an allylic rearrangement to dimethylvinylcarbinol ("isoprene alcohol") (Rep. 1923, 59). With bromine water the chief product is 1-bromo-2-Me-buten-2-ol-4.

Bromine, in aqueous EtOH, gives about 45%

$$BrCH_2CMe=CHCH_2OH$$

and 15%

$$BrCH_2CMe(OH)CH=CH_2$$

and a little $HOCH_2CMe=CHCH_2Br$ thus showing that the attack on the conjugated system starts mainly at the 1-carbon (Ingold 1931).

If Thiele's conception of partial valences gives the true explanation of 1,4-addition the reduction of isoprene would be expected to give mainly trimethyl ethylene and isopentane. Reduction with a platinum catalyst using equimolar proportions of hydrogen and isoprene gave isopentane, 30%, $Me_3$-ethylene, 15%, *unsym*-MeEt-ethylene, 13%, isopropylethylene, 12% and unchanged isoprene, 30%. Similar results were obtained with butadiene-1,3, pentadiene-1,3 and 2,3-$Me_2$-butadiene-1,3. Diisobutenyl,

$$Me_2C=CHCH=CMe_2$$

on the other hand gave 1,4-addition as the sole primary process (Lebedef, Rep. 1928, 72).

Isoprene with Na or K and EtBr gives 1,4-addition of the free ethyl radical to give 4-Me-octene-4 (Rep. 1930, 88) (Midgley). This is analogous to the addition of free triphenylmethyl radicals to get $(C_6H_5)_3CCH_2CMe=CHCH_2C(C_6H_5)_3$ (Conant 1933).

Isoprene, in glacial acetic acid, treated with NaSCN and bromine gives a dithiocyano addition product, m. 77°, probably $NCSCH_2CH=C(Me)CH_2SCN$ (Bruson 1928).

Isoprene adds $SO_2$ to form the cyclic sulfone, 2-Me-butene-2-sulfone-1,4, m. 63° (Rep. 1930, 90) (EP 655).

Isoprene was known to react at 180° with benzoquinone to give a product m. 234° containing two molecules of the diene for one of the quinone (v. Euler 1920) for some time before the discovery of the general reaction of conjugated dienes with $\alpha\beta$-unsaturated carbonyl compounds. (Diels, Alder 1928.)

The *polymerization* of isoprene is a most complex subject. In nature it may give rise to the terpenes and rubber and related

vegetable products. In the laboratory it gives products at least as complicated (Conant 1932).

The dimerization of isoprene was formerly thought to give a dimethyl cyclo-octatriene (Harries) but the process is actually an ordinary polymerization resulting in menthadienes (Rep. 1931, 87). If, instead of ring closure, the polymerization produces long chains of the type,

$$Me_2C=CHCH_2(CH_2CMe=CHCH_2)_nCH=CMeCH=CH_2$$

the product is caoutchouc.

Isoprene, with glacial acetic and sulfuric acids, gives geraniol, cyclogeraniol, linalool, $\alpha$-terpineol and 1,4- and 1,8-cineole (Rep. 1932, 151). This complex process involves only ordinary changes which may be analyzed as follows:

1. An H+ ion adds to the more active double bond of an isoprene molecule leaving the second carbon with only 6 electrons (indicated as *)

$$CH_2=C(Me)CH=CH_2 + H+ \rightarrow Me_2C^*CH=CH_2$$

2. This carbon relieves its deficiency by attracting an electron pair from the double bond of the next carbon, leaving the fourth carbon deficient and giving $Me_2C=CH-CH_2^*$. If this unites with an acetate or bisulfate ion it gives $Me_2C=CHCH_2OAc$ or the acid sulfate.

3. It reacts with another isoprene molecule exactly as the H+ did originally

$$Me_2C=CHCH_2^* + CH_2=C(Me)^*CH=CH_2 \rightarrow Me_2C=CHCH_2CH_2C^*(Me)CH=CH_2$$

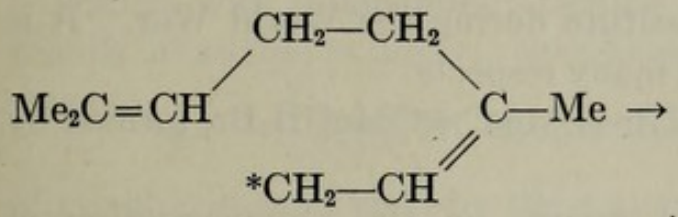
4. This undergoes a similar electron shift to that in 2, giving

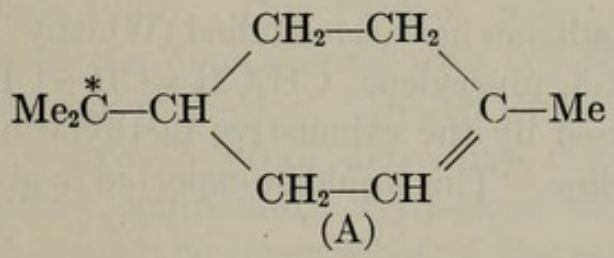
$$Me_2C=CHCH_2CH_2C(Me)=CHCH_2^*$$

This fragment can undergo various changes.

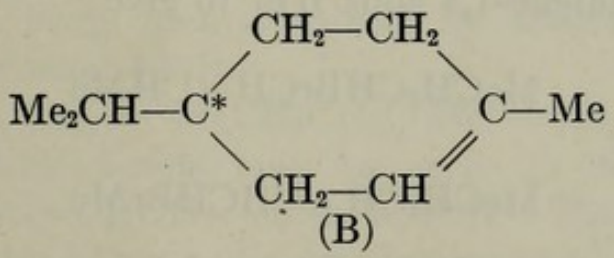
5. Union with an acetate or bisulfate ion followed by hydrolysis gives geraniol, $Me_2C=CHCH_2CH_2C(Me)=CHCH_2OH$.

6. The *C can approach the 6-C in space and can add to its double bond to form a 6-ring.





(A)



(B)

7. (A) can undergo several changes, one of the easiest of which is the union of the *C with acetate or bisulfite ion to give a product which on hydrolysis forms *α-terpineol* having OH in place of the *.

8. The *C can attract an electron pair from the adjacent tertiary C together with the attached H to give (B). This could give terpineol-4 with OH in place of *.

9. Addition of an H+ to α-terpineol from (7) would give $Me_2C(OH)-CH(CH_2CH_2)_2C^*Me$. In this the *C and the OH can approach each other in space. The H is expelled as H+ and the *C unites with the O to form ordinary cineol (1,8), an inner ether containing a 6-membered ring.

10. Entirely similar processes with the product of (8) would give 1,4-cineol, an internal ether containing a 5-ring.

The products formed are evidently those most stable under the conditions of the experiment.

The exaltation in the molecular refraction due to the conjugation of the double bonds in isoprene is 0.87.

**Methylisoprene,** 2,3-$Me_2$-butadiene-1,3, diisopropenyl,

$$CH_2=C(CH_3)C(CH_3)=CH_2, \text{ b. } 70°,$$

is made by the catalytic dehydration of pinacol, $Me_4$-ethylene

glycol, formed by the bimolecular reduction of acetone. Its polymerization by aniline hydrobromide as a catalyst gives *methyl rubber* used as a rubber substitute during the World War. It is inferior to natural rubber in many respects.

The chief product with HBr is $Me_2C=CMeCH_2Br$, formed by 1,4-addition.

The influence of methyl groups on the polymerization of substituted butadienes has been studied (Whitby, Rep. 1932, 113).

**Pentadiene-1,3,** piperylene, $CH_3CH=CH-CH=CH_2$, b. 43°, has been obtained by the exhaustive methylation of piperidine, hexahydropyridine. This would be expected to give the 1,4-diene. (EP 637.)

**1,4-$Me_2$-butadiene-1,3** adds HBr to give

$$MeCH_2CHBrCH=CHMe$$

and

$$MeCH_2CH=CHCHBrMe$$

in 9 : 1 ratio. Thus the chief addition is 1,2. This may be interpreted as indicating that there is less tendency for the group

$$Me-CH_2-\overset{*}{C}H-CH=CH-Me$$

to undergo the allylic rearrangement to form

$$Me-CH_2-CH=CH-\overset{*}{C}H-Me$$

than for

$$Me-\overset{*}{C}H-CH=CH_2$$

to change to $Me-CH=CH-CH_2$* as in the 1,4-addition to butadiene.

Higher alkylated dienes of the type, $Me_2C=CHC(Me)=CHR$, can be made by dehydrating the product of mesityl oxide with $RCH_2MgX$.

The best substitute for isoprene for rubber manufacture is *chloroprene*, 2-chlorobutadiene-1,3, (p. 98) which polymerizes more readily than isoprene and gives a rubber (Neoprene) superior

to ordinary rubber in its insolubility in hydrocarbons such as petroleum products.

**Dienes with Independent Double Bonds.** Of these the most readily available is diallyl, hexadiene-1,5,

$$CH_2=CHCH_2CH_2CH=CH_2, \text{ b. } 61°,$$

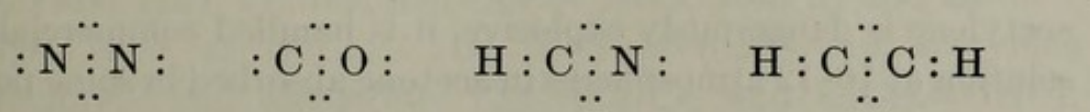
obtainable in good yield by the action of sodium on allyl bromide or iodide (Cortese 1929). This type of diolefin shows the ordinary reactions of the double bond with complications due to the possibility of ring formation. Diallyl with benzoyl peroxide (Rep. 1927, 87) gives a furan derivative instead of the expected tetrahydroxy compound. Hydration with sulfuric acid gives 2,5-epoxyhexane, the inner ether of the expected glycol.

1,4-Diolefins have been obtained by Boord's bromoether synthesis (Shoemaker 1931).

**Diisobutenyl,** $CH_2=CMeCH_2CH_2C(Me)=CH_2$, b. 114°. The effect of 1-double bonds may be seen by comparing with *diisocrotyl*, $Me_2C=CHCH=CMe_2$, b. 128°. The latter also has conjugated double bonds and a very symmetrical molecule which would ordinarily be expected to lower the boiling point. Under the influence of alcoholic KOH or silica catalysts at 200° diisobutenyl changes to the extent of 80% into the conjugated compound, diisocrotyl (Lebedef 1934).

## 2. Acetylenes, Alkines or Alkynes

The acetylenes resemble the olefins in being unsaturated. The unsaturation is localized at two adjacent carbon atoms, each of these atoms being capable of *adding* two univalent groups or their equivalent. This unsaturation is indicated by a *triple bond* between the two carbons. Although an acetylene can add twice as much as an olefin, the *ease of addition* to a triple bond may be less than that to a double bond. This lowered activity of the triple bond is perhaps due to an electronic structure resembling those of nitrogen, carbon monoxide and hydrocyanic acid (Lewis). In each case the *pair* of atoms has a complete octet.



The physical properties of the acetylenes resemble closely those of the paraffins and olefins.

### Acetylene, ethine, ethyne, $HC \equiv CH$

**Acetylene** is formed during many thermal decompositions of organic material. Thus it is found in illuminating gas. It is also formed in partial combustion of hydrocarbons as in the flame of a Bunsen burner which is burning at the base. The synthesis of acetylene from carbon and hydrogen in the electric arc by Berthelot in 1862 was of great theoretical interest because it opened up the synthesis of nearly all types of organic compounds from the elements and definitely overthrew any remaining idea that organic and inorganic materials obeyed different laws. Acetylene is also formed during the electrolysis of solutions of sodium fumarate and sodium maleate. The treatment of bromoform, or iodoform, $CHX_3$, with metals such as Zn or Ag forms acetylene.

*Preparation.* 1. Since 1892 when Willson made calcium carbide, $CaC_2$, available commercially, acetylene has been made by the action of water on that substance (Metal carbides, Ahr. 1896, 1–46).

2. Acetylene is also made on the large scale by passing hydrocarbons through an electric arc.

3. It can be made by the action of alcoholic KOH on ethylene bromide to remove 2 HBr. The reaction proceeds in two steps, vinyl bromide being formed first. Since vinyl bromide is volatile, the yield is cut down correspondingly. Moreover, considerable vinyl ethyl ether, $CH_2 = CHOEt$, is formed.

*Properties.* Acetylene is a gas with a very slight odor when pure. The odor of the impure gas is caused by traces of $H_2S$ and $PH_3$ due to impurities of sulfates and phosphates in the lime used for making commercial calcium carbide. It dissolves at ordinary temperature in water, benzene, ethanol and acetone to the extent of 1, 4, 6, and 25 volumes respectively. Since pure compressed acetylene is dangerously explosive, it is handled commercially in solution at 10–12 atmospheres in acetone absorbed in some porous

material (Prestolite tanks). The b.p. of acetylene is −84° while the m.p. is −82°. The liquid and solid are violently explosive, as it is a highly endothermic compound.

Studies of the specific heat of acetylene indicate that acetylene exists in equilibrium with isoacetylene (acetylidene, Nef), ($H_2C=C$) (Ingold 1923).

The normal vibrations of acetylene have been calculated from its infra-red spectrum (Olson 1932).

Acetylene is poison because it forms a stable compound with hemoglobin. In small amounts it has a narcotic effect (*Narcylene*).

*Reactions.* 1. With oxygen. Since acetylene is an endothermic compound, its combustion gives more heat than would be obtained by burning the same weight of pure carbon and hydrogen. The acetylene-oxygen flame is also superior to the oxy-hydrogen flame because the temperature of dissociation of carbon monoxide is far above that of steam. Consequently the hottest part of the acetylene flame is correspondingly hotter than the hydrogen flame. The brilliant white flame of acetylene burning in a special burner in air is due to the incandescent particles of carbon formed during the combustion. This gave acetylene its former wide use as an illuminant. At present the chief use of acetylene is for cutting and welding metals.

Acetylene forms explosive mixtures with air over the wide limits from 3 to 82% acetylene. This behavior is unusual. Thus methane and ethylene form explosive mixtures with air only between the limits 5 and 13% and 4 and 22% respectively. The kinetics of the slow oxidation of acetylene by oxygen are very complex (Kistiakowsky 1930).

2. With hydrogen. One or two molecules of hydrogen can be added to acetylene catalytically. It has been reported that chromous chloride solution, $CrCl_2$, will reduce $-C\equiv C-$ to $-CH=CH-$.

3. While acetylene and chlorine react explosively to give carbon and HCl, the reaction can be moderated by the use of a catalyst such as $SbCl_5$. The chief products are acetylene tetrachloride and dichloride, $Cl_2CHCHCl_2$ and $ClCH=CHCl$.

Smaller amounts of pentachloro- and hexachloro-ethane are obtained.

Bromine acts similarly.

Iodine at 150° gives solid *trans* and liquid *cis* acetylene diiodide (Rep. 1911, 97). The configurations have been determined by conversion to fumaric and maleic acids respectively. The addition of two univalent groups to a triple bond to give a *trans* olefin has been observed in many cases but has not been satisfactorily explained.

4. Halogen acids add to form vinyl halides and ethylidene halides, $CH_2=CHX$ and $CH_3-CHX_2$. The latter addition is in accord with Markownikoff's Rule. Traces of peroxides cause the reverse addition to give ethylene halides, $XCH_2CH_2X$ (Kharasch 1933).

5. Water can be added to acetylene in presence of mercuric sulfate and sulfuric acid to form acetaldehyde (b.p. 20°) which distills out of the reaction mixture and can be used for many important industrial syntheses. Another conversion of acetylene to acetaldehyde is by a $B_2O_3$ and $H_3PO_4$ catalyst at 360°.

6. Acetic acid can also be added in the presence of mercuric salts to form vinyl acetate, $CH_2=CHOCOCH_3$, and ethylidene diacetate, $CH_3CH(OCOCH_3)_2$, (Rep. 1921, 63).

7. Acetylene with oleum gives $(HO)_2CHCH(SO_3H)_2$ which, with barium hydroxide, forms $CH_2(SO_3)_2Ba$ and Ba formate.

8. Alcohols in the presence of $BF_3$ and mercuric compounds give acetals, $CH_3CH(OR)_2$ (Nieuwland 1930).

9. Aromatic compounds add to acetylene in presence of cuprous catalysts according to Markownikoff's Rule. Thus phenol gives $(HOC_6H_4)_2CHCH_3$ (Nieuwland 1928).

Acetylene with benzene and $AlCl_3$ gives a complex mixture containing 1,1-diphenylethane and 9,10-dimethyldihydroanthracene and only traces of styrene (Rep. 1921, 81).

10. Acetylene adds to itself (polymerizes) under the influence of cuprous catalysts to give vinyl acetylene and divinyl acetylene, $CH_2=CH-C\equiv CH$ and $CH_2=CH-C\equiv C-CH=CH_2$, and higher polymers (Nieuwland 1931). Vinyl acetylene is industrially important as the parent substance of chloroprene used in making Duprene rubber (Carothers 1932).

When heated, acetylene polymerizes to a great variety of products including benzene (Berthelot 1862) and a complex mixture of hydrocarbons called cuprene (EP 691). The silent electric discharge and ultraviolet light produce similar results (Lind 1932).

Acetylene is not polymerized by sulfuric acid. Different concentrations of acid give acetaldehyde and crotonaldehyde, $CH_3CH=CHCHO$.

The effect of heat on acetylene has been extensively studied (Rep. 1912, 74; 1919, 57; 1920, 53; 1928, 68; 1932, 112; Egloff 1932; EP 81).

10. Acetylene reacts when heated under the proper conditions with S or $NH_3$ to give thiophene or pyrrole (Rep. 1922, 61). Under other conditions $NH_3$ gives acetonitrile.

11. In a silent electric discharge, acetylene and nitrogen form HCN.

12. Acetylene reacts with $AsCl_3$ in presence of $AlCl_3$ (Nieuwland) to form chlorovinyl dichloroarsine, $ClCH=CHAsCl_2$ (the war gas, Lewisite, Lewis 1923) and the more highly substituted arsines, $(ClCH=CH)_2AsCl$ and $(ClCH=CH)_3As$.

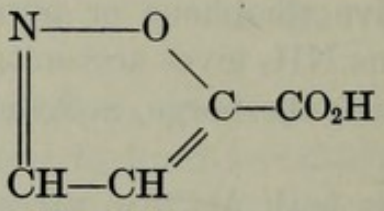
13. The hydrogens in acetylene have definitely acidic properties. Treatment of acetylene with ammonical cuprous or ammonical silver solutions precipitates cuprous and silver acetylides. These are explosive when dry. Treatment with acids regenerates acetylene. One or both hydrogens of acetylene can be replaced by heating with metallic sodium (Guernsey 1926) or potassium or by passing acetylene into a solution of the metal or metal amide in liquid $NH_3$. These compounds differ from the heavy metal acetylides in being stable when dry. They are completely hydrolyzed by water. Acetylene reacts like an acid with Grignard reagents forming the corresponding hydrocarbon and $HC\equiv CMgX$ or $XMgC\equiv CMgX$. These acetylene Grignard reagents can be used in the usual Grignard syntheses. Acetylene reacts with dilute alkaline solutions of organomercuric halides, RHgX, to give precipitates of organomercuric acetylides, $RHgC\equiv CHgR$, of characteristic melting points (Spahr 1933). The melting points (°C.) for the derivatives of the *n*-alkyls from methyl to

decyl are 233, 196, 151, 126, 92, 105, 96, 108, 98, and 111. Those of the derivatives of isopropyl, *sec*-butyl and isoamyl are 111, 106 and 107. Acetylene is regenerated by the action of acid.

Many C—H compounds other than acetylenic compounds of the type C≡CH show feebly acidic properties (Conant 1933).

14. The hydrogen atoms in acetylene can be *replaced* by iodine by the action of an alkaline solution of iodine. The product, diiodoacetylene, is a very insoluble solid of peculiar odor. The mono and disubstituted acetylenes containing chlorine and bromine are spontaneously inflammable.

15. Acetylene with nitric acid gives isoxazole-$\alpha$-carboxylic acid (EP 683).




16. Acetylene adds HCN in presence of a catalyst of barium cyanide and carbon to give vinyl cyanide, acrylonitrile, $CH_2=CHCN$.

17. Acetylene reacts with ketones in presence of sodamide to give ethynyl dialkyl carbinols, RR′C(OH)C≡CH (Ruzicka 1923, Carothers 1933).

18. Acetylene with chlorine water gives dichloracetaldehyde.

**Allylene,** methylacetylene, propyne, $CH_3C\equiv CH$, b. −23.3°.

Allylene can be made by the action of alcoholic potash on propylene dibromide (1,2-dibromopropane) or on acetone dichloride (2,2-dichloropropane). In each case allene ($CH_2=C=CH_2$) is also formed. This can be converted to MeC≡CNa by treatment with Na in ether. Allylene can also be made by a modified Wurtz reaction by methyl iodide or methyl sulfate with monosodium acetylide in liquid $NH_3$ (Maass 1931) or the mono Grignard reagent of acetylene, HC≡CMgX.

Allylene gives all the addition reactions of acetylene. These follow Markownikoff's Rule. Thus mercuric salts cause the addition of water to form acetone.

Allylene also shows the acid H reactions of acetylene. With

alkaline $Hg(CN)_2$ solution it gives $(MeC{\equiv}C)_2Hg$, m. 204°. This is a general reaction valuable for identifying α-acetylenes (Johnson 1926, Vaughn 1933). The corresponding derivatives of $RC{\equiv}CH$ in which R corresponds to the *n*-alkyl groups ethyl to decyl have melting points of 163, 118, 96, 61, 80, 68, 80, 79, and 85.

$MeC{\equiv}CNa$ reacts with acetaldehyde, ethyl formate, acetyl chloride and $CO_2$ to give pentyn-3-ol-2, butyn-2-al, pentyn-3-one-2 and methylpropiolic acid (1-carboxypropyne-1). The sodium derivatives of monosubstituted acetylenes in general form the best sources of αβ-acetylenic alcohols, aldehydes, ketones and acids (Moureu 1900–1902). In these syntheses they act exactly like Grignard reagents.

The polymerization of allylene by sulfuric acid yields mesitylene (*sym*-trimethylbenzene). Heat converts it to allene which then polymerizes.

**Ethylacetylene,** butyne-1, $C_2H_5C{\equiv}CH$, b. 8°, can be made similarly to its lower homolog and also from 1,1-dichlorobutane with alkali or, better, with sodamide. This is a good general method for making higher 1-acetylenes starting with aldehydes (Bourguel 1925).

Long heating with alcoholic KOH at 150° converts butyne-1 to butyne-2. This is a general reaction of alpha acetylenes of the type $RCH_2C{\equiv}CH$. Those of type, $RR'CHC{\equiv}CH$, are converted to allenes, $RR'C{=}C{=}CH_2$, while those of type, $R_3CC{\equiv}CH$ are stable to alcoholic KOH at 200° (Favorsky 1888).

Methylallene, $MeCH{=}C{=}CH_2$ in ether with Na gives $EtC{\equiv}CNa$.

At best, the yields of acetylene homologs by any elimination reaction are poor. Thus 1,2-dibromobutane with alcoholic KOH gives 1- and 2-bromobutene-1, 1- and 2-ethoxybutene-1, butadiene-1,2 and butyne-1 and -2 in varying amounts.

The addition and polymerization reactions of butyne-1 are like those of propyne.

**Crotonylene,** dimethylacetylene, butyne-2, $CH_3C{\equiv}CCH_3$, b. 29°, can be made in the usual ways. Since it contains no $C{\equiv}CH$ group it does not react with ammonical solutions of silver and

cuprous salts. Heating with metallic sodium or sodamide however isomerizes it with the formation of the sodium derivative of butyne-1. Thus acetylenes of the 1- and 2- types are interconvertible. The conversion to alpha acetylenes is a general property of disubstituted acetylenes even when the acetylene linkage is far removed from the end of the chain. Thus diamyl acetylene, $C_5H_{11}C{\equiv}CC_5H_{11}$, heated for seven hours at 210° in mineral oil with sodamide, gives decylacetylene, $C_{10}H_{21}C{\equiv}CH$ (Vaughn 1933).

Disubstituted acetylenes give no reaction with the Grignard reagent (Gilman 1925). With chlorine water they give dichloroketones, $RCCl_2COR'$.

**Higher Acetylenes.** The boiling points of pentyne-1 ($\alpha$-valerylene), pentyne-2 and 3-methylbutyne-1 are 40°, 55° and 35°, illustrating the effect of branching in the chain and of the position of the triple bond at the end or nearer the center of the molecule. Those of hexyne-1 and -2 are 71° and 84°, of heptyne-1 (Oenanthylidene), -2 and -3 are 110°, 113° and 106°; and of octyne-1 (caprylidene), and -2 are 125° and 133°.

*t*-Butylacetylene, $Me_3$-allylene, $(CH_3)_3CC{\equiv}CH$, b. 39°, is the lowest boiling compound of six carbons. It is obtained from pinacolone by treatment with $PCl_5$ followed by alcoholic KOH. No rearrangement takes place. It is unchanged by alcoholic KOH at 200°.

Because of the ready availability of heptaldehyde from castor oil cracking, heptyne-1 is the commonest higher acetylene. Its sodium derivative, in common with all sodium acetylides, reacts with $CO_2$ to give an acetylene acid. The methyl ester is a perfume, "methyl heptine carbonate."

Heptyne-1 with an alcoholic KOH solution of isopropylmercuric bromide forms an oil, $AmC{\equiv}CHgCHMe_2$, $d_4^{20}$ 1.628 (Spahr 1933).

Higher alpha acetylenes containing an even number of carbons can be made from an alkyl halide and disodium acetylide in liquid ammonia to give $RC{\equiv}CR$ which can be rearranged by $NaNH_2$ to $R'C{\equiv}CH$ (Vaughn 1933). Decyne-1 and dodecyne-1 have been made thus from *n*-butyl and *n*-amyl halides.

Acetylenes are more active than olefins with acid oxidizing agents. They split readily at the triple bond giving organic acids.

### Unsaturated Hydrocarbons, $C_nH_{2n-4}$, Alkenynes, and $C_nH_{2n-6}$, Alkadiynes

**Vinyl acetylene,** butenyne, $CH_2=CHC\equiv CH$, is obtained from acetylene and a cuprous chloride catalyst (DuPont). It adds HCl to give an unstable 1 : 4 addition product $ClCH_2-CH=C=CH_2$, which rearranges spontaneously, or more rapidly in presence of excess HCl, to give *chloroprene*, $CH_2=CHCCl=CH_2$, the raw material for Duprene rubber (Nieuwland, Carothers). Divinylacetylene, $CH_2=CH-C\equiv C-CH=CH_2$, is similarly obtained. On standing it polymerizes to a dangerously explosive solid resin. When partly polymerized and dissolved in a suitable solvent it forms a useful synthetic drying oil (S.D.O.).

**Diacetylene,** butadiyne, $HC\equiv CC\equiv CH$, is obtained as the cuprous derivative by heating ammonium diacetylene dicarboxylate with ammoniacal cuprous solution. Treatment with KCN gives the hydrocarbon. The Cu compound is violet red and the Ag compound is yellow. The latter is violently explosive even when wet.

**Dipropargyl,** hexadiyne-1,5, is made from the tetrabromide of diallyl with alcoholic KOH at 110°. It forms a liquid tetrabromide and an octabromide, m. 141°. It polymerizes readily. Heating with alcoholic KOH in a sealed tube rearranges the triple bonds in the usual way.

$$\underset{\text{m. } -6^\circ,\ \text{b. } 87^\circ}{HC\equiv CCH_2CH_2C\equiv CH} \rightarrow \underset{\text{m. } 64^\circ,\ \text{b. } 130^\circ.}{CH_3C\equiv CC\equiv CCH_3}$$

The substances are isomeric with benzene, m. 5°. b. 80°.

**$Me_2$-diacetylene,** hexadiyne-2,4, $CH_3C\equiv C-C\equiv C-CH_3$, is made from allylene by oxidizing the cuprous compound with potassium ferricyanide. It is also formed by heating dipropargyl with alcoholic KOH. In contrast to its isomer it is very stable.

The poly-olefins or polyenes are very important because of their occurrence in plant products. In general such substances have many conjugated double bonds.

## II. HALOGEN DERIVATIVES OF THE PARAFFINS

### *A.* Alkyl halides, $C_nH_{2n+1}X$, RX

Methyl fluoride, chloride and bromide and ethyl fluoride and chloride are gases. The other alkyl halides to about $C_{16}$ are liquids with sweetish odors. The freezing points of the chlorides and iodides of methyl and *n*-butyl are respectively −103°, −66° and −123°, −103°. The densities for the same pairs are respectively 0.95, 2.29 and 0.91 and 1.64.

Boiling Points of Alkyl Halides, °C.

| | Fluorides | Chlorides | Bromides | Iodides |
|---|---|---|---|---|
| Methyl | − 78 | − 24 | + 4.6 | 42.6 |
| Ethyl | − 32 | + 12.2 | 38.4 | 72.2 |
| *n*-Propyl | − 2 | 46.6 | 70.9 | 102.4 |
| *iso*-Propyl | | 36.5 | 59.6 | 89.5 |
| *n*-Butyl | | 77.9 | 101.6 | 127. |
| *sec*-Butyl | | 66.5 | 91. | 120. |
| *iso*-Butyl | | 68.5 | 92. | 119. |
| *ter*-Butyl | | 51.5 | 72. | 100. |
| *n*-Amyl | | 106.6 | 127.9 | 156. |
| *ter*-Amyl | | 85. | 108. | 127. |
| Neopentyl | | 84.4 | 105. | 133. |
| *n*-Hexyl | 85 | 134. | 156. | 177. |
| *n*-Heptyl | 119 | 159. | 178. | 204. |
| *n*-Octyl | 142 | 180. | 202. | 221. |

The alkyl halides are nearly insoluble in water, soluble in ether, in hydrocarbons and in alcohols. They are insoluble in cold concentrated sulfuric acid. This fact is used in removing impurities of alcohols from the halides. Doubt has been cast on this method of purification (McCullough 1929).

While the alkyl halides have a halogen atom in place of one hydrogen of a paraffin they are not usually prepared by direct halogenation. Fluorine reacts violently with paraffins giving hydrogen fluoride and carbon. The chlorination of hydrocarbons usually gives mixtures of various chlorides. In spite of an enormous amount of work on the chlorination of methane the process

is still unsatisfactory for the preparation of methyl chloride. In recent years the chlorination of *n*- and *iso*-pentane has been developed commercially to give monohalides which are important intermediates for the amyl alcohols (Sharples). Similar processes are being studied for the butanes. While the bromination of paraffins is possible, the process has received little study. The iodination of paraffins is not possible, the reverse action of an alkyl iodide and hydrogen iodide to give a paraffin and $I_2$ taking place too readily.

The numbers of alkyl halides theoretically possible have been calculated (Blair 1932). Thus there are 1,553 decyl chlorides for which formulas can be written.

Alkyl iodides form dichlorides, iodoso, and iodoxy compounds similar to those of the aromatic series. The aliphatic compounds are much less stable, however.

The preparations and chemical reactions of alkyl halides, RX, cannot be safely generalized except for the first two members. This is because of the frequent occurrence of molecular rearrangements both in the preparation and the reactions of the higher members and because of the great differences in *primary, secondary* and *tertiary halides*, $RCH_2X$, RR′CHX, and RR′R″CX.

The halides may be divided into several classes within each of which generalization is fairly safe except that knowledge of this important series is still inadequate.

1. **The primary halides,** MeX, EtX and the general type $RCH_2CH_2X$ can be prepared from the corresponding alcohols in good yields as follows: (a) Chlorides by means of HCl and pressure, HCl and $ZnCl_2$ heated (OS), HCl + $H_2SO_4$, NaCl + $H_2SO_4$, $PCl_3$ (alone or with $ZnCl_2$), $PCl_5$, $SOCl_2$ (with pyridine, Darzens 1911); (*b*) Bromides by the corresponding bromine cpds.; (*c*) Iodides by $I_2$ and P (OS) or from the corresponding chloride and KI in methanol or acetone. The reactions of the alcohols are slow especially with the halide acids. The first action is undoubtedly the formation of an oxonium salt, ROH.HX or $(ROH)_2HX$ which reacts gradually to give RX. Thus there is no real resemblance to the action of an acid with a base in spite of the apparent similarity of the two equations.

$$ROH + HX \rightarrow RX + H_2O$$
$$MOH + HX \rightarrow MX + H_2O$$

In the latter case, the base first dissociates into ions which then react. In the organic reaction the *first process is one of addition followed by slower decomposition.* This difference between inorganic and organic reactions is common.

Formerly the only primary halides which could be made by adding halide acid to olefins were the ethyl halides. It is now known that Markownikoff's Rule can be reversed by the addition of HX to an olefin in the presence of peroxides (Kharasch 1933–4), 1-olefins producing primary halides instead of the usual 2-derivatives. Thus propylene and pentene-1 can give *n*-propyl bromide and *n*-amyl bromide (Kharasch 1934, Sherrill 1934).

The halides of Class 1 give ordinary metathetical reactions, without rearrangement, with AgOH ($Ag_2O + H_2O$), Ag salts, inorganic cyanides, etc. The iodides are most reactive and the chlorides least. The bromides are usually preferred to the chlorides because they are made more easily and are more reactive without too great cost.

Type 1 halides include those of the normal alkyl groups, $Me(CH_2)_n-$, and others such as isoamyl, $Me_2CH(CH_2)_2-$, and neopentylcarbinyl (*β-t*-butylethyl), $Me_3C(CH_2)_2-$. In other words, if the halogen is on the No. 1 carbon and there is no branch in the chain nearer than the No. 3 carbon rearrangements are unlikely both in the preparation and reactions of the halides.

2. **Primary halides of the type** $RR'CHCH_2X$ can be obtained in only fair yields from the corresponding alcohols. Examples are isobutyl, $Me_2CHCH_2-$ and "active amyl," *sec*-butylcarbinyl, $MeEtCHCH_2-$. The best yields are obtained by $SOCl_2$ or $PBr_3$ under carefully controlled conditions. The halides of Type 2, in metathetical reactions, give mixtures of the expected product with the corresponding tertiary compound, depending on the conditions of the experiment. Thus isobutyl bromide with silver acetate, without a solvent, gives mainly isobutyl acetate whereas, in the presence of glacial acetic acid, the chief product is tertiary butyl acetate. Isobutyl iodide with AgNCO

gives the tertiary and iso derivatives in the ratio 2 : 1. Isobutyl iodide with alcoholic $AgNO_3$ gives ethyl *t*-butyl ether.

3. **Primary halides of the type** $RR'R''CCH_2X$ cannot be made from the corresponding alcohols except in very small yields, the main product being a tertiary halide formed by the shift of one of the alkyl groups. The only halides of this type which have been obtained pure are those of the neopentyl group, $Me_3CCH_2-$. The chloride is obtained by the direct chlorination of neopentane, tetramethylmethane. The chloride reacts normally with Mg to give the Grignard reagent which reacts with mercuric chloride to give neopentylmercuric chloride. This, with bromine and iodine, gives neopentyl bromide and iodide. The latter cannot be made from the chloride and an inorganic iodide. In fact all of the neopentyl halides are unusually inert. The iodide, for instance, reacts with alcoholic KOH only at 180°. Then the reaction is remarkable in giving neopentane as the chief product.

4. **Secondary halides of propane and butane** can be made from isopropyl alcohol and *sec*-butyl alcohol without complications. The chlorides can be made by treating the alcohols with HCl and $ZnCl_2$ in the cold. The reactions of these halides are entirely normal.

5. **Secondary halides of the normal paraffins beginning with pentane** are difficult to prepare pure. Thus the identities of the 2- and 3-halogen derivatives of *n*-pentane are still unsettled. Either secondary alcohol is likely to give a mixture of the two halides. The reactions of this type of halides are little known.

6. **Secondary halides having a branch on the carbon next to the carbinol group,** $RR'CHCHXR''$, cannot be made from the corresponding alcohol even under the mildest conditions. Thus methylisopropylcarbinol, $MeCHOHCHMe_2$, under all known conditions gives the *ter*-amyl halide exclusively (Whitmore 1933). The desired secondary chloride can be obtained only by adding HX to isopropylethylene. Even this reaction gives an equal amount of tertiary halide. It is interesting that the secondary isoamyl chloride when once formed is unusually unreactive and stable, showing no tendency to rearrange to the tertiary chloride. Thus the rearrangement takes place during the change of the alcohol to the chloride. This tendency to rearrangement can

be made useful in synthesis. Thus diisopropylcarbinol, which is available as a by-product of the synthesis of methanol from CO, reacts smoothly with HCl to give dimethylisobutylcarbinyl chloride $Me_2CHCH_2C(Cl)Me_2$.

7. **Secondary chlorides having two branches on** a carbon atom adjacent to the carbinyl carbon, RR′R″CCHXR‴, are unknown. Pinacolyl alcohol, $Me_3CCHOHMe$, gives the tertiary halides, $Me_2CXCHMe_2$, exclusively. The addition of HX to *ter*-butylethylene, $Me_3CCH=CH_2$, might be expected to give the desired product. As a matter of fact this addition proceeds contrary to Markownikoff's Rule and gives the primary halide, $Me_3CCH_2CH_2X$.

8. **Tertiary halides,** RR′R″CX, are formed with the greatest ease by the action of the tertiary alcohols with HX either in concentrated solution or as gas. Thus *ter*-butyl alcohol reacts almost instantaneously with hydrochloric acid.

The reactions of tertiary halides have been inadequately studied. With water they undergo hydrolysis to give tertiary alcohols if conditions are carefully controlled. Otherwise the chief product is an olefin. The reaction of tertiary halides with cold water can be used to remove them from a mixture with primary and secondary halides (Michael). This method is less valuable with higher tertiary halides because of their greater insolubility in water and consequent low reaction velocity. With reagents which would be expected to give metatheses the result with tertiary halides is usually merely the removal of HX to give the olefin. In other cases they may be very inactive as in the case of *t*-butyl chloride and NaI in which the reaction is only one fiftieth as fast as that on *n*-butyl chloride (Conant 1925).

### General Reactions of Alkyl Halides

The alkyl halides are among the most reactive of organic compounds. Their reactions are far from the simple metathetical type ordinarily pictured. They are nearly always far from complete and are accompanied by side reactions.

1. Effect of Heat.

Primary halides of Class 1 decompose only at high temperatures. The pyrolysis of *n*-butyl chloride without a catalyst gives

butene-1. With $CaCl_2$ as catalyst the chief products are *trans* and *cis* butene-2 (Hass 1932). With no catalyst, *sec*-butyl chloride gives butene-1 and *trans* and *cis* butene-2 in yields of 33, 44 and 22%. With $CaCl_2$ the yield of butene-1 falls to 15%. If the primary carbon bearing the halogen has a tertiary hydrogen next to it (Class 2) the temperature at which a change takes place is lowered. Thus isobutyl bromide is converted to tertiary bromide rapidly by heating at 230°. This is a true rearrangement and not a decomposition and recombination (Michael).

Secondary halides lose halide acid more easily than primary, and tertiary halides are least stable of all. Tertiary chlorides containing over six carbon atoms cannot be distilled at atmospheric pressure without considerable decomposition into halide acid and olefin. Tertiary iodides are very unstable.

2. Reducing Agents.

Powerful reducing agents such as sodium amalgam and alcohol, hydriodic acid and sodium in alcohol or liquid ammonia and metals with acids replace the halogen in alkyl halides by hydrogen producing saturated hydrocarbons. Alkaline reagents tend to, give olefins with tertiary halides. The reduction of neopentyl iodide to neopentane by conc. alcoholic KOH at 180° is unusual.

3. Bases and Hydrolysis (EP 781).

(*a*) Aqueous bases convert primary halides mainly to alcohols but always give some olefin. With secondary halides the proportion of olefin increases at the expense of the alcohol formed. With tertiary halides practically no alcohol is formed unless the base is very dilute and the temperature is low. This increasing tendency to olefin formation in the series primary, secondary and tertiary halides holds with practically all reagents especially with all which are capable of reacting with halide acids.

(*b*) Alcoholic bases give olefins with by-products of the corresponding ethyl ethers in the case of the primary and secondary halides. Often the ether is formed in as large amount as the olefin (p. 82). Neopentyl iodide is abnormal as it gives mainly neopentane with alcoholic KOH (p. 73). In the case of the tertiary halides, olefin formation is rapid and there is practically no ether formation. Hydrolysis by water in alcohol solution is

more rapid with secondary halides than with primary (Nicolet 1928).

4. Ammonia adds alkyl halides, especially those of Class 1, giving substituted ammonium halides. A complicated equilibrium system is set up.

$$\begin{aligned} RX + NH_3 &\rightarrow RNH_3X \\ RNH_3X + NH_3 &\rightleftharpoons NH_4X + RNH_2 \\ RNH_2 + RX &\rightarrow R_2NH_2X \\ R_2NH_2X + NH_3 &\rightleftharpoons NH_4X + R_2NH \\ R_2NH + RX &\rightarrow R_3NHX \\ R_3NHX + NH_3 &\rightleftharpoons NH_4X + R_3N \\ R_3N + RX &\rightarrow R_4NX \end{aligned}$$

The addition of alkyl halides to amines follows the same course. It is important in exhaustive methylation (p. 195). In addition to these reactions the ammonia or amine can act also as a base removing HX from the halide, slightly in the case of the primary halides, appreciably with the secondary halides and practically completely with the tertiary. Thus amines of tertiary alkyl groups are not obtainable from the halide.

5. Metals.

(*a*) Sodium reacts with most primary halides either in anhydrous ether or without a solvent to give fair yields of hydrocarbons (Wurtz).

$$2\,RX + 2\,Na \rightarrow R{-}R + 2\,NaX$$

The reaction is best with iodides and poorest with chlorides. Sodium vapor with gaseous MeBr or EtBr gives NaBr and the free radicals. These react in various ways (Rice 1934). Two ethyl radicals can form butane or ethylene and ethane or ethylene and hydrogen. The reaction in a solvent is more complex. Thus if a higher olefin is used as a solvent it takes part in the reaction (Reid 1935). When the Wurtz reaction is carried out in ether solution the sodium alkyl, RNa, can react with the ether to form EtONa and RH (Schorigin 1908) (Carothers 1930). With secondary halides the amount of unsaturated by-products increases enormously and with tertiary halides they form the main product.

(*b*) The one reaction which apparently takes place with all types of halides is that with magnesium and ether to give the Grignard reagent, RMgX. With the simpler alkyl halides of all types it is possible to approach 100% yields by the use of proper precautions. This is true with Class 1 halides as high as *n*-dodecyl bromide. With tertiary halides higher than amyl the yield falls rapidly due to the increasing tendency to remove HX with olefin formation. The surest method of converting an alkyl halide to the corresponding alcohol without possibility of rearrangement is to convert it to the Grignard reagent and treat the latter with oxygen (Whitmore 1933).

(*c*) Zinc-copper alloy reacts with the lower primary bromides and iodides to give zinc dialkyls which are volatile and spontaneously inflammable (Frankland). Secondary and tertiary halides yield mainly olefins.

(*d*) Sodium amalgam in the presence of a trace of ethyl acetate as a catalyst reacts with primary bromides and iodides to form mercury dialkyls (Frankland). These are high boiling very toxic liquids.

(*e*) Mercury reacts with methyl iodide in sunlight to form crystalline methylmercuric iodide (Frankland). A trace of mercurous iodide catalyzes the reaction (Maynard). The reaction fails with other halides.

(*f*) Sodium-lead alloy and ethyl chloride under pressure are used to make the enormous tonnage of tetraethyllead now used in anti-knock gasoline ("Ethyl gas").

6. Salts and Related Compounds.

(*a*) Cyanides and sodioketoesters. The reactions of alkyl halides most frequently mentioned in textbooks are those of synthetic importance like the action with KCN or NaCN and with sodiomalonic ester, sodioacetoacetic ester and sodiocyanoacetic ester. These reactions work well only with halides of Class 1 (p. 71). The yields with those of Class 2 are much poorer. With halides of Classes 3 to 6 the reactions either fail completely, give poor yields or result in olefins or rearranged products. With tertiary halides, olefins are the main products. Small yields of cyanides, RR′R″CCN, are reported from the action of the tertiary iodides with the double cyanide of Hg and K

and with silver cyanide, mercuric cyanide or cuprous cyanide (available for use in anti-fouling paint for boat bottoms).

The preparation of a higher halide, $RCH_2X$ from RX is often very important. The steps commonly given are $RX \rightarrow RCN \rightarrow RCH_2NH_2 \rightarrow RCH_2OH \rightarrow RCH_2X$. The first step is likely to give trouble unless R is of Class 1. The second step gives relatively little trouble although there is a tendency to form some secondary amine, $(RCH_2)_2NH$. The third step spoils the entire process since the yield of normal product is poor even when R belongs to Class 1. A better process for converting the primary amine, $RCH_2NH_2$ to $RCH_2Cl$ consists in converting it to the benzoyl derivative which reacts with $PCl_5$ to give $RCH_2Cl$, $C_6H_5CN$ and $POCl_3$ (von Braun, Rep. 1911, 87).

A process for going up the series which offers fewer difficulties involves the action of monochloromethyl ether (from methanol, formaldehyde and HCl) with the Grignard reagent followed by the splitting of the resulting ether with HBr (Rep. 1926, 101).

$$RX \rightarrow RMgX \rightarrow RCH_2OMe \rightarrow RCH_2Br$$

The advantages of this method are (1) the formation of the Grignard reagent offers fewer complications than any other reaction of alkyl halides, (2) alpha halogenated ethers are easily prepared and react nearly quantitatively with Grignard reagents, and (3) the splitting of methyl ethers by HBr offers no complications unless R in the above compounds is tertiary.

The *addition of two carbon atoms* can be accomplished by the use of sodiomalonic ester in the following steps:

$$RX \rightarrow RCH(CO_2Et)_2 \rightarrow RCH_2CO_2H \rightarrow RCH_2CO_2Et \rightarrow RCH_2CH_2OH \rightarrow RCH_2CH_2X$$

Once again the first step is likely to fail unless RX belongs to Class 1.

An alkyl halide may be lengthened by *three carbon atoms* by treating its Grignard reagent with $\gamma$-chloropropyl *p*-toluenesulfonate (Rossander 1928).

$$RMgX + Tol{-}SO_3(CH_2)_3Cl \rightarrow R(CH_2)_3Cl + Tol{-}SO_3MgX$$

The preparation of a *lower alkyl halide from a higher member* of the series is also often important. The classical series of steps is as follows: $RCH_2X \rightarrow RCH_2OH \rightarrow RCHO \rightarrow RCO_2H \rightarrow RCOCl \rightarrow RCONH_2 \rightarrow RNH_2 \rightarrow ROH \rightarrow RX$. The first step will involve trouble unless RX is of Class 1. The steps from the alcohol to the primary amine all give excellent yields. It is interesting that these are *not metathetical* processes. Even the action of the acid chloride with $NH_3$ probably involves an addition to the carbonyl group rather than a simple metathesis which might be indicated. Again the conversion of the primary amine to the alcohol presents serious difficulty but the amine can be converted to the halide through von Braun's benzoyl method (p. 78). A useful modification of the above set of steps is the treatment of the acid chloride with sodium azide ($NaN_3$) to give the amine (Naegeli 1932) which can then be treated by von Braun's method.

$$RCOCl \rightarrow RCON_3 \rightarrow RNH_2 \rightarrow RNHCOC_6H_5 \rightarrow RCl + C_6H_5CN$$

(*b*) Silver salts. Esters not readily available in other ways may sometimes be made from alkyl halides and the silver salts of the desired acids. Even this reaction works well only with halides of Class 1.

The action of alkyl halides with $AgNO_2$ has been very thoroughly studied (Reynolds 1929). Both nitro compound and nitrite are obtained in all cases, the combined yield being 60–90%. As might be expected, the tertiary halides give the lowest yield but react most rapidly. The bromides give more nitro compound than the chlorides or iodides.

(*c*) Other salts. Higher boiling halides react on heating with anhydrous sodium acetate ("fused") to give the corresponding acetates. This process is used commercially to prepare amyl acetates from the chlorination products of the pentanes. As would be expected the yields from secondary chlorides are poor and tertiary chlorides are converted entirely into olefins.

A special method for replacing primary and secondary halogen by hydroxyl is to reflux with anhydrous potassium formate in absolute methyl alcohol. The first step probably converts the halide to the formate which then undergoes "alcoholysis"

$HCO_2R + MeOH \rightarrow HCO_2Me + ROH$. An easy way to be sure of having anhydrous potassium formate is to add thoroughly dried potassium hydroxide to a mixture of anhydrous methyl formate and methanol and reflux before adding the halide (OS).

The replacement of one halogen by another is often possible. Thus chlorides with $AlBr_3$ give bromides, with NaI, KI (Conant 1925) or $CaI_2$ give iodides; bromides with NaI etc. give iodides less readily, with $SbCl_5$ give chlorides; iodides with $CuBr_2$ give bromides, with $HgCl_2$ give chlorides and with AgF or $HgF_2$ give fluorides. As usual these replacement reactions give good results only with primary halides of Class 1. Thus isobutyl iodide with ICl gives $I_2$ and *tertiary* butyl chloride exclusively.

(*d*) Anhydrous aluminum chloride reacts vigorously with alkyl halides giving HX and rearrangement and polymerization products. This type of reaction has not been adequately studied.

(*e*) Dialkylzinc compounds, Grignard reagents and organolithium compounds, with alkyl halides, give higher hydrocarbons in poor yields. These reactions are used only as a last resort (Marvel 1927, Noller 1929, Edgar 1929).

## Individual Alkyl Halides

These will be considered, either because of their importance or as illustrations of typical processes.

1. **Methyl fluoride** is prepared (1) by heating KF with $MeKSO_4$ and washing the products with conc. $H_2SO_4$ to remove ethylene and methyl ether; (2) by heating $Me_4NF$.

**Methyl chloride** is available liquefied in tanks. It is prepared from methanol with NaCl and $H_2SO_4$ or with hydrochloric acid and zinc chloride in autoclaves. It has also been made by heating trimethylamine with HCl, the former being obtained by the decomposition of betaine during the destructive distillation of sugar beet residues. Its preparation by the direct chlorination of methane has not been practical. It is used as a refrigerant. Because of its toxic character and very slight odor, it may be mixed with a small amount of a warning agent (ethyl mercaptan) for use in refrigeration. It is easily converted to the Grignard reagent, MeMgCl.

**Methyl bromide** can be generated conveniently by warming a mixture of sodium bromide, methanol and sulfuric acid. It is a useful methylating agent (Lucas 1929).

**Methyl iodide** is best made from methanol, iodine and phosphorus (OS). One possible equation for this complex reaction is

$$10\ CH_3OH + 5\ I_2 + 2\ P \rightarrow 10\ CH_3I + 2\ H_3PO_4 + 2\ H_2O$$

It can also be prepared by heating dimethyl sulfate (poisonous, odorless) with sodium iodide. Methyl iodide has been much used as a methylating agent. Thus methyl glucoside with MeI and $Ag_2O$ gives polymethyl ethers. Ketones, with sodamide and MeI, have alpha H atoms replaced by Me groups.

2. **Ethyl chloride** is prepared like methyl chloride and is available in tanks. Small amounts of ethyl chloride can be made conveniently by heating an alcoholic solution of $CaCl_2$ with $Et_2SO_4$. Recently the preparation from ethylene and HCl has become important. Ethyl chloride has replaced the bromide used for the preparation of lead tetraethyl (anti-knock). It is also used for making ethyl mercaptan, EtSH, for the preparation of sulfonal. It is used as a refrigerant, in thermo-regulators for house heating and as a local freezing anesthetic for minor operations.

**Ethyl bromide** is prepared from ethanol, sodium bromide and sulfuric acid or from ethanol and a mixture of HBr and $H_2SO_4$ obtained from bromine, a limited amount of water and sulfur dioxide (OS). Recently the tendency for commercial preparation is to use the action of HBr with ethylene. The conversion of ethyl bromide to HBr and ethylene has been studied as a typical monomolecular reaction (Daniels 1932).

**Ethyl iodide** is prepared like methyl iodide. Infra-red spectrum studies have been made on the ethyl halides (Daniels 1933).

3. ***n*-Propyl chloride** is best prepared from propanol-1 (from fusel oil or methanol synthesis) by heating with concentrated hydrochloric acid and zinc chloride (Norris). It can also be prepared by means of $PCl_3$, $PCl_5$ or $SOCl_2$. In addition to the normal reactions giving the alkyl chloride there is always some loss due to the formation of the esters, $R_3PO_3$, $R_3PO_4$ and $R_2SO_3$.

***n*-Propyl bromide** is prepared like ethyl bromide. It can also be prepared with $PBr_3$. The pentabromide is less suitable because it readily dissociates into the tribromide and free bromine and thus has an oxidizing effect on the alcohol. *n-Propyl iodide* is made like methyl iodide. *Isopropyl chloride* is made from isopropyl alcohol (Petrohol) by hydrochloric acid and zinc chloride. *Isopropyl bromide* and *iodide* are made like the corresponding normal compounds. The iodide can also be made from glycerol, phosphorus, water and iodine. The latter substances give HI which reacts to replace the three hydroxyls by iodine. Since iodine atoms on adjacent carbon atoms are easily lost to give a double bond the 1,2,3-triiodopropane changes to allyl iodide (3-iodopropene-1). This then adds HI to give 1,2-diiodopropane which loses iodine to give propylene. This adds HI to form isopropyl iodide. At a time when isopropyl alcohol was not available commercially, this was the best method for obtaining an isopropyl halide.

4. ***n*-Butyl halides** are readily prepared from butanol-1 by the same methods as the ethyl halides. *sec-Butyl halides* are prepared from butanol-2 (from cracked gases) like the isopropyl halides. *Isobutyl halides* are obtained from isobutyl alcohol (from fusel oil or from methanol synthesis) in rather poor yields. This is due to the presence of the tertiary H atom next to the carbinol group. Considerable amounts of isobutylene and tertiary butyl halides are formed. The isobutyl halides are best prepared by thionyl chloride, either alone or with pyridine, by phosphorus tribromide and by phosphorus and iodine. In such processes two types of reaction can occur.

$$3\ ROH + PX_3 \rightarrow 3\ RX + H_3PO_3$$
$$3\ ROH + PX_3 \rightarrow R_3PO_3 + 3\ HX$$

The factors controlling these have never been studied adequately.

Isobutyl bromide, on heating, is partly converted to *ter*-butyl bromide by a true intramolecular rearrangement (Michael) and not by dissociation and reverse addition of HBr as is often assumed.

**Tertiary butyl halides,** in common with tertiary halides in general, are prepared with extreme ease by merely treating

tertiary butyl alcohol (from cracked gases) with the proper halide acid. The reaction is almost as rapid and complete as between a base and an acid. The only precaution which has to be used with the tertiary halides is due to the ease with which they lose halide acid to give olefins at higher temperatures. *t*-Butyl iodide is very unstable.

5. **Amyl halides.** The commercial chlorination of *n*- and *iso*-pentane (Sharples) gives all the possible amyl chlorides except neopentyl chloride. The amounts in which the individual chlorides appear is still unsettled (Hass 1935). The preparation of the pure amyl halides may be discussed as typical of higher halides of the corresponding types.

***n*-Amyl halides,** $Me(CH_2)_4X$, are now readily available from *n*-amyl alcohol (Sharples). Before this alcohol or *n*-butyl alcohol was available *n*-amyl bromide was made by von Braun (1911) as follows: Benzoylpiperidine was treated with $PCl_5$ under conditions to break only one of the C—N bonds, thus giving $Cl(CH_2)_5NHCOC_6H_5$. This, with NaI in alcohol, gave the corresponding iodide in which the iodine could be replaced by H on treatment with zinc dust and acid. The *n*-amylbenzamide thus obtained gave *n*-amyl chloride or bromide by action with $PX_5$.

**Isoamyl halides,** $Me_2CHCH_2CH_2X$, have long been available by the usual methods from isoamyl alcohol from fusel oil.

**Active amyl halides,** $Me_2EtCHCH_2X$, are obtained from active amyl alcohol from fusel oil. The yields are poor because of the nearby branch in the chain.

**Neopentyl halides** ($Me_3CCH_2X$) are available only by special reactions (p. 73).

**Secondary *n*-amyl halides** (2- and 3-) are difficult to prepare pure. Probably the best methods are the use of the alcohols with thionyl chloride or phosphorus tribromide with pyridine in each case.

**Secondary isoamyl halides,** $Me_2CHCHXMe$, are available only by the addition of HX to isopropyl ethylene.

**Tertiary amyl halides,** $Me_2EtCX$, are readily available by the action of HX with commercial *t*-amyl alcohol.

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**Higher alkyl halides** have been made in great number. In most cases their preparation depends on the preparation of the higher alcohol. A method of adding several carbons to a given halide consists in treating its Grignard compound with the tolyl sulfonate of a 1-chloro-ω-hydroxy compound obtained from a polymethylene glycol (Marvel 1928).

$$C_7H_7SO_3(CH_2)_nCl + RMgX \rightarrow R(CH_2)_nCl + C_7H_7SO_3MgBr$$

**Identification of Alkyl Halides.** This is possible by conversion to a variety of crystalline compounds. Among these are the acyl-anilides formed from phenyl isocyanate ($C_6H_5NCO$) and the Grignard reagent.

$$RMgX + C_6H_5NCO \rightarrow C_6H_5NHCOR$$

The m. (°C.) for the acyl-anilides from the simpler alkyl groups follow (Schwartz 1931): Me 114, Et 105, *n*-Pr 92, *iso*-Pr 103, *n*-Bu 63, *iso*-Bu 114, *sec*-Bu 111, *t*-Bu 132, *n*-Am 96, 2-*sec*-Am 95, 3-*sec*-Am 124, *iso*-Am 112, *sec-iso*-Am 78, *Active*-Am 88, *t*-Am 92, *neo*-Am 132, *n*-Hex 69, *n*-Hep 57, 2-*sec*-Octyl 73. Correspondingly α-naphthyl isocyanate gives naphthalides, $RCONHC_{10}H_7$, m. (°C.): Me 160, Et 126, *n*-Pr 121, *n*-Bu 112 (Gilman 1928).

Another method of identification is the reaction with potassium 3-nitrophthalimide to give $(NO_2)C_6H_3(CO)_2N-R$. The m. (°C.) of typical derivatives follow: Me 113, Et 106, *n*-Pr 85, *n*-Bu 72, *iso*-Am 94. Obviously this method can give best results only with halides of Class 1.

Still another means is the conversion to the Grignard reagent, treatment with oxygen and identification of the resulting alcohol in one of the usual ways (p. 142).

Alkyl halides have been identified by conversion to RHgX through the Grignard reagents (Marvel 1923, Hill 1928, Vaughn 1933). The resulting alkylmercuric halides are readily crystallized (poison) and have definite melting points. This method fails with tertiary halides and is only fair with secondary. The mercury compounds can be treated in alkaline solution with acetylene to give $RHgC{\equiv}CHgR$, compounds of high melting points (p. 65) (Spahr 1933).

## *B.* Saturated Dihalides, $C_nH_{2n}X_2$

### Methylene Halides, $CH_2X_2$

**Methylene chloride,** b. 39.8°, is obtained as a by-product in the commercial reduction of carbon tetrachloride to chloroform. It is remarkably stable and unreactive (Carlisle, Levine 1932). *Methylene bromide,* b. 99°, and *methylene iodide,* b. 181°, are obtained by reducing bromoform and iodoform with alkaline arsenite solution (OS). The iodide is used as a heavy liquid (d. 3.3) in separating heavy minerals such as sulfides from materials such as silicates which have densities below 3. Lighter minerals can be separated by diluting the iodide with lighter liquids to give a mixture in which one mineral will float and others will sink. The iodide exists in two crystalline forms, m. 5.5° and 6.0° (stable form) (Stone 1932). $CH_2I_2$ acts with mercury to give iodomethylmercuric iodide, $ICH_2HgI$, and di-iodomercuri-methane, $CH_2(HgI)_2$, depending on the amount of metal used (Sakurai 1880–2). These products are insoluble solids.

The halogen atoms in the methylene halides are less active than those in methyl halides. They react readily only with strongly alkaline reagents. The bromide and iodide react with Al to give $CH_2{=}AlX$ which is decomposed by water or alcohol to give $CH_4$ (Rep. 1922, 62).

**Ethylidene Halides,** $CH_3CHX_2$. Ethylidene chloride, b. 58°, is made from acetaldehyde with phosphorus pentachloride or phosgene, the other product being $POCl_3$ or $CO_2$. It can be made by passing ethylene chloride over $Al_2O_3$ at 400° to give vinyl chloride and HCl which combine in presence of $AlCl_3$ at 125° to give ethylidene chloride. The bromide is more difficult to prepare from acetaldehyde and $PBr_5$, because the ready dissociation to $PBr_3$ and $Br_2$ causes bromination of the alpha carbon. The best preparation of ethylidene bromide or iodide is from HBr or HI and acetylene. Hydrolysis of the ethylidene halides gives acetaldehyde.

**Ethylene Halides,** $XCH_2CH_2X$, are obtained by direct addition of the halogens to ethylene.

**Ethylene chloride,** b. 84°, is available as a very cheap by-

product of the production of ethylene chlorohydrin from ethylene and chlorine water (EP 468). It is "the oil of the Dutch chemists" (p. 30). It can also be made from liquid chlorine and dry ethylene (Curme 1921). It is characterized by great chemical stability and high solvent power. Like all polyhalides it is non-combustible. Under pressure it gives ordinary halide reactions. Thus, with NaCN, it gives ethylene dicyanide, succinonitrile. With $SO_3$ it gives, $ClCH_2CH_2SO_2Cl$, beta-chloroethane sulfonyl chloride, which reacts with CaO to give ethylene oxide. A rubber substitute, Thiokol, which is resistant to solvents which attack ordinary rubber, has been made from ethylene chloride and $Na_2S_x$. This consists of high polymers containing alternate ethylene and polysulfide residues. Ethylene diamine is also made from the chloride. Treatment of the chloride with bases under pressure produces vinyl chloride, $CH_2=CHCl$. When sodium acetate is used vinyl chloride and acetate are obtained. These readily polymerize (Vinylite resins).

The U. S. Dept. of Agriculture has a publication giving a complete summary of the chemistry and uses of ethylene chloride with 470 references to the literature. Misc. Publication No. 117 (1932).

**Ethylene bromide,** b. 131°, m. 9°, is made in enormous amounts (over one million pounds per month in 1936) for use with tetraethyl lead in anti-knock fuel. It supplies bromine to convert the lead to lead bromide which escapes as such from the exhaust of the engine. If no bromide is used, lead oxide is formed and acts as a flux with the oxide coating of the spark points and so eats them away. Chlorides cannot be used in place of bromides because lead chloride hydrolyzes to the oxide under motor conditions. The amount of ethylene bromide used for this purpose is so great that processes have been developed for extracting the bromine from sea water (Stewart 1934). Sea water contains 65–70 parts per million of bromine whereas it contains less than 5 parts per *billion* of gold (Gurevich 1933).

As would be expected, ethylene bromide is more reactive than the chloride. In addition to the reactions of primary alkyl bromides it reacts with zinc dust to give the olefin, a reaction typical of 1,2-dibromides.

**Ethylene iodide,** m. 81°, is formed from ethylene and iodine wet with alcohol. It reverts to ethylene and iodine on heating (Kistiakowsky 1933). The instability of 1,2-diiodides is utilized for making olefins by heating the corresponding chloride or bromide with NaI.

**Ethylene chlorobromide,** $ClCH_2CH_2Br$, b. 107°, is obtained by passing ethylene into bromine containing an equivalent amount of chlorine ("bromine chloride"). For a time it was used in Ethyl fluid in place of the bromide until it was found that only the bromine in the compound was effective. Its reactions are practically identical with those of the bromide or chloride. There is little difference in the reactivity of the two different halogen atoms in the molecule. One exception is the reaction with sodium sulfite which takes place practically entirely with the bromine giving sodium $\beta$-chloroethyl sulfonate, $ClCH_2CH_2SO_3Na$.

**Ethylene chloroiodide,** $ClCH_2CH_2I$, b. 140°, is prepared from ethylene and iodine monochloride, ICl. Similarly *ethylene bromoiodide,* b. 163°, has been prepared.

Ethylidene and ethylene halides react with an excess of alcoholic potash to give acetylene.

**Propylidene Halides,** 1,1- or $\alpha\alpha$-, $CH_3CH_2CHX_2$. These are made from propionaldehyde similarly to the ethylidene halides. $EtCHCl_2$, b. 86°; $EtCHBr_2$, b. 130°.

**Acetone Dihalides,** 2,2- or $\beta\beta$-, $CH_3CX_2CH_3$. The chloride is prepared from acetone and phosphorus pentachloride in poor yield. A considerable amount of $CH_3CCl=CH_2$ is formed. Phosphorus pentabromide acts as a brominating agent, introducing bromine into the methyl groups. The bromide and iodide are obtained by adding HX to methylacetylene.

**Propylene Halides,** 1,2- or $\alpha\beta$-, $CH_3CHXCH_2X$. These are made by adding halogens to propylene. In the addition of iodine chloride to propylene the chief product is 1-iodo-2-chloropropane. Thus the iodine is the positive part of the addend.

The propylidene, propylene and acetone dihalides give methyl acetylene with reagents like alcoholic potash and sodamide.

**Trimethylene Halides,** 1,3- or $\alpha\gamma$-, $XCH_2CH_2CH_2X$. These are obtained from trimethylene glycol (1,3-dihydroxypropane), a by-product of glycerol manufacture, by the ordinary methods for

making alkyl halides. The addition of HBr to allyl bromide, $CH_2=CHCH_2Br$, in the presence of peroxides takes place rapidly to give the 1,3-dibromide. In the presence of antioxidants the addition is slow and produces the 1,2-compound (Kharasch 1933). The two halogen atoms act independently and almost exactly like other primary halides. It is possible to replace one or both of them under suitable experimental conditions. The dichloride is important as an intermediate for the general anesthetic, cyclopropane. For this purpose it is made by chlorinating propane (Hass). Heating with Zn gives cyclopropane (Mallinckrodt) (Hass 1936).

**Dihalides of butane and isobutane** are available by the methods already outlined. Special methods may be named for the following:

*a.* Tetramethylene dibromide, $Br(CH_2)_4Br$, has been made from trimethylene dibromide (Marvel 1922) and from tetramethylene diamine (v. Braun 1922). The reactions follow:

$$Br(CH_2)_3Br + PhONa \rightarrow PhO(CH_2)_3Br$$

$$\xrightarrow{KCN} \xrightarrow[H_2SO_4]{EtOH} \xrightarrow{Na} \xrightarrow[EtOH]{HBr} Br(CH_2)_4Br$$

$$H_2N(CH_2)_4NH_2 \rightarrow PhCONH(CH_2)_4NHCOPh$$

$$\xrightarrow{PBr_5} PhCN + Br(CH_2)_4Br$$

The hydrolysis of dibromides containing a tertiary bromine gives aldehydes or ketones by rearrangement (p. 265) (Evers 1933). Thus isobutylene dibromide and $Me_3$-ethylene dibromide give isobutyraldehyde and methyl isopropyl ketone respectively.

Many *higher dihalides* have been prepared. In general the aldehydes react with phosphorus pentachloride to give $RCHCl_2$. These substances react readily with sodamide to give monosubstituted acetylenes. Ketones with the same reagent give dichlorides, $RCCl_2R'$, but in even poorer yields than with acetone. The dihalides, $RCHXCHXR'$, in which $R'$ is either an alkyl group or hydrogen, are obtained in the usual way from halogens and the corresponding olefins. Amylene dichlorides are available

commercially (Sharples). A special method is available for preparing dibromides of the type $RR'CBr-CHBrR''$ in which R'' is an alkyl group or hydrogen. Tertiary alcohols heated to about 80° are treated with bromine as rapidly as the latter is decolorized. The process may be illustrated by means of tertiary amyl alcohol

$$(CH_3)_2C(OH)CH_2CH_3 + Br_2 \rightarrow (CH_3)_2CBrCHBrCH_3 + H_2O$$

This process is simpler than the preparation of the olefin and addition of bromine to it.

The higher $\alpha\omega$-dihalides, $X(CH_2)_nX$ can be prepared by the ordinary methods from the corresponding glycols obtained by the reduction of dibasic esters by means of a large excess of sodium and absolute alcohol (Bouveault and Blanc) or by hydrogenation with Cu chromite type catalysts (Adkins). The reactions of these dihalides are like those of the corresponding propane derivatives. They give the ordinary reactions of Class 1 alkyl halides (p. 71). Decamethylene bromide with sodium and ether gives higher paraffins, $H-[(CH_2)_{10}]_n-H$, in which $n$ is 2 to 7 and higher (Carothers 1930).

### *C.* Trihalides

### Methine Halides, Haloforms, $CHX_3$

All attempts to prepare fluoroform in quantities large enough to study have failed. The action of $SbF_3$ with $CHCl_3$ gave chlorodifluoromethane, $CHClF_2$, a colorless gas of faint sweet odor, b. −40°, very soluble in water but not hydrolyzed. It is non-toxic (Booth 1932). Dichlorofluoromethane, $CHCl_2F$, b. 15°, has similar properties but is more reactive and is toxic.

**Chloroform,** $CHCl_3$, b. 61°, is now prepared by the reduction of carbon tetrachloride with moist iron. An older method, still employed somewhat, is the action of bleaching powder with ethanol or acetone. Chlorination probably first takes place with the production of chloral, $CCl_3CHO$, and trichloromethyl methyl ketone, $CCl_3COCH_3$ respectively. These then react with the lime to give chloroform with formates and acetates. The grouping, $X_3C-CO-$, reacts readily with bases to give $CHX_3$ and a salt. The first step is apparently the addition of the base to the

carbonyl group. With complex compounds in which such addition is blocked the haloform reaction fails (Fuson 1934).

Chloroform was one of the first anesthetics. It acts very rapidly. For such use it has to be protected from oxygen which reacts with it to give phosgene, $COCl_2$, and HCl, both very toxic (Hill 1932). Chloroform U.S.P. (United States Pharmacopeia) and D.A.B. (Deutches Arzneibuch) contains a trace of alcohol to convert any phosgene to harmless diethyl carbonate.

Chloroform, with anhydrous alcohol and sodium, gives ethyl orthoformate, $HC(OEt)_3$. With sodium ethylate it gives the same product but also CO, sodium formate, ethyl ether and some ethylene. Alcoholic KOH converts chloroform to potassium formate.

With primary amines, in presence of a base, chloroform gives an isocyanide (carbylamine) of intensely disagreeable odor.

$$CHCl_3 + RNH_2 + 3\ KOH \rightarrow RNC + 3\ KCl + 3\ H_2O$$

The carbylamine test is very delicate for a haloform or a primary amine.

Chloroform adds to acetone in the presence of a trace of alkali (aldol condensation) to give trichloro-*tert*-butyl alcohol, $(Cl_3C)Me_2COH$, which is used as an antispasmodic (chloretone, Mothersills remedy for seasickness).

Chloroform has a pleasant odor and a sweet burning taste. It is slightly soluble in water but completely miscible with most organic liquids. It is a good solvent for fats, waxes and hydrocarbons. It is used as an antiseptic to prevent fermentation.

**Bromoform,** $CHBr_3$, b. 151°, m. 7.7°, d. 2.9, is most conveniently made by treating acetone with sodium hydroxide and bromine.

**Iodoform,** $CHI_3$, m. 120°, can be prepared similarly to its analogs by adding iodine and alkali to any substance containing the grouping $CH_3CHOH-$ or $CH_3CO-$ (Iodoform test, Lieben). Because of the cost of iodine these methods are not satisfactory. A better method involves the carefully controlled electrolysis of an aqueous solution of alcohol, an inorganic iodide and sodium carbonate. In this way, practically all the iodide is converted to iodoform. Iodoform was formerly much used as a disinfectant for wounds but its penetrating slightly disagreeable odor led to

the use of odorless substitutes such as Aristol and Diiodoform ($C_2I_4$) and mixtures of iodoform with substances which disguise its odor such as paraformaldehyde (Ekaiodoform) and thymol (Anozel). Modern medical practice is making little use of dusting powders for wounds, however.

### Trihalides of Ethane

**Methyl chloroform,** $CH_3CCl_3$, b. 74°, is made by chlorinating ethylidene chloride or from acetyl chloride and phosphorus pentachloride.

**1,1,2 Trichloroethane,** vinyl trichloride, $Cl_2CHCH_2Cl$, b. 113°, is made by chlorinating ethylene chloride.

The only readily obtainable *trihalides of propane* are of the 1,2,3 type.

**Glyceryl chloride,** trichlorohydrin, $CH_2ClCHClCH_2Cl$, b. 158°, is readily obtained from glycerol and $PCl_5$. The corresponding bromide is readily obtained by adding bromine to allyl bromide, $CH_2=CH-CH_2Br$. The corresponding iodide loses two atoms of iodine spontaneously giving allyl iodide, the product of the action of glycerol with phosphorus and iodine in the absence of water.

### *D.* Tetrahalides

**Carbon tetrafluoride,** b. −130°, is obtained by electrolyzing fused $KHF_2$ using a soft carbon anode (LeBeau 1926). It is very inert.

Dichlorodifluoromethane, $CCl_2F_2$, b. −30°, is made from $CCl_4$ and $SbF_3$ as an important refrigerant (Freon, F-12, Kinetic No. 12) (EP 707–10), is non-toxic, non-corrosive and non-inflammable. Its thermodynamic properties are ideal (Thompson 1932).

**Carbon tetrachloride,** b. 76.7°, (Ahr. 1905, 116 pp.), is the compound most readily obtained by the chlorination of methane because the intermediate products are more easily chlorinated than methane itself. This process is not yet commercial. The commerical preparation of carbon tetrachloride is from $CS_2$ with sulfur monochloride in the presence of iron as a catalyst (p. 546).

Carbon tetrachloride is rather inactive. With alcoholic KOH at 100° it gives CO and formates but no $K_2CO_3$ and no orthocarbonate. This peculiar behavior is probably due to the primary replacement of one chlorine by hydrogen under the influence of the base. This difference in one of the four halogen atoms is even more noticeable with the bromide and iodide.

Carbon tetrachloride reacts with fuming sulfuric acid to give phosgene, $COCl_2$, and pyrosulfuryl chloride, $S_2O_5Cl_2$. This reaction is convenient for generating small amounts of phosgene (poison).

Reduction of $CCl_4$ with moist iron gives chloroform. Methylene chloride, hexachloroethane and tetrachloroethylene are obtained as by-products.

Carbon tetrachloride is used in fire extinguishers because of its high volatility and the incombustibility of its heavy vapors (Pyrene). It is effective in fires near electrical equipment where water would cause short circuits. Its use may involve danger because it reacts with water vapor at flame temperature to give phosgene which is dangerously toxic. Thus a space in which a fire has been extinguished by carbon tetrachloride should be ventilated at once.

Carbon tetrachloride is an excellent solvent. Alone and mixed with hydrocarbons it is widely used in dry cleaning (Carbona).

Carbon tetrachloride was formerly used to eliminate certain internal parasites (hook worm). For this purpose it had to be carefully freed from traces of impurities such as $CS_2$.

**Carbon tetrabromide,** b. 189°, m. 94°, is obtained from bromoform and sodium hypobromite solution on long standing. Boiling with alkali readily gives bromoform and a hypobromite. Thus one bromine atom acts as if "positive." With alcoholic KOH, carbon tetrabromide gives mainly CO and ethylene but no carbonate. $CBr_4$ has been used as a brominating agent (Hunter 1932).

**Carbon tetraiodide** (solid) is obtained from $CCl_4$ and $AlI_3$. It reacts even with water to give iodoform. It reacts similarly with bases, alcoholates and cyanides. Thus, of the three tetrahalides, iodoform has the greatest tendency to have a positive halogen.

***Sym*-Tetrachloroethane,** acetylene tetrachloride, $Cl_2CHCHCl_2$,

b. 146°, is obtained by passing acetylene and chlorine into antimony pentachloride. This moderates the explosive reaction which would take place between chlorine and acetylene gases if mixed directly. Another device for moderating this violent reaction is to pass the gases into a chamber filled with fine sand. It reacts readily with bases to give trichloroethylene, another valuable solvent. With air and steam in ultraviolet light it gives mainly dichloroacetic acid together with a small amount of $C_4H_2Cl_8$.

Tetrachloroethane is the most powerful solvent in the chlorinated series. It is an excellent solvent for cellulose acetate, varnishes, paints and general organic compounds. It is more toxic than the unsaturated chlorides and must be used in special apparatus to avoid industrial hazards. In the presence of moisture it attacks metals with the production of unsaturated chlorides.

The tetrabromide is made similarly. The tetraiodide does not exist.

***Unsym*-Tetrachloroethane,** $ClCH_2CCl_3$, b. 130° is obtained by chlorinating ethylene chloride.

### *E.* Higher Halides

**Hexafluoroethane,** b. −79°, has been prepared (Swarts 1933).

The reaction of chlorine with acetylene gives as by-products *pentachloroethane*, b. 162°, m. −29°, and *hexachloroethane*, a white crystalline solid of camphor odor which melts and sublimes at 186°. $C_2Cl_6$ is also obtained as a by-product in making chloroform from $CCl_4$. Vigorous chlorination of perchloroethane gives two molecules of carbon tetrachloride. Similarly after most hydrocarbons are exhaustively chlorinated, further chlorination breaks a carbon to carbon linkage giving smaller completely chlorinated molecules. Pentachloroethane is a valuable high boiling solvent. It is toxic and must be used with proper care. Hexachloroethane is used in safety explosives, smoke screens and insecticides.

Treatment of a normal hydrocarbon with bromine and ferric bromide results in the introduction of one bromine on each carbon. This is probably because ferric bromide catalyzes the

removal of HBr leaving a double bond which adds bromine. A more practical method of making 1,2,3,4-tetrabromobutane is from crude butadiene obtained from 2,3-dibromobutane or from crotyl chloride (Jacobson 1932).

It was formerly believed that chlorine acted differently from bromine with aliphatic hydrocarbons, in that the chlorine tended to accumulate on the carbon where chlorination started. This is due to the fact that no catalyst is needed with chlorine. In the presence of ferric chloride the result would probably be the same as with bromine.

***Asym*-Heptachloropropane,** $Cl_2CHCCl_2CCl_3$, b. 248°, m. 30°, is readily obtained by the action of chloroform and tetrachloroethylene in presence of aluminum chloride.

**Highly chlorinated hydrocarbons** and their action with $AlCl_3$ have been studied (Prins 1932). Highly chlorinated paraffin wax is used with aromatic hydrocarbons and $AlCl_3$ to give complex materials such as Paraflow which inhibit the separation of wax from lubricating oils on cooling (pour-point depressers). Chlorinated wax with phenols and naphthols in presence of $AlCl_3$ give similar compounds which can be esterified with dibasic acids such as phthalic acid (Santopour) (Reiff 1936).

Many chlorides of carbon are known. They are perchlorohydrocarbons. $CCl_4$, b. 77°; $C_2Cl_4$, b. 121°; $C_2Cl_6$, b. 187°; $C_3Cl_6$, b. 210°; $C_3Cl_8$, m. 160°, b. 269°; $C_4Cl_6$, perchlorobutadiene, m. 32°, b. 269°; $C_4Cl_6$, perchlorobutyne, m. 39°, b. 284°; $C_4Cl_8$, b. 275°; $C_6Cl_6$, hexachlorobenzene, m. 226°, b. 326°.

### *F.* Unsaturated Halides, $C_nH_{2n-1}X$

1. **Vinyl halides,** $CH_2=CHX$, are obtained by the action of alcoholic KOH on the corresponding ethylene and ethylidene dihalides. They are also formed by the addition of HX to acetylene and by the action of HX with $CaC_2$ (Rep. 1922, 73). As is general for halogens attached to unsaturated carbon atoms, those in the vinyl halides are very unreactive. Almost the only reaction which they give readily is with an excess of alkali to form acetylene. The vinyl halides add HX to form ethylidene halides. In the presence of peroxides, vinyl bromide adds HBr contrary to Markownikoff's Rule to give ethylene bromide

(Kharasch 1933). Vinyl halides polymerize readily (Vinylite resins) (Rep. 1930, 93). *Vinyl fluoride* b. −51°, *chloride* b. −13.9°, *bromide* b. 16°, *iodide* b. 56°.

2. *a* The **allyl halides,** $CH_2=CH-CH_2X$, are made by the the usual methods for alkyl halides from allyl alcohol obtained from glycerol. The iodide can be made from glycerol, phosphorus and iodine under anhydrous conditions. Probably 1,2,3-triiodo-propane is formed and loses two iodine atoms from adjacent carbons. The allyl halides act like alkyl halides of Class 1 (p. 71) but are more reactive. The freedom from side reactions is due to lack of tendency to form the related unsaturated compound, allene, $CH_2=C=CH_2$, and to the fact that a 1 : 3 shift of the double bond would give an identical product.

$$CH_2=CHCH_2X \rightarrow QCH_2CH=CH_2$$

When HCl or HBr is added to an allyl halide in the absence of peroxides (presence of antioxidants) the product is a propylene halide (1,2) while in the presence of peroxides a trimethylene dihalide (1,3) is formed (Kharasch 1933). The addition in the presence of peroxides is more rapid than in their absence. Addition to allyl halides without any special precautions gives varying proportions of the two dihalides depending on the amount of oxidation which the double bond has undergone. The addition of HI follows Markownikoff's Rule since it effectively reduces peroxides.

**Allyl chloride,** b. 44°, on standing, changes slowly to a mixture of polymers with $n=9$, 12, 5, 25, 11 and 7 in order of decreasing amount (Rep. 1930, 93).

**Allyl bromide,** b. 71°; *iodide,* b. 102°. Allyl iodide reacts 60 times as rapidly with sodium ethylate as does *n*-propyl iodide.

Treatment of allyl bromide with Mg ordinarily gives diallyl. Good yields of the Grignard reagent can be obtained by using large amounts of ether (Gilman 1929).

*b.* The **alpha** and **beta halogen propylenes,** $XCH=CHCH_3$ and $CH_2=CXCH_3$ are obtained by removing one HX from propylidene and acetone dihalides respectively. The halogen atoms attached to unsaturated carbon atoms are inactive except to alcoholic potash which removes HX. The compounds react with dilute

acids to give propionaldehyde and acetone respectively. This is because they add water under the influence of the acid and form compounds containing the grouping, C(OH)X, which loses HX spontaneously to give a carbonyl group.

$$ClCH=CHMe, \text{ b. } 36°; \qquad CH_2=CClMe, \text{ b. } 23°.$$

3. *a.* **Crotyl halides,** $CH_3CH=CHCH_2X$, present interesting examples of 1 : 3 or allylic rearrangements. Crotyl alcohol, $CH_3CH=CHCH_2OH$, obtained by the reduction of crotonic aldehyde, reacts with $PBr_3$ and pyridine to give crotyl bromide (Young 1933). The same product is obtained from the action of HBr with methylvinylcarbinol, $CH_3CHOHCH=CH_2$, obtained from acrolein $CH_2=CHCHO$ and MeMgX. When the halogen in a crotyl halide is replaced by hydroxyl the product is not pure crotyl alcohol but a mixture with methylvinylcarbinol.

$$CH_3CHOHCH=CH_2 \underset{AgOH}{\overset{HX}{\rightleftarrows}} CH_3CH=CHCH_2X$$

This type of change is very common (Rep. 1923).

*b.* 1-Halogenbutene-1, $EtCH=CHX$, can be obtained from a butylidene halide. Its halogen is unreactive.

*c.* 4-Halogenbutene-1, $XCH_2CH_2CH=CH_2$, can be made from a tetramethylene dihalide. It gives the reactions of a primary halide and an olefin without the mutual influence exhibited in the allyl halides.

*d.* **Methallyl halides,** β-methylallyl halides, $CH_2=CMeCH_2X$, are obtained by removing HX from isobutylene dihalides, $Me_2CXCH_2X$. Isocrotyl halides, $Me_2C=CHX$, form the chief products. *Methallyl chloride,* b. 72° is available commercially (Shell) from the action of chlorine with isobutylene. Even at 0° no dichloride is obtained in this process. This is an example of Kondakoff's Rule (p. 42). It is often assumed that this type of change involves the formation of the dichloride which then loses HCl. Since bromides are more reactive than chlorides it is hard to explain on this basis why isobutylene and bromine give isobutylene dibromide which is stable. It is also interesting that methallyl chloride combines with fuming HCl at 100° to give

isobutylene dichloride. A possible solution depends on the addition of a halogen molecule to a double bond in steps. The second step would involve the addition of a negative halide ion to the tertiary carbon in isobutylene. In the case of chlorine it is easier to remove a hydrogen nucleus to form a molecule of HCl and leave the unsaturated chloride. With bromine, the tendency to form HBr is less and consequently the second bromine adds to the tertiary carbon. Many other cases of the formation of unsaturated halides from the action of halogens on olefins are known. For instance, the diisobutylenes (p. 42) fail to give dichlorides and dibromides, in both cases giving unsaturated halides and HX. The processes involved are probably like that involved in the ready halogenation of an enol (pp. 242, 260).

Methallyl halides react like allyl halides being very reactive and giving normal replacement reactions.

*e.* **Isocrotyl chloride,** $Me_2C=CHCl$, b. 68°, is formed by the action of bases with isobutylidene chloride, $Me_2CHCHCl_2$ and from isobutylene and chlorine. Its halogen is inactive. Treatment with acid gives isobutyraldehyde. This involves addition of water contrary to Markownikoff's Rule or, more probably, a rearrangement like that in the hydrolysis of isobutylene dibromide to give isobutyraldehyde (p. 123). Isocrotyl bromide reacts with sodium alcoholates at 140° to give the unsaturated ethers, $Me_2C=CHOR$. These react with dilute acids in sealed tubes forming isobutryaldehyde.

4. *a.* ***n*-Pentenyl halides** resemble the other unsaturated halides in their preparation and reactions depending on the relation of the halogen and the double bond. Those with the halogen on an unsaturated carbon are inactive. With the halogen and double bond in the allyl arrangement, $C=C-CX$, the halogen is very reactive and allylic rearrangements take place. With farther separation of the halogen and the double bond they act independently.

*b.* **3,3-Dimethylallyl halides,** $Me_2C=CHCH_2X$, offer an example of complete allylic rearrangement. Treatment of dimethylvinylcarbinol with $PX_3$ gives only the primary halide while replacement of the primary halogen gives only the tertiary alcohol. Isoprene with HBr gives $Me_2C=CHCH_2Br$ (EP 646).

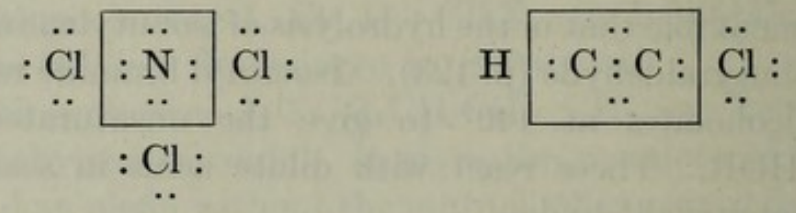
### *G.* Unsaturated Halides, $C_nH_{2n-3}X$

1. **Chloroprene,** 2-chlorobutadiene-1,3, $CH_2=CClCH=CH_2$, is the most important member of this group because of its relation to Neoprene rubber (p. 60). It is made from vinyl acetylene and HCl (Rep. 1932, 108, 125).

2. **Monohalogen acetylenes,** $HC\equiv CX$, are obtained from sym-dihalogenated ethylenes and bases. Both the bromo and chloro compounds have been made and are violently explosive, spontaneously inflammable, have strong odors and are toxic. Nef explained these peculiar properties on the basis that the halogenated acetylenes contain bivalent carbon much as do the isocyanides (1897).

$$XHC = C \qquad X_2C = C \qquad RN = C$$

On the other hand compounds $R-C\equiv C-X$ are stable non-toxic unobjectionable substances. The explosive nature of monohalogen acetylenes suggests that of the halides of nitrogen in which the halogen atoms are regarded as positive. The following analogy may be significant,



$RNCl_2$ and $RC\equiv CCl$ have none of the properties of $NCl_3$ and $C_2HCl$ except that hydrolysis gives HOCl. In the absence of water they are stable.

3. *a.* **Propargyl halides,** propiolic halides, $HC\equiv C-CH_2X$, can be made from propargyl alcohol by the usual reagents. They give normal reactions much like those of the allyl halides.

*b.* **Allylene halides,** $CH_3C\equiv CX$, are obtained from allylene and hypohalite solutions. The iodo compounds can best be made from the acetylene and iodine in liquid $NH_3$. They react with mercuric cyanide solution to give $(RC\equiv C)_2Hg$, crystalline compounds of high melting points (Vaughn 1933). The halogen in $R-C\equiv CX$ is reactive but does not behave like that in an alkyl halide but rather like halogen in combination with O or N. Thus

NaOEt gives the acetylene and a hypohalite. The stability of $RC_2X$ is in sharp contrast to the instability of $HC_2X$.

*c.* Many higher acetylenic halides have been prepared. In many cases they involve rearrangements similar to those of the substituted allyl halides.

**Unsaturated polyhalides** are obtained by removing HX or $X_2$ from higher halides.

1. **1,1-Dichloroethene,** acetylidene dichloride, $CH_2=CCl_2$, b. 37°; *Dibromo*, b. 92°.

2. 1,2-Dihalogen ethenes, acetylene dihalides, exist in *cis* and *trans* forms (EP 674).

| | | | |
|---|---|---|---|
| HCCl | | HCCl | |
| ‖ | | ‖ | |
| HCCl | | ClCH | |
| *cis* | b. 48° | *trans* | b. 60° |

Direct addition of $Cl_2$ to excess acetylene at 200° gives both forms. The commercial product is a mixture, b. 52° ±, obtained by the reduction of acetylene tetrachloride with iron. In common with other halogenated solvents, *dichloroethylene* is non-inflammable. Its halogen atoms are very unreactive. Consequently there is no danger of corrosion. It is an excellent solvent for the extraction of materials ranging from plant perfumes to rubber. It can be used in place of ordinary ether for general extractions.

Unsaturated iodides form polyvalent iodine derivatives having a fair degree of stability. They thus resemble the corresponding aromatic compounds. Thus $Cl_2$ in an inert solvent will react with the iodine atom of 1-Cl-2-I-ethylene. The dichloride reacts with sodium carbonate to give the iodoso compound and the latter disproportionates on warming to give the iodo and iodoxy compounds (Thiele).

$$ClCH=CHI \rightarrow ClCH=CHICl_2$$
$$\rightarrow ClCH=CHIO \rightarrow ClCH=CHIO_2$$

3. **Trichloroethene,** $ClCH=CCl_2$, b. 87°, is made from acetylene tetrachloride and bases. Its chlorine is inactive. Dilute acids convert it to chloroacetic acid probably by the

following steps:

$$ClCH=CCl_2 \rightarrow ClCH_2-CCl_2(OH) \rightarrow ClCH_2COCl \rightarrow ClCH_2CO_2H$$

It reacts violently with conc. $HNO_3$ to give dichlorodinitromethane, $Cl_2C(NO_2)_2$. With formaldehyde and $H_2SO_4$ it gives $O(CH_2CHClCO_2H)_2$ by a peculiar combination of condensation, hydrolysis and dehydration.

**Trichloroethylene** (Triclene, Westrosol), is the most important of the chlorinated solvents. It is inactive and stable except on exposure to light. It is a powerful solvent for fats, resins, bitumens, rubber, sulfur and phosphorus. It is a valuable non-inflammable substitute for benzene and petroleum hydrocarbons in dry cleaning. It is used for extracting the residual oil from vegetable oil cakes left after pressing out most of the oil, for degreasing leather, textiles and metals and as an assistant in soaps for scouring textiles.

4. **Tetrachloroethene, perchloroethylene,** $Cl_2C=CCl_2$, b. 120°, is made from pentachloroethane obtained as a by-product in the action of chlorine with acetylene and from hexachlorethane obtained in the same way and as a by-product in the reduction of carbon tetrachloride. With conc. $HNO_3$ it gives mainly $CO_2$. With formaldehyde and $H_2SO_4$ it forms $HOCH_2CCl_2CO_2H$. Tetrachloroethylene is more expensive than the other chlorinated solvents. It has been used in place of $CCl_4$ for treatment of hook worms, and similar parasites.

5. Bases, with trichloropropane from glycerol, give γ-chloroallyl chloride, $ClCH=CHCH_2Cl$, which contains an active and an inactive chlorine. It and the dibromo compound, with Grignard reagents, give $RCH_2CH=CHX$ from which $NaNH_2$ gives 1-acetylenes.

6. A special method for making unsaturated triiodo derivatives is the treatment of cuprous acetylides with iodine to give $RCI=CI_2$ (Lespieau).

7. **Dichloroacetylene,** b. 32°, and **dibromoacetylene,** b. 77° are toxic and have odors like isocyanides. Like the monohalogen acetylenes they are formulated as derivatives of acetylidene, $H_2C=C$, (p. 98) (Nef 1897) (EP 675). Evidence that the two

halogen atoms are on the same carbon is given by the following reactions of dibromoacetylene:

*a.* It oxidizes readily in air to give CO and $C_2Br_4$

$$2\,Br_2C{=}C + O_2 \rightarrow 2\,[Br_2C{=}C{=}O] \rightarrow 2\,CO + Br_2C{=}CBr_2$$

The intermediate product is a ketene which would be expected to give the observed products.

*b.* Oxidation with nitric acid gives $Br_2CHCO_2H$.

*c.* Addition of HI gives $Br_2C{=}CHI$.

Strangely diiodoacetylene, $C_2I_2$, is an inert solid, m. 80°.

## III. ALCOHOLS

### *A.* Saturated Alcohols, $C_nH_{2n+1}OH$

These are mono hydroxyl derivatives of the paraffin hydrocarbons. The reactions of the OH group are like those of water but are modified by the length and structure of the attached carbon skeleton. The carbon attached to the hydroxyl is rendered more reactive than in the paraffins. The reactions of both the C and O in the system COH are profoundly influenced by the number of alkyl groups attached to the C. Hence the important classification into *primary, secondary* and *tertiary alcohols* or *mono-, di-* and *tri- substituted carbinols,* $RCH_2OH$, RR′CHOH and RR′R″COH in which the alkyl groups may be alike or different.

The alcohols range from non-viscous liquids of b.p. 66° and density 0.8 to solids (*n*-decyl alcohol, m. 7°, b. 230°, d. 0.84). Alcohols higher than $C_{10}$ are waxy solids increasingly like the higher hydrocarbons as the carbon content rises. The boiling points of the alcohols are much higher than those of the corresponding hydrocarbons because of the *association* of the liquids. This constitutes another resemblance to water. These differences in boiling points are 230°, 171°, 102°, 58°, and 57° for the $C_1$, $C_2$, $C_5$, $C_{10}$ and $C_{16}$ members. Evidently the association effect decreases as the alcohols lose their resemblance to water.

The first three alcohols are completely soluble in water. The higher ones become less soluble as the carbon content increases.

Many primary alcohols occur in natural products, usually in the form of esters.

In contrast to the paraffins, the alcohols are very reactive with a great variety of chemical reagents. Apparently the introduction of the oxygen atom into the completely non-polar hydrocarbon molecule decreases the stability and inactivity of the latter. Moreover, the oxygen atom through its ability to form oxonium compounds offers an active spot in the molecule.

It is impossible to generalize satisfactorily on either the preparations or reactions of alcohols, R—OH, since the nature of the alkyl group has such a profound effect. Consequently the individual alcohols will be considered until enough members of the series have been presented to show all the many peculiarities produced by changes in the alkyl group attached to the hydroxyl. It is not possible to generalize accurately even according to the three classes of alcohols. The alcohols form the best refutation to the older idea that knowledge of the first two or three members of an homologous series makes possible the prediction of the reactions of the higher members.

### Individual Alcohols

**Methanol,** methyl alcohol, wood alcohol, wood spirit, *carbinol*, $CH_3OH$, b. 66°, occurs in nature in a few esters such as methyl salicylate, in oil of wintergreen and as complex methyl ethers in the lignin portion of wood and many alkaloids and natural dyes. Pine lignin contains 15% methoxyl (Hibbert 1931).

The crude pyroligneous acid which separates from the tar obtained in wood distillation contains up to 3% methanol along with a smaller amount of acetone and a larger amount of acetic acid. The latter is neutralized with lime and the methanol and acetone are removed and separated by distillation. The methanol first obtained contains impurities which render it specially suitable as a denaturant for ethanol.

The modern method of preparing methanol is from carbon monoxide and hydrogen in the presence of a zinc chromite catalyst at about 450° and 3000 lb. pressure. The process can be operated to give practically pure methanol or methanol mixed with higher alcohols and related products. The present tendency is to allow

the formation of these products since they can readily be separated from the methanol and have many uses (pp. 114, 119, 139).

Although the hydrolysis of methyl chloride is the subject of many patents it has never been successfully developed for the preparation of methanol.

Although methanol is assumed to be an intermediate in the oxidation of methane (Bone) it is not readily obtained in that way because it is so much more easily oxidized than $CH_4$. With a 9 : 1 mixture of methane and oxygen at 360° and 100 atm. 17% of the methane oxidized was recovered as methanol. Less than 1% of formaldehyde was obtained. The other products were CO, $CO_2$ and $H_2O$. No $H_2$ was found. (Newitt 1931?)

Methanol forms azeotropic mixtures (constant b.p.) with many liquids. Such a mixture with $CHCl_3$ (b. 61°) boiling at 53° is useful in separating methanol (b. 66°) from acetone (b. 58°) (Rep. 1921, 61). The per cent of the second liquid and the boiling points of several such mixtures follow: acetone, 86, 56°; carbon disulfide, 86, 38°; benzene, 60, 58°; carbon tetrachloride, 79, 56°; chloroform, 87, 53°; methyl iodide, 93, 39°; *n*-hexane, 73, 50°. A commercial azeotrope of methanol and acetone is sold as "*methyl acetone.*" Dynax, a special fuel for speed boats (DuPont) contains a methanol-benzene blend. Some mixtures of substances which cannot be separated by simple distillation can be mixed with methanol and fractionated because one forms an azeotrope and the other does not. If the liquid desired is insoluble in water the methanol can then be washed out.

Since it forms no azeotrope with water it can be separated from the latter by careful fractionation (difference from ethanol).

The purest methanol can be obtained:

1. By converting to the solid compound $CaCl_2.4$ MeOH which can be heated to 100° to remove all impurities not removable from the methanol by distillation. Treatment of the compound with water and distillation gives pure methanol.

2. By conversion to the oxalate, $(CO_2Me)_2$, and purification by crystallization, m. 54°, and treatment with a base, followed by distillation.

As a matter of fact the best grade of synthetic methanol is practically as pure as any ever obtained.

Acetone in wood distillation methanol can be detected as iodoform (odor, yellow crystals) by treating with a base and iodine.

Methanol, in common with all compounds containing the group MeO−, can be determined by the Zeisel methoxyl method which consists in treating with constant boiling HI, distilling MeI formed, reacting it with $AgNO_3$ and determining the AgI formed.

Methanol dissolves solid carbon dioxide.

The most important reactions of methanol are:

1. Mild oxidation or dehydrogenation to give formaldehyde, $H_2CO$, important as a disinfectant and as an intermediate in synthetic resins. This is accomplished at a moderate temperature in contact with silver or copper gauze either with or without the admission of air. More vigorous oxidation of methanol gives formic acid and finally $CO_2$.

Most methods for the qualitative and quantitative determination of methanol depend on its conversion to formaldehyde.

2. With sulfuric acid to form dimethyl ether, $Me_2O$, used as a refrigerant. Conditions which might be expected to dehydrate the methanol to give methylene, $CH_2=$, give ethylene and higher polymers instead. Under other conditions the acid sulfate can be formed. This on distillation gives the volatile dimethyl sulfate (toxic, odorless). $2\ MeHSO_4 \rightarrow Me_2SO_4 + H_2SO_4$.

3. Halide acids yield methyl halides. The chloride is best formed by HCl and $ZnCl_2$ under pressure. The bromide is formed readily from a mixture of methanol, sodium bromide and concentrated $H_2SO_4$.

The action of alcohols with halide acids is very different from that of a base and an acid. It undoubtedly takes place through the formation of an *oxonium salt* which then decomposes to give the halide.

$$MeOH + HX \rightleftarrows \left[\begin{array}{c} H—O—H \\ | \\ Me \end{array}\right]^{+} X^{-} \rightleftarrows H_2O + MeX$$

Both these reactions are reversible but the second is less easily reversed. The fact that HI acts much more readily than HCl with methanol and most alcohols is due to the greater ease with which it forms oxonium salts.

In the case of some of the higher alcohols crystalline oxonium salts with halide acids are obtained (p. 139).

4. With halides of phosphorus to give methyl halides. The only actual reaction used is that with phosphorus and iodine to give methyl iodide (p. 81).

5. With metals to give methylates (methoxides). Sodium and potassium react violently giving MeONa and MeOK which crystallize with MeOH. It is difficult to remove the latter without decomposing the alcoholates. Aluminum (amalgamated to give a clean surface) reacts readily. Even magnesium reacts with no difficulty (difference from higher alcohols). The easiest way to obtain *absolute methanol* is to make a suspension of magnesium methylate in a portion of the alcohol and add it to the rest. Any trace of water reacts to give insoluble MgO

$$(MeO)_2Mg + H_2O \rightarrow 2\ MeOH + MgO$$

Magnesium methylate is valuable in removing the last traces of water (0.1–0.2%) from ordinary "absolute" ethyl alcohol for use as a solvent in malonic ester and acetoacetic ester syntheses and similar reactions in which a small trace of moisture is very harmful and a little methanol is harmless.

6. With organic acids to give esters.

$$HCO_2H + CH_3OH \rightleftharpoons HCO_2CH_3 + H_2O$$

In this case the formic acid is a strong enough acid to require no other catalyst. In the case of higher acids, it is advisable to add a trace of sulfuric acid or to saturate the mixture of acid and alcohol with dry hydrogen chloride gas. Since methanol is cheap the reversible reaction can be forced more nearly to completion by using a large excess of the alcohol. More $H_2SO_4$ may be added to use up the $H_2O$ formed.

7. When esters of more expensive acids are needed it is advisable first to convert the acid to its chloride by $PCl_5$ or $SOCl_2$

$$RC(=O)—Cl + CH_3OH \rightarrow RC(=O)—OCH_3 + HCl$$

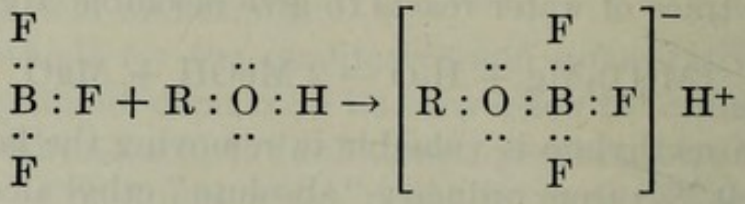
This reaction is not reversible.

8. Methanol reacts with fused alkalies to give hydrogen, formates and finally carbonates (Fry 1928).

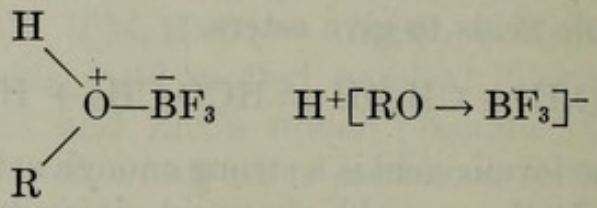
$$CH_3OH \rightarrow HCO_2K + 2\,H_2 \rightarrow K_2CO_3 + H_2$$

9. Methanol combines with many substances as alcohol of crystallization: $CaCl_2.4\,MeOH$, $MgCl_2.6\,MeOH$, $CuSO_4.2\,MeOH$, $BaO.2\,MeOH$, $MeOK.MeOH$ etc. Since the union with $CaCl_2$ is a common property of alcohols they cannot be dried with this substance.

10. Boron trifluoride with methyl and ethyl alcohols gives highly conducting solutions (Rep. 1932, 104). This is another example of the tendency for completion of an octet.



The linkage between the oxygen and boron is a coordinate link and may be represented as follows



The chief uses of methanol are:

1. Denaturing ethyl alcohol to free it from beverage taxes: The methanol is much more toxic than ethyl alcohol. Sub-lethal doses are likely to cause blindness. When prepared by wood distillation it contains impurities which give the resulting denatured alcohol a bad taste and odor. During the prohibition era in the United States many tragedies resulted from the removal of the disagreeable materials from denatured alcohol without the removal of the methanol before the mixture was diverted to beverage uses. Ethyl alcohol completely denatured with methanol (10%) can be used successfully even for making ethyl esters.

2. Solvent for shellac and varnishes.

3. Antifreeze for automobile radiators. For this use, it has the advantage of low molecular weight but the disadvantage of rather high volatility.

4. Production of formaldehyde for resins.

5. Methylation of various intermediates and dyes.

6. Production of MeCl and $Me_2O$ as refrigerants.

The analytical reactions of methanol have been assembled (Ahr. *20*, 1913).

**Ethanol,** ethyl alcohol, alcohol, grain alcohol, methylcarbinol, spirits of wine, $CH_3CH_2OH$, b. 78.3°.

The oldest preparation of ethyl alcohol is still the most important, namely the fermentation of glucose and materials related to it. In the United States practically all ethanol is made from black strap molasses, mainly from Cuba. In other countries potatoes and various grains are used as the source of glucose. During the prohibition era in the United States enormous amounts of crude "yellow chip" glucose from corn starch was used in the illegal production of alcohol.

The net reaction for the production of ethanol by the enzymes of yeast is

$$C_6H_{12}O_6 \rightarrow 2\ C_2H_5OH + 2\ CO_2$$

Much study of this important process and its by-products has led to the conclusion that the steps involved may be somewhat as follows (Neuberg) (Backhaus 1931):

1. Glucose $\rightarrow 2\ H_2O + 2$ MeCOCHO, pyruvic aldehyde.

2. $2$ MeCOCHO $\rightarrow$ $MeCOCO_2H$ + $MeCOCH_2OH$, acetol.

3. $MeCOCH_2OH \rightleftharpoons CH_2{=}COHCH_2OH$

$\rightarrow CH_2OHCHOHCH_2OH$, glycerol.

4. $MeCOCO_2H \rightarrow MeCHO + CO_2$.

5. $MeCHO + MeCOCHO \rightarrow MeCH_2OH + MeCOCO_2H$.

In confirmation of (1) it has been possible to isolate pyruvic aldehyde from the reaction products of glucose and very dilute alkalies. Equation (2) represents the oxidation and reduction (disproportionation) of a substance in an intermediate stage of

oxidation (Cannizzaro). It is very common in biological processes. Equation (3) represents the processes of enolization and hydration of the enol. It would be expected that water would add to the enol to give $CH_3C(OH)_2CH_2OH$ (Markownikoff). This is merely the hydrated form of acetol and would revert to that substance and be again capable of enolization. In other words glycerol can form and survive because it is the end product of a series of reactions only the last of which is not easily reversed. Reaction (4) is caused by "carboxylase" in the yeast. If a substance which combines with acetaldehyde, such as calcium bisulfite, is added to the fermenting mixture, an addition product of acetaldehyde is actually obtained. This would prevent reaction (5) from taking place. Thus all the pyruvic aldehyde would follow reaction (2) and give more glycerol. On this principle is based a commercial process for making glycerol by fermentation. Reaction (5) is of the same type as (2) except that dissimilar molecules take part in the oxidation and reduction. In ordinary fermentation (5) continues uninterrupted, producing ethanol and pyruvic acid which starts again the cycle of (4) and (5). This utilizes another molecule of pyruvic aldehyde which would otherwise follow (2). It is thus evident that (2) should take place only to a limited extent. This would also limit (3) and the formation of glycerol. It has long been known that glycerol accompanies the formation of alcohol but only to the extent of 2–3% unless some reagent is used which can use up acetaldehyde.

The fermented liquid contains about 10% ethanol which is concentrated by careful fractional distillation. The fore-run always contains acetaldehyde. The alcohol is obtained in various concentrations depending on its ultimate use. The maximum obtainable is an azeotropic mixture with water containing 95.6% alcohol by weight and boiling at 78.2° whereas absolute ethanol boils at 78.4°.

Protein impurities in the starting material give fusel oil containing *n*-propyl, isobutyl, isoamyl and active amyl alcohols together with smaller amounts of a very complex mixture of higher alcohols and oily compounds (Schorigin 1933). The amount of fusel oil is about 3–11 parts per 1000 of ethanol pro-

duced. Part of the fusel oil is fractionated to give *n*-propyl, isobutyl and mixed amyl alcohols. The latter cannot be separated by distillation in any ordinary equipment (p. 127). Since the amount of the first two alcohols is relatively small, about 5 and 20% respectively, fusel oil is usually converted directly to crude amyl acetate for use as a solvent. In the days before nitrocellulose lacquers it adequately filled the need for this type of solvent. It could not be expanded to meet the new need because of its by-product nature. The need has been met by *n*-butyl alcohol from corn or molasses (C.S.C.), by amyl alcohols from the pentanes (Sharples), by *sec*-butyl and *sec*-amyl alcohols from cracked gases (Stanco, Shell) and by *n*-propyl, isobutyl and higher alcohols obtained as by-products in the action of hydrogen and carbon monoxide (DuPont).

The residue ("slops") after the alcohol is distilled from the fermentation mixture is worked up for glycerol and potash salts. The final step is to burn the residue giving an ash containing about 30% $K_2O$.

During the fermentation the weight of $CO_2$ produced nearly equals that of the ethanol. This is nearly pure and free from air. It is compressed and sold as liquid in tanks or as solid $CO_2$ (Dry Ice) for special refrigeration purposes. (Fermentation, Ahr. 1902, 50 pp.; 1914, 46 pp.; 1924, 48 pp.; Rev. *3*, 41–80, 1926.)

Another preparation for ethyl alcohol which is assuming increasing commercial importance is the hydration of ethylene from cracked gases. (EP 332.) The ethylene is absorbed in sulfuric acid to form ethyl hydrogen sulfate. This is diluted and heated to hydrolyze the ester to ethyl alcohol. The dilute sulfuric acid is then concentrated and used again. The cost of concentration has been reduced to a small fraction of the cost of fresh acid. Ethyl ether is obtained very cheaply as a by-product of this process. A possible alternative to the concentrating of the dilute acid is its conversion to ammonium sulfate for fertilizer.

The history of the production of ethanol from ethylene goes back to 1826 when Hennell in Faraday's laboratory made it in that way. The process was rediscovered by Berthelot in 1855. In 1862 Cotelle organized a company to make alcohol from the ethylene in illuminating gas but failed financially. It was not

until 1929 that the process became a commercial reality (C. and C.).

Any marked increase in the cost of molasses, such as would be caused by a high tariff, would probably increase the production of ethanol from ethylene enormously because the cracked gases of the petroleum refineries of the United States offer an almost unlimited supply of ethylene (p. 36).

A potential source of ethanol which was used during the World War is acetaldehyde, $CH_3CHO$, from the catalytic hydration of acetylene by mercuric salts (p. 64). The acetaldehyde can be catalytically hydrogenated to ethanol. Since a considerable amount of ethanol is converted to ethyl acetate, another possibility is the catalytic conversion of acetaldehyde directly to ethyl acetate in the presence of aluminum ethylate. This is a special type of disproportionation.

$$2\ CH_3CHO \rightarrow CH_3CO_2CH_2CH_3$$

A practically unlimited source of glucose for alcohol production exists in the hydrolysis of cellulose (from sawdust or any cheap vegetable waste) by HCl under pressure (Bergius).

Absolute ethyl alcohol is usually made by treating the 96% alcohol with fresh quicklime, CaO. The 100% alcohol is very hygroscopic and should not be exposed to moist air. Anhydrous alcohol is made commercially by distilling the 96% alcohol with dry benzene. A tertiary mixture of benzene, water and alcohol distills at 64.8°, followed by a binary mixture of benzene and alcohol, b. 68.2° and finally by absolute alcohol at 78.3° (Keyes 1929). The benzene can be recovered and used again. This method of drying by distillation with dry benzene is very useful with a variety of organic materials.

Anhydrous ethanol is also prepared by heating the 95% alcohol with a fused mixture of anhydrous potassium and sodium acetates.

Ethanol of 99.5% can be obtained by a special use of calcium chloride (Noyes 1923).

BaO is soluble in absolute alcohol. When such a solution is added to alcohol containing even a trace of water, insoluble $Ba(OH)_2$ is formed.

The density of absolute alcohol at 20° is 0.789 while that of 96% alcohol is 0.801.

Proof spirit (U.S.) contains 50% ethanol by volume. Thus 90% alcohol (by volume) is 180 proof and absolute alcohol is 200 proof. In Great Britain proof spirit is 49.3% ethanol by weight or 57% by volume. A distilled liquor was originally defined as proof spirit if when poured over gun powder and lighted, it would burn and finally ignite the powder. If the ethanol content is less than 49.3% by weight the water left after the burning of the alcohol is sufficient to prevent the powder from burning.

Denatured alcohol is ethanol containing materials which prevent its use as a beverage. It is exempt from the tax on beverage alcohol. The nature of the denaturants used varies in different countries and at different times. The commonest are crude wood alcohol, benzene, and pyridine bases.

Alcohol finds very wide and increasing uses in industry. About 40% of the production in the United States is used in antifreeze for automobiles. It is a valuable solvent and chemical intermediate. Ethanol has been widely used outside the United States as a motor fuel both alone and mixed with gasoline (petrol). Absolute alcohol is fairly soluble in gasoline. The absorption of a small amount of water causes a separation of aqueous alcohol. This can be prevented by adding to the mixture benzene and higher alcohols.

Ethanol is used for preserving biological specimens. Because of its affinity for water (48 cc. $H_2O$ + 52 cc. abs. EtOH give only 96.3 cc. of mixture, all measured at 20°) it is used for dehydrating such materials. For this purpose it should be free from traces of aldehyde. This is best removed by adding a small amount of potassium hydroxide and zinc dust or sodium amalgam, refluxing and then distilling the alcohol (Schuette 1933?).

In pharmaceutical chemistry, solutions in ethanol are known as *tinctures*.

Ethyl alcohol has been isolated in minute amounts from brain, blood and liver of non-alcoholic humans, dogs and pigs (Gettler 1932).

Ethanol unites with salts as methanol does, forming $CaCl_2 . 4$ EtOH etc.

Ethanol gives *reactions* similar to those of methanol:

1. Dehydrogenation and oxidation give acetaldehyde, $CH_3CHO$. The easiest small scale preparation is by the oxidation of ethyl alcohol with "chromic acid mixture" (a dichromate and sulfuric acid). Although acetaldehyde is much more sensitive to oxidation than ethanol, this process is effective because of the greater volatility of acetaldehyde, b. 20°. More vigorous oxidation of ethanol gives acetic acid which is stable to oxidation. Oxidation with half the theoretical amount of chromic acid mixture gives ethyl acetate.

Oxidation with nitric acid involves the methyl as well as the carbinol group, the products including glycollic acid, glyoxal, glyoxylic acid and oxalic acid. In the presence of bases alcohol is readily oxidized even by air. The aldehyde formed is changed to resinous materials by the base. Alcoholic potash (KOH) is a reducing agent especially for nitro compounds.

2. Treatment with sulfuric acid gives diethyl ether or ethylene according to the conditions. *p*-Toluene sulfonic acid (a by-product of saccharin manufacture) is sometimes used in place of sulfuric acid because it gives fewer side reactions. The best way to make pure ethylene from ethanol is by passing its vapor with superheated steam over a dehydrating catalyst such as $Al_2O_3$ at about 1000°. At about 300° alumina gives a good yield of ether and very little ethylene (Alvarado 1928).

Ethanol with sulfur trioxide gives beta hydroxyethane sulfonic acid, *isethionic acid*. There is also formed the acid sulfate of this acid, $HOSO_2-OCH_2CH_2SO_3H$, *ethionic acid*.

3. The reactions with halide acids and halides of phosphorus are the same as with methanol.

4. The reactions with metals are the same as with methanol except that magnesium does not react readily and aluminum reacts to give $Al(OEt)_3$, m. 130°, which can be distilled under reduced pressure (b. 205°/14 mm.) and serves as a useful catalyst and reagent. Aluminum alkoxides unite with alcohols to form *alkoxyacids* (Meerwein). $Al(OR)_3 + ROH \rightarrow H^+[Al(OR)_4]^-$. These are strong acids which can be titrated with indicators. The acid radical bears a striking resemblance electronically to those of sulfuric, phosphoric and perchloric acids each involving

a system of a central atom, four oxygen atoms, and 32 electrons. Sodium ethylate or ethoxide, EtONa.2 EtOH, is converted to EtONa at 200°.

The treatment of nearly anhydrous ethanol with metallic sodium will not remove the last trace of water because of the equilibrium

$$C_2H_5OH + NaOH \rightleftharpoons C_2H_5ONa + H_2O$$

If $Mg(OMe)_2$ is used, the last traces of water are removed because no soluble base is formed. Metallic calcium can be used because the $Ca(OH)_2$ and CaO formed are insoluble. Ba ethylate can be made by boiling absolute alcohol with BaO when $Ba(OEt)_2$ precipitates.

5. Ethanol reacts with acids to form esters slightly less rapidly than methanol.

6. It reacts with acid chlorides and acid anhydrides to give esters. Ethyl benzoate, $C_6H_5CO_2Et$, has a characteristic odor. The *p*-nitro compound, $NO_2C_6H_4CO_2Et$, m. 57° whereas the Me ester m. 97°. The Me and Et esters of 3,5-dinitrobenzoic acid m. 107.8° and 92.7° respectively.

7. With fused alkalies ethanol at 500° reacts to give hydrogen and acetates and then carbonates and methane (Fry 1928).

8. Ethanol reacts with chlorine to give chloral, $Cl_3CCHO$ which forms the hydrate, $Cl_3CCH(OH)_2$. With alkalies this gives $CHCl_3$. With $I_2$ and a base, ethanol gives iodoform (odor, yellow crystals). This is not a test for ethanol because other substances containing the grouping $CH_3CO$ such as acetaldehyde, acetone, and isopropyl alcohol also give it.

Reactions of Ethyl Alcohol, Morris, Rev. 1932, pp. 465–94.

## Propyl Alcohols

1. **Normal propyl alcohol,** propanol-1, ethylcarbinol, $CH_3CH_2CH_2OH$, b. 97°.

This alcohol constitutes 3–7% of the fusel oil from ordinary alcoholic fermentation. The amount is so small that most distillers do not separate it and the potential supply from this source has been very limited. The fusel oil from the Nipa palm

of the Philippines is said to contain more propyl and butyl alcohols than other fusel oil.

The mode of formation of propanol-1 during fermentation is not known. It may be due to changes such as the following:

1. $2\ MeCOCHO \rightarrow MeCOCO_2H + MeCOCH_2OH$, acetol
2. $MeCOCH_2OH \rightarrow MeCHOHCH_2OH$
3. $MeCHOHCH_2OH \rightarrow MeCH_2CHO$
4. $MeCH_2CHO \rightarrow MeCH_2CH_2OH$

Reaction (1) is probably a step in alcoholic fermentation (p. 107). When acetol is added to a rapidly fermenting mixture of sugar it is converted to 1,2-propylene glycol as in reaction (2) (OS). The change in reaction (3) is a rearrangement common in organic chemistry. Reaction (4) is of the same type as the final conversion of acetaldehyde into ethyl alcohol in ordinary fermentation. An alternative possibility is that it may be formed from the small amount of $\alpha$-amino-*n*-butyric acid in proteins (Abderhalden).

*n*-Propyl alcohol is now available in considerable amounts as a by-product of the action of CO and $H_2$. This source could probably be expanded as needed by a study of catalysts and reaction conditions.

If it were necessary to prepare propanol-1 synthetically, a variety of processes could be used. The first two are suitable in general for primary alcohols of the type, $RCH_2OH$.

1. Ethyl Grignard reagent with formaldehyde.

$$EtMgCl + HCHO \rightarrow EtCH_2OMgCl$$
$$EtCH_2OMgCl + HCl \rightarrow C_2H_5CH_2OH + MgCl_2$$

There is a minimum of side reactions in making the Grignard reagent and in the other steps. As in all cases involving lower alcohols and formaldehyde, care must be taken not to have the two present as they readily form stable formals, $H_2C(OR)_2$. This is easily avoided by using only a small excess of formaldehyde and boiling out that excess before the reaction mixture is acidified.

The cost of the magnesium and the anhydrous ether would be prohibitive commercially.

2. Reduction of ethyl propionate from acids obtainable by the fermentation of kelp (war time potash source).

(*a*) By sodium and alcohol (Bouveault and Blanc).

$$EtCO_2C_2H_5 + 2\,EtOH + 4\,Na \rightarrow EtCH_2ONa + 3\,EtONa$$

The cost of the metallic sodium (large excess) and the extremely anhydrous alcohol needed would be serious.

(*b*) By high pressure catalytic hydrogenation (Adkins, Schrauth).

$$CH_3CH_2CO_2C_2H_5 + 2\,H_2 \rightarrow CH_3CH_2CH_2OH + C_2H_5OH$$

This reaction works better with esters of higher acids. It has become very important with the $C_{10}-C_{16}$ alcohols (p. 141).

3. From propane from natural gas. This could be chlorinated to give a mixture of monochlorides rich in the normal chloride. The normal and iso chlorides could be separated by fractionation since there is a difference of 10° in their boiling points. Because of their low boiling points a fractionation with high reflux ratio would not be costly. The purified *n*-propyl chloride could then be converted to the alcohol by heating under pressure with aqueous sodium hydroxide and some emulsifying agent such as sodium oleate.

4. From glycerol. Heating with formic or oxalic acid converts it to allyl alcohol, $CH_2=CH-CH_2OH$. This could be hydrogenated catalytically with nickel at moderate temperature and pressure to give propanol-1.

5. The preparation from propionitrile from ethyl bromide and sodium cyanide would not be practical even in the laboratory. The nitrile can be reduced to *n*-propylamine by sodium and absolute alcohol or catalytically. The trouble would be that the amine with nitrous acid would give both propanol-1 and propanol-2 formed by rearrangement (pp. 78, 192).

The *reactions* of *n*-propyl alcohol, a typical primary alcohol, $RCH_2OH$, are like those of ethyl alcohol. For instance oxidation, as with all primary alcohols, gives an aldehyde and then an acid of

the same carbon content as the alcohol, in this case EtCHO, propionaldehyde, and $EtCO_2H$, propionic acid.

*n*-Propyl alcohol heated with an equimolecular amount of Na *n*-propylate under pressure at 250° undergoes a change characteristic of primary and secondary alcohols, $RCH_2CH_2OH$ and RMeCHOH (Guerbet 1898), in which the net result is the removal of the ONa group with an alpha hydrogen (on carbon next the carbinol group) from another molecule to form NaOH and 2-Me-pentanol-1. By more vigorous treatment it is possible to obtain "tripropyl alcohol," probably 2,4-$Me_2$-heptanol-1.

$$Pr-ONa + HCH(Me)CH_2OH \rightarrow Pr-CH(Me)CH_2OH$$
$$\rightarrow Pr-CH(Me)CH_2-CH(Me)CH_2OH$$

Propanol-1 with fused alkalies at 500° gives methane and $H_2$ in the ratio 4 : 1 and carbonates (Fry 1928). Some carbonization takes place.

2. **Isopropyl alcohol,** propanol-2, "isopropanol," Petrohol. Ikohol, dimethylcarbinol, $(CH_3)_2CHOH$, b. 82.4°.

This alcohol is available in practically unlimited amounts from the hydration of propylene from cracked gases. The propylene is dissolved in sulfuric acid, the isopropyl hydrogen sulfate is diluted and hydrolyzed by heating. The isopropyl alcohol is distilled out and the dilute sulfuric acid is concentrated for re-use. The product finds many uses formerly filled by ethyl alcohol. About 0.2% of methylisobutylcarbinol is obtained as a by-product. This is probably the result of the hydration of a dimer of propylene. No *n*-PrOH is formed even under favorable conditions for peroxide formation (Brooks 1934). Diisopropyl ether is obtained as a by-product at a price less than that of ordinary ethyl ether.

Isopropyl alcohol cannot be used in beverages and is not subject to the legal restrictions of ethyl alcohol.

Formerly isopropyl alcohol was obtained by the reduction of acetone. Now considerable quantities of acetone are made by the catalytic dehydrogenation of isopropyl alcohol.

Isopropyl alcohol forms an azeotrope with 12% water, b. 80.4°. It forms many other azeotropes. The following give the per cent isopropyl alcohol and the boiling point of the azeotrope with the

substance indicated: chloroform, 4.2, 60.8°; $CCl_4$, 18, 67°; ethylene dichloride, 45, 74°; trichloroethylene, 28, 74°; tetrachloroethylene, 80.6, 81.7°; *n*-hexane, 22, 61°; cyclohexane, 33, 68.6°; benzene, 33.3, 71.9°; toluene, 69, 80.6°.

The reactions of isopropyl alcohol, a typical secondary alcohol, RR'CHOH, differ from those of its normal isomer in several respects.

1. Ether formation is more difficult.
2. Dehydration to olefins is easier. This is true of secondary alcohols as compared with the corresponding primary alcohols.
3. Reaction with metals is more difficult.
4. Esterification with acids is much slower.
5. Alkalies or the alcoholate and the alcohol give condensation products between two or more molecules (Guerbet). As usual an alpha H atom is involved. The chief products are "diisopropyl alcohol," 4-Me-pentanol-2, methylisobutylcarbinol and "triisopropyl alcohol," 4,6-$Me_2$-pentanol-2. The first of these is now being produced commercially (C. and C.). Fused alkalies at high temperature (500°) give carbonates, methane and $H_2$ quantitatively without any carbonization (Fry 1928).
6. Oxidation gives the three carbon ketone, acetone, $CH_3COCH_3$, instead of an aldehyde as obtained from a primary alcohol. The acetone is rather stable to oxidation whereas the aldehyde is readily oxidized to an acid of the same number of carbon atoms. More vigorous oxidation converts the acetone to acids but only by breaking the carbon chain thus giving acetic and formic or carbonic acids. This difference between propanol-1 and propanol-2 on oxidation is general for all primary and secondary alcohols, $RCH_2OH$ and RR'CHOH.
7. It reacts in a complex way with bromine giving mainly brominated acetones such as $BrCH_2COCBr_3$ and isopropyl bromide.

### Butyl Alcohols

Unlike the lower alcohols these are not completely soluble in water.

1. **Normal butyl alcohol,** butanol-1, "Butanol," *n*-propylcarbinol, $CH_3CH_2CH_2CH_2OH$, b. 117.7°.

Since the World War this has been the most largely used of the butyl alcohols. During the War larger amounts of acetone were needed for smokeless powder manufacture than could be made from pyroligneous acid even by converting the calcium acetate into acetone. A fermentation process was developed for producing acetone (Weizmann, Fernbach) (C.S.C.). The yield of acetone was about 30%. At the same time a yield of about 60% of *n*-butyl alcohol was obtained. This had no adequate outlet until the development of the modern lacquer industry. Now acetone is the by-product of the process. Other by-products are ethanol, hydrogen and carbon dioxide. The latter two were formerly converted into methanol catalytically.

The mechanism of the butylic fermentation may involve the aldol condensation of acetaldehyde formed from pyruvic acid (p. 107). (Johnson 1933.) The following disproportionation could take place

$$2\ MeCHOHCH_2CHO \rightarrow MeCH_2CH_2CH_2OH + MeCOCH_2CO_2H$$

The acetoacetic acid on decarboxylation would yield $CO_2$ and acetone.

The supply of butanol-1 is limited only by the demand since it is a primary product and the process starts with corn or molasses. (Killeffer 1927.)

*n*-Butyl acetate is made by the reduction of crotonic aldehyde by metals and acetic acid. The crotonic aldehyde is made by condensing acetaldehyde prepared from acetylene.

$$MeCH=CHCHO + 5\ MeCO_2H + 2\ Zn \rightarrow MeCO_2CH_2CH_2CH_2CH_3 + H_2O + 2\ (MeCO_2)_2Zn$$

*n*-Butyl alcohol is also made by the catalytic hydrogenation of crotonic aldehyde (C. and C.)

Butanol-1 has been made by merely heating ethanol with Ba ethylate under pressure (Guerbet). It was identified by conversion to *n*-butyramide.

Butanol-1 is found in minute amounts in fusel oil (Emmerling 1902, Olewine 1936). This is probably formed from the small amount of norvaline in the proteins of the molasses.

The *reactions* of butanol-1 are essentially like those of ethyl alcohol.

Before secondary butyl alcohol was available from cracked gases it was made from *n*-butyl alcohol by dehydration to butene-1 and -2 followed by hydration by means of $H_2SO_4$.

2. **Isobutyl alcohol,** 2-methylpropanol-1, isopropylcarbinol, $(CH_3)_2CHCH_2OH$, b. 108°.

This is the longest known of the butyl alcohols, being obtained from fusel oil formed in ordinary alcoholic fermentation. The amount available from this source is relatively small. Isobutyl alcohol is not formed from glucose but from valine, $\alpha$-amino-isovalerianic acid obtained by the hydrolysis of the protein impurities in the fermenting mixture. The zymase of the yeast removes $CO_2$ and hydrolyzes off ammonia.

$$\underset{\text{Valine}}{Me_2CHCH(NH_2)CO_2H} + H_2O \rightarrow Me_2CHCH_2OH + NH_3 + CO_2$$

The valine is dextro rotatory but no asymmetric carbon is left in isobutyl alcohol. Consequently the latter is optically inactive. Fermentation isobutyl alcohol contains a minute impurity of a nitrogen compound which gives a scarlet color with sodium pentacyanosulfitoferroate (Johnson, Baudisch). It is possible to distinguish the fermentation and synthetic isobutyl alcohols by this test in 1 : 1000 dilution in water.

Isobutyl alcohol is also a by-product from synthetic methanol manufacture (Frolich, Cryder 1930).

Isobutyl alcohol gives the reactions typical of a primary alcohol except that the presence of the branched chain next to the carbinol group makes rearrangements unusually easy. Thus if the directions for converting *n*-butyl alcohol to its bromide by sodium bromide and sulfuric acid (OS) are applied to isobutyl alcohol a much poorer yield is obtained. Considerable amounts of tertiary butyl bromide and isobutylene and its polymers are obtained. A good example of the tendency for rearrangement is the fact that isobutyl alcohol with HBr gas even at −15° gives 11% tertiary butyl bromide (Michael).

The best preparation of isobutyl bromide is by means of $PBr_3$.

This type of reaction is usually represented as follows:

$$3\ ROH + PBr_3 \rightarrow 3\ RBr + H_3PO_3$$

As a matter of fact the reaction is much more complex. It is probable that the primary reaction involves the formation of an alkyl phosphite, $(RO)_3P$ and HX. These react in steps giving $(RO)_2POH$, $ROP(OH)_2$, $P(OH)_3$ and RX (Rep. 1918, 51). If this is correct it would seem desirable to pass a stream of HX gas through the mixture during the reaction.

The extreme case of rearrangement of isobutyl alcohol is obtained in dehydration at high temperatures which gives normal butylenes as well as isobutylene. In this case a methyl group rearranges. It has been shown that this rearrangement depends on the presence of acid (Ipatieff). Dehydration of isobutyl alcohol with $Al_2O_3$ completely free from acid gives pure isobutylene.

Isobutyl alcohol with fused alkalies at 500° gives much carbonization. This is apparently characteristic of alcohols having at least the chain, CCCO, and is in sharp contrast to the behavior of isopropyl and tertiary butyl alcohols (Fry 1928).

3. **Secondary butyl alcohol,** butanol-2, methylethylcarbinol, $CH_3CH_2CHOHCH_3$, b. 100°.

This alcohol is available in any desired amount from the hydration of *n*-butylenes from cracked gases by means of sulfuric acid. The isobutylene is first removed by means of more dilute acid than that necessary to dissolve the *n*-butylenes.

In addition to the preparation from the butylenes, butanol-2 can be obtained as follows:

1. By reduction of methyl ethyl ketone obtained with acetone in wood distillation. Now the pure ketone is obtained from the secondary alcohol by dehydrogenation (Shell). The reduction of a ketone is a general method for making secondary alcohols. Some bimolecular reduction product (a pinacol) is practically always formed as a by-product (p. 252).

2. The action of ethyl magnesium halide with acetaldehyde.

$$EtMgBr + MeCHO \rightarrow EtCHOHMe$$

The same product could be obtained from MeMgX and propionaldehyde but the starting materials would be more expensive.

In general secondary alcohols, RR'CHOH, can be made in this way by the proper selection of the aldehyde and Grignard reagent provided the R groups are not both tertiary (Conant 1929).

Since butanol-2 has an asymmetric molecule it can exist in two enantiomorphic optically active forms, dextro-rotatory and levo-rotatory. The synthetic material contains these in equal amounts (racemic mixture) and is optically inactive. Treatment with phthalic anhydride gives the acid phthalic esters, $C_6H_4(CO_2H)CO_2R$. The acid esters formed by the *d*- and *l*-alcohols are still enantiomorphic and cannot be separated because their properties are identical except their behavior to plane polarized light. The racemic mixture of the two acid esters is then treated with an optically active base, such as *d*-brucine. This gives two salts which may be represented as *d*-acid . *d*-brucine and *l*-acid . *d*-brucine. These salts are no longer enantiomorphs, parts of the two molecules are asymmetric and enantiomorphic and parts are asymmetric and identical. In such pairs of substances the properties are not identical as with enantiomorphic pairs. In this case there is enough difference in solubility between the two salts to allow their separation by fractional crystallization. The progress of the separation can be followed by finding the optical rotation of each of the fractions. When material is obtained which has the same specific rotation after repeated crystallizations the separation is assumed to be complete. The product is then treated, first, with acid to remove the brucine and then, with alkali to liberate the alcohol.

This process for resolving racemic mixtures of asymmetric secondary alcohols is due to Pickard and Kenyon (1911) and has been widely used.

The specific rotation (if $\alpha$ is the angle through which the plane of polarization of the light is rotated by a solution of $g$. grams in 100 g. of solution of density $d$ in a tube $l$ decimeters long $\left[\alpha\right] = \frac{100\alpha}{gdl}\Big)$ of the *d*-form of butanol-2 at 20° for the D line of the sodium spectrum, $[\alpha]_D^{20}$ is + 13.87°; $[\alpha]_D^{50}$ + 12.48°.

The reactions of butanol-2 are similar to those of isopropyl alcohol. It is a typical secondary alcohol. Thus it esterifies

more slowly and reacts with oxidizing agents to form methyl ethyl ketone which gives acetic acid on more vigorous oxidation. With fused alkalies it gives "di-*sec*-butyl alcohol," 5-Me-heptanol-3. A hydrogen of the methyl group reacts rather than one from the alpha methylene group.

$$EtMeCHONa + HCH_2CH(OH)Et \rightarrow EtCH(Me)-CH_2CH(OH)Et$$

4. **Tertiary butyl alcohol,** trimethylcarbinol, $(CH_3)_3COH$, b. 82.8°, m. 25.5°.

This alcohol is readily available from the hydration of isobutylene from cracked gases. Its supply is dependent on the demand for secondary butyl alcohol. At present the potential supply is far in excess of the demand. Whether there are adequate uses for tertiary butyl alcohol or not, the isobutylene has to be taken out in order to avoid contamination of the secondary butyl alcohol by the tertiary. This is done by a more dilute sulfuric acid than will absorb the *n*-butenes. The successful conversion of the small amounts of isobutylene contained in cracked gases into high anti-knock gasoline for aviation makes possible the utilization of this material.

Before tertiary butyl alcohol was available commercially, it was made as follows:

1. By dehydration of isobutyl alcohol to isobutylene which was then hydrated with sulfuric acid.

2. By the action of MeMgCl on acetone.

$$Me_2CO + MeMgCl \rightarrow Me_3COMgCl \rightarrow Me_3COH$$

This is a general method for tertiary alcohols. Selection of the proper ketone and Grignard reagent will give any alcohol RR′R″COH unless there is too much branching in the R groups (Conant, Blatt 1929).

The reactions of tertiary butyl alcohol are typical of tertiary alcohols and are radically different from those of primary and secondary alcohols.

1. Acids.

(*a*) Even dilute inorganic acids dehydrate it on heating to give isobutylene.

(*b*) Concentrated halide acids or the gaseous hydrogen halides react rapidly and completely giving tertiary butyl halides and water. The reaction is almost like that between an acid and a base.

(*c*) Organic acids form esters very slowly and incompletely. This is the reason an impurity of a tertiary alcohol in a secondary alcohol is harmful since the chief use of the latter is in making esters for solvents.

2. Acid chlorides present an interesting series of reactions with *ter*-butyl alcohol as with other tertiary alcohols. Acetyl chloride in the cold gives *t*-butyl chloride and acetic acid quantitatively (Butlerow). When the two reagents are heated a nearly 1 : 1 mixture of chloride and acetate is obtained. The acetate can be obtained in quantitative yield by adding dimethyl aniline to combine with the HCl as fast as liberated in the normal reaction (Norris).

$$Me_3COH + MeCOCl \rightarrow HCl + MeCO_2CMe_3$$

If the HCl is not removed it reacts more or less completely with the tertiary ester to give the chloride and acetic acid.

Another preparation for acetates of tertiary alcohols which should be useful with the less readily available ones is to treat the alcohol with MeMgX to form $CH_4$ and ROMgX which can then be treated with acetic anhydride.

3. The acetate of *ter*-butyl alcohol can also be obtained by heating with acetic anhydride and a small amount of Zn dust (Norris).

4. Another evidence that tertiary butyl alcohol is more "basic" than "acidic" is the slowness with which it reacts with the alkali metals.

5. With bromine, there is no chance for oxidation as with the primary and secondary alcohols. Instead a dibromide is formed corresponding to the olefin which would be obtained by dehydrating the alcohol, namely, isobutylene.

$$Me_2C(OH)CH_3 + Br_2 \rightarrow Me_2CBrCH_2Br + H_2O$$

This dibromide suffers an interesting rearrangement on refluxing with water, giving isobutyraldehyde, $Me_2CHCHO$.

6. Fused NaOH at 500° gives sodium carbonate and methane quantitatively (Fry 1928).

7. Mild oxidizing agents have no effect on tertiary butyl alcohol. More vigorous ones split it into acetone, acetic acid and $CO_2$. Acid oxidizing agents give a peculiar by-product, isobutyric acid, $Me_2CHCO_2H$ (Butlerow 1872). Probably the first step is the dehydration to isobutylene followed by a peculiar oxidation and rearrangement. Similar processes take place in the oxidation of diisobutylene and triisobutylene (Whitmore 1934).

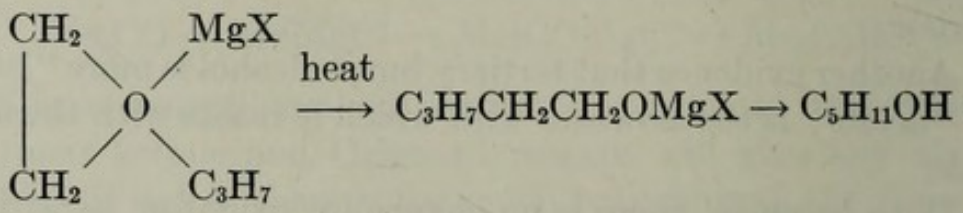
### Amyl Alcohols

All eight of the theoretically possible structural isomers have been prepared.

1. **Normal amyl alcohol,** pentanol-1, *n*-butylcarbinol,

$$CH_3\text{-}(CH_2)_3CH_2OH \text{ b. } 137°.$$

This alcohol has recently become available by the hydrolysis of 1-chloropentane formed by the direct chlorination of pentane from natural gasoline (Sharples). Before that, it could be prepared from a *n*-butyl Grignard reagent and formaldehyde. Before *n*-butyl alcohol was available it could be made from *n*-propyl Grignard reagent and ethylene oxide. An "oxonium" addition compound is first formed which on heating gives a derivative of the desired alcohol. Decomposition of the first product with acid gives propane and ethylene glycol.




This is a general method for building up higher primary alcohols from primary and secondary halides. It does not work with tertiary Grignard reagents.

Another method of preparation is the reduction of ethyl *n*-valerate with sodium and alcohol (Bouveault and Blanc). The ester is made by converting *n*-butyl halide to the cyanide and then treating with ethyl alcohol and sulfuric acid.

Minute traces of *n*-amyl alcohol have been identified in fusel oil. It is probably formed from norleucine, α-amino-*n*-caproic acid, in the same way that isobutyl alcohol is formed from valine. Older attempts failed to find this alcohol in fusel oil. Thus Tissier (1893) fractionally distilled 1600 l. of fusel oil in the search of this alcohol which was believed to be present because the dehydration of fusel oil amyl alcohol gave some normal amylenes. It is now known that these come from the rearrangement of *sec*-butylcarbinol.

*n*-Amyl alcohol gives the reactions of primary alcohols.

2. **Secondary butylcarbinol,** " active amyl alcohol," 2-methyl-butanol-1, $CH_3CH_2(CH_3)CHCH_2OH$, b. 128°.

This alcohol has long been available, mixed with about seven times as much isoamyl alcohol in fusel oil. The separation has been difficult. Active amyl alcohol is so-called because of its optical activity. It is formed during fermentation from isoleucine derived from the proteins in the material fermented (F. Ehrlich). The net change is

$$MeEtCHCHNH_2CO_2H + H_2O \rightarrow MeEtCHCH_2OH + CO_2 + NH_3$$

The isoleucine has two asymmetric carbons and is optically active as are practically all natural products which have asymmetric molecules. In the change to the alcohol only one of the asymmetric atoms is rendered symmetrical. Hence the product is still optically active. Although it is levorotatory, $[\alpha]_D^{20} = -5.9°$, it is called *d*-amyl alcohol because on oxidation it gives *d*-valerianic acid (*d*-methylethylacetic acid) which is dextrorotatory (Marckwald 1902). This apparent inconsistency in the naming of optically active compounds is general. The symbols *d*- and *l*- simply show the chemical relationship of the substance named to some standard reference substance. Thus *d*-fructose is levorotatory. It is called *d*- because it has three asymmetric carbon atoms like those in *d*-glucose, the reference substance in the hexose series.

The separation of active amyl alcohol (*d*-sec-butylcarbinol) from isoamyl alcohol was formerly a problem of great interest and was attacked by many able workers beginning with Pasteur.

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The mixture of alcohols may be treated with sulfuric acid to give the acid amyl sulfates which are then neutralized with barium hydroxide to give the barium amyl sulfates. Repeated crystallizations of the mixture give fractions differing in optical properties but the rate of separation is surprisingly slow. While the barium amyl sulfates differ slightly in solubility they crystallize in the *same type* of crystals and are capable of forming *mixed crystals* in all proportions. This ability to form mixed crystals occurs with all the derivatives of these two amyl alcohols. This property is not surprising in view of the close similarity of the structures of the two alcohols. Both are primary alcohols and differ only in the position of one methyl group and in the possession of an asymmetric carbon atom by the "active" alcohol. Other derivatives which have been used to separate these alcohols are the ester acids of 3-nitrophthalic acid. When the anhydride of 3-nitrophthalic acid (OS) is treated with the alcohol the 2-carboxyl is esterified whereas the treatment of the acid with the alcohol and HCl gas esterifies the 1-carboxyl. Salts of the ester acids are repeatedly recrystallized to separate the esters of active and iso-amyl alcohols which are then hydrolyzed to obtain the alcohols.

Better results are obtained by recrystallizing the amyl carbamates $C_5H_{11}OCONH_2$. This is probably because the molecules are smallest here and consequently the slight difference in the two amyl groups makes a relatively greater difference in the solid derivatives.

The best separation is obtained by combining the crystallization method with the utilization of a slight difference in chemical activity between the two alcohols. Isoamyl alcohol at its boiling point reacts more *rapidly* with hydrogen chloride than does the "active" amyl alcohol. The mixture of the two alcohols is thus treated with HCl gas to convert about ninety per cent of the mixture to chlorides and then fractionally distilled to remove the chlorides. The remaining mixture of alcohols is richer in the "active" amyl alcohol. The enriched mixture is then converted to suitable crystalline compounds and recrystallized until no increase is obtained in the rotation of the fraction having the greatest optical activity.

Thus the separation of pure optically active *sec*-butylcarbinol was extremely difficult until distilling columns having the equivalent of one hundred theoretical plates were used to distill fusel oil (Olewine 1936, Fenske 1936).

The proportion of "active" amyl alcohol in amyl alcohol from fusel oils varies very decidedly according to the material fermented. Apparently the largest amount is obtained in the fermentation of beet-molasses.

At present the best sources for racemic secondary-butylcarbinol is the hydrolysis of 1-chloro-2-methylbutane obtained by chlorinating isopentane (Sharples) and as a by-product in methanol synthesis. Obtained thus the alcohol is optically inactive being a racemic mixture of the *d*- and *l*-forms in equal amounts.

Secondary-Butylcarbinol has also been made synthetically by use of the secondary butyl Grignard reagent with formaldehyde.

The reactions of this alcohol are like those of isobutyl alcohol, that is, the reactions of the primary alcohol group are complicated by the adjacent tertiary H and the fork in the chain. Thus it gives some tertiary halide and on dehydration gives some normal amylenes (Tissier).

3. **Isoamyl alcohol,** 3-methylbutanol-1, isobutylcarbinol, $(CH_3)_2CHCH_2CH_2OH$, b. 131°.

This is the principal amyl alcohol contained in fusel oil. It is formed during fermentation from leucine, $\alpha$-amino-isocaproic acid. Although the leucine is optically active, the resulting alcohol is not because it does not have an asymmetric molecule.

Isoamyl alcohol is readily available from the chlorination products of isopentane (Sharples).

The reactions of isoamyl alcohol are those of a primary alcohol.

Ordinary dehydration of isoamyl alcohol gives very little isopropylethylene since that substance readily rearranges to $Me_3$-ethylene in presence of the acid dehydrating agent.

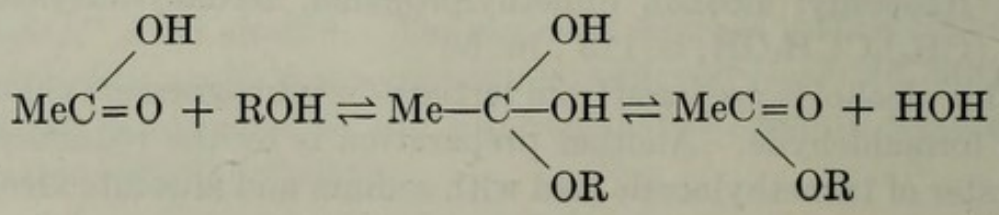
4. **Neopentyl alcohol,** dimethylpropanol, tertiary-butylcarbinol, $(CH_3)_3CCH_2OH$, b. 113°, m. 50°.

This alcohol is prepared from tertiary-butylmagnesium chloride and formaldehyde. Another preparation is by the reduction of an ester of trimethylacetic acid with sodium and absolute alcohol.

An unusual reaction is the formation of neopentyl alcohol in nearly quantitative yield by the action of pivalyl chloride with an excess of *t*-butyl Grignard reagent (Whitmore 1936).

$$Me_3C-COCl + Me_3CMgCl \rightarrow Me_3C-CH_2OH + Me_2C=CH_2$$

It reacts as a primary alcohol with oxidizing agents, with the alkali metals, with organic acids, and with acyl halides. With all reagents which would be expected to remove or replace the hydroxyl group, such as halide acids, inorganic acid chlorides and dehydrating agents it gives little or none of the expected product but largely undergoes rearrangement with the formation of trimethylethylene and tertiary amyl derivatives (Whitmore 1932, 1934). The fact that all reactions which result in the removal of the hydroxyl from neopentyl alcohol result in *ter*-amyl products can be used in studying the mechanism of *esterification of alcohols* with carboxylic acids. The older and natural conception is that the process resembles the neutralization of a base with an acid and that the alcohol supplies the OH group and the acid supplies the H. More recently evidence has accumulated indicating that the alcohol supplies the H and the acid supplies the OH (Norris). If the older conception is correct, the esterification of neopentyl alcohol would deprive it of its OH and give a *ter*-amyl derivative. If the newer conception is sound, only the H would be removed from the neopentyl alcohol, the C—O linkage would not be broken at any time during the process, no opportunity for rearrangement would be given and the product would be a neopentyl compound. The fact is that neopentyl alcohol can be converted to neopentyl acetate and hydrolyzed back to the same alcohol without the slightest evidence of rearrangement. This confirms the idea that the alcohol supplies only H in esterification and gives added weight to the conception that both esterification and hydrolysis take place through addition to the carbonyl group (Henry, Rep. 1910, 66).



The initial step in each process is the addition of H+ to the oxygen of the carbonyl group of the acid or ester.

5. **Pentanol-2,** methylpropylcarbinol,

$$(CH_3CH_2CH_2)(CH_3)CHOH, \text{ b. } 119°.$$

This is another of the amyl alcohols from chlorinated pentane (Sharples). The hydrolysis of 2-chloropentane gives considerable olefin and consequently a poorer yield of alcohol than the hydrolysis of the primary halides.

Pentanol-2 is also available from the hydration of pentene-1 obtained in the cracking process (cf. isopropyl and secondary butyl alcohols) (Shell). Commercial secondary amyl alcohol from cracked gases contains the 2- and 3-isomers in the ratio 4 : 1 (Brooks 1934).

Pentanol-2, made by either of these methods, always contains pentanol-3. To obtain the pure alcohol it is best to use the general method for making a secondary alcohol, namely the action of a Grignard reagent on an aldehyde. The desired result can be obtained from acetaldehyde and *n*-propyl Grignard reagent or from *n*-butyraldehyde and methyl Grignard reagent. The *d*-form of the alcohol has been obtained, $[\alpha]_D^{20} = +13.7°$.

Another general method for making secondary alcohols is the reduction of ketones. In this case methyl propyl ketone would be used. This could be made through the acetoacetic ester synthesis using ethyl bromide as the halide and splitting the final product with *dilute* alkali and acid (p. 441). The reduction of ketones practically always gives as by-products pinacols, in this case 4,5-dimethyloctandiol-4,5.

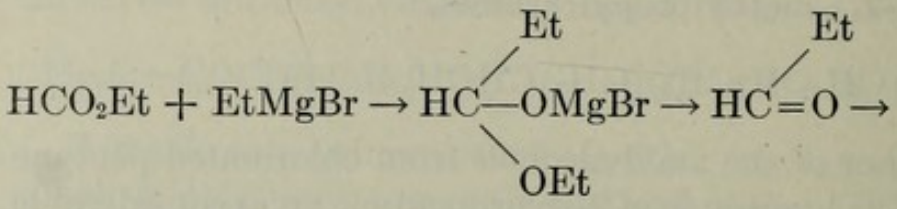
Pentanol-2 shows the usual reactions of secondary alcohols. If halides are made from it by the ordinary methods (acid and heat) a mixture of the 2- and 3- compounds is obtained. Thionyl chloride and pyridine or HCl gas at *room temperature* give the pure 2-chloropentane.

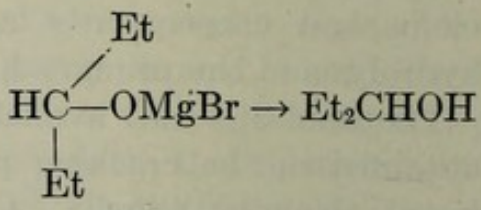
6. **Pentanol-3,** diethylcarbinol, $(C_2H_5)_2CHOH$, b. 117°.

This alcohol is obtained from 3-chloropentane in the usual way (Sharples).

Before this method was available it could be made by the

Grignard reaction in two ways: (a) Propionaldehyde and EtMgX (b) Ethyl formate and EtMgX.





These steps, except the last, take place when an excess of Grignard reagent is added to a formate. The grouping $C(OR)OMgX$ is unstable like $C(OH)_2$ and loses ROMgX and becomes $C=O$.

The action of a Grignard reagent with a formate is a general method for making symmetrical secondary alcohols of the type $R_2CHOH$.

Another preparation is by the reduction of diethyl ketone formed by the dry distillation of calcium propionate or by passing the vapors of propionic acid over manganous carbonate. The pinacol formed as a by-product of the reduction would be 3,4-$Et_2$-hexandiol-3,4.

The reactions of pentanol-3 are like those of pentanol-2 including the tendency for rearrangement.

7. **Methylisopropylcarbinol,** secondary isoamyl alcohol, 3-methylbutanol-2, $(CH_3)_2CHCHOHCH_3$, b. 112°.

This alcohol is not obtained from the chlorination products of isopentane. The corresponding chloride probably loses HCl very rapidly to give trimethylethylene, etc.

It is prepared by MeMgX and isobutyraldehyde. This gives a better over-all yield than the use of an isopropyl Grignard reagent with acetaldehyde.

Another method of preparation is by the reduction of methyl isopropyl ketone. This has recently become available by the hydrolysis and rearrangement of trimethylethylene dibromide

obtainable by the direct bromination of tertiary amyl alcohol (OS).

8. **Tertiary amyl alcohol,** 2-methylbutanol-2, dimethylethylcarbinol, "Amylene Hydrate," $(CH_3CH_2)(CH_3)_2COH$, b. 102°.

This alcohol is available in large amounts because the chlorination of isopentane and the hydrolysis of the resulting products give large amounts of trimethylethylene. When this is hydrated by means of 50% sulfuric acid, tertiary amyl alcohol is obtained.

*t*-Amyl alcohol may also be made by means of suitable Grignard reagents with acetone, methyl ethyl ketone and ethyl propionate.

The reactions of tertiary amyl alcohol are practically identical with those of tertiary butyl alcohol. It is even more easily dehydrated. *t*-Amyl alcohol with dilute $H_2SO_4$ in a sealed tube gives two layers (olefin and aqueous acid) on warming. On cooling one layer is formed again (Butlerow 1877).

With bromine it gives trimethylethylene dibromide directly. This, on hydrolysis, rearranges to form methyl isopropyl ketone.

*ter*-Amyl alcohol is valuable in the dry cleaning industry for removing spots before treatment with the usual solvents and for the dry cleaning of Celanese (cellulose acetate fiber). It is sold as K.O.S. (Sharples).

A crude mixture of the amyl alcohols obtained by the hydrolysis of chloropentanes by NaOH and an emulsifying agent such as soap is marketed as Pentasol for use as a solvent alone and in making Pentacetate (Sharples). Pentasol contains approximately the following percentages of amyl alcohols: *sec*-butylcarbinol, 32; *n*-amyl alcohol, 26; pentanol-3, 18; isoamyl alcohol, 16; and pentanol-2, 8. The method of hydrolysis converts any *t*-amyl chloride and 2-chloro-3-Me-butane in the chlorinated pentanes into amylenes and traces of the corresponding alcohols.

## Hexyl Alcohols

All seventeen of the theoretically possible hexyl alcohols are known. Most of them have been prepared in a variety of ways. Only the most typical of these will be considered. The reactions of these alcohols are like those of the lower homologs of the corresponding classes. The alcohols are grouped as primary, secondary and tertiary.

1. ***n*-Hexyl alcohol,** hexanol-1, $CH_3(CH_2)_4CH_2OH$, b. 157°.

This alcohol is available commercially (C and C). Presumably it is made as follows:

$$CH_3CH_2CH_2CHO + CH_3CHO \rightarrow CH_3CH_2CH_2CH{=}CHCHO \rightarrow CH_3(CH_2)_4CH_2OH$$

It can be synthesized in a variety of other ways.

*a.* Reduction of ethyl caproate or caproamide by sodium and absolute alcohol (Bouveault and Blanc 1904). A modification of these reactions is the reduction of ethyl caproate by sodium in liquid ammonia. It can also be reduced by $H_2$ and a copper chromium oxide catalyst under pressure.

*b.* *n*-Butyl magnesium bromide with ethylene oxide (p. 373), obtained from ethylene chlorohydrin and alkali (OS).

*c.* A similar reaction is that of *n*-PrMgX with trimethylene oxide obtained from 3-chloropropanol-1 (trimethylene chlorohydrin) and alkali.

*d.* Since *n*-amyl alcohol is readily available it could be made from *n*-amyl Grignard reagent and formaldehyde.

2. **2-Methylpentanol-1,** $(CH_3CH_2CH_2)(CH_3)CHCH_2OH$, b. 148°.

This alcohol is obtained in fair amounts as a by-product of synthetic methanol. It has also been made as follows:

*a.* By heating propyl alcohol with sodium propylate at 220° (Guerbet).

*b.* By converting 2-chloropentane to the Grignard reagent and treating with trioxymethylene (polymerized formaldehyde).

*c.* By the sodium and absolute alcohol reduction of methylpropylacetoacetic ester.

$$MeCOCMePrCO_2Et + Na + EtOH \rightarrow MeCO_2Na + MePrCHCH_2OH$$

The splitting of the grouping $MeCO-C-CO_2Et$ by vigorous treatment with NaOEt is characteristic.

3. **3-Methylpentanol-1,** $(CH_3CH_2)(CH_3)CHCH_2CH_2OH$, b. 154° (Norris 1925), is best made synthetically from secondary butylcarbinol through the Grignard reagent and formaldehyde. It occurs as an ester in Roman Camomile oil. The natural

alcohol is optically active $[\alpha]_D^{20.5} = +8.8$. Its structure was proved by oxidation to known $\beta$-Me-valeric acid.

4. **Isohexyl alcohol,** 4-Methylpentanol-1,

$$(CH_3)_2CH(CH_2)_2CH_2OH, \text{ b. } 148°,$$

*a.* From isoamyl magnesium bromide and formaldehyde.

*b.* By heating isobutyl acetoacetic ester with sodium and absolute alcohol.

5. **2-Ethylbutanol-1,** diethylcarbincarbinol, 3-methyolpentane, 3-hydroxymethyl-pentane, $(C_2H_5)_2CHCH_2OH$, b. 146°.

This is commercially available (C. and C.) presumably from the product of an aldol condensation of acetaldehyde and *n*-butyraldehyde, the former contributing the carbonyl group and the latter the alpha H, exactly the reverse of the process which would give hexanol-1 after reduction (p. 132).

*a.* By catalytic reduction of ethyl diethylacetate obtained from ethyl diethylmalonate, available as an intermediate for veronal.

*b.* From the hydrochloride of the corresponding amine and an excess of silver nitrite. Such a process would certainly be expected to produce rearrangement products (p. 192).

Dehydration of diethylcarbincarbinol gives a mixture of rearrangement products with a minimum amount of the normally expected product. It gives hexene-3, hexene-2, 3-Me-pentene-2, and 2-Et butene-1 (Karnatz 1932).

6. **Tertiary-Amylcarbinol,** 2,2-dimethylbutanol-1,

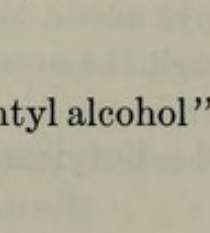
$$(CH_3CH_2)(CH_3)_2CCH_2OH, \text{ b. } 135°.$$

*a.* By reduction of the ethyl ester of dimethylethylacetic acid with sodium and absolute alcohol.

*b.* From *ter*-amyl magnesium chloride and ethyl formate. This involves an addition and a reduction by the Grignard reagent.

*c.* From the *ter*-amyl Grignard reagent and formaldehyde.

This alcohol reacts abnormally with acids, undergoing the usual rearrangement of the "neopentyl alcohol" grouping



(p. 128). Dehydration gives the olefins $MeEtC=CHMe$, $Et_2C=CH_2$, $Me_2C=CHEt$ and $MePrC=CH_2$.

7. **Neopentylcarbinol,** 3,3-dimethylbutanol-1,

$$(CH_3)_3CCH_2CH_2OH, \text{ b. } 143°.$$

The preparation of this alcohol from acetone illustrates a wide range of synthetic processes.

1. Acetone $\xrightarrow{\text{reduction}}$ pinacol, $Me_2C(OH)C(OH)Me_2$
2. pinacol $\xrightarrow{\text{acid}}$ pinacolone, $Me_3CCOMe$
3. pinacolone $\xrightarrow{\text{reduction}}$ pinacolyl alcohol, $Me_3CCHOHMe$
4. pinacolyl alcohol $\xrightarrow[NaOH]{CS_2}$ sodium pinacolyl xanthate $\xrightarrow{MeI}$ methyl pinacolyl xanthate
5. xanthate $\xrightarrow{\text{heat}}$ *ter*-butylethylene
6. *ter*-butylethylene $\xrightarrow{HBr}$ $Me_3CCH_2CH_2Br$
7. bromide $\xrightarrow{CH_3CO_2Na}$ acetate
8. acetate $\xrightarrow{KOH}$ $Me_3CCH_2CH_2OH$.

Step 6 represents an addition contrary to Markownikoff's Rule possibly due to the presence of peroxides in the olefin.

Neopentylcarbinol forms halides with the same ease as does butanol-1 and also without rearrangement. This is in marked contrast to its lower homolog neopentyl alcohol (p. 128).

8. **2,3-Dimethylbutanol-1,** $(CH_3)_2CH(CH_3)CHCH_2OH$, b. 145°.

This alcohol has been made only by the reduction of the ethyl ester of methyl isopropyl acetic acid with sodium and alcohol. The ester is made through the acetoacetic ester or malonic ester synthesis for acids.

9. **Hexanol-2,** methyl-*n*-butylcarbinol, $CH_3CHOH(CH_2)_3CH_3$, b. 141°.

*a.* By reduction of methyl butyl ketone by sodium in a mixture of ether and water, by catalytic hydrogenation (Sabatier), and by sodium amalgam and dilute acid. The methyl butyl ketone is obtained from sodium acetoacetic ester and *n*-propyl bromide (OS).

*b.* By treating hexene-1 from *n*-PrMgBr and allyl bromide with 85% sulfuric acid, diluting and distilling.

*c.* From *n*-butyl magnesium bromide and acetaldehyde.

10. **Hexanol-3,** ethylpropylcarbinol,

$$CH_3CH_2CH_2CHOHCH_2CH_3, \text{ b. } 135°.$$

*a.* By reduction of ethyl propyl ketone by sodium amalgam and water.

The ketone can be obtained from a mixture of propionic and *n*-butyric acids either through the calcium salts or by hot manganous oxide.

*b.* A better preparation would be from EtMgX and *n*-butyraldehyde.

11. **3-Methylpentanol-2,** methyl-*sec*-butylcarbinol,

$$(CH_3CH_2)(CH_3)CHCHOHCH_3, \text{ b. } 134°.$$

By the reduction of methyl *sec*-butyl ketone by sodium and wet ether. The ketone is made by introducing a methyl and an ethyl group into acetoacetic ester in the usual way and splitting by dilute alkali.

12. **Methylisobutylcarbinol,** 4-Me-pentanol-2,

$$(CH_3)_2CHCH_2CHOHCH_3, \text{ b. } 132°.$$

This alcohol is available commercially presumably from the catalytic dehydration and hydrogenation of diacetone alcohol.

The dextrorotatory form has been made through the brucine salt of the acid phthalic ester. $[\alpha]_D^{21.3} = +20.4°$. The levorotatory form has been obtained similarly from the brucine salt of the acid succinic ester, $[\alpha]_D^{14} = -20.8°$.

The *dl*-alcohol has been made as follows:

*a.* From isovaleraldehyde and zinc dimethyl.

*b.* By the reduction of mesityl oxide, $Me_2C=CHCOMe$, with sodium and alcohol or catalytically.

*c.* By the reduction of methyl isobutyl ketone with sodium and a mixture of ether and water. The ketone is obtained from sodium acetoacetic ester and isopropyl bromide.

*d.* From acetaldehyde and isobutyl magnesium bromide.

*e.* From the action of zinc or magnesium on a mixture of isobutyl iodide and acetic anhydride. This is undoubtedly a Grignard reaction followed by reduction.

*f.* From isopropyl alcohol, either by heating it with KOH or by heating it with sodium isopropylate to 200°. As usual, the ONa combines with an alpha hydrogen.

13. **Ethylisopropylcarbinol,** 2-methylpentanol-3,

$$(CH_3)_2CHCHOHCH_2CH_3, \text{ b. } 128°.$$

The dextrorotatory form has been obtained by means of the strychnine salt of the half phthalic ester. $[\alpha]_D^{21.4} = +12.4°$. The *dl*-alcohol has been made as follows:

*a.* From isobutyryl chloride and zinc diethyl. The ethyl isopropyl ketone first formed is reduced to the carbinol instead of adding another molecule of zinc alkyl.

$$Me_2CHCOEt + ZnEt_2 \rightarrow Me_2CHCH(Et)OZnEt + C_2H_4$$

*b.* From isobutyraldehyde and EtMgBr.

*c.* By hydrogenating ethyl isopropyl ketone.

14. **Pinacolyl alcohol,** methyl-*ter*-butylcarbinol, 2,2-dimethylbutanol-3, $(CH_3)_3CCHOHCH_3$, m. 5.5°, b. 121°.

The *d*-form has been made in the usual way. $[\alpha]_D^{20} = +7.7°$. The *dl*-material has been prepared as follows:

*a.* Reduction of pinacolone by sodium amalgam.

*b.* Acetaldehyde and tertiary butylmagnesium chloride.

This alcohol contains the neopentyl alcohol grouping (p. 128). Since there are three alpha H atoms in the molecule, it might be expected that dehydration would involve one of them to give *ter*-butylethylene. This normal product is obtained to the extent of only 3%. The main products are those of rearrangement, namely, tetramethylethylene and *unsym*-methylisopropylethylene in 61 and 31% yields (Whitmore 1933). The normal dehydration

product from pinacolyl alcohol can be obtained without rearrangement by an indirect process involving the decomposition of the methyl xanthate (Fomin 1913) (p. 47). This process gives the unrearranged olefin in many cases in which ordinary dehydration gives only rearranged products.

Conversion of pinacolyl alcohol to halides gives those related to dimethylisopropylcarbinol by rearrangement of the neopentyl alcohol grouping.

15. **2-Methylpentanol-2,** dimethyl-*n*-propylcarbinol,

$$(CH_3CH_2CH_2)(CH_3)_2COH, \text{ b. } 123°.$$

*a.* *n*-Butyryl chloride and zinc dimethyl. This method served as the equivalent of the Grignard reaction until about 1900.

*b.* Ethyl *n*-butyrate and excess methyl Grignard reagent.

*c.* Acetone and *n*-propyl magnesium bromide.

This tertiary alcohol, in common with all tertiary alcohols of $C_6$ and higher, is dehydrated by refluxing with a trace of iodine (Hibbert). *t*-Butyl and *t*-Amyl alcohols boil at too low a temperature to give this reaction. The latter is dehydrated slowly by refluxing with iodine at two atm. pressure.

16. **Methyldiethylcarbinol,** 3-methylpentanol-3, $MeEt_2COH$, b. 123°.

*a.* From acetyl chloride and zinc diethyl.

*b.* From ethyl acetate and excess ethyl magnesium bromide. A modification of this reaction has been made by using calcium acetate with the Grignard reagent.

This method is general for making tertiary alcohols of the type, $RR_2'COH$. A ketone is probably formed as an intermediate in the reaction mixture (p. 138). With more complex esters and Grignard reagents the corresponding ketone is obtained instead of the tertiary alcohol (Bachmann 1932).

17. **Dimethyl-isopropylcarbinol,** 2,3-Dimethylbutanol-2, $(CH_3)_2CHC(OH)(CH_3)_2$, b. 122°.

This alcohol has been made by a great variety of methods.

*a.* By the ordinary Grignard reactions using isopropyl magnesium bromide with acetone, and methyl isobutyrate with excess methyl magnesium bromide, and trimethylethylene oxide with methyl magnesium bromide. The last two methods are prefer-

able. The forked Grignard reagent, isopropyl magnesium bromide gives side reactions with the ketone including its reduction to isopropyl alcohol and its condensation to mesityl oxide and more complex products. Thus the yield of the desired alcohol is only 35–40%.

*b.* By more complex actions of MeMgX with alpha chloro isobutyraldehyde and with the chlorohydrin of trimethylethylene. The intermediate product in both cases is trimethylethylene oxide.

*c.* By similar reactions of zinc dimethyl with isobutyryl chloride, chloral, dichloroacetyl chloride, and alpha bromopropionyl bromide. The first of these is an ordinary "Grignard" type of reaction. The other three are somewhat more complex although the individual steps are entirely normal.

*d.* At the present time the way to make this alcohol is from MeMgX and methyl isopropyl ketone, since the latter is readily available from tertiary amyl alcohol.

### Heptyl Alcohols

Of the 39 theoretically possible heptyl alcohols about half have been made. The reactions used are no different from those described for the hexyl alcohols except in the case of triethylcarbinol which is best made from an excess of EtMgX and ethyl carbonate. This is a general method for symmetrical tertiary alcohols, $R_3COH$ (Tschitschibabin 1905) (OS). The following changes probably take place in the reaction mixture (cf. Ivanov 1932).

$$(EtO)_2C{=}O \rightarrow (EtO)_2C\begin{matrix}\diagup\,OMgX\\ \diagdown\,Et\end{matrix} \rightarrow$$

$$EtOMgX + EtCO_2Et \rightarrow Et_2C\begin{matrix}\diagup\,OMgX\\ \diagdown\,OEt\end{matrix} \rightarrow$$

$$EtOMgX + Et_2C{=}O \rightarrow Et_3COMgX \rightarrow Et_3COH$$

Even if less than 3 mols of Grignard reagent are used, considerable tertiary alcohol is formed because the ketone and ester formed as intermediates are considerably more reactive than ethyl carbonate.

***n*-Heptyl alcohol,** $CH_3(CH_2)_5CH_2OH$, b. 176°, has long been available as a reduction product of heptaldehyde (OS) obtained by the pyrolysis of castor oil.

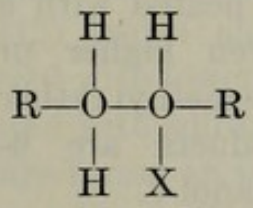
Methyl-*n*-amylcarbinol is made by the reduction of the corresponding ketone.

**Diisopropylcarbinol,** 2,4-$Me_2$-pentanol-3,

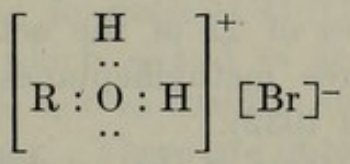
$$(CH_3)_2CHCHOHCH(CH_3)_2,$$

is the chief secondary alcohol obtained as a by-product of methanol synthesis (Graves 1931). This alcohol gives a crystalline oxonium salt $(ROH)_2.HBr$, m. 69°. (Favorsky 1913).

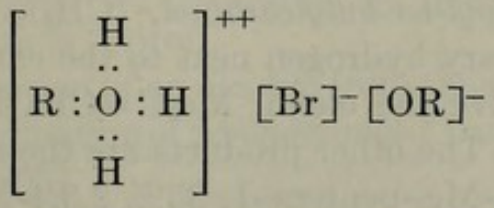
While the oxonium salts of most alcohols are difficult to isolate, many highly branched alcohols give stable crystalline compounds. The "structure" suggested is



The formation of the simplest possible oxonium salt, ROH.HX, like MeOH.HBr which is stable only at low temperatures, may involve the coordination of a hydrogen ion by the oxygen



The more complex oxonium salt would then be



**2,4-$Me_2$-pentanol-1** (Marvel 1931) and *4-Me-hexanol-1* are also

obtained in the methanol synthesis but in smaller amounts than the other by-product alcohols.

**Pentamethylethanol,** 2,3,3-$Me_3$-butanol-2, m. 17°, b. 131°, forms a crystalline hydrate, $(ROH)_2 . H_2O$, m. 83°, which sublimes even at room temperature.

Of the unknown heptyl alcohols the ones which would offer serious difficulties in synthesis are those related to 2,3-$Me_2$-pentane and many of the primary alcohols related to the highly branched heptanes.

### Octyl Alcohols

Of the 89 possible isomers less than one-third are known.

**Octanol-1,** $CH_3(CH_2)_6CH_2OH$, b. 195°, occurs as esters in various plants.

**Capryl alcohol,** octanol-2, methyl-*n*-hexylcarbinol,

$$CH_3CHOH(CH_2)_5CH_3,$$

b. 178°, has long been available from the action of bases with castor oil (OS). When heated with alkali it gives di- and tri-capryl alcohols and even higher products (Guerbet). The condensation involves the methyl rather than the alpha methylene group. Thus the products are 9-Me-pentadecanol-7 and 11-Me-9-*n*-Hex-heptadecanol-7.

**2-Et-hexanol-1** is available commercially (C and C). It could be obtained from the aldol condensation product of *n*-butyraldehyde by catalytic dehydration and hydrogenation or by the action of alkali on butanol-1 (Guerbet).

An interesting series of 22 of the octyl alcohols related to *n*-octane and the three methylheptanes has been made and studied (Reid, Stewart 1932).

The dehydration of some of the octyl alcohols throws further light on the peculiar reactions of the neopentyl alcohol grouping (p. 128). *Isopropyl-ter-butylcarbinol,* $(CH_3)_2CHCHOHC(CH_3)_3$, containing a tertiary hydrogen next to the carbinol group would be expected to give the olefin, $Me_2C=CHCMe_3$. Only 2% of this is obtained. The other products are the result of rearrangements, 18% 2,4,4-$Me_3$-pentene-1, 35% 2,3,4-$Me_3$-pentene-1, and 40% 2,3,4-$Me_3$-pentene-2.

The two simplest *tertiary* alcohols containing the neopentyl alcohol system which could lose $H_2O$ *either* with or without rearrangement are *methylethyl-ter-butylcarbinol* and *dimethyl-ter-amylcarbinol.* These dehydrate almost normally giving not over 20% of rearranged products (Whitmore 1932).

## Higher Alcohols

Many higher alcohols have been made by the methods outlined above.

An unusual preparation of complex tertiary alcohols was developed by Grignard himself (1904) by passing $CO_2$ in one RMgX solution, boiling out the excess $CO_2$ and then adding 2 mols of R′MgX thus obtaining $RR'_2COH$. In this way he made *diethylisoamylcarbinol* and *isobutyldiisoamylcarbinol.*

**Lauryl alcohol,** dodecanol-1, $CH_3(CH_2)_{10}CH_2OH$, has long been available by the Na and absolute alcohol reduction of ethyl laurate prepared from cocoanut oil. With the development of the catalytic hydrogenation of esters, $RCO_2Et$, to primary alcohols, $RCH_2OH$ (p. 345) lauryl alcohol has become commercially important. Mixed with lower and higher alcohols it is sold as Lorol. When treated with sulfuric acid and converted to the sodium salt this mixture forms an important detergent with many properties superior to those of ordinary soap (Gardinol, S.L.S. Dreft etc.). They can be used in slightly acid solutions which would precipitate the fatty acids from ordinary soaps and in salt water and hard waters. The relation to ordinary soaps is shown by the formulas, $CH_3(CH_2)_nCH_2OSO_3Na$ and $CH_3(CH_2)_mCO_2Na$ in which $n$ and $m$ are 10 or more. Pure sodium lauryl sulfate is not as useful a detergent as a mixture with its higher homologs. These are obtainable from oleic and stearic esters as well as from the mixture of esters obtainable from higher acids produced by oxidation of petroleum fractions. Cetyl sodium sulfate is Avirol.

A notable preparation of an alcohol from the next higher acid is illustrated by the formation of *pentadecanol-1* from silver palmitate and $I_2$ (Simonini 1893).

$$2\,C_{15}H_{31}CO_2Ag + I_2 \rightarrow 2\,AgI + CO_2 + C_{15}H_{31}CO_2C_{15}H_{31}$$

Saponification of the resulting ester gives the desired alcohol.

*Waxes* contain higher alcohols in the form of esters. *Cetyl alcohol* (ethal) hexadecanol-1, $C_{16}H_{33}OH$, m. 49°, was obtained by Chevreul from spermaceti (cetyl palmitate) over a century ago (Youtz 1925). It is now more cheaply prepared from ethyl palmitate by hydrogenation. *Carnaubyl alcohol*, $C_{24}H_{49}OH$, m. 69°, occurs as esters in wool grease. *Ceryl alcohol*, $C_{26}H_{53}OH$, m. 79°, occurs as ceryl cerotate in chinese wax. *Montanyl alcohol*, $C_{28}H_{57}OH$ in montan wax and in cotton. *Ginnol*, nonacosanol-10 ($C_{29}$). *Melissyl* or *myricyl alcohol*, $C_{30}H_{61}OH$ or $C_{31}H_{63}OH$, m. 85°, occurs as esters in beeswax and Carnauba wax. An isomer *gossypyl alcohol* and its $C_{32}$ and $C_{34}$ homologs are found in the wax of American cotton (Rep. 1925, 69). *Lacceryl alcohol*, $C_{32}H_{65}OH$. *Psyllastearyl* or *psyllicyl alcohol*, $C_{33}H_{67}OH$, m. 79°.

### Identification of Alcohols

Several series of crystalline derivatives of the alcohols have been studied. The commonest consists of the *3,5-dinitrobenzoates* obtained from the acid chloride and the alcohol alone or in the presence of pyridine. Solid aryl urethanes are obtained by the action of phenyl isocyanate, $\alpha$-naphthylisocyanate, *p*-nitrophenylisocyanate, or 4-diphenylisocyanate. The alcohol used must be anhydrous since water changes the isocyanate to the corresponding diarylurea. Similarly most tertiary alcohols cannot be identified by this method because they lose a molecule of water so easily.

$$ArNCO + ROH \rightarrow ArNHCO_2R$$
$$2\,ArNCO + H_2O \rightarrow (ArNH)_2CO$$

Some higher tertiary alcohols form phenyl urethanes. For example 3-Et-octadecanol-3, from Et palmitate and EtMgBr, reacts with phenyl isocyanate to give both a phenyl urethane, m. 55°, and diphenylurea.

Alcohols which can be converted to alkyl halides without rearrangement can be identified by means of the latter (p. 84).

A special method for identifying primary and secondary alcohols is to make their esters with pyruvic acid, $CH_3COCO_2H$,

and convert these to semicarbazones (Bouveault 1904). Tertiary alcohols are dehydrated by this procedure.

### *B.* Olefinic Alcohols

1. Vinyl alcohol, $CH_2=CHOH$, is known only in the form of derivatives such as its ether, b. 35.5° which may be made from $\beta\beta'$-dichlorodiethyl ether and alkalies.

$$(ClCH_2CH_2)_2O \rightarrow (CH_2=CH)_2O$$

Vinyl sulfide, b. 101°, can similarly be made from mustard gas.

Reactions which would be expected to give vinyl alcohol result in the formation of acetaldehyde

$$CH_2=CHOH \rightarrow CH_3-\overset{H}{\overset{/}{C}}=O$$

This type of change takes place in most cases in which a hydroxyl is attached to an ethylenic or acetylenic carbon. The change is seldom complete, however, a condition of equilibrium being reached

$$\underset{\text{enol form}}{C=C-OH} \rightleftharpoons \underset{\text{keto form}}{CH-C=O}$$

This equilibrium system is very general. It may be expressed in a generalized form

$$M=Q-Z-H \rightleftharpoons MH-Q=Z$$

in which M, Q and Z represent various elements, especially various combinations of C, N, O and S atoms. The commonest of these systems are

$$\underset{\text{Aldehydes, ketones, etc.}}{C=C-OH \rightleftharpoons CH-C=O} \qquad \underset{\text{Thio analogs of aldehydes, etc.}}{C=C-SH \rightleftharpoons CH-C=S}$$

$$\underset{\text{Oximes. In this case the "enol" is the stable form.}}{C=NOH \rightleftharpoons CH-N=O}$$

$$\underset{\text{Cyanic acid derivatives}}{N=C-OH \rightleftharpoons NH-C=O} \qquad \underset{\text{Isothiocyanic acid derivatives}}{N=C-SH \rightleftharpoons NH-C=S}$$

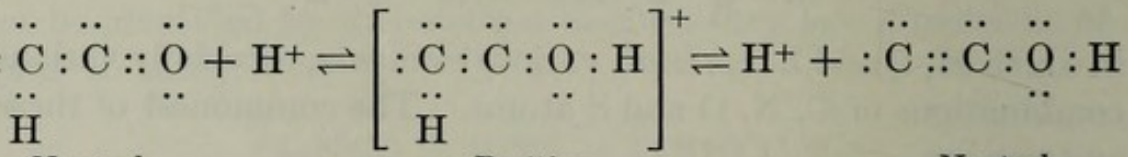
Such equilibria are called tautomeric equilibria and the substances are referred to as tautomers.

Many of the reactions of aldehydes, ketones and acids and their derivatives can best be explained on the basis that the keto system, $CH-C=O$, which they contain is in equilibrium with the enol system, $C=C-OH$.

It was formerly assumed that the change between keto and enol forms involved an actual transfer of H from one part of a given molecule to another part of that molecule. It is now generally recognized that the change is *intermolecular* rather than *intramolecular* and that it usually involves the solvent. The change involves the addition to one part of the molecule of a hydrogen ion from the medium (the solvent or the substance itself) and the loss of a hydrogen ion from another part of the molecule. The changes may take place in the reverse order, hydrogen ion being removed from one part of the molecule and added at another point. In either case the net result is the same as in an actual intramolecular shift of H. The process may be illustrated by acetaldehyde and vinyl alcohol.

$$H^+ + CH_3-CHO \rightleftharpoons [CH_3-CH(OH)]^+ \rightleftharpoons H^+ + CH_2=CH(OH)$$

Regarded electronically, the conversion of a keto to an enol form involves the addition of H to one of the electron pairs of the carbonyl oxygen to form a complex ion which can lose H either from the oxygen or from the alpha carbon. In the latter case, the enol results. The changes are reversible.

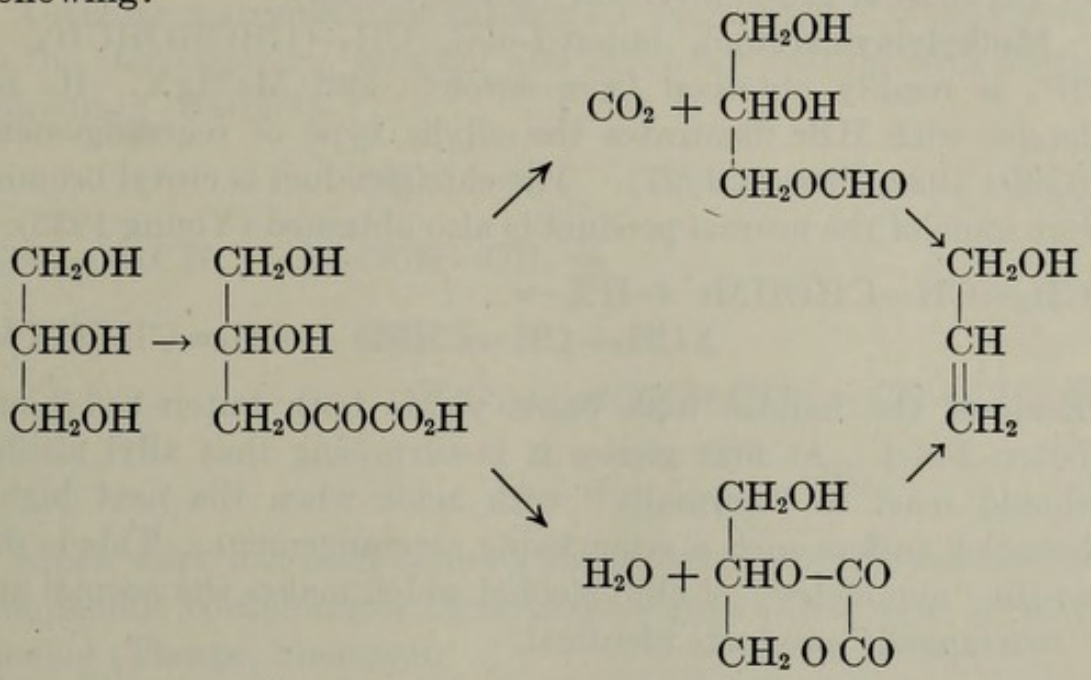


Neutral keto form. Positive complex ion. Neutral enol form.

**Propenol-1,** $CH_3CH=CHOH$, and propenol-2, $CH_3COH=CH_2$, are merely the enol forms of propionaldehyde and acetone respectively, and are not capable of independent existence. There is good evidence, however, that these forms exist in equilibria with the ordinary $CH=CO$ forms.

**Allyl alcohol,** propenol-3, vinyl carbinol, $CH_2=CH-CH_2OH$, b. 97°, is prepared by heating glycerol with formic or oxalic acid

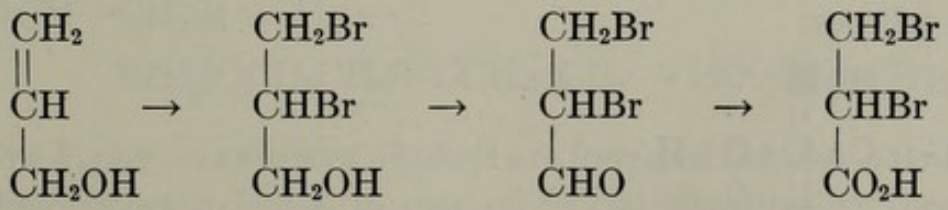
and a trace of ammonium chloride to 220°. The steps are the following:




It gives the reactions of a primary alcohol except that there is no tendency for dehydration. It gives the ordinary addition reactions of an olefin and also adds $KHSO_3$ when refluxed with a concentrated solution of that substance.

$$CH_2{=}CHCH_2OH + KHSO_3 \rightarrow CH_3{-}CH(SO_3K)CH_2OH$$

Oxidation by dilute $KMnO_4$ gives glycerol. In order to oxidize the alcohol group alone, the ethylenic linkage must be "protected." This is done by adding bromine, which can later be removed by means of zinc.




By removing bromine from the last two products, acrolein, $CH_2{=}CHCHO$, and acrylic acid, $CH_2{=}CHCO_2H$ would be obtained.

**Hypohalous acids** add to allyl alcohol contrary to Markownikoff's Rule to give beta glycerol halohydrins,

$$HOCH_2CHXCH_2OH$$

Addition takes place more rapidly from aqueous solutions of $Cl_2$ or $Br_2$ than of HOCl or HOBr (Hibbert 1931).

**Methylvinylcarbinol,** buten-1-ol-3, $CH_2=CHCHOHCH_3$, b. 97°, is readily obtained from acrolein and MeMgX. Its behavior with HBr illustrates the allylic type of rearrangement. (Gillet 1922, Prevost 1927). The chief product is crotyl bromide but some of the normal product is also obtained (Young 1935).

$$CH_2=CH-CHOHMe + HX \rightarrow XCH_2-CH=CHMe + CH_2=CHCHXMe$$

Each of the halides with bases yields both buten-1-ol-3 and buten-2-ol-1. At first glance it is surprising that allyl alcohol should react so "normally" with acids when the next higher homolog suffers such a remarkable rearrangement. This is due to the "symmetry" of allyl alcohol which makes the normal and "rearranged" products identical.

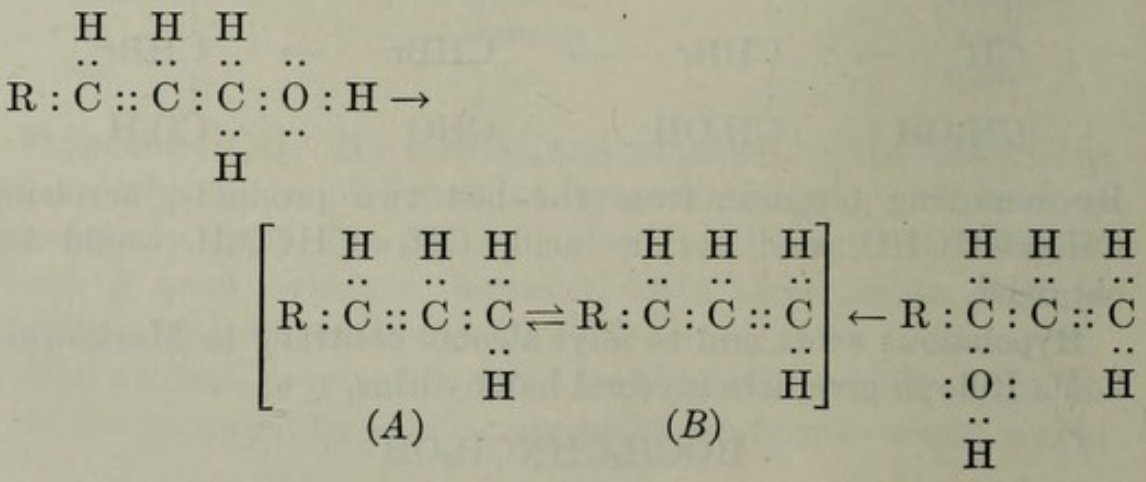
$$CH_2=CH-CH_2OH \rightarrow CH_2=CH-CH_2X + XCH_2-CH=CH_2$$

**Crotyl alcohol,** crotonyl alcohol, propenylcarbinol, buten-2-ol-1, $CH_3CH=CHCH_2OH$, b. 121°, is difficultly obtainable from crotonaldehyde by ordinary methods. Reduction by Al isopropoxide gives a 60% yield (Young 1935).

$$3\ RCHO + Al(OCHMe_2)_3 \rightarrow (RCH_2O)_3Al + 3\ Me_2CO$$

Crotyl alcohol with HBr gives crotyl bromide and the rearranged methylvinylcarbinyl bromide.

An electronic picture of the *three carbon* or *allylic rearrangement* is as follows:



The bromide ion attaches itself to the electronically deficient carbon in (*A*) or (*B*).

A similar rearrangement takes place when linalool is converted to the stereoisomers, geraniol and nerol, by heating with acetic anhydride (Barbier)

$$(CH_3)_2C{=}CHCH_2CH_2\overset{\displaystyle OH}{\overset{|}{\underset{\displaystyle CH_3}{\underset{|}{C}}}}CH{=}CH_2 \rightarrow$$

$$(CH_3)_2C{=}CHCH_2CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH{-}CH_2OH$$

Much work has been done on the glutaconic acids and similar compounds containing a three carbon system like that in allyl alcohol (Thorpe, Shoppee).

**Allylcarbinol,** buten-1-ol-4, $CH_2{=}CHCH_2CH_2OH$, b. 114°, has been made by heating $NH_2(CH_2)_4NH_2$ with $AgNO_2$ and HCl.

Unsaturated esters other than $\alpha\beta$ can be reduced by Na and EtOH to unsaturated primary alcohols without reducing the double bond. Thus *oleyl alcohol,* octadecen-9-ol-1, is available from oleic esters.

**Penten-1-ol-5,** $CH_2{=}CH(CH_2)_3OH$, is obtained by a peculiar reaction of Mg with tetrahydrofurfuryl bromide (Robinson 1936)

$$\begin{array}{l} CH_2{-}CH_2 \\ |\quad\ \ | \\ CH_2OCH{-}CH_2Br + Mg \rightarrow \end{array}$$

$$BrMgOCH_2CH_2CH_2CH{=}CH_2 \rightarrow HO(CH_2)_3CH{=}CH_2$$

A few *higher unsaturated alcohols* are found in nature: *citronellol,* 2,6-dimethylocten-1-ol-8, in rose oil as the levorotatory form, in oil of citronella as the dextrorotatory form, and in geranium oil in both forms; its isomer rhodinol, 2,6-dimethylocten-2-ol-8; phytol, 3,7,11,15-tetramethylhexadecen-2-ol-1, a constituent of chlorophyll (Willstaetter).

### *C.* Acetylenic Alcohols

The simplest possible member would be *ethynol* (ethinol), $HC{\equiv}C{-}OH$. This exists only in the tautomeric form, $H_2C{=}C{=}O$, ketene.

**Propargyl alcohol,** propiolic alcohol, propynol, $HC{\equiv}CCH_2OH$, b. 115°, can be made from glycerol tribromohydrin by treatment with alcoholic KOH, hydrolyzing with water and further treatment with alcoholic KOH.

$$BrCH_2CHBrCH_2Br \rightarrow CH_2{=}CBrCH_2Br \rightarrow CH_2{=}CBrCH_2OH \rightarrow CH{\equiv}CCH_2OH$$

The product from the first step is easily isolated. One Br is inactive and the other unusually active being an "allyl" halogen. The removal of the last Br to give the triple bond is the most difficult step. The effect of unsaturation on physical properties is seen in the series propyl, allyl and propargyl alcohols, with m. −127°, −129°, −17°; b. 97°, 97°, 115°, and d. about 0.80, 0.85, 0.97. The effect of the triple bond is much more marked than that of the double bond. Propargyl alcohol shows the group reactions typical of a primary alcohol group and of a terminal acetylene linkage. Thus HBr gives Br-allyl alcohol, $PBr_3$ gives propargyl bromide, and ammoniacal Ag and cuprous solutions give characteristic precipitates.

**Higher acetylenic alcohols** may be made by the action of acetylenic Grignard reagents, $HC{\equiv}CMgX$ and $RC{\equiv}CMgX$ or the corresponding sodium derivatives with aldehydes and ketones. Another general method is the action of the sodium derivative of the enol form of a ketone (formed by sodamide, $NaNH_2$) with acetylene. Thus

$$\begin{array}{ccccc} CH_3 & & CH_3 & & CH_3 \\ | & & | & & \diagdown \\ CO & \rightarrow & C{-}ONa & \rightarrow & HC{\equiv}C{-}C{-}OH \\ | & & \| & & \diagup \\ CH_3 & & CH_2 & & CH_3 \end{array}$$

An example of the practical utilization of this process is the conversion of 2-methylhepten-2-one-6 ("methylheptenone" from citral) into 3,7-dimethyloctyn-1-en-6-ol-3 which is then partially

hydrogenated to the perfume material linalool, 3,7-dimethyl-octadien-1,6-ol-3.

## IV. ETHERS, R—O—R, R—O—R′

These are the oxides of the alkyl groups, $C_nH_{2n+1}$. The absence of the H attached to oxygen makes them much less reactive than the corresponding alcohols. They are, however, much more reactive than the corresponding hydrocarbons. They range from b. −25° to high boiling liquids and finally solids. The ethers differ from the alcohols and water in not having associated molecules. Thus the boiling points are much lower than those of the related alcohols and near to those of the hydrocarbons of the same number of atoms in a chain. Thus: propane, −45°; $CH_3OCH_3$, −24.5°; $CH_3OH$, 66°; *n*-pentane, 36°, EtOEt, 35°.

1. **Methyl ether,** dimethyl ether, $CH_3OCH_3$, b. − 24.5° can be prepared from methanol and concentrated sulfuric acid. The reaction takes place in definite steps:

(*a*) cold $\quad MeOH + H_2SO_4 \rightarrow MeOSO_3H + H_2O$
(*b*) hot $\quad MeOH + MeOSO_3H \rightarrow Me_2O + H_2SO_4$

An alternative or supplementary mechanism for the formation of ethers from alcohols and sulfuric acid involves the addition of alcohol to sulfuric acid in the same way water adds to it. (Oddo 1901). Just as $H_2SO_4$ can add 2 $H_2O$ to give the unstable ortho acid $S(OH)_6$ it can add 2 ROH to give $(RO)_2S(OH)_4$ which could lose $R_2O$ and $H_2O$ leaving sulfuric acid to start the cycle again. The action of sulfuric acid is a general method for making ethers. With higher alcohols, especially those with branched chains, the tendency to form olefins even at moderate temperatures increases greatly. This can be diminished by operating at 140–145° under pressure (Oddo).

If one alcohol is treated with sulfuric acid to make the acid ester and then a different alcohol is added during the heating, a *mixed ether*, ROR′, is obtained.

Methyl ether as now commercially available is obtained from methanol catalytically (DuPont). It is also a by-product of the preparation of dimethylaniline from aniline, MeOH and HCl.

Another method of preparation is from sodium methylate and methyl halide, preferably the iodide (Williamson 1852). In the case of the methyl compounds this reaction gives an excellent yield. With higher halides there is increasing tendency to form olefins. The Williamson preparation of simple and mixed ethers is the best proof of their structure.

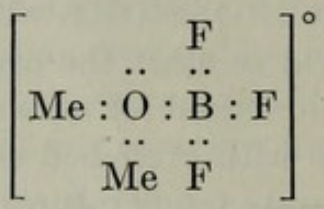
Methyl ether is soluble 600 : 1 (by volume) in conc. sulfuric acid. Its vapor pressure at 20° is 5 atm.

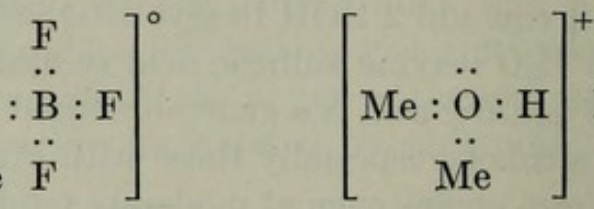
As a refrigerant, it is unique in that it can be allowed to come in direct contact with foodstuffs during "quick freezing" without giving any foreign taste or odor. The advantage of quick freezing is that the crystals of water formed are so small that they do not rupture the cell walls and thus alter the characteristics of the food.

Because of its remarkable properties as a solvent and because it can be handled as readily as $NH_3$ and $SO_2$ in the liquid state, methyl ether is likely to find many uses.

Dimethyl ether, like its homologs, forms complex compounds with many types of substances. $Me_2O.C_2H_2$, $Me_2O.NH_3$, $Me_2O.AlCl_3$, $Me_2O.2\,AlCl_3$, $Me_2O.CaCl_2$, $Me_2O.HCl$, (Friedel 1875), $Me_2O.4\,HCl$ etc. Many of these are known to be oxonium compounds.

Of the same nature as the oxonium compounds but characterized by greater stability is the coordination compound $Me_2O.BF_3$, b. 128°.





In case of an over-production of by-product methyl ether, it can be converted smoothly to methanol by water and catalysts at 400°.

Methyl ethyl ether, b. 10.8°, is readily made from MeI and NaOEt or from EtI and NaOMe. If needed commercially it could readily be made from the two alcohols.

2. **Ethyl ether,** "ether," "sulfuric ether," $C_2H_5OC_2H_5$, b. 34.5°, is made from ethanol and sulfuric acid at 130–140°. The

process is not perfectly continuous because (1) most of the water formed remains in the acid and dilutes it and (2) much of the ethanol is dehydrated to give ethylene which partly polymerizes to give materials capable of reacting with the sulfuric acid and reducing it to sulfur dioxide. Other by-products such as isethionic acid, $HOCH_2CH_2SO_3H$, are also formed. Ethyl ether is now available as a by-product of the preparation of ethanol by hydrating ethylene with sulfuric acid. This source of ether makes it independent of fluctuations in the price of ethanol (C and C). The preparation of ethyl ether from ethylene was attempted as long ago as 1900 in an effort to avoid the use of taxed ethanol. The direct catalytic hydration of ethylene to ether has never been mastered.

A modification of the sulfuric acid preparation is to heat ethanol with an aromatic sulfonic acid, always keeping an excess of alcohol present. The process is much like that using sulfuric acid except that a higher temperature can be used without reducing the acid. The cheapest sulfonic acid is paratoluene sulfonic acid (from saccharin manufacture).

$$ArSO_3H + EtOH \rightarrow ArSO_3Et + H_2O$$
$$ArSO_3Et + EtOH \rightarrow Et_2O + ArSO_3H$$

Ethyl ether is obtained in good yield when ethanol is passed over alumina at 250–300° (Senderens). A trace of a heavy metal salt like ferric chloride catalyzes ether formation (Oddo).

Ethyl ether has been made by Williamson's method (80% yield from EtI + EtONa). The formation of ethyl ether from $Ag_2O$ and EtI is additional evidence of its structure.

Ethyl ether is a typical ether in its reactions.

1. It dissolves in concentrated $H_2SO_4$. At higher temperatures it reacts.

$$Et_2O + H_2SO_4 \rightarrow EtOSO_3H + EtOH$$

2. Concentrated HI solution splits it even at room temperature.

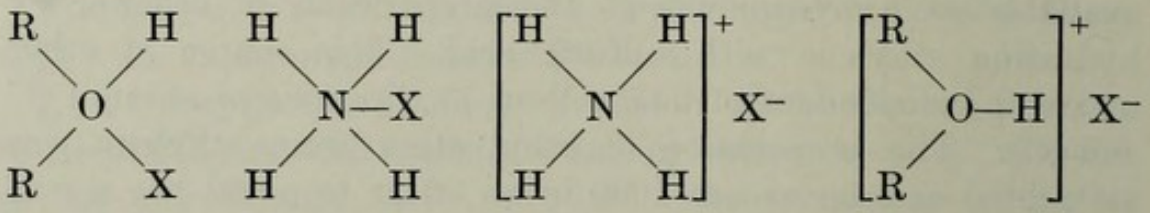
$$Et_2O + HI \rightarrow EtI + EtOH$$

Hydrobromic acid produces a similar change but less readily.

3. With sodium it does not react at its boiling point. This gives the best way of removing the last traces of water and alcohol

from ether for use in making Grignard reagents. The assumption that *higher ethers* will not react with Na is erroneous. On heating they react to give alcoholates, olefins and $H_2$.

4. It forms "oxonium salts" with halide acids, $R_2O.HX$. These compounds may be represented as having tetravalent oxygen,



In many ways these resemble ammonium salts which were formerly represented as $NH_3.HX$. Just as these are related to the unstable radical, $NH_4$, the oxonium salts are related to an even less stable oxonium ion $[H_3O]^+$ (Baeyer, Villiger). The oxonium salts are completely ionized (Oddo 1910).

5. Ether reacts slowly with oxygen to give complex "peroxide" compounds and aldehydes. Ether thus contaminated is dangerous in anesthetic use. Evaporation of "old" ether sometimes leaves dangerous amounts of this highly explosive material. Ether has been successfully preserved by storage with asbestos impregnated with alkali and either pyrogallol or permanganate (Palkin 1929).

6. Acid iodides split ethers (Gustus 1933).

$$Et_2O + MeCOI \rightarrow EtI + MeCO_2Et$$

Acid chlorides and acid anhydrides in the presence of anhydrous $ZnCl_2$ give a similar splitting (Meerwein).

7. Phosphorus pentachloride reacts with ethers but, contrary to the ordinary conception, gives complex chlorinated products instead of simple alkyl chlorides (Whitmore 1933).

8. Chlorine and bromine react with ethers much as with paraffin hydrocarbons. The first H atom replaced is one on the C attached to O. Then those of the next carbon are attacked (Oddo). Finally perchloroether, $(C_2Cl_5)_2O$, is obtained as a solid with an odor like camphor. At low temperatures ether combines with bromine to give the compound, $Et_2O.Br_2$, m. 24°. At higher temperatures this loses bromine with bromination of the ether.

Since ether is largely used because of its chemical inertness, it is useful to remember that it does not react under ordinary conditions with metals, Grignard reagents, acid chlorides, organic acids, phosphorus trihalides, permanganates and bases.

The most important use of ether is as the commonest general anesthetic. This property was probably first observed by Faraday. The actual use as an anesthetic was made independently by Drs. Long, Morton, and Simpson of Georgia, Boston, and Edinburgh in 1842, 1846 and 1848 respectively.

Ether is a very important general solvent in organic chemistry because it is only slightly soluble in water (7%) and dissolves a great variety of materials which are also soluble in water. It is thus used for extracting many materials from their dilute solutions in water (Soxhlet, etc.). It is used for extracting acetic acid from pyroligneous acid (Suida Process).

U.S.P. Ether contains about 4% ethanol and traces of water. Absolute, anhydrous, or "dry" ether can be made from it by removing the alcohol with solid $CaCl_2$, decanting and distilling from $P_2O_5$ or Na. The product is satisfactory for making Grignard reagents. Final traces of water and alcohol can be removed by refluxing with a small amount of a cheap Grignard reagent such as MeMgCl or EtMgBr and distilling the ether.

Methyl *n*-propyl ether, b. 39°; ethyl *n*-propyl ether, b. 64°; and ethyl isopropyl ether, b. 54° have been made in the usual way.

3. (*a*) ***n*-Propyl Ether,** $C_3H_7OC_3H_7$, b. 90.4°, is made by the same reactions as ethyl ether. The tendency for olefin formation is greater both by the acid and the Williamson methods. Its reactions are like those of ethyl ether.

(*b*) **Isopropyl Ether,** $(CH_3)_2CHOCH(CH_3)_2$, b. 69°, is available as a by-product of the hydration of propylene to isopropyl alcohol (C and C). Its higher boiling point and its even lower mutual solutility with water gives it advantages over ethyl ether as an extracting agent. It is specially useful in extracting acetic and lactic acids from their dilute water solutions. Since it is actually cheaper than ethyl ether it will undoubtedly find wide uses as a solvent and extractant. It is apparently less useful in the Grignard reaction than ethyl ether and the higher normal ethers.

Isopropyl ether is used in high anti-knock fuels for airplanes.

4. Higher ethers can be obtained by the regular methods, the amount of olefin increasing with the size and branching of the alcohols or halides used. *n*-Butyl ether, b. 178°, is valuable as a high boiling ether for the Grignard reagent. It can be made by the action of 50% sulfuric acid with butanol-1. Mixed amyl ethers, b. 170–190°, are available as a by-product of the preparation of amyl alcohols from pentanes (Sharples). Mixed higher ethers containing the *t*-butyl group and a Me, Et, *n*-Pr, *n*-Bu or isopropyl have been made by heating the mixtures of alcohols with a 15% solution of sulfuric acid or $NaHSO_4$. In this process there is little or no tendency to form the simple ethers. To prepare ethers containing primary and secondary alkyl groups it is necessary to use 50% acid. All three possible ethers were formed in each case, the mixed ethers predominating (Norris 1932). This preparation of ethers is all the more important because of the good yields obtained. Thus ethyl *t*-butyl ether, b. 73°, was made in 95% yield and isopropyl *t*-butyl ether, b. 87°, in 82%.

Mixed primary-tertiary and secondary-tertiary ethers are obtained by adding primary or secondary alcohols to olefins related to tertiary alcohols, in presence of catalysts, usually acidic in nature (Edlund 1934). Thus methanol and isopropyl alcohol with isobutylene give respectively $MeOCMe_3$ and $Me_2CHOCMe_3$.

As would be expected, ethers containing tertiary groups are readily split by acids like HCl to give a tertiary chloride and the alcohol corresponding to the other radical.

**Higher ethers** can be made by the action of the Grignard reagent with an alpha chloro or bromomethyl ether (Hamonet 1904) obtained from formaldehyde, an alcohol and HX (Henry).

$$ROH + CH_2O + HX \rightarrow ROCH_2X + H_2O$$
$$ROCH_2X + R'MgX \rightarrow ROCH_2R'$$

Beta halogenated ethers are less active but can be caused to react with Grignard reagents by using a higher temperature made possible by the use of a higher ether such as *n*-butyl ether. Thus $\beta\beta'$-dichloroethyl ether, $(ClCH_2CH_2)_2O$, gives $(RCH_2CH_2)_2O$.

Trimethylethylene with methanol and sulfuric acid gives a methyl amyl ether (Reychler 1907).

The higher ethers, because of their higher boiling points, are more easily caused to react than the more volatile lower members. Thus refluxing amyl ether with phosphoric anhydride gives amylene and with sodium gives sodium amylate and amylene.

Higher ethers also react with Na on heating.

$$2\ RCH_2CH_2OR' + 2\ Na \rightarrow 2\ R'ONa + 2\ RCH{=}CH_2 + H_2$$

Alkyl derivatives of hydrogen peroxide such as EtOOH, liquid, and EtOOEt, b. 65°, are known. They are strong oxidizing agents and are explosive.

## V. ALIPHATIC SULFUR COMPOUNDS

Almost all organic compounds on heating with sulfur give $H_2S$ and substitution products containing sulfur. Usually these are of unknown complexity.

While some of the simpler sulfur compounds resemble the corresponding oxygen compounds in their formulas they differ in many ways:

1. The sulfur atom can be oxidized (can give electrons) whereas the oxygen atom cannot. This ability makes possible compounds such as the sulfoxides, sulfones, sulfonic acids and sulfinic acids, $R_2SO$, $R_2SO_2$, $RSO_3H$ and $RSO_2H$ respectively.

2. The $-S-S-$ linkage is stable whereas the $-O-O-$ linkage is very unstable.

3. The -onium compounds of sulfur are very stable whereas those of oxygen are unstable.

Considerable amounts of aliphatic sulfur compounds occur in many crude petroleums. The removal of such compounds from petroleum products is troublesome and expensive. It is stated that the danger of corrosion from small amounts of sulfur compounds is greatly exaggerated (Egloff 1930).

Organic sulfur compounds, under hydrogenation conditions, give up all their sulfur as $H_2S$ which can readily be separated. The older catalytic processes were stopped by sulfur compounds

but the modern sulfide catalysts used in the hydrogenation of petroleum and coal are not poisoned in this way (Haslam). This conversion of complex organic sulfur compounds to $H_2S$ represents one of the chief advantages of hydrogenation as a method of refining.

*Mercaptans*, thioalcohols, alkan-thiols, RSH, resemble alcohols only as to formulas. The lower members have remarkably disagreeable odors. Ethyl mercaptan can be detected by smell in as small an amount as $2 \times 10^{-12}$ gram (E. Fischer 1887). This is less than 1/200 of the smallest amount of Na detectable with the spectroscope. The offensive odor decreases with the homologs until the $C_9$ member has a pleasant odor (Reid). The lower mercaptans boil lower than the corresponding alcohols just as $H_2S$ boils lower than $H_2O$. This difference steadily decreases. For the first six normal members the *differences* (°C) between the boiling points of the alcohols and mercaptans are 58, 41, 30, 20, 12, and 7. The higher mercaptans ($C_7$ etc.) boil at almost the same point as the alcohols. With these substances association has largely disappeared. The mercaptans are insoluble in water but soluble in alcohols and ethers. The reactions of the mercaptans and alcohols differ profoundly. The reactions of the mercaptans can be generalized more safely than those of the alcohols largely because the C—S linkage is not broken as is the C—O linkage in most reactions. Even the preparation of mercaptans from alkyl halides apparently involves less rearrangement than does that of the alcohols. This may well be due to the ability of sulfur to *add* alkyl halides as in the formation of sulfonium halides.

*Preparation of Mercaptans.*

1. By passage of an alcohol and $H_2S$ over hot thorium oxide. This method was used during the World War to make *n*-BuSH, the odor of which resembles that of *Mephitis mephitica.*

2. By heating NaSH solution (NaOH saturated with $H_2S$) with a solution of a salt of an alkyl sulfuric acid (a solution of an alcohol in sulfuric acid, diluted and exactly neutralized with a base).

$$NaSH + RNaSO_4 \rightarrow RSH + Na_2SO_4$$

3. By treatment of an alkyl halide with concentrated KSH solution. This has the disadvantages of the insolubility of the alkyl halide and the basic nature of the reagent which tends to remove HX from some halides. This reaction has not been studied with all types of alkyl halides (p. 71–4).

4. In special cases by treatment of a Grignard reagent with sulfur (Rep. 1905, 105).

$$RMgX \rightarrow RSMgX \rightarrow RSH$$

In this way neopentyl mercaptan, $Me_3CCH_2SH$, and related compounds have been made available whereas the ordinary methods fail.

*Reactions of Mercaptans.* The stability of the C—S linkage is much like that of the C—N linkage thus differing very much from the C—O linkage.

1. Mercaptans form metal derivatives, mercaptides or thiolates, much more readily than alcohols form alcoholates. Thus they are soluble in base solutions and react with HgO to give RSNa, $(RS)_2Hg$, etc. They also form mixed compounds like RSHgCl, valuable for identification purposes because of their crystalline character and high melting points, and RSHgR′ of value therapeutically when one of the R groups contains a solubilizing group (Kharasch).

Mercaptans in gasoline are removed by sodium plumbite solution (lead salt with excess of NaOH). This precipitates the lead mercaptides, $(RS)_2Pb$ (Bergstrom 1929). Some stay in solution as RSPbONa, etc. Treatment with lead plumbite solution ("Doctor solution") is known as "sweetening." With higher mercaptans the mercaptides may be soluble in the hydrocarbons.

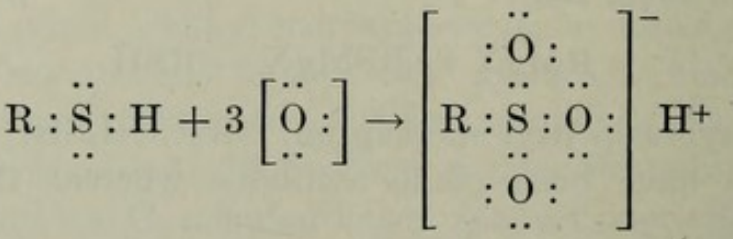
2. Gentle oxidation merely removes the hydrogen from the —SH group giving a disulfide

$$2RSH + [O] \rightarrow H_2O + RS{-}SR$$

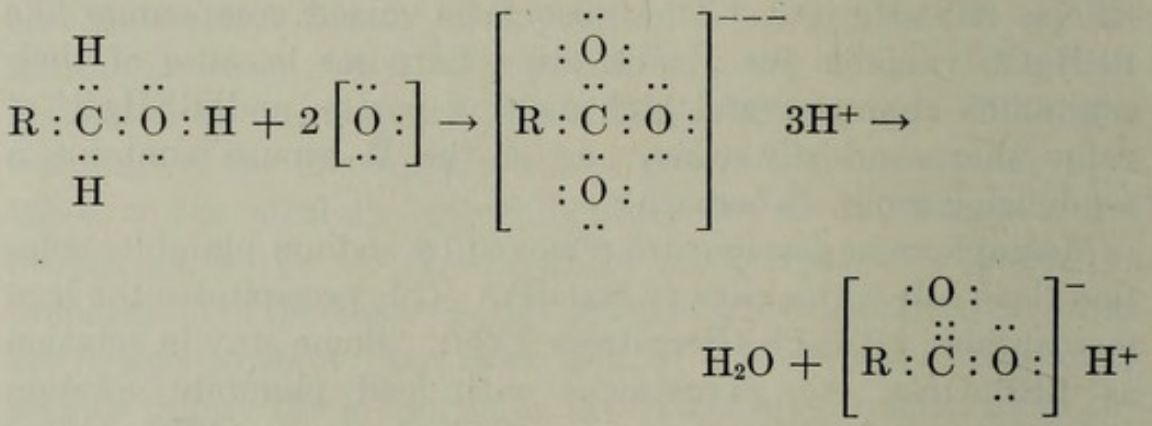
This process takes place even more easily with the soluble mercaptides. Thus a mercaptan in presence of ammonia solution is oxidized by air to a disulfide. The process is easily reversed by reducing agents. The oxidation-reduction system represented by the mercaptans and their disulfides is of great

biological importance in the action of substances like cystine and glutathione.

3. Vigorous oxidation converts the $-SH$ group to the *sulfonic acid* group $-SO_3H$. The intermediate *sulfinic acid*, $RSO_2H$, cannot be isolated because of its ease of oxidation. Omitting the intermediate steps, the oxidation may be represented as follows:



Any representation of double bonds between sulfur and oxygen as ordinarily given in the "structure" formulas of sulfuric acid and sulfonic acids is contrary to fact (Lewis 1916, Sidgwick 286). The difference between this type of oxidation and that of the oxidation of an alcohol may be emphasized as follows:



This illustrates important differences between sulfur and oxygen and sulfur and carbon.

*a*. The difference between the small kernel of oxygen which can only take electrons and the larger one of sulfur which can also give electrons.

*b*. The difference between sulfur with six valence electrons and carbon with four.

*c*. The difference between the small kernel of carbon and the large one of sulfur in that the former cannot have a stable "orthocarbonic" *ion*, $RCO_3^{---}$.

4. Just as alcohols react with carbonyl compounds to give hemiacetals, acetals and esters, mercaptans give similar reactions but with greater ease. Whereas alcohols give acetals with aldehydes but do not react with unsubstituted ketones, mercaptans give *mercaptals* with aldehydes and *mercaptols* with ketones in presence of HCl.

$$=C=O \qquad =C(OH)SR \qquad =C(SR)_2$$

The RS− groups are readily removed by treatment with mercuric compounds and water. $=C(SR)_2+HgO\rightarrow=C=O+(RS)_2Hg$. This gives a method of "protecting" the aldehyde group while other groups in the molecule are being studied.

With carboxylic acids, the mercaptans give monothioesters and water. The mechanism is probably like that of esterification with an alcohol.

$$RC(=O)OH + R'SH \leftrightarrows RC(SR')(OH)OH \rightleftharpoons H_2O + RC(=O)SR'$$

The R−S linkage is not broken in the process. This agrees with the conclusion that the *R−O linkage in alcohols is not broken during esterification with carboxylic acids* (p. 128).

Mercaptans do not react with halide acids as do alcohols. Thus the most prolific source of rearrangements in alcohols is lacking with the mercaptans just as it is with the amines.

5. Mercaptans add to $\alpha\beta$-unsaturated ketones and related compounds (Rep. 1905, 115).

$$RCH=CHCOR' \rightarrow RCH(SR'')CH_2COR'$$

*Mercaptans can be identified* by the mixed sulfides formed by the action of their sodium compounds with the active chlorine atom in 2,4-dinitrochlorobenzene (Bost 1932). The melting points for the compounds $R-S-C_6H_3(NO_2)_2$ for the first nine normal alkyl groups (°C.) are 128, 115, 81, 66, 80, 74, 82, 78, 86 and cetyl, $C_{16}$, 91. Potassium permanganate in acetic acid

oxidizes these sulfides to sulfones with the following melting points for $C_1$ to $C_9$, 189, 160, 127, 92, 83, 97, 101, 98, 92.

**Methyl mercaptan,** methanthiol, $CH_3SH$, b. 7.6°, is formed by the decay and hydrolysis of various proteins. Presumably its source is methionine, $MeSCH_2CH_2CH(NH_2)CO_2H$, or related compounds.

**Ethyl mercaptan,** ethanthiol, $CH_3CH_2SH$, b. 37°, is made commercially from $NaEtSO_4$ for the preparation of the soporifics *Sulfonal* and *Trional.* $EtSH.18H_2O$, crystals below 8°; $(EtS)_2Hg$, m. 76°; $(EtS)_2Pb$, m. 150°; BuSH, b. 97°.

1- and 2- mercaptans through $C_9$ have been made and their properties studied in detail (Ellis 1932).

Higher mercaptans to $C_{18}$ have been prepared (Collin 1933).

Mercaptans, Malisoff, Rev. 1930, 493–547.

**Alkyl sulfides,** thioethers, $R_2S$, are prepared by alkali sulfides with alkyl halides or alkyl sodium sulfates. Mixed alkyl sulfides can be made from alkyl iodides and mercaptides, $RSNa + R'I \rightarrow NaI + RSR'$. Grignard reagents treated with one atomic equivalent of sulfur and then with $R'X$ give alkyl sulfides. $RMgX \rightarrow RSMgX \rightarrow RSR'$ (Rep. 1905, 105). The alkyl sulfides are pleasant smelling (when pure) and are insoluble in water. They boil higher than the corresponding mercaptans and ethers. The effect of $-S-$ is about equal to that of $-CH_2OCH_2-$. Thus the boiling points of the following pairs (°C.) are: $Me_2S$, $Et_2O$, 38, 35, and $Et_2S$, $Pr_2O$, 92, 91 (Reid).

The alkyl sulfides form addition products with a great variety of substances including mercuric salts, halogens, and alkyl halides to form $R_2S.HgX_2$, $R_2S.X_2$, and $R_3SX$. The first two are not molecular compounds in any indefinite sense but are sulfonium compounds.

$$\left[\begin{array}{c} R \\ \vdots \\ R:S:Hg \\ \vdots \end{array}\right]^{++} X_2^{--} \qquad \left[\begin{array}{c} R \quad \vdots \\ \vdots \\ R:S:X: \\ \vdots \quad \vdots \end{array}\right]^{+} X^- \qquad \left[\begin{array}{c} R \\ \vdots \\ R:S:R \\ \vdots \end{array}\right]^{+} X^-$$

The second compound is interesting in that one halogen atom is part of the cation and the other forms the anion.

$Me_2S$, b. 38°; $Et_2S$, b. 92°; $Bu_2S$, b. 182°.

Mild oxidation converts the sulfides to sulfoxides, $R_2SO$, and more vigorous oxidation to sulfones, $R_2SO_2$.

The splitting of a C—S linkage is difficult. The sulfides can be split by treatment with cyanogen bromide.

$$RSR' + BrCN \rightarrow RSCN + R'Br$$

In most cases R > R′ (Rep. 1923, 87).

Polymethylene dimercaptans, $HS(CH_2)_nSH$ react with polymethylene bromides, $Br(CH_2)_mBr$ and bases to give polymeric cyclic sulfides in great variety (Reid).

$\beta\beta'$-Dichloroethyl sulfide, Mustard Gas, Yprite, $(ClCH_2CH_2)_2S$, b. 218°, was the most important vesicant developed during the World War (Rep. 1920, 58; 1922, 23). The two methods for its preparation start from ethylene, sodium chloride and sulfur. Thus the folly of any attempted legislation against materials for war "gases" is obvious. In the German method (V. Meyer 1886), ethylene chlorohydrin is treated with $Na_2S$ and the resulting thiodiglycol gives the chloride with HCl. The other method (Guthrie 1860) adds sulfur monochloride, $S_2Cl_2$, to ethylene to give the sulfide and free S which remains in colloidal form.

$$C_2H_4 \rightarrow ClCH_2CH_2OH \rightarrow S(CH_2CH_2OH)_2 \rightarrow S(CH_2CH_2Cl)_2$$
$$C_2H_4 + S_2Cl_2 \rightarrow S + S(CH_2CH_2Cl)_2$$

The vesicant properties depend on the $\beta$-position of the Cl. $ClCH_2CH_2SMe$ has similar properties but $ClCH_2SMe$ does not (Kirner 1928). The best method for rendering mustard gas harmless is by chlorination (Lawson 1927). The potential production of mustard gas in all countries at the time of the Armistice was of the order of 300 tons a day. The more highly developed ethylene industry of the present day stands as a powerful argument for peace.

Mixed tetra-thioethers, $C(CH_2SR)_4$, have been made from the tetra bromide of pentaerythritol and mercaptides from $C_5$ to $C_{12}$ (Backer 1932).

Allyl sulfide, $(CH_2{=}CHCH_2)_2S$, b. 140°, occurs in onions and garlic. It is readily prepared from the allyl halides.

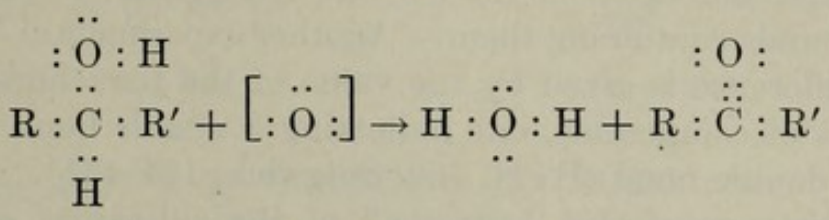
*The sulfonium halides,* trialkyl sulfinium halides, RR′R″SX, are obtained from alkyl halides and dialkyl sulfides. They resemble ammonium and other -onium salts. Heating alkyl iodides with sulfur gives a similar result to that obtained with phosphorus (p. 208) forming periodides $R_3SI_3$ which can easily be reduced to $R_3SI$. Treatment of sulfonium halides with AgOH gives the sulfonium hydroxides, strong soluble bases. Asymmetric sulfonium compounds have been obtained as optically active enantiomers. The sulfonium compounds form stable products with mercuric salts, halogens, etc. The electronic nature of the substances may be closely related to that of the sulfonium salts

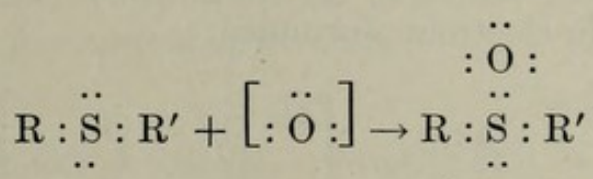
$$\left[\begin{array}{c} R \\ \vdots \\ R:S: \\ \vdots \\ R \end{array}\right]^{+} X^{-} \qquad \left[\begin{array}{c} R \\ \vdots \\ R:S:Hg \\ \vdots \\ R \end{array}\right]^{+++} 3\,X^{-} \qquad \left[\begin{array}{c} R \\ \vdots \quad \vdots \\ R:S:X: \\ \vdots \quad \vdots \\ R \end{array}\right]^{++} 2\,X^{-}$$

**Alkyldisulfides,** RS—SR, may be made by oxidizing the mercaptans cautiously or from alkali disulfides and alkyl sodium sulfates. Reduction gives mercaptans. Mild oxidation converts one sulfur to a sulfone grouping thus giving a thiosulfonic acid ester, $RSO_2SR$, sometimes incorrectly called a *disulfoxide.* After oxidation starts, the monosulfoxide next goes to a monosulfone before the second sulfur is attacked. Vigorous oxidation gives a disulfone, $RSO_2SO_2R$, and finally two molecules of a sulfonic acid, $RSO_3H$. The —S—S— is broken not only by reduction and oxidation but by the action of alkyl iodides which give sulfonium compounds. $Me_2S_2$, b. 112°, $Et_2S_2$, b. 153°.

**Alkyl sulfoxides,** $R_2SO$, are obtained by the action of nitric acid with the sulfides. The first product is a "nitrate," $R_2SO.HNO_3$ which is decomposed by water or mild bases. A better preparation is from the sulfides and an organic peroxide such as benzoyl hydroperoxide, $PhCO_3H$. The lower sulfoxides are liquids which solidify on cooling. They are soluble in water, alcohol and ether. The highers ones are solids insoluble in water. $Pr_2SO$, m. 15°; $Bu_2SO$, m. 32°; $Hept_2SO$, m. 70°. Reduction changes them back to sulfides.

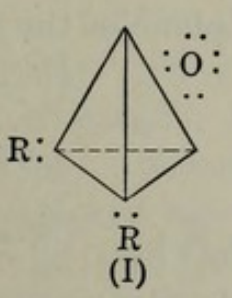
Any superficial resemblance between the SO and the CO groupings must not be accepted as real. This will be clearer from a consideration of the mode of formation of the two types of groups. Using electronic formulas:



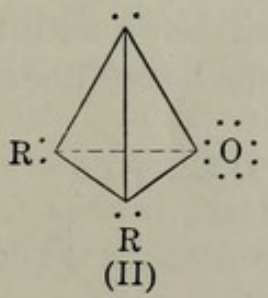


Sulfoxide

In the case of the ketone there is a true double bond involving a sharing of four electrons by the C and O to *complete* both octets. In the case of the sulfoxide there is no double bond although this type of linkage is sometimes referred to as a *semipolar double bond.* It is more properly classed as a *coordinate link* (Sidgwick, 60). It is also represented as $R_2S \rightarrow O$, $R_2S \rightleftharpoons O$ and $R_2S^+ - O^-$. The difference between the CO and SO groups can be shown better with space models, using tetrahedra to represent the C and S atoms.



(I)



(II)

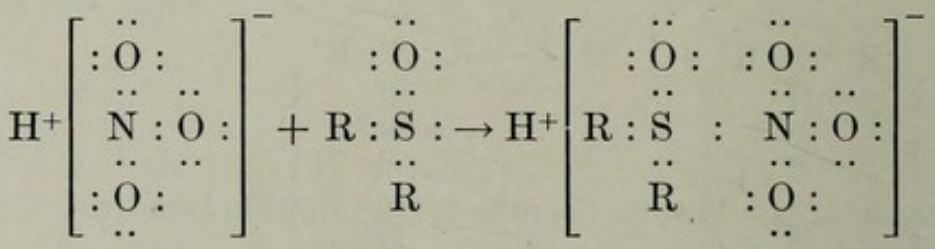
It will be seen that the ketone (I) has a plane of symmetry through R, R′ and the O atom while the sulfoxide (II) has no such plane. This agrees with the experimental fact that sulfoxides can be obtained as optically active isomers (Kenyon, Rep. 1926, 106, 111, 126). This would be obviously impossible

with a structure RR′S=O which would have a plane of symmetry and could not exist in enantiomeric forms.

The differences between sulfoxides and ketones extends to nearly all their properties (Shriner 1930).

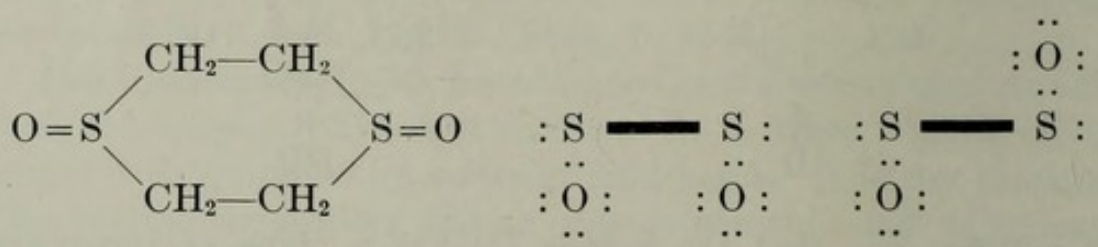
The difference between the SO and CO groupings persists in all compounds containing them. Another experimental evidence of this difference is given by the value of the parachors for the two types of compounds, one indicating a double bond and the other no double bond (H, II, 169; Sidgwick, 124–131).

The existence of the "nitrates" of the sulfoxides offers an interesting possibility in electronic formulas:



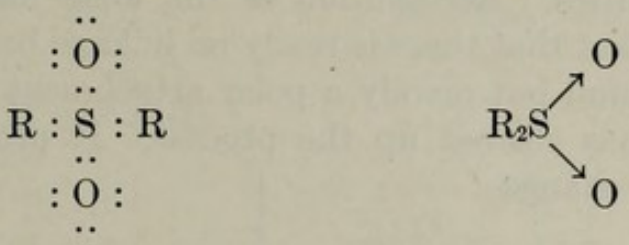
Such complex acids (not true nitrates) could not be produced by ordinary acids whose negative ions have complete octets and so could not form a coordinate link with the "free" electron pair of the sulfoxide.

Further evidence for the coordinate linking in sulfoxides is given by the existence of *cis* and *trans* forms of certain disulfoxides such as those of 1,4-dithian. The double bond formula is inadequate to express this isomerism. The coordinate link formulas are shown with the edge of the plane of the ring represented by the heavy line.



**Alkyl sulfones,** $R_2SO_2$, are stable, crystalline, odorless solids obtained by vigorous oxidation of the sulfides or by treating sodium alkyl sulfinates with alkyl halides. They are not attacked by reducing agents or by $PCl_5$. Their properties are

reflections of the effect of the two coordinate links and the resulting strong electrical fields within the materials.



$Me_2SO_2$, m. 109°, b. 238°; $Et_2SO_2$, m. 70°, b. 248°.

Soporifics of the *sulfonal* type are disulfones obtained by oxidizing mercaptols of ketones.

$$Me_2CO + 2EtSH \xrightarrow{HCl} Me_2C(SEt)_2 \xrightarrow{Ox} Me_2C(SO_2Et)_2$$

Trional and tetronal are similarly related to methyl ethyl ketone and diethyl ketone respectively. Many variations have been achieved by using different ketones and mercaptans. The general reactions by which these are made follow:

$$RCHO \rightarrow RCH(SR')_2 \rightarrow RCH(SO_2R')_2 \xrightarrow{NaOEt,\ R''X} RR''C(SO_2R')_2$$

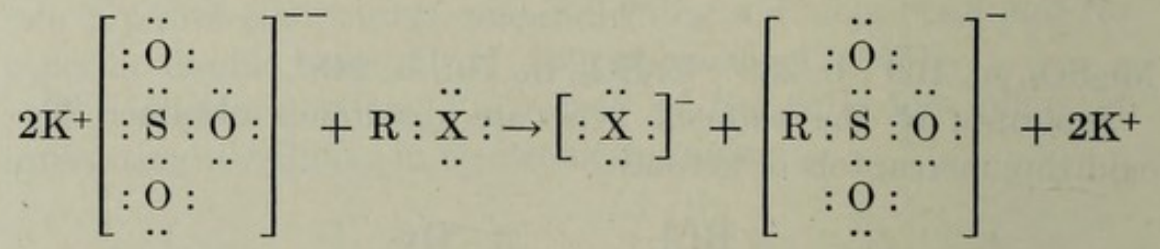
The H on the carbon between the two sulfone groups is replaceable like that between two carbonyl groups.

**Alkyl sulfonic acids,** $RSO_3H$, are soluble, strong acids. Contrary to the usual conception, sulfonic acids can be distilled: *n*-$BuSO_3H$, b. 145° (0.2 mm.); *iso*-$AmSO_3H$, b. 178° (0.2 mm) (v. Braun 1934). They are obtainable in certain cases by direct sulfonation of paraffin hydrocarbons with fuming sulfuric acid (Worstall 1898). Secondary and, especially, tertiary hydrogen atoms are attacked more readily. Thus normal paraffin hydrocarbons can be freed from isomers by long treatment with oleum or chlorosulfonic acid (Midgley).

Better preparations for the sulfonic acids are: 1. Oxidation of mercaptans, which proves the C—S linkage in the sulfonic acids; 2. Action of an alkyl halide (probably only of Class 1, p. 71) with an alkali sulfite

$$K_2SO_3 + RX \rightarrow KX + RSO_3K$$

The formation of a C—S compound, presumably by replacement of K in a K—O linkage, formerly presented considerable theoretical difficulties. Recognition of the ionic nature of such a salt and the fact that there is really no linkage between K and O in the compound but merely a polar attachment of the ions $K^+$ and $SO_3^{--}$, has cleared up the process. It probably involves the following changes:



The alkyl group, deprived of its X attaches itself to the lone pair of electrons of the sulfur thus forming the alkyl sulfonate ion. A similar change occurs between the alkyl sodium sulfates and an alkali sulfite.

Additional evidence on this process is given by the fact that $Ag_2SO_3$ and alkyl halides give alkyl esters of the alkyl sulfonic acids, $RSO_2OR$. In this case after one R has attached itself to the lone pair of electrons, the other has to attach itself to one of the oxygen atoms thus forming an ester (Hunter 1932).

3. Grignard reagents with $SO_2$ give sulfinic acids which are readily oxidized to sulfonic acids.

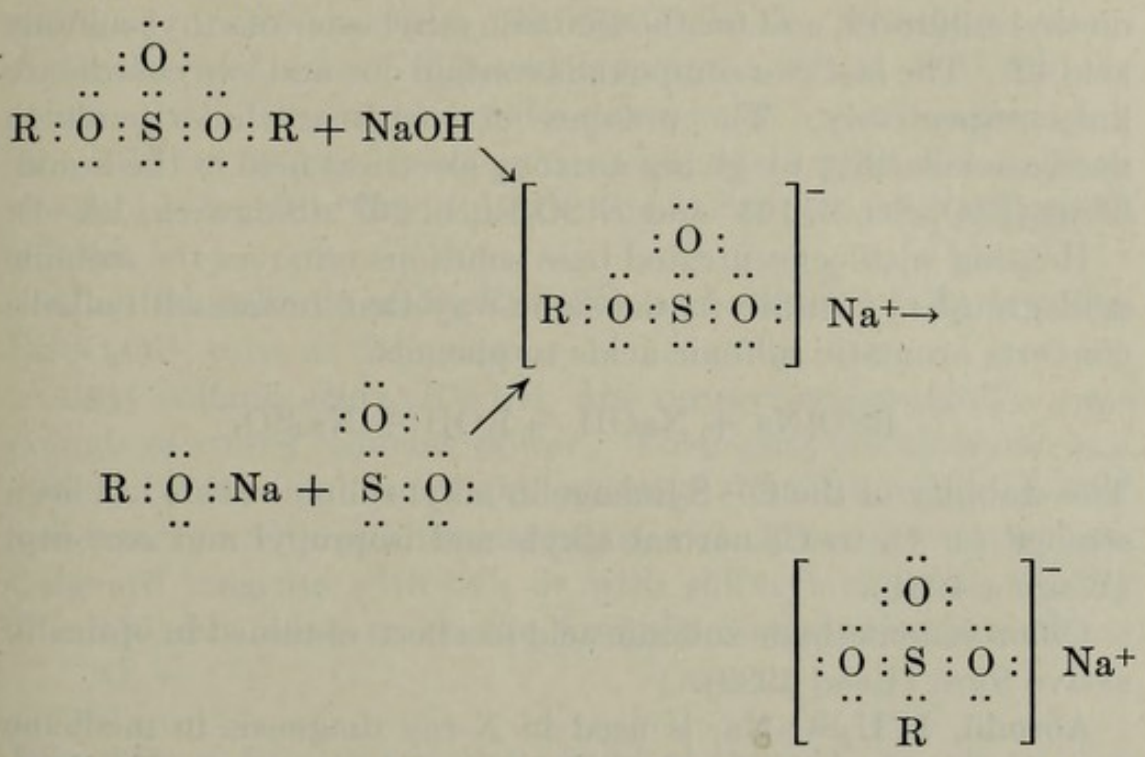
4. Alkali salts of ethyl sulfonic acid are formed by two rearrangements which have long caused confusion in the study of sulfites and related compounds.

*a*. Of diethyl sulfite, $Et_2SO_3$ (formed from thionyl chloride, $SOCl_2$ and alcohol), under the action of 1 mol of dilute base

$$(EtO)_2SO + KOH \rightarrow EtOH + EtSO_3K$$

*b*. Of an alkali ethyl sulfite, $NaEtSO_3$ (obtained from NaOEt and $SO_2$), under the influence of salts like NaI. This type of sulfite is usually represented as having Na attached directly to sulfur, $NaSO_2OEt$.

These reactions are cleared when considered in terms of electronic structures.



The change of the sodium alkyl sulfite to the isomeric sodium alkyl sulfonate is readily followed experimentally because the former reduces iodine and permanganate solutions while the latter does not. In the older system the reducing action was explained on the basis of the S—Na linkage while the more modern view ascribes it to the lone electron pair which can add a nascent oxygen (with 6 electrons). The shift of the R from O to S within the ion is still not entirely clear.

Alkyl sulfonic acids, $C_9$ to $C_{14}$, have been made (Noller 1933).

The alkyl sulfonic acids are stable to hot acids and alkalis. With $PCl_5$, they give sulfonyl chlorides, $RSO_2Cl$. These react with water, bases, alcohols, ammonia and amines to give $RSO_3H$, $RSO_3Na$, $RSO_3R'$, $RSO_2NH_2$, $RSO_2NHR'$ and $RSO_2NR'R''$. With zinc and acid they give mercaptans while with zinc in neutral or slightly alkaline solution they give zinc sulfinates, $(RSO_2)_2Zn$.

The alkyl esters of the alkyl sulfonic acids, $RSO_2OR'$, are isomeric with the dialkyl sulfites, $(RO)_2SO$. The former on hydrolysis either in acid or base lose only one R group. Vigorous hydrolysis of the latter by excess of acid or base removes both R groups forming $SO_2$ or alkali sulfites.

The presence of a coordinate link in a compound greatly

increases its dielectric constant. The value of this constant for a hydrocarbon is about 2, for a carboxylic ester about 7, for diethyl sulfite 19, and for the isomeric ethyl ester of ethyl sulfonic acid 42. The last two compounds contain one and two coordinate links respectively. The presence of coordinate links tends to decrease volatility by giving a strong electrical field in the liquid. Thus $(EtO)_2SO$, b. 161° and $EtSO_3Et$, b. 207° (Sidgwick, 123–4).

Heating with concentrated base solutions removes the sulfonic acid group as a sulfite in the same way that fusion with alkalis converts aromatic sulfonic acids to phenols.

$$RSO_3Na + NaOH \rightarrow ROH + Na_2SO_3$$

The stability of the C—S linkage in alkyl sulfonic acids has been studied for $C_1$ to $C_5$ normal alkyls and isopropyl and *sec*-butyl (Wagner 1931).

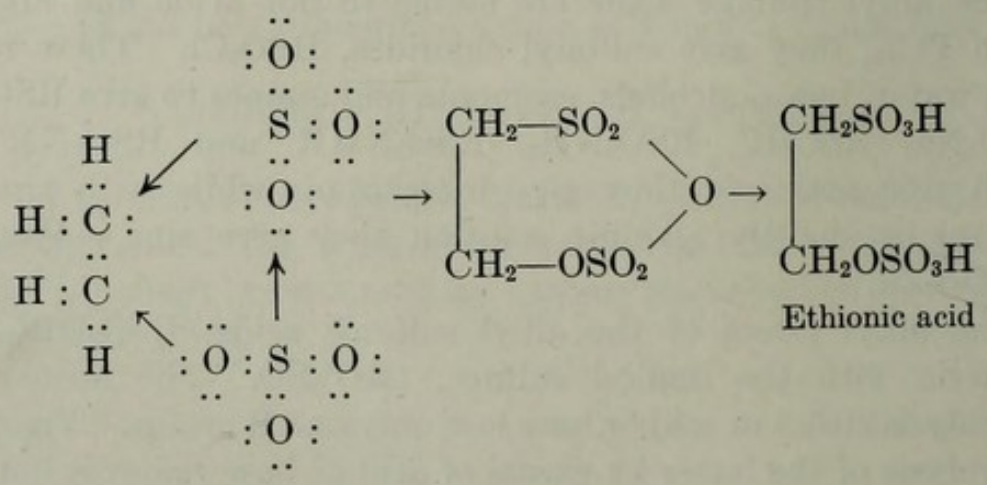
Chloroiodomethane sulfonic acid has been obtained in optically active form (Read 1932).

**Abrodil,** $ICH_2SO_3Na$, is used in X-ray diagnosis in medicine because of the opaqueness of the heavy iodine atom (**Skiodan**).

Di- and tri-sulfonic acids of methane have been extensively studied (Baker 1930). Methionic acid, $CH_2(SO_3H)_2$, can be made by hydrolyzing the product from the action of acetylene with fuming sulfuric acid.

$$(HO)_2CHCH(SO_3H)_2 \rightarrow HCO_2H + CH_2(SO_3H)_2$$

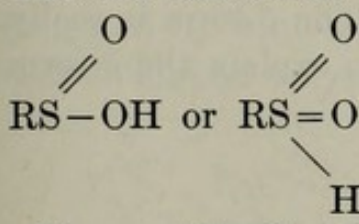
Carbyl sulfate is the inner anhydride of ethionic acid, formed by the action of $SO_3$ with ethylene. Formulation of this process on electronic lines follows:



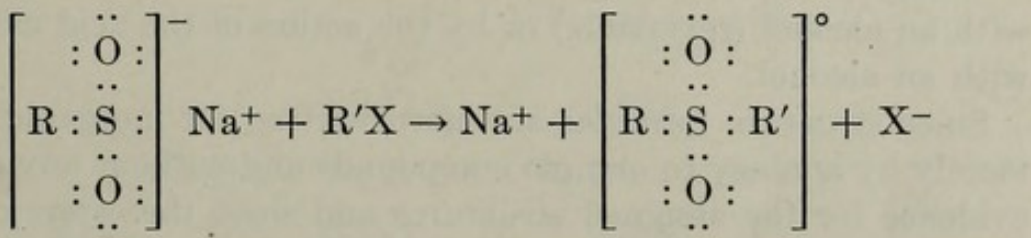
**Vinyl sulfonic acid,** $CH_2=CHSO_3H$, can be prepared as follows: ethylene chlorohydrin is converted to the mercaptan and oxidized to *isethionic acid*, $HOCH_2CH_2SO_3H$. When the acetyl derivative of a salt of this acid is boiled, a salt of vinyl sulfonic acid results. The double bond is not reduced by sodium amalgam as would be the case in $\alpha\beta$-unsaturated carboxylic acids. Thus the double bond in vinyl sulfonic acid is not part of a conjugated system.

**Alkyl thiosulfonic acids,** $RSO_2SH$, and **alkyl thiosulfuric acids,** $RSSO_2OH$, exist as their salts.

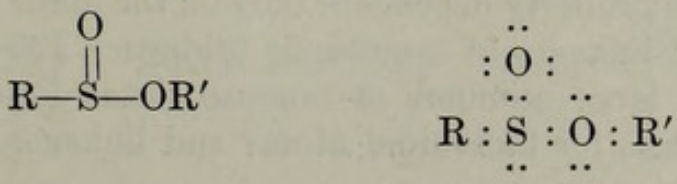
**Alkyl sulfinic acids,** $RSO_2H$, are syrupy, water-soluble compounds of strong reducing power. Their salts are available in a variety of ways: 1. From alkyl sulfonyl chlorides with zinc dust and water or with sodium mercaptides; 2. From zinc dialkyls or Grignard reagents with $SO_2$ or with sulfuryl chloride, $SO_2Cl_2$. The old discussion as to the formula of the sulfinic acids as



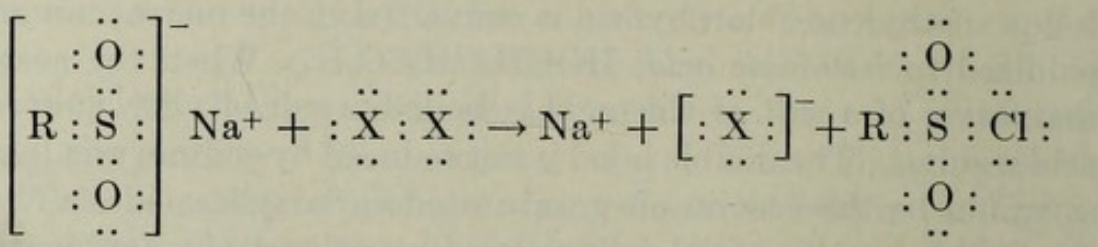
and the action of the sodium salt to give sulfones with alkyl halides and the existence of esters RSO(OR′) isomeric with the sulfones, all become clear in electronic notation.



Sulfinic esters of the type, $RSO_2R'$, have been obtained in optically active forms in the aromatic series (Phillips, Rep. 1925, 111). The older formula containing a double bond does not represent an asymmetric molecule. Moreover the parachors of these esters indicate the absence of any double bond (Sidgwick, 127). Thus the electronic formula is indicated on two counts.



Sodium sulfinates, with halogens, give sulfonyl chlorides.



Organic compounds of selenium and tellurium analogous to those of sulfur are known. The bivalent compounds are even less pleasant. These of tellurium are actually dangerous in that they persist in the body for long periods and give an unbearable odor.

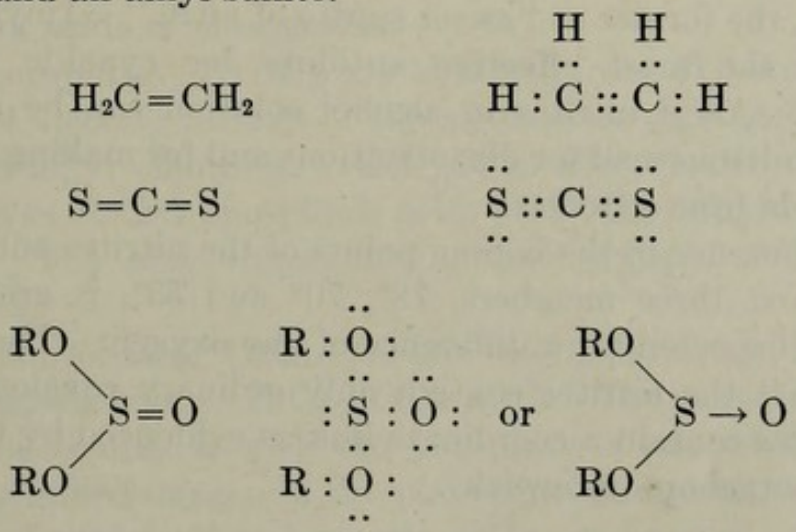
A type of tellurium compound which is sufficiently different from the sulfur compounds to deserve mention is dimethyl telluronium diiodide, $Me_2TeI_2$, which was reported as existing in two stereoisomeric forms (Sidgwick, 286). This has been shown to be incorrect (Rep. 1929, 80–1). The $\beta$-form is really $Me_3TeI.MeTeI_3$. The change postulated to explain the $\beta$-form involves a pinacolic type of rearrangement.

## VI. ESTERS OF INORGANIC ACIDS

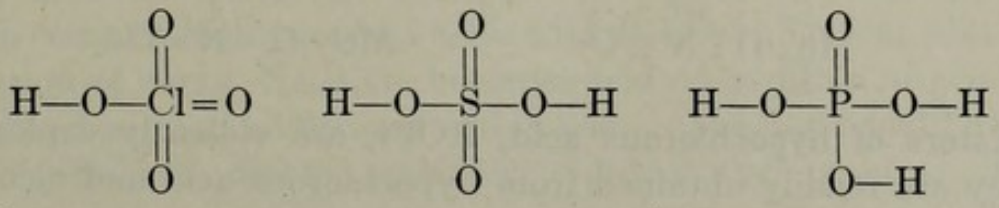
These are obtained either by direct esterification of the acid with an alcohol (reversible) or by the action of the acid chloride with an alcohol.

Since structure formulas are often written for inorganic acids merely by analogy to organic compounds and without any direct evidence for the assigned structures and since the esters of the inorganic acids give means for judging these formulas it is well to consider the experimental evidence regarding these structures. A purely physical demonstration of the existence of a double bond was given by Sugden in 1924 in his introduction of the conception of the *parachor* of a compound (essentially, the product of its molecular volume by the fourth root of its surface tension) as a truly additive property dependent only on the kinds and numbers of atoms and linkages in a molecule (Sidgwick 125–31). Measurements on large numbers of non-associated liquids give the following values for individual atoms and linkages: H, 17.1; C,

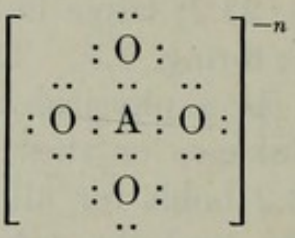
4.8; N, 12.5; O, 20.0; F, 25.7; Cl, 54.3; Br, 68.0; I, 91.0; S, 48.2; P, 37.7; double linkage, 23.2; triple linkage, 46.4; 3-ring, 15.5; 4-ring, 11.6; 5-ring, 9.3; 6-ring, 7.7. The most valuable use of the parachor has been as a physical means of determing the presence of multiple linkages or their absence in given compounds. The value 23.2 holds for all double linkages, C=C, C=O, C=N, C=S, etc., and the value 46.4 holds for C≡C, C≡N, etc. In many cases in which double bonds were written under the older conceptions, determinations of the parachor show that there are not double bonds but coordinate linkages. Thus olefins, ketones, esters, alkyl nitrites, $CS_2$, and isothiocyanates are found to contain the double bonds usually indicated. Nitro compounds and alkyl nitrates are found to have only *one* double linkage instead of the two usually indicated. $POCl_3$, alkyl phosphates, $SOCl_2$, $SO_2Cl_2$, alkyl sulfites and alkyl sulfonates are found to contain *no* double linkages. These conceptions may be illustrated by bond and electronic formulas for ethylene, carbon disulfide and an alkyl sulfite.




Similarly the older "structural" formulas of acids like perchloric acid, sulfuric acid and orthophosphoric acid must be replaced by formulas which agree with the fact that these acids do not contain double linkages (Lewis 1916).



In each case the ion of the acid is more correctly represented by



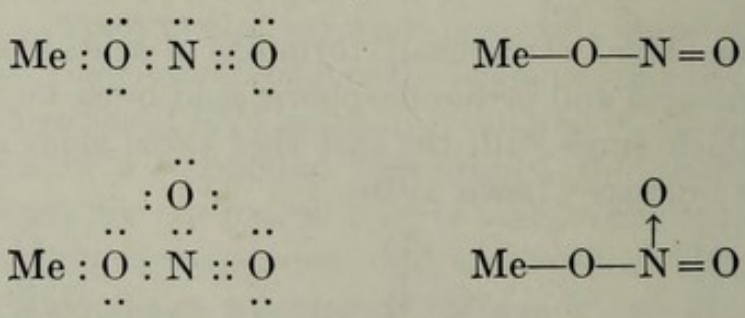
The negative change on the ion is the difference between the 32 electrons in this stable arrangement and the total valence electrons of 4 oxygen atoms and the element A. $n = 32 - (24 + v) = 8 - v$.

**Esters of nitric acid** can be made from nitric acid and an alcohol in the presence of urea to remove nitrous acid.

$MeONO_2$, b. 66°; $EtONO_2$, b. 87°; $PrONO_2$, b. 110°. Nitric acid esters are explosive.

**Esters of nitrous acid** are obtained from an alcohol with a nitrite and sulfuric acid. MeONO, b. −12°; EtONO, b. 17°; PrONO, b. 57°. Ethyl nitrite and amyl nitrite are used in medicine, the former as "sweet spirits of nitre." Amyl nitrite is probably the most effective antidote for cyanide poisoning (Clowes). Alkyl nitrites in alcohol solution can be used as a source of nitrous acid for diazotizations and for making isonitroso compounds from ketones.

The difference in the boiling points of the nitrites and nitrates, for the first three members, 78°, 70° and 53°, is greater than would be expected for a difference of one oxygen. The explanation is that the nitrites contain only ordinary covalences while the nitrates contain a coordinate link as evidenced by the values of their parachors (Sidgwick).



**Esters of hypochlorous acid,** ROCl, are violently explosive. They are readily obtained from hypochlorous acid and alcohols

either in aqueous solution or in mixed water and carbon tetrachloride solution. They decompose in the cold and explode on exposure to sunlight or heat. Tertiary hypochlorites are less unstable than those of primary and secondary radicals. The main processes of decomposition are as follows:

$$RCH_2OCl \rightarrow RCHO + HCl$$
$$RR'CHOCl \rightarrow RR'CO + HCl$$
$$R_3COCl \rightarrow RCl + R_2CO$$

The changes are all exothermic.

Ethyl hypochlorite finds use in the preparation of pure calcium hypochlorite, $Ca(OCl)_2$, (HTH) as contrasted with bleaching powder CaCl(OCl).

$$EtOH \rightarrow EtOCl \xrightarrow{Ca(OH_2)} Ca(OCl)_2 + 2\,EtOH$$

MeOCl, b. 12°; EtOCl, b. 36° (Rep. 1923, 66; 1925, 69).

**Esters of acids of phosphorus.**

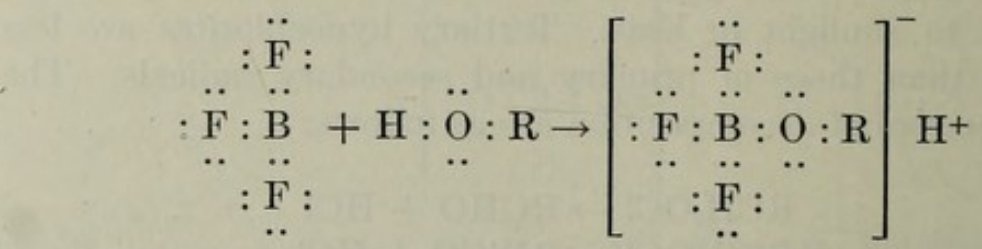
Alkyl phosphites, $P(OR)_3$, are obtained from $PCl_3$ and NaOR. The use of alcohols instead of the alcoholates give unstable acid esters and alkyl chlorides. $(EtO)_3P$, b. 156°, heated with MeI at 220° gives methyl phosphinic acid, $MePO_3H_2$, ethyl iodide and ethylene. The alkyl phosphites absorb oxygen and become phosphates.

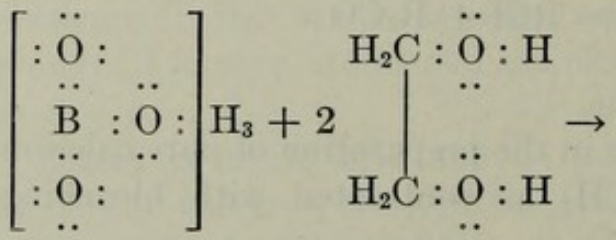
Alkyl phosphates, $(RO)_3PO$, can be made from $H_3PO_4$ or $POCl_3$ with alcohols. $(EtO)_3PO$, b. 216°. The increase of 50° in the b.p. as compared with the phosphite is related to the co-ordinately linked oxygen in the phosphate (Sidgwick, 123).

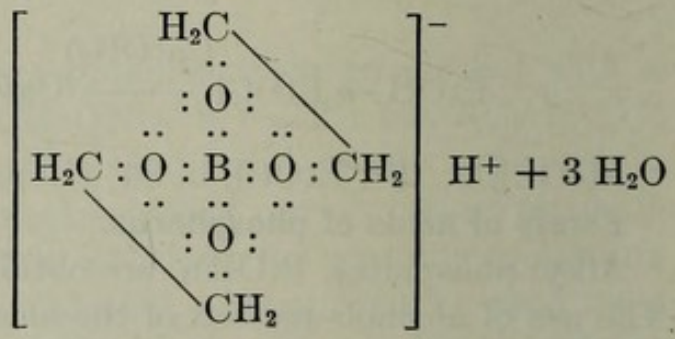
**Esters of arsenious and arsenic acids** are known. $(EtO)_3As$, b. 166°; $(EtO)_3AsO$, b. 149° (60 mm.).

**Boric acid esters,** $(RO)_3B$, are obtained from $BCl_3$ and alcohols and from boric anhydride, $B_2O_3$, and alcohols (Webster 1933). $BF_3$ with alcohols gives strongly acid $H(BF_3OR)$. 1,2-Glycols form complex highly ionized acids with $H_3BO_3$. Thus an alkaline solution of borax, $Na_2B_4O_7$, becomes acid on addition of glycerol or glycol and can be titrated with a base. The boric acid formed by hydrolysis unites with the 1,2-hydroxyl groups. This

property is also used in determining configurations in sugars.







$(MeO)_3B$, b. 65°; $(EtO)_3B$, 120°.

**Esters of silicic acid** are known.

$$(EtO)_4Si,\ \text{b. } 165°;\ (EtO)_3SiOSi(OEt)_3,$$

hexaethyl disilicate, b. 236°.

**Esters of sulfuric acid.**

1. **The acid esters or alkyl sulfuric acids,** $ROSO_3H$ are made by simply dissolving the alcohol in sulfuric acid. If the compound is desired pure the mixture can be neutralized with barium hydroxide and filtered hot from the $BaSO_4$ formed. Cooling or evaporation of the filtrate gives $Ba(RSO_4)_2$. Treatment of this with the exact amount of dilute $H_2SO_4$ to precipitate the barium leaves a solution of $RHSO_4$. The salts such as $KEtSO_4$ are well crystallized. They are used in many reactions in place of alkyl halides because of their ready solubility in water.

2. **Dialkyl sulfates.** Methyl sulfate, $Me_2SO_4$, b. 188° can be

obtained by heating methylhydrogen sulfate or by treating dimethyl ether with $SO_3$. It is odorless and extremely poisonous. It is a more vigorous alkylating agent than $NaMeSO_4$.

Ethyl sulfate, $Et_2SO_4$, b. 208°, is made from ethylene and sulfuric acid under pressure (Curme 1920) or by the vacuum distillation of $NaEtSO_4$. It is an important ethylating agent (Cade 1924, 1926).

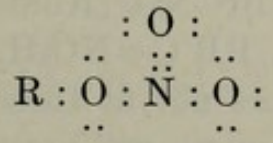
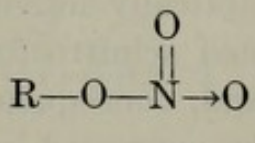
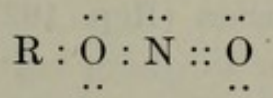
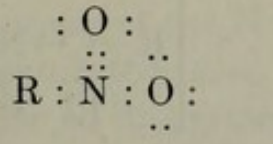
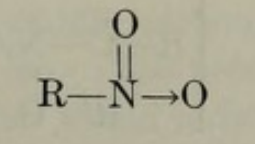
Di-isopropyl sulfate is stable if free from acid. Methylene sulfate, $CH_2SO_4$, and ethylene sulfate $C_2H_4SO_4$ are known. Mixed alkyl sulfates have been made (Rep. 1924, 65).

**Esters of sulfurous acid** are best obtained from thionyl chloride, $SOCl_2$, and alcohols. The alkali alkyl sulfites, $NaRSO_3$ are obtained from alcoholates and $SO_2$. The peculiar relations of the sulfites and the sulfonic acids are discussed under the latter (p. 166).

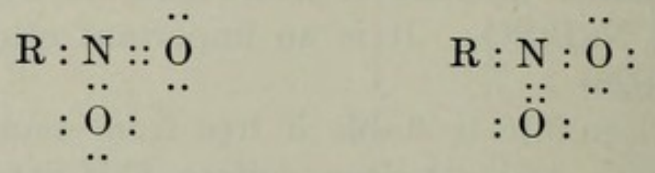
## VII. ALIPHATIC NITRO AND NITROSO COMPOUNDS

*Aliphatic nitro compounds*, $RNO_2$, are distinguished from the isomeric alkyl nitrites in several ways.

1. They boil nearly 100° higher. This is presumably because of the semipolar double bond or coordinate link which they contain. The parachor for nitromethane shows that it contains only *one* double bond. Thus the ordinary formula which is written with two double bonds is unsound (Sidgwick, 123, 127). The formulas of the nitrates, nitrites and nitro compounds may be expressed as follows:

| | | b.p. of $CH_3$ cpd. |
|---|---|---|
|  |  | 66° |
|  | $R—O—N=O$ | −12° |
|  |  | 101° |

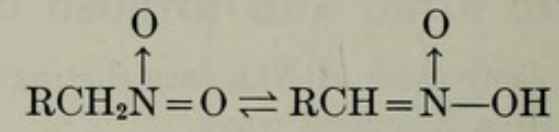
The apparent lack of symmetry in the electronic structure of the nitro group does not agree with the facts as determined by dipole moment measurements. Thus the two oxygen atoms are probably equivalent because of a condition of resonance



2. Reduction gives a primary amine, $RNH_2$ proving the C—N linkage.

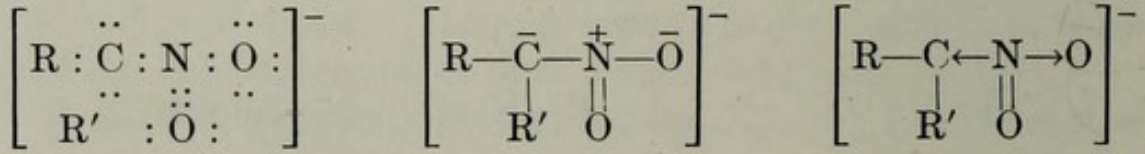
3. They cannot be hydrolyzed as are the nitrites.

4. If the alkyl radical is primary or secondary, sodium salts can be formed. Such nitro compounds are pseudo acids. (Hantzsch 1899; Branch, Rep. 1927, 107). An alpha H undergoes a tautomeric change to give an aci-nitro form.



When R is phenyl the true nitro and the acinitro forms have been isolated. The latter is formed by acidifying the sodium derivative at low temperatures. It is instantly soluble in NaOH while the true nitro compound dissolves only slowly.

The question of the structure of the nitro and acinitro compounds has been reopened by the study of optically active 2-nitrobutane which, gives an optically active sodium compound which, in turn, gives optically active $MeEtBrCNO_2$ (Kuhn 1927). The ordinarily assumed acinitro formula, $RR'C=NO_2H$, has a plane of symmetry and, consequently, does not fit these facts. The following formula, expressed in three ways, will account for them since it contains an asymmetric carbon (Rep. 1927, 103, 108).



*Preparation of Alkyl Nitro Compounds.*

1. Direct nitration of tertiary hydrocarbons gives

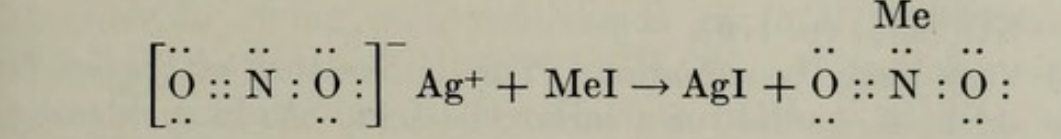
$$RR'R''C-NO_2.$$

Other aliphatic hydrocarbons are more difficultly nitrated (Konowaloff 1892, Worstall 1898, EP 1040–5, Hass 1935–36).

2. Nitro methane, $CH_3NO_2$, b. 101°, can be made from MeI and silver or mercurous nitrite but better from sodium chloroacetate and sodium nitrite (OS) (Adkins 1931).

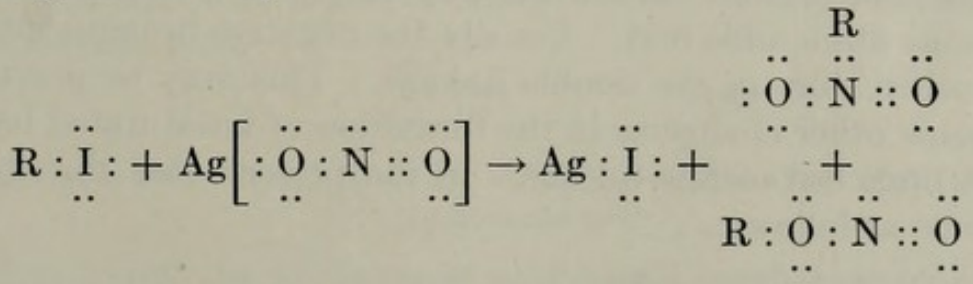
$$ClCH_2CO_2Na \rightarrow O_2NCH_2CO_2Na \rightarrow CH_3NO_2 + NaHCO_3$$

The formation of a nitro compound from a nitrite is another example of an ion giving a non-ionized product of different structure. It is the same type of change as the conversion of a sulfite to a sulfonic acid, a sulfinate to a sulfone and an arsenite to an arsonic acid. It can best be expressed electronically.



Ethyl iodide gives about equal amounts of nitroethane and ethyl nitrite. Higher iodides in general give increasing amounts of the nitrites. Bromides give more nitro compound than the corresponding iodides. (Reynolds 1929.)

It is apparently possible for the nitrite ion to attach itself to the alkyl in two ways:



The larger group in general tends to attach itself to one of the oxygen electron pairs at the ends of the ion rather than to the lone electron pair of the N in the middle, although that is apparently the unsaturated point in the ion. The process is apparently not as simple as this generalization would indicate (Reynolds 1929).

Thus methyl sulfate with a concentrated solution of a nitrite gives some nitromethane whereas a dilute solution gives only methyl nitrite.

Nitromethane and nitroethane are obtained as by-products in the vapor-phase nitration of propane and higher paraffin hydrocarbons (Hass 1936).

Tertiary nitro compounds can be made from the amine of a tertiary radical by oxidation. A better method is the action of a zinc alkyl on the bromination product of a secondary nitro compound (Bewad 1893).

$$Me_2BrCNO_2 + Me_2Zn \rightarrow Me_3CNO_2 + MeZnBr$$

*Reactions of Nitro Compounds.*

1. All are reduced to primary amines.

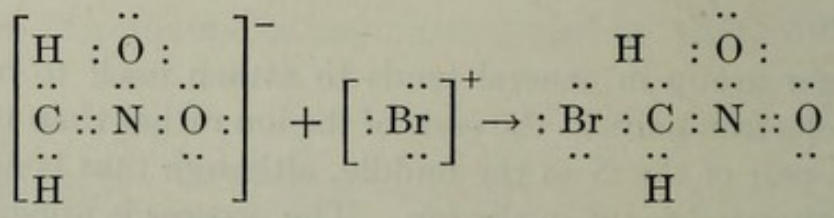
2. Primary and secondary nitro compounds, $RCH_2NO_2$ and $RR'CHNO_2$ are characterized by reactions due to *alpha* hydrogen.

(*a*) Formation of salts of the acinitro form (*nitronic acid*), $-C=NO(ONa)$ (p. 176).

(*b*) Very ready bromination. This is like that of the $\alpha-H$ in an aldehyde, ketone, or a carboxylic acid. As in such cases, an "enolization" process is involved.

$$CH_3NO_2 \rightarrow CH_2=NO_2Na \xrightarrow{Br_2} CH_2BrNO_2 + NaBr$$

It is not necessary to assume that the second bromine atom adds to the N and then splits off as NaBr. As happens in the addition of bromine to an ordinary ethylenic bond, the *positive* bromine atom adds first. Usually the negative bromine adds to the other atom of the double linkage. This may be prevented by some other change as in the formation of unsaturated halides from branched olefins (p. 32). In the present case the change may be as follows:



The bromine with only six electrons attracts the extra pair of

electrons in the double bond to fill its own octet. The $Br^-$ and $Na^+$ ions remain in solution.

(*c*) Action with nitrous acid. The primary compounds up to $C_8$ give *nitrolic* acids, $RC(NO_2)=NOH$, crystalline acids which give deep *red* salts. The secondary compounds up to $C_5$ give *pseudo nitroles*, $[R_2C(NO_2)NO]_2$, white crystalline materials which are *blue* when dissolved or fused, due to dissociation into the monomolecular nitroso compounds.

These reactions are the basis for the "red, white and blue test" for the nature of alcohols. The alcohol to be tested is converted to the iodide, treated with silver nitrite, made alkaline, treated with $NaNO_2$, acidified and then made alkaline again. A red color indicates a primary alcohol, a blue color secondary and no color tertiary because in the last there is no alpha H and no action. This test is largely of historical interest since it is successful only with lower alcohols which are now well-known.

(*d*) The alpha H atoms give the aldol condensation with formaldehyde giving such compounds as $RCH(NO_2)CH_2OH$, $RC(NO_2)(CH_2OH)_2$ and $RR'C(NO_2)CH_2OH$. With higher aldehydes the products are $RCH=CHNO_2$, $RCH=C(R')NO_2$ and $RCHOH-C(R'R'')NO_2$.

(*e*) Reduction with stannous chloride, $SnCl_2$, gives oximes, $RCH=NOH$ and $RR'C=NOH$ which can be hydrolyzed to carbonyl compounds (v. Braun 1911).

3. Primary nitro compounds, boiled with hydrochloric acid give carboxylic acids and hydroxylamine hydrochloride. This involves a complicated series of changes probably going through the hydroxamic acid.

$$RCH_2NO_2 \rightarrow \underset{\text{Hydroxamic acid}}{RC(H)(O\uparrow)=N-OH} \rightarrow RC(OH)=NOH \rightarrow RC(OH)=O + H_2NOH$$

The formation of the hydroxamic acid would involve a peculiar intramolecular oxidation of the alpha H by the coordinately linked oxygen. With aliphatic nitro compounds readily available by the vapor-phase nitration of paraffin hydrocarbons (Hass 1936) this reaction gives a practical method for making acids like propionic and butyric acids from the corresponding hydrocarbons.

4. Conc. KOH gives the following changes:

$$2\,CH_3NO_2 \rightarrow \underset{\text{Salt of } \textit{methazonic acid}}{HON{=}CH{-}CH{=}NO_2K} \rightarrow$$

$$N{\equiv}C{-}CH{=}NO_2K \xrightarrow{H_2O} O_2NCH_2CO_2H$$

*Nitroacetic acid*, m. 87°

$EtNO_2$, b. 115°; *n*-$PrNO_2$, b. 126°; *iso*-$PrNO_2$, b. 118°; *n*-$BuNO_2$, b. 151°; *n*-$OctNO_2$, b. 208°.

**Dinitromethane,** $CH_2(NO_2)_2$, is obtained by the reducing action of sodium arsenite with $Br_2C(NO_2)_2$ which can be made by the vigorous action of nitric acid on various dibromo compounds. It is strongly acid in solution, probably existing as $O_2NCH{=}NO_2H$. This behavior is reminiscent of the strong tendency of 1 : 3 dicarbonyl compounds to enolize to $-COCH{=}C(OH)-$.

$Cl_2C(NO_2)_2$ and $Br_2C(NO_2)_2$ are obtained by the action of nitric acid on the trihalogen anilines.

The Ag cpd. of *dinitroethane* gives two different reactions with MeI, one the expected alkylation to give dinitropropane (I) and the other the production of formaldehyde and ethyl nitrolic acid (II).

$$[MeC(NO_2)_2]Ag \xrightarrow{MeI} \begin{cases} Me_2C(NO_2)_2 & \text{(I)} \\ MeC(NO_2){=}NOH + H_2CO & \text{(II)} \end{cases}$$

The latter reaction can be regarded as an internal oxidation-reduction process taking place in an O—Me cpd. formed simultaneously with the C—Me cpd. (I).

$$MeC(NO_2){=}NO_2Me$$

$$Me{:}C(NO_2){::}N{:}O{:}CH_3 \rightarrow Me{:}C(NO_2){::}N{:}O{:}H + H_2CO$$

**Trinitromethane,** nitroform, $CH(NO_2)_3$, m. 15°, is obtained by the action of bases on $C(NO_2)_4$, a reaction like that of $CI_4$ with bases. It is explosive on heating. In water it forms a stable strongly acid solution. It can be obtained in the aci-form, $(O_2N)_2C=NO_2H$, m. 50°.

**Tetranitromethane,** $C(NO_2)_4$, m. 13°, b. 126°, is best made from acetic anhydride and fuming nitric acid. (Chattaway 1910). It reacts as though one of the four groups were different from the other three. This is much like the action of carbon tetrahalides. Thus KOMe give K nitroform and $KNO_2$. Potassium ferrocyanide gives the K salt of acitrinitromethane $(O_2N)_2C=NO_2K$ (Rep. 1916, 94).

Tetranitromethane in petroleum ether gives intense colorations with C=C compounds of all types including enols (Ostromisslensky 1911). In methyl alcohol it adds to double bonds:

$$C=C + MeOH + C(NO_2)_4 \rightarrow \underset{\underset{OMe}{|}}{\overset{}{C}}\!\!-\!\!\!-\!\!\underset{\underset{NO_2}{|}}{\overset{}{C}} + CH(NO_2)_3$$

(Rep. 1912, 106).

The temptation to assign an unsymmetrical formula to tetranitromethane is probably unsound since the Raman spectrum indicates a symmetrical molecule, as does the low value of 2.3 for its dielectric constant (Sidgwick, 124).

Tetranitromethane can also be made from nitric acid and acetylene (Orton 1920).

**Nitroethylene,** $CH_2=CHNO_2$, b. 98°, is made from β-nitroethanol and $P_2O_5$. It is a lachrymator. Like $CH_2=CHCHO$ it polymerizes readily. Its addition reactions have been studied (Flürscheim 1932).

**1-Nitroisobutylene,** $(CH_3)_2C=CHNO_2$, b. 155°, is readily obtained by the action of nitric acid with *t*-butyl alcohol. On hydrolysis it gives acetone and $CH_3NO_2$.

Other αβ-unsaturated nitro compounds can be obtained by condensing aldehydes with aliphatic nitro compounds. The α−H of the nitro compound adds to the carboxyl oxygen in an aldol condensation.

$$RCHO + CH_3NO_2 \rightarrow [RCHOHCH_2NO_2] \rightarrow RCH=CHNO_2$$

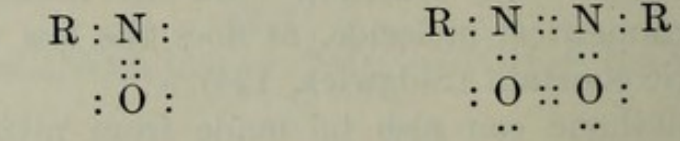
**Chloropicrin,** $Cl_3CNO_2$, b. 112°, is obtained from bleaching powder and picric acid by a series of reactions still unexplained. It is a very effective lachrymator. In contrast to the action of carbon tetrachloride, chloropicrin reacts readily with sodium ethylate to give ethyl orthocarbonate, $C(OEt)_4$, and with ammonia to give guanidine, $HN=C(NH_2)_2$.

Hyponitrous esters, $RON=NOR$, can be made from alkyl halides and silver hyponitrite. Hydrolysis involves oxidation-reduction,

$$MeON=NOMe \rightarrow N_2 + MeOH + CH_2O$$

**Aliphatic nitroso compounds,** RNO, are known only when R is a tertiary radical. *t*-nitrosoisobutane, $Me_3CNO$, can be made from the amine by oxidation with Caro's acid (monopersulfuric acid, $H_2SO_5$) or from the Grignard reagent and NOCl. As solids, the nitroso compounds are colorless dimers. In solution or fused, they are blue monomers. The relation is like that between brown $NO_2$ and colorless $N_2O_4$.

The relation of the nitroso cpds. and their dimers may be expressed electronically as follows



Reactions which would be expected to give primary or secondary nitroso compounds, give the *oximes* instead. Hence these are sometimes called *isonitroso* compounds. The grouping $=CHNO$ becomes $=C=NOH$, a complete "enolization." An exception to this generalization is the compound, 1-chloro-1-nitrosoethane, $CH_3CHCl(NO)$, obtained by chlorine and acetaldoxime. It exists as a colorless dimer which melts to the blue monomer at 85°. On long heating it becomes colorless again by conversion to the oxime of acetyl chloride, $MeCCl=NOH$.

**Nitroso chloroform,** $Cl_3CNO$, is a blue oil obtained in good yield by the action of nitric acid on trichloromethyl sulfinic acid, $Cl_3CSO_2H$ obtained from the sulfone chloride by reaction with $H_2S$. Oxidation by chromic acid gives chloropicrin.

## VIII. AMINES, ALKYL DERIVATIVES OF AMMONIA

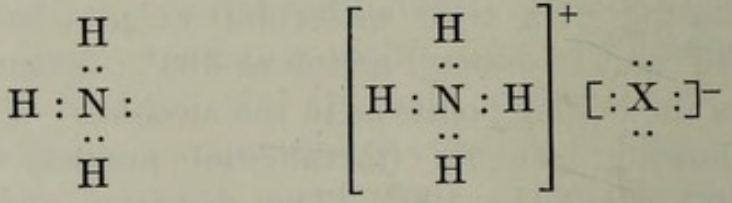
Depending on the number of H atoms replaced in $NH_3$, the amines are primary, secondary and tertiary, $RNH_2$ (amino group, $-NH_2$), RR′NH (imino group, $=NH$), and RR′R″N respectively. They have the basic properties of ammonia but form more strongly basic solutions probably because of the greater stability of their "hydrates" as compared with that of ammonia. The primary and secondary amines are "alcohols of the ammonia system" (Franklin) while the tertiary amines are "ethers" on the same basis. The amines have characteristic odors somewhat resembling that of $NH_3$. The three methyl amines and primary ethyl amine boil below 20°. The others are liquids with boiling points increasing with their molecular weights to heptadecyl amine at 340° and tri-*n*-octyl amine at 366°. Branching of the chain lowers the boiling points as in the alcohols. This is shown by the following isomeric (metameric) amines: $Et_3N$, 90°; $Pr_2NH$, 110°; $HexNH_2$, 129°. The densities of the amines range about 0.66 to 0.77.

The preparations and reactions of the amines can be more safely generalized than can those of the alcohols. This is because the alcohols give many apparently *metathetical* reactions and amines do not. This is related to the greater additive power of nitrogen and the greater stability of the C—N linkage as compared with the corresponding properties of oxygen. Thus there are few reactions of amines in which the C—N linkage is broken whereas most reactions of alcohols involve the breaking of the C—O linkage. The outstanding example of the breaking of a C—N linkage, the action of nitrous acid with a primary amine presents even more irregularities than any alcohol reaction (p. 192).

The amines unite with HX in the same way that $NH_3$ does, forming $NH_4Cl$, $RNH_3Cl$, $R_2NH_2Cl$, $R_3NHCl$ etc. The substituted ammonium salts (amine hydrochlorides etc.) have much the same properties as the parent substance. They are very soluble crystalline compounds. They are more soluble in organic liquids than the simple ammonium salts. Ammonia and the amines add certain alkyl halides to give ammonium salts having

one more alkyl group than the starting material. The last possible stage is a *quaternary ammonium* compound $R_4NX$. The corresponding bases, $RNH_3OH$, $R_2NH_2OH$, $R_3NHOH$, $R_4NOH$, substituted ammonium hydroxides act as stronger bases than $NH_4OH$. $Me_4NOH$ can be obtained as a solid resembling KOH in physical and chemical properties. On heating, however, it decomposes giving $Me_3N$ and MeOH. Secondary amines give stronger bases than either the corresponding primary or tertiary amines (Hall 1931, 1932).

The valence of nitrogen and the "shape" of its atom have long been a source of discussion (Meisenheimer 1932). This is a case where the electronic conceptions of valence are helpful in organic chemistry. This is illustrated by $NH_3$ and an ammonium salt.



The related organic compounds simply have R groups in place of H atoms. Thus the peculiar additive power of ammonia and the amines is due to their active electron pair which can combine with a positively charged group to give a positive ammonium ion, either simple or substituted. The ammonium compounds give good examples of *polar* and *non-polar* linkages. The former exist between the two charged ions each of which has a complete octet while the latter exist between the nitrogen and the organic groups in which a pair of electrons is shared by the two atoms, each having a complete octet only by means of the shared pair.

The tetrasubstituted ammonium ion is undoubtedly tetrahedral rather than pyramidal as was formerly supposed (Rep. 1927, 102). This is confirmed by the occurrence of various complex ammonium compounds in enantiomorphic optically active forms. With the electronic conception it is easy to see that the four electron pairs and their attached groups must assume a tetrahedral arrangement in space. The older conception of a pyramidal nitrogen atom with the "fifth" group attached at the apex becomes impossible. The fifth group is attached only ionically as is chlorine to sodium. Werner in 1902 in his coordination

theory hit upon the true nature of the ammonium compounds long before the electronic theory.

While nitrogen was believed to be quinquevalent in the sense that carbon is quadrivalent, many attempts were made to prepare compounds such as $Me_5N$ but these failed until more complex groups were used and $Me_4NC(C_6H_5)_3$ and $Me_4NCH_2C_6H_5$ were obtained (Schlenk, Rep. 1916, 111; 1917, 117). These proved not to be true quinquevalent nitrogen compounds but merely a new type of ammonium "salt," the properties resembling those of an organic sodium compound. Water hydrolyzes them giving $Me_4NOH$ with triphenylmethane and toluene respectively.

*Preparation of Amines.* A mixture of the three classes can be obtained by treating certain alkyl halides with ammonia, usually in alcoholic solution. The halides which work best are those of Class 1 and isopropyl and isobutyl halides. Even with Class 1 halides, the higher members become increasingly sluggish and give lesser amounts of tertiary and secondary amines. The other classes of halides either do not react or merely lose HX to give olefins and $NH_4X$.

The action of alkyl chlorides with $NH_3$ is accelerated by a trace of an inorganic iodide.

The addition of alkyl halides to $NH_3$ and amines is greatly influenced by the solvent used (Menschutkin). Thus isopropyl bromide and $Et_2NH$ react very slowly without a solvent but readily in glycerol or ethylene glycol (Caspe 1932).

The reaction of $NH_3$ with RX may be pictured as:

$$\begin{array}{ccccc} & H & & H & \\ & \cdot\cdot & & \cdot\cdot & \\ H:N: & + & R:X: & \rightarrow & H:N:R + :X: \\ & \cdot\cdot & & \cdot\cdot & \\ & H & & H & \end{array}$$

The mixing of a suitable alkyl halide with a solution of $NH_3$ can give all four possible ammonium halides (p. 76). Treatment with a base converts the first three to amines leaving the quaternary ammonium salt unchanged in the solution. The others can be distilled out and separated by distillation, contrary to the ordinary conception of the difficulty of separating the three amines of a given radical. Thus the boiling points (°C.) of the

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three ethyl amines and the three *n*-butyl amines are 19, 56, 90 and 78, 160, 216 respectively.

**Primary amines,** free from other amines, can be obtained in a variety of ways.

1. The hydrolysis of alkyl isocyanates was the method used by Wurtz in his discovery of the first amine.

$$RN=C=O \rightarrow RNHCO_2H \rightarrow CO_2 + RNH_2$$

The difficulty is that isocyanates can be prepared readily only from alkyl halides of Class 1.

2. Hofmann's degradation of an acid amide by a hypochlorite or hypobromite or by halogen and a base. This gives the net change $RCONH_2 \rightarrow RNH_2$. The intermediate steps involve the formation of an N-bromoamide and its action with the basic solution to give an isocyanate which is then hydrolyzed to the primary amine.

$$RCONH_2 \rightarrow RCONHBr \rightarrow RNCO \rightarrow RNH_2$$

If the reaction is not carefully controlled some of the amine may unite with unchanged isocyanate to give a disubstituted urea, RNHCONHR. Also the amine may react with any excess of hypohalite to give a cyanide, $RCH_2NH_2 \rightarrow RCN$. These side reactions are easily avoided and yields approaching 100% of primary amine are obtainable from an acid amide in spite of the many steps involved. The process is successful for *all types of primary amines.* Thus although tertiary butyl amine, $Me_3CNH_2$, and neopentyl amine, $Me_3CCH_2NH_2$ cannot be made from the corresponding halides they are readily obtained from the amides of trimethylacetic and *t*-butylacetic acids. The advantage of this method is obvious from the fact that *t*-butyl chloride and $NH_3$ give only a 3% yield of amine (Brandes 1918).

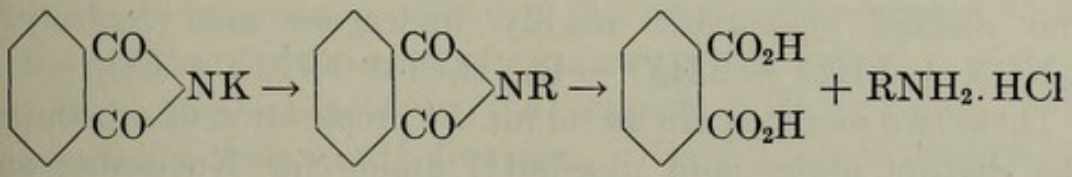
3. The Curtius conversion of an acid azide, $RCON_3$, to $RNH_2$. As in the Hofmann reaction the isocyanate is an intermediate product. This method is best carried out by heating an acid chloride with sodium azide, $NaN_3$, in toluene, filtering off the NaCl and heating with an excess of HCl to give the amine hydrochloride.

4. Reduction of an oxime, $C=NOH$, or a hydrazone, either unsubstituted or substituted, $C=NNH_2$, $C=NNHQ$, gives $C-NH_2$. Thus pinacolyl amine (2,2-$Me_2$-3-aminobutane), $Me_3CCH(NH_2)Me$, cannot be made by any of the ordinary ways because the necessary intermediates are lacking or react in other ways. Pinacolone, $Me_3CCOMe$, however, can readily be converted to its oxime which is easily reduced to the primary amine. A similar result can be obtained with the hydrazone, or the phenylhydrazone.

5. The reduction of a cyanide (nitrile), $RCN \rightarrow RCH_2NH_2$. Acid reducing conditions are avoided as they favor the formation of secondary amines probably by the hydrolysis of the intermediate product $RCH=NH$ to give the aldehyde, RCHO, which combines with the amine to form $RCH=NCH_2R$, a Schiff's base. This is reduced to $(RCH_2)_2NH$.

6. Reduction of an acid amide with sodium and absolute alcohol, $RCONH_2 \rightarrow RCH_2NH_2$.

7. Gabriel's phthalimide synthesis (1887) is useful in preparing special primary amines. It consists in the action of an alkyl iodide (usually of Class 1) with potassium phthalimide. The resulting N-alkyl phthalimide is hydrolyzed by HCl under pressure.




In cases in which hydrolysis is difficult, hydrazine ($H_2NNH_2$) can be used to give the amine (Ing 1926).

8. The best preparation of a primary amine of a tertiary alkyl is that from the Grignard reagent and chloroamine, $ClNH_2$ (Coleman 1929). This method gives over 60% yields with *t*-amyl amine, $Me_2EtCNH_2$.

9. While reduction of nitroso and nitro compounds gives primary amines the process is useful only in making primary amines of tertiary alkyl radicals. Nitroso compounds of primary and secondary radicals usually change to a bimolecular form or to oximes of the related aldehyde or ketone. Primary and sec-

ondary nitro compounds are usually less available than the corresponding amine. This condition is likely to be changed by the ready availability of the nitro cpds. by vapor-phase nitration of paraffin hydrocarbons (Hass 1936). The nitroso and nitro derivatives of tertiary butyl give tertiary butyl amine. The former compound can be made from *t*-butylmagnesium chloride and nitrosyl chloride. The second is made from the nitration of isobutane in the vapor phase (Hass 1934).

10. Alkyl halides heated with hexamethylene tetramine, $(CH_2)_6N_4$, give only primary amines (Delepine). Presumably this process would be most successful with Class 1 halides.

**Secondary amines,** free from other types, may be prepared:

1. From the N-disubstituted anilines through the para nitroso compounds which are easily prepared by the action of nitrous acid and are readily hydrolyzed by bases to give *p*-nitrosophenol and the secondary amine.

$$R_2NC_6H_5 \rightarrow R_2NC_6H_4NO \rightarrow HOC_6H_4NO + R_2NH$$

2. From disodium cyanamide $Na_2NCN$ and an alkyl halide. The sodium compound is obtained by the action of sodium carbonate on commercial calcium cyanamide (Kalkstickstoff). The dialkyl cyanamide readily undergoes acid hydrolysis $R_2NCN + 2\,HCl + 2\,H_2O \rightarrow R_2NH_2Cl + NH_4Cl + CO_2$.

These two methods are useful for the preparation of substances like diethyl amine and di-*n*-butyl amine for Novocaine and Butyn manufacture.

3. Secondary amines, especially mixed amines, RR′NH, can be made by the reduction of the condensation products of aldehydes with primary amines (Schiff's bases), RCH=NR′.

Secondary amines of secondary and tertiary alkyl groups are unknown except diisopropyl amine, b. 84°.

**Tertiary amines** are best prepared by the action of an excess of alkyl halide with ammonia and a base. Distillation of the alkaline solution gives the tertiary amine which can be distilled with steam. The residual quaternary salt may be evaporated and distilled with solid KOH to give more of the tertiary amine.

The fourth group is removed as an olefin except in the case of methyl which appears as MeOH.

A special preparation of tertiary amines is the action of a Grignard reagent with an $\alpha$-dialkylamino-ether obtainable from a secondary amine and an alpha chloro ether which can be made from HCl, an aldehyde and an alcohol (Rep. 1923, 87).

$$RMgX + R'R''NCH_2OEt \rightarrow RCH_2NR'R'' + EtOMgX$$

Tertiary amines containing three secondary or tertiary groups are unknown except that tri-isopropyl amine is reported as one of the reduction products of acetone oxime, $Me_2C{=}NOH$.

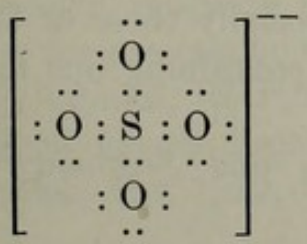
Trialkyl amines such as *n*-Bu and *n*-Am are good inhibitors of corrosion (Mann 1936).

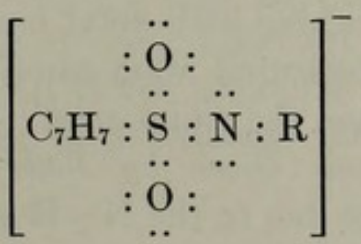
Tri-*n*-butyl amine is used as an anti-oxidant for gasoline (DuPont).

**The separation of the three amines of a given alkyl radical** has been the subject of much study.

1. The best method is by fractional distillation.
2. The Hinsberg Method (1890) may be useful in certain cases. The mixture of amines is treated with an aromatic sulfonyl chloride, originally benzene sulfonyl chloride but now usually the *p*-toluene compound although the beta-anthraquinone sulfonyl chloride has been suggested as more advantageous.

The $ArSO_2Cl$ acts on the primary and secondary amines because of their N—H grouping. The mixture is made alkaline and the tertiary amine is distilled from it. The treatment with alkali decomposes a "salt" formed from the tertiary amine and the sulfone chloride. The latter is converted to the sulfonate of the alkali used. The alkaline mixture contains insoluble $ArSO_2NR_2$ and a soluble salt of the primary sulfonamide, $(ArSO_2NR)K$. This salt probably resembles a sulfate in electronic arrangement.





The usual formulas in which the metal is attached directly to N or to O, $-SO_2NK(R)$ and $-SO(OK)=NR$, are less probable. These salts are not as readily hydrolyzed as N—K compounds usually are and apparently a doubly linked sulfur atom as in S=N is improbable.

When the alkaline mixture, left after the removal of the tertiary amine, is filtered the residue contains the derivative of the secondary amine and the filtrate contains the salt of the primary amine compound. On acidification, the latter gives $ArSO_2NHR$. After purification by crystallization, it and the secondary amine compound can be hydrolyzed by HCl under pressure to give the hydrochlorides of $RNH_2$ and $R_2NH$.

3. The three classes of amines can also be separated by heating with diethyl oxalate, with which the tertiary amines do not react, the primary give crystalline diamides, $(CONHR)_2$, and the secondary give oily mono-amides, $EtO_2CCONR_2$. The latter compounds are easily separated and can be hydrolyzed to the amines. With higher primary amines there is difficulty due to the stopping of the reaction at $EtO_2CCONHR$ which would appear with the secondary amine compound.

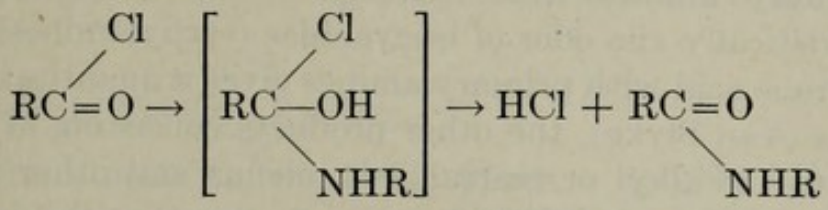
4. Primary amines form insoluble Schiff's bases $C_6H_5CH=NR$ with benzaldehyde, while secondary and tertiary amines do not react. Acid hydrolysis regenerates $RNH_2.HX$.

*Tests for Primary, Secondary and Tertiary Amines* have been devised in great numbers. They are best considered under the reactions of the three classes.

*Reactions Given by All Three Classes.* These are due to the basic properties of the nitrogen atom, ability to combine with hydrogen ions (protons). They all combine with acids to form substituted ammonium salts, $[(Amine)H]_nQ$, in which $n$ is the valence of the acid radical Q. This includes complex acids such as chloro-auric and chloroplatinic acids, $HAuCl_4$ and $H_2PtCl_6$. They combine with alkyl halides, especially those of Class 1, to form substituted ammonium halides containing one more alkyl group than the amine used.

*Reactions Given by Both Primary and Secondary Amines.* These are due to the N—H grouping.

1. Acid chlorides and anhydrides give N-alkylated acid amides. The active H of the amine adds to the oxygen of the carbonyl and the N adds to the C.



The HCl formed unites with another molecule of the amine to form its hydrochloride. Tertiary amines form addition compounds with acid chlorides which are decomposed by water whereas the amides are not. The action of sulfonyl chlorides has already been considered.

2. They can be further alkylated to give more highly substituted ammonias while tertiary amines are converted directly to quaternary ammonium salts. Amines may be methylated by MeI, by $Me_2SO_4$ or by heating with formalin solution ($H_2CO$).

3. With alkali metals they form RNHNa, $R_2NNa$ etc. substances analogous in the ammonia system to NaOEt in the water system.

4. They react with chlorine and with bromine to give N-halogen derivatives, RNHX, $RNX_2$ and $R_2NX$ and complex compounds with an excess of halogen. The halogen attached to nitrogen is "positive" and resembles that attached to oxygen as in hypohalous acids. Indeed they act as the hypohalous "acids" of the ammonia system. Thus they are powerful oxidizing agents. One halogen attached to N liberates two iodine atoms from an iodide solution. This is the test for positive halogen.

5. With $CS_2$ they give amine salts of N-alkylated dithiocarbamic acids, $RNHCS_2NH_3R$ and $R_2NCS_2NH_2R_2$. Treatment of the former with $HgCl_2$ gives HgS and a mustard oil, an isothiocyanate, RN=C=S. Since the mustard oils have a characteristic odor this can be used as a test for primary amines.

6. Grignard reagents form RNHMgX and $R_2NMgX$ from which the amines can be regenerated by acid (Hibbert 1912).

7. Nitroamines, $RNHNO_2$ and $RR'NNO_2$ are obtainable only by indirect means because nitric acid oxidizes the amines. Nitroamines, Ahr. 1912, 119 pp.

*Reactions Given Only by Primary Amines*

These are due to the amino group $-NH_2$.

1. Primary amines with chloroform and a base give the characteristically vile odor of isocyanides (carbylamines), RNC.

2. Nitrous acid with primary amines gives a quantitative yield of $N_2$ gas (Van Slyke), the other products consisting of alcohols (related to the alkyl or rearranged), olefins and other products (Whitmore 1933). It is important to observe that the action of a primary amine with nitrous acid is never a good preparative method for an alcohol (p. 78). Even with methyl amine, the chief product is methyl ether instead of methanol.

Secondary amines give oily nitroso compounds, $R_2NNO$.

3. Primary amines can be changed to the corresponding halides by benzoylation and treatment with $PBr_5$ or $PCl_5$ (p. 78). (v. Braun 1932.)

4. A solution of a primary amine containing copper powder absorbs air on warming and forms an aldehyde which can be distilled out and tested (Rep. 1906, 106).

5. Primary amines, $RCH_2NH_2$, with monopersulfuric acid (Caro's acid, $H_2SO_5$), give hydroxylamines, $RCH_2NHOH$, oximes, $RCH=NOH$, and finally hydroxamic acids,

$$RC(OH)=NOH$$

which form violet colors with ferric chloride. Amines of secondary groups $RR'CHNH_2$ give ketoximes, $RR'C=NOH$, while those of tertiary groups give nitroso and nitro compounds.

6. Thionyl chloride, $SOCl_2$, gives thionyl amines, RNSO. These are liquids of sharp odor which unite with water to form thionaminic acids, $RNHSO_2H$. Excess water gives hydrolysis to the amine sulfite.

*Reactions Given Only by Secondary Amines*

These are due to the imino group, $=NH$.

1. Nitrous acid gives insoluble oily nitrosamines, $R_2NNO$ from which the amines can be regenerated by concentrated HCl. Primary amines give $N_2$ gas and tertiary do not act in the cold.

The nitrosamines, $R_2NNO$, when heated with phenol and

sulfuric acid, diluted and made alkaline, give a blue-violet color (Liebermann reaction).

2. Oxidation with hydrogen peroxide forms hydroxylamines, RR'NOH.

*Reactions of Tertiary Amines*

1. Nitrous acid, in the cold, forms a soluble nitrite. On heating this gives a nitrosamine, RR'NNO and ROH or related products.

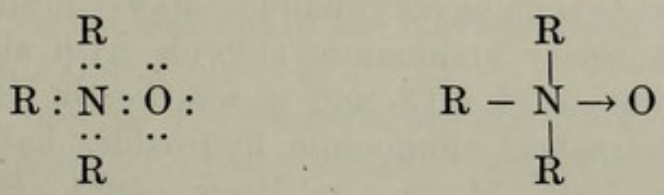
2. Acid chlorides form compounds, $RCOCl.R_3N$ (Dehn 1912). Heating under pressure gives $RCONR_2$ and RCl. Treatment with water gives $RCO_2H$ and $R_3NHCl$. The best diagnosis of a tertiary amine as distinguished from a primary or secondary amine is its failure to give substituted amides with *cold* acetyl chloride.

3. Hypochlorous acid gives secondary amines (or their N-chloro derivatives) and aldehydes or related compounds.

4. Hydrogen chloride under pressure gives RCl and $NH_4Cl$.

5. Cyanogen bromide gives $R_2NCN$ and RBr (v. Braun 1900).

6. Oxidation by hydrogen peroxide forms *amine oxides*, $R_3NO$. A formula, $R_3N=O$, indicating pentavalent nitrogen does not agree with the properties of these substances (Jones 1926). The value of the parachor for the amine oxides shows no increment such as would correspond to the *double bond*, (H, II, 169). Thus further experimental evidence is given for the electronic structure (p. 170).



Thus the N=O linkage in the amine oxides is impossible as is the S=O linkage in the sulfoxides (p. 171) and similar compounds.

Amine oxides have been obtained as optically active enantiomers (Meisenheimer Rep. 1911, 75).

*Identification of Amines*

Primary and secondary are best converted to crystalline derivatives.

1. Sulfonamides, by treatment with sulfonyl chlorides such as *p*-toluene-, benzyl-, and methyl- (Marvel 1927, 1929).

2. Ureas, by isocyanates such as phenyl-, *p*-nitrophenyl- and *α*-naphthyl.

$$ArNCO + RNH_2 \rightarrow ArNHCO(NHR)$$

Potassium cyanate and acid give substituted ureas, $RNHCONH_2$ and $RR'NCONH_2$.

3. Thioureas, by means of phenyl-, *p*-tolyl-, *o*-tolyl- and *α*-naphthyl-mustard oils.

$$ArNCS + RNH_2 \rightarrow ArNHCS(NHR)$$

4. Acetyl and benzoyl derivatives, $CH_3CONHR$, and $-NR_2$, $C_6H_5CONHR$, and $-NR_2$, of many primary and secondary amines have characteristic melting points.

5. All amines form chloroplatinates and chloroaurates just as $NH_3$ forms $(NH_4)_2PtCl_6$ and $NH_4AuCl_4$.

6. They also form characteristic picrates (with trinitrophenol) and picrolonates (with 1-*p*-nitrophenyl-3-Me-4-nitropyrazolone-5).

*Quaternary Ammonium Compounds and Exhaustive Methylation*

As has been seen, the treatment of an alkyl halide with ammonia gives some quaternary ammonium halide, $R_4NX$. This can be produced more effectively from ammonia or amines by alkylating agents such as alkyl halides, alkyl sulfates, etc., and a base. A quaternary ammonium chloride with alcoholic KOH gives a precipitate of KCl and a solution of $R_4NOH$. The stability of tetraalkyl ammonium hydroxides has been widely studied (Ahr. 1899, 54 pp.; v. Braun 1931, Stewart 1932; Ingold 1933). The following results of heating these substances are typical

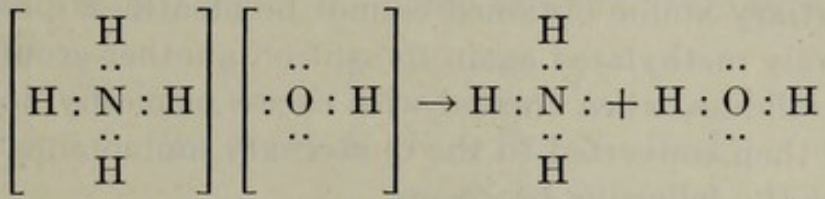
1. $Me_4NOH \rightarrow Me_3N + MeOH$

2. $EtMe_3NOH \rightarrow Me_3N + H_2C{=}CH_2 + H_2O$

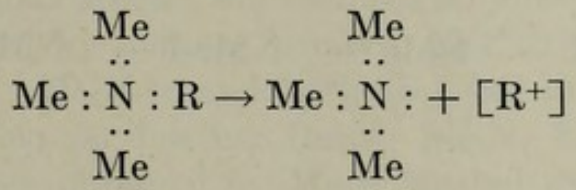
3. $(Me_2CHCH_2)Me_3NOH \rightarrow Me_3N + Me_2C{=}CH_2 + H_2O$

4. $(Me_3CCH_2)Me_3NOH \rightarrow Me_3N + Me_3CCH_2OH$

The formation of olefins cannot be regarded as due to dehydration of alcohols first formed because the temperatures used are far below those required for such dehydrations. The process may be regarded as analogous to the decomposition of ordinary $NH_4OH$.



The new combination is more stable.



If the hypothetical $R^+$ contains a hydrogen on the carbon alpha to the carbon which was left with only six electrons by the decomposition of the complex ammonium ion, then that hydrogen is expelled as a proton ($H^+$) and an olefin is formed

$$R^+ \rightarrow H^+ + \text{olefin}$$

If, however, such a loss of a proton is not possible as with the methyl (1) or the neopentyl group (4) the $R^+$ combines with the $OH^-$ to give ROH.

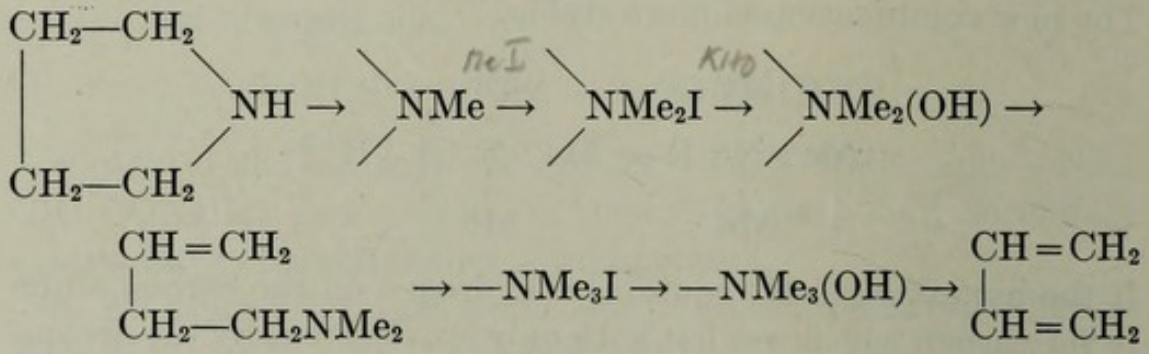
Whereas the decomposition of a quaternary ammonium hydroxide results in the detachment of the largest group, the more difficult decomposition of the corresponding halide gives a methyl halide if that is possible.

The useful process of *exhaustive methylation* is based on the ready decomposition of quaternary ammonium hydroxides. The process will be illustrated by several examples.

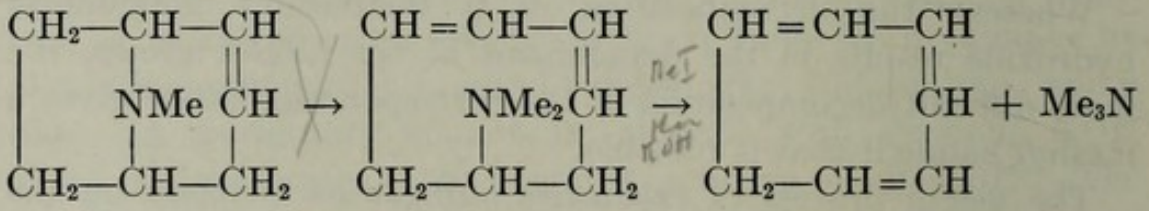
1. An amine, $C_6H_{15}N$, with nitrous acid, gives no $N_2$ but gives an oily nitroso compound from which the original amine can be regenerated. There are some 14 secondary amines of this formula. Treatment with an excess of MeI and NaOH gives a quaternary ammonium salt, $C_8H_{20}NI$. The ammonium hydroxide, obtained by $Ag_2O$ and water, decomposes on heating to give a gas which is identified as isobutylene and a tertiary amine,

$C_4H_{11}N$, which must be ethyl dimethyl amine. Thus the original amine was either ethyl isobutyl amine or ethyl *t*-butyl amine. The identity as between these two would have to be decided by synthesis and the preparation and comparison of derivatives. If the tertiary amine obtained cannot be identified directly it is exhaustively methylated again to split off another group.

2. Pyrrolidine, when treated with excess of methyl iodide and base and then converted to the quaternary ammonium salt, etc. undergoes the following processes:



3. Many naturally occurring products contain cyclic structures having a nitrogen bridge as in tropine and related compounds. The first formation of a quaternary base and its decomposition removes the N from one of its attachments across the ring and the second exhaustive methylation detaches it entirely. Thus tropidine would go through the following steps to cycloheptatriene-1,3,5.

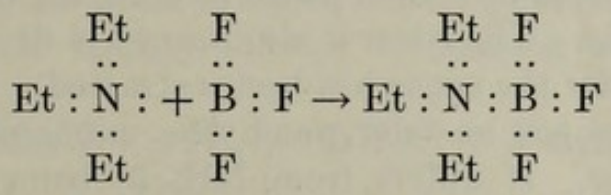


*Free tetra-alkyl ammoniums* are very unstable. They are obtained by electrolysis of the salts at low temperatures. They decompose to give tertiary amines and products corresponding to the free radical involved. With a mercury cathode tetramethylammonium amalgam has been prepared (McCoy 1911). It resembles ammonium amalgam.

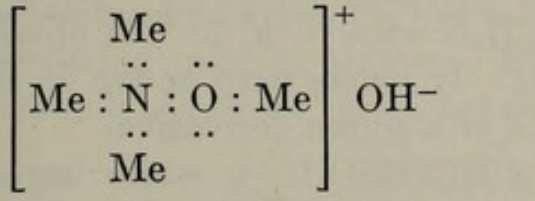
A solution of free tetramethyl ammonium has been formed in liquid ammonia by treating a solution of tetramethyl ammonium chloride with metallic lithium.

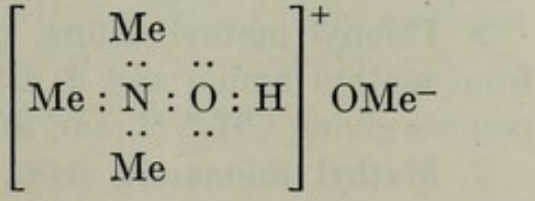
Quaternary ammonium halides form complex polyhalides of the types, $R_4NX_n$ in which $n$ is 3, 5, 7, 9, and 13 (Rep. 1923, 87).

The compound $Et_3N.BF_3$, m. 29°, is undoubtedly formed by a *coordinate link* made possible by the free electron pair of the amine and the ability of the boron atom to share such a pair.



The non-equivalence of the valences of quinquevalent nitrogen has been shown by making isomers, $Me_3N(OH)(OR)$ (Meisenheimer 1913). $Me_3N$ treated with MeI and then NaOH gives a substance which on heating forms $Me_3N$, HCHO and $H_2O$ while the isomer obtained by $Me_3N$ treated with HCl and then with NaOMe gives $Me_3NO$ and MeOH. These are easily understood in the ammonium ion notation





*Individual Amines*

*Methyl amines* are best obtained by the catalytic dehydration of a mixture of methanol and ammonia (Sabatier). The relative amounts of the three amines can be modified somewhat by controlling the concentrations of the reactants and by changing the conditions. The resulting mixture can be distilled under increased pressure to avoid low temperature distillation although that is possible according to the technique developed for separating propane and the butanes from natural gas. The boiling points of the three methyl amines are −7°, +7° and +3.5°, the tertiary being exceptional. All other tertiary amines boil considerably higher than the corresponding secondary amines.

Although the methyl amines are readily available, adequate uses have not yet been found for them.

In the laboratory, methyl amine and trimethyl amine can be

made from formalin solution and paraformaldehyde with ammonium chloride (OS).

$$2\,H_2CO + NH_4Cl \rightarrow CH_3NH_2.HCl + HCO_2H$$
$$3\,(H_2CO)_3 + 2\,NH_4Cl \rightarrow 2\,(CH_3)_3NHCl + 3\,CO_2 + 3\,H_2O$$

Di- and trimethyl amines are formed in decaying fish and similar organic materials. The latter is also formed in dry distillation of beet residues after the sugar has been extracted.

Methyl amine has an odor much like ammonia and is very soluble in water. It differs from $NH_3$ in being inflammable. Its hydrochloride, m. 225°, resembles ammonium chloride. Picrate, m. 215°.

Several individual compounds related to methylamine may be considered here:

1. **N-Dichloro methyl amine,** $CH_3NCl_2$, b. 59°, is made from methyl amine with chlorine and alkali. It reacts with water and alcohols to give hypochlorous acid and its esters. With iodides it liberates iodine. Thus the halogen atoms are "positive."

2. **Thionyl methyl amine,** $CH_3N{=}S{=}O$, b. 58°, is obtained from methyl amine and $SOCl_2$. It reacts with active H compounds giving $CH_3NH_2$ and $SO_2$ or a sulfite derivative.

3. **Methyl thionamic acid,** $CH_3NHSO_2H$, a white unstable solid, is obtained directly from the amine and $SO_2$.

4. **Methyl nitroamine,** $CH_3NHNO_2$, m. 38°, is prepared by nitrating N-methyl urethane and treating the product with ammonia. It gives explosive salts.

$$MeNHCO_2R \xrightarrow{HNO_3} MeN(NO_2)CO_2R \xrightarrow{NH_3} MeNHNO_2 + NH_2CO_2R$$

The imino H is replaceable by alkali metals and thus by organic radicals.

$$Me{-}NH{-}NO_2 \rightarrow MeN{=}NO(OH) \rightarrow Me{-}N{=}NO(ONa) \xrightarrow{RX} Me{-}N(R){-}NO_2$$

The resulting disubstituted nitroamines may be reduced to unsymmetrical *disubstituted hydrazines*, $CH_3RNNH_2$.

Dimethyl amine forms a hydrochloride which is soluble in chloroform. The nitroso compound, $Me_2NNO$, b. 149°, forms a hydrochloride which is hydrolyzed by water. The nitroamine, $Me_2NNO_2$, is a solid, m. 57°, b. 187°.

Trimethyl amine when obtained as a by-product can be utilized by conversion to methyl chloride by heating with HCl under pressure.

$$Me_3N + 4\ HCl \rightarrow NH_4Cl + 3\ MeCl$$

*Ethyl amines* are best prepared from ethyl chloride and ammonia under pressure. Their separation offers no difficulty. The preparation from ethanol and $NH_3$ is not practical because of the large amount of olefin formed. This applies even more to higher alcohols.

Ethylamine on pyrolysis gives ethylene and acetonitrile as the chief products. At higher temperatures methane is the chief hydrocarbon (Hurd).

**C-Halogenated amines** are obtainable by the standard methods for preparing ordinary amines. Ethylene dibromide through the phthalimide synthesis, gives beta-bromoethyl amine,

$$BrCH_2CH_2NH_2$$

(Gabriel 1889). Such a substance, containing two groups which can react with each other but too close to form a stable ring within the molecule, tends to form a ring between two molecules. In this case the product is the dihydrobromide of piperazine,

$$HBr.NH(CH_2CH_2)_2NH.HBr.$$

Gamma halogenated propyl amines give similar 8-membered rings. Delta halogenated butyl amines readily form pyrrolidines. 3-Bromopropyl- and 4-bromobutyl-diethyl amines have been prepared by a series of reactions illustrative of the possibilities in making compounds containing two very active groupings (Marvel 1927).

$$Br(CH_2)_3Br \rightarrow PhO(CH_2)_3Br \rightarrow PhO(CH_2)_3NEt_2$$
$$\rightarrow Br(CH_2)_3NEt_2$$
$$PhO(CH_2)_3Br \rightarrow PhO(CH_2)_3CN \rightarrow PhO(CH_2)_4NH_2$$
$$\rightarrow Br(CH_2)_4NEt_2$$

The splitting of the phenyl ether takes place with HBr without difficulty. The amines are obtained as their salts. The free amines form cyclic quaternary compounds. The bromine gives the reactions of Class 1 halides including that with sodium malonic ester.

A general method for making omega ($\omega$) halogenated tertiary amines depends on the following reactions (Gilman):

$$R_2NH + RMgX \rightarrow R_2NMgX + RH$$
$$R_2NMgX + Tol-SO_3(CH_2)_nCl \rightarrow R_2N(CH_2)_nCl + Tol-SO_3MgX$$

*Unsaturated amines* are obtained by different reactions depending on the relation of the double bond to the amino group.

1. **Δ-1,2-Amines, Vinyl amine,** $CH_2=CHNH_2$, would be expected from the removal of HBr from bromoethyl amine. The product obtained is probably the cyclic ethylene imine, $(CH_2)_2NH$ corresponding to ethylene oxide (Euler 1903). Neurine is a related quaternary base, $CH_2=CH-NMe_3OH$. The formula, $CH_2=CHNH_2$, corresponds to an enol $CH_2=CHOH$. Nitrous acid would be expected to give this enol which would tautomerize to acetaldehyde. As a matter of fact the product is ethylene glycol showing the relation of the substance to ethylene diamine.

Alpha beta unsaturated amines, $-CH=CHNH_2$, are in equilibrium with the form, $-CH_2-CH=NH$, which is readily hydrolyzed to $-CH_2-CHO$. Thus the Hofmann degradation of $\alpha\beta$-unsaturated acid amides gives the next lower aldehyde instead of the unsaturated amine,

$$RCH=CH-CONH_2 \rightarrow RCH_2CHO$$

(Rep. 1920, 80). Conjugated unsaturated amines,

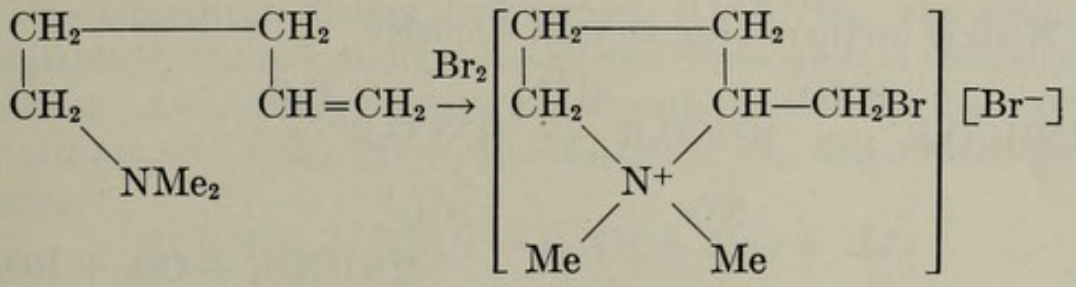
$$RCH=CHCH=CHNH_2,$$

have been obtained (Muskat). The amino group is only weakly basic.

2. **Δ-2,3-Amines, Allyl amine,** $CH_2=CH-CH_2NH_2$, b. 57°, can be made from the halides but is most readily obtained by hydrolyzing allyl isothiocyanate (mustard oil). It is only about one tenth as strong a base as *n*-propyl amine. Its quaternary

compounds, $CH_2=CHCH_2NMe_3X$ are much less poisonous than its lower homolog, the naturally occurring neurine.

**Δ-3,4- and Δ-4,5-Amines** are obtainable from the corresponding C-bromo amines. They show a decided tendency to ring formation. Thus 5-dimethylaminopentene-1, with bromine gives the quaternary bromide of 2-bromomethyl-NN-dimethyl pyrrolidine.



The Br with only six electrons probably adds to the extra electron pair of the olefinic linkage, thus leaving the second carbon with only six electrons. The second carbon can satisfy this deficiency by union with the unshared electron pair of the nitrogen atom in the 1,5-position to it. The resulting quaternary ammonium ion unites with the Br with eight electrons from the bromine.

## IX. ALKYL HYDRAZINES AND RELATED COMPOUNDS

**Alkyl hydrazines,** derivatives of hydrazine, $H_2NNH_2$ (diamide). These are less important than the corresponding aromatic compounds. The alkyl hydrazines resemble the amines in most of their properties but are much less volatile and partake of the properties of hydrazine itself in being powerful reducing agents.

**Primary hydrazines,** $RNHNH_2$, are prepared:

1. From alkyl sulfates and excess of hydrazine and a base.

$$R_2SO_4 + N_2H_4 + NaOH \rightarrow RNHNH_2 + NaRSO_4 + H_2O$$
$$RNaSO_4 + N_2H_4 + NaOH \rightarrow RNHNH_2 + Na_2SO_4 + H_2O$$

An excess of alkylating agent adds more alkyl groups to the same N, the final result being an amino quaternary ammonium salt, $[R_3NNH_2]X$.

2. From primary amines through substituted ureas by treatment with nitrous acid, reduction and hydrolysis by conc. HCl.

$$RNH_2 \xrightarrow{COCl_2} RNHCONHR \xrightarrow{HNO_2} RN(NO)CONHR \rightarrow$$

$$RN(NH_2)CONHR \xrightarrow{HCl} CO_2 + RNH_2.HCl + RNHNH_2.HCl$$

N-alkyl urethanes can be used similarly.

$$RNHCO_2R \xrightarrow{HNO_2} \underset{\displaystyle NO}{\overset{|}{RNCO_2R}} \xrightarrow{4[H]} \underset{\displaystyle NH_2}{\overset{|}{RNCO_2R}} \xrightarrow{H_2O}$$

$$RNHNH_2 + CO_2 + ROH$$

In the same way that the amines are more basic than $NH_3$, the alkylated N in $RNHNH_2$ is more strongly basic than the other N. Thus MeI adds to the first N. Probably HCl does the same

$$\begin{matrix} H:\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}:R \\ H:\underset{\cdot\cdot}{\overset{\cdot\cdot}{N}}:H \end{matrix} \rightarrow \left[\begin{matrix} Me \\ H:\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}:R \\ H:\underset{\cdot\cdot}{\overset{\cdot\cdot}{N}}:H \end{matrix}\right] I \rightarrow \left[\begin{matrix} Me \\ Me:\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}:R \\ H:\underset{\cdot\cdot}{\overset{\cdot\cdot}{N}}:H \end{matrix}\right] I$$

The quaternary iodide will add no more MeI under ordinary conditions. Heated at 125° with excess MeI, it reacts with a splitting of the N—N linkage to give $Me_4NI$.

The inertness of the free $NH_2$ in the hydrazines is further evidenced by their behavior with isocyanates and mustard oils which give $RN(CONHR')NH_2$ etc. Thus the H attached to the substituted N is more reactive than the other two. A reaction of the free $NH_2$ group is that with $SOCl_2$ giving thionyl derivatives, RNHNSO.

The alkylhydrazones, formed with aldehydes and ketones, are usually liquids and consequently are not valuable for identification purposes as are the aromatic compounds.

**Methyl hydrazine,** $CH_3NHNH_2$, b. 87°, may be obtained by reducing nitro or nitroso N-methyl urethanes and hydrolyzing the products. Methyl hydrazine resembles methyl amine in many respects but is a powerful reducing agent, reacting with Fehling's solution even in the cold. The oxidation of methyl hydrazine by HgO gives considerable amounts of mercury

dimethyl, $Me_2Hg$ (very poisonous). Methyl hydrazine reacts with potassium pyrosulfate to give potassium methyl hydrazine sulfonate.

$$MeNHNH_2 + K_2S_2O_7 \rightarrow MeNHNHSO_3K + KHSO_4$$

$EtNHNH_2$, b. 102°.

**Unsymmetrical dialkyl hydrazines,** $RR'NNH_2$, are readily available by the reduction of the nitroso compounds of secondary amines. A surprising reaction is that with the calculated amount of nitrous acid which gives $N_2O$ instead of $N_2$, and a secondary amine.

$$R_2NNH_2 + HNO_2 \rightarrow R_2NH + N_2O + H_2O$$

Mercuric oxide gives a tetrazone, $R_2NN{=}NNR_2$.

Alkylation gives the same unsymmetrical products as the monoalkyl hydrazines

$Me_2NNH_2$, b. 63°. $Et_2NNH_2$, b. 98°.

Symmetrical dialkyl hydrazines, hydrazo alkanes, RNHNHR, are difficult to prepare. They are not available by the alkylation of hydrazine nor a monoalkyl hydrazine because this takes place asymmetrically. The diformyl derivative of hydrazine can, however, be alkylated on both nitrogen atoms (Harries 1894). Treatment of the product with conc. HCl gives a poor yield of the desired product.

$$HCONHNHCOH \rightarrow HCONRNRCOH \rightarrow 2\,HCO_2H + RNHNHR$$

More vigorous treatment with HCl gives $RCl + NH_4Cl$. Mercuric oxide with the ethyl compound gives diethyl mercury and $N_2$ instead of the expected azo-cpd. Nitrous acid splits the compound to give ethyl nitrite. Thus the symmetrical molecule has a much less stable N—N linkage then the unsymmetrical ones.

Careful oxidation of *sym*-$Me_2$-hydrazine dihydrochloride with potassium dichromate solution gives azomethane, $MeN{=}NMe$, b. 2°. Its decomposition, thermal, photochemical and catalytic, have been carefully studied (Ramsberger 1929, Emmett 1932). The thermal decomposition gives mainly $CH_4$ and $N_2$.

Azomethane with HCl gives formaldehyde and methylhydra-

zine hydrochloride. This is due to a tautomeric change in which the N=N linkage plays the part usually played by C=O. $H^+$ adds to one N and is expelled from the carbon in the 3-position. Hydrolysis then gives the observed products.

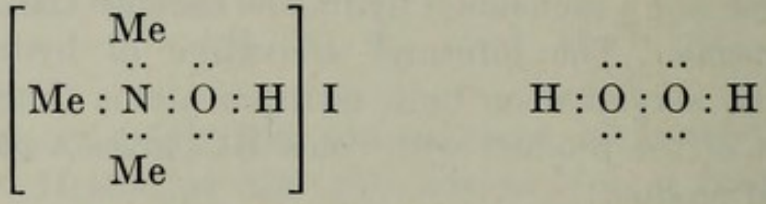
$$CH_3—N=N—CH_3 \xrightarrow{H^+} [CH_3\overset{*}{N}—NHCH_3]^+ \rightarrow$$

$$H^+ + CH_2=N—NHCH_3 \rightarrow CH_2O + CH_3NHNH_2.HCl$$

*sym*-Diisopropylhydrazine and azo-isopropane have been prepared (Lochte 1921–2). The decomposition of the latter is homogeneous and unimolecular, giving $N_2$ and diisopropyl as the chief products (Ramsberger 1928). EtNHNHEt, b. 85°.

**Alkyl hydroxylamines,** derivatives of $H_2NOH$, occur as O-derivatives (*alpha*) and N-derivatives (*beta*).

Direct alkylation of hydroxylamine with methyl iodide gives the quaternary ammonium salt, $Me_3N(OH)I$. It is to be noted that the hydroxyl group is not ionized but forms part of the inner complex. The electronic linkage N : O is like the O : O linkage in hydrogen peroxide.



With ethyl and higher halides, it is possible to interrupt the alkylation at $R_2NOH$, the N,N- or $\beta\beta$-dialkylhydroxylamine.

Alkyl nitrites with Grignard reagents give N,N-dialkylhydroxylamines (Bewad 1907).

$$2\,RMgX + R'ONO \rightarrow R_2NOMgX + R'OMgX + RH$$

When heated with acetic acid N,N-diethylhydroxylamine gives ethyl amine acetate and acetaldehyde. The formation of the latter is due to the oxidizing action of the peroxide-like oxygen.

O-Alkyl hydroxylamines, alkoxylamines, $H_2NOR$, cannot be obtained by direct alkylation because of the additive power of the nitrogen for all alkylating agents. On the other hand oximes, $R_2C=NOH$, can be alkylated and then hydrolyzed to give the desired products. The alkoxylamines can be split by HCl.

They can be alkylated to N,O-dialkyl derivatives, R′NHOR, and finally to quaternary salts $[R_3NOR]X$.

N-Alkyl hydroxylamines, RNHOH, can be obtained by the electrolytic reduction of nitroparaffins and by the splitting of N,O-dialkylhydroxylamines.

The N-alkyl derivatives are more powerful reducing agents than the O-alkyl compounds.

**β-Methyl hydroxylamine,** $CH_3NHOH$, m. 41°, is obtained by the reduction of nitromethane by zinc dust and water. It reduces Fehling's solution. **α-Methyl hydroxylamine,** $NH_2OCH_3$ does not reduce Fehling's solution. When heated with HCl it gives formaldehyde.

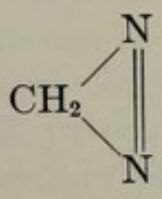
$EtONH_2$, b. 68°; hydrochloride, m. 128°.

EtNHOH, m. 60° dec; $Et_2NOH$, b. 134° dec; EtNHOEt, b. 83°.

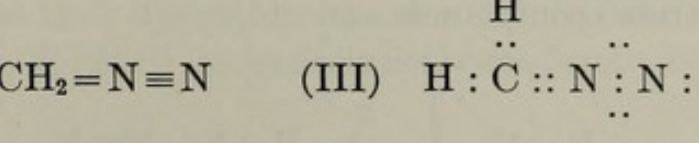
**Diazoparaffins,** $RCHN_2$, are of little importance compared with the corresponding aromatic compounds. The simplest member, diazomethane, azomethylene, $CH_2N_2$ (v. Pechmann 1894) is important as a special methylating agent. It is a yellow poisonous gas which liquefies at −24°. It is used in ether solution. It is prepared from nitroso methyl urethane and alkali. The steps are as follows, starting with methyl amine.

$$MeNH_2 + ClCO_2Et \rightarrow MeNHCO_2Et \rightarrow$$
$$MeN(NO)CO_2Et \rightarrow CH_2N_2$$

An alcoholic solution of nitroso methyl urethane with NaOEt can be used as nascent diazomethane (Rep. 1919, 86). It can also be formed from hydrazine, $CHCl_3$ and KOH and from hydroxylamine and N-dichloromethyl amine. The structure of diazomethane is written as (I) and (II) (Rep. 1917, 87). In all probability this is another case in which electronic formulas are useful (III)

(I) 

(II) $CH_2=N\equiv N$

(III) 

This indicates the ease with which a molecule of $N_2$ can be

liberated leaving the active methylene residue. Thus with $HgCl_2$ and organomercuric chlorides it gives $N_2$ and $ClCH_2HgCl$ and $ClCH_2HgR$ (Hellerman 1932). Iodine gives $N_2$ and $CH_2I_2$, while HCl gives methyl chloride.

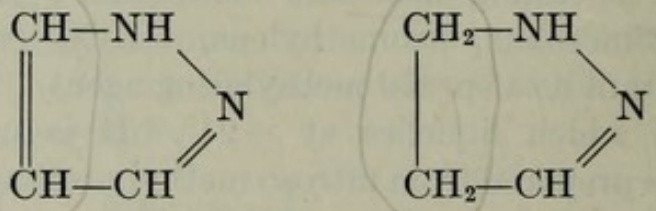
Diazomethane converts acids and phenols to methyl esters and methyl ethers. This action is valuable in the treatment of costly or sensitive substances.

It reacts with acid chlorides and with aldehydes to give chloromethyl ketones and methyl ketones respectively (Rep. 1928, 86–7).

Acetone, in presence of a little water, reacts with diazomethane to give a 40% yield of methyl ethyl ketone (Rep. 1928, 89).

It should be remembered that diazomethane fails to methylate in many special cases which are not as yet thoroughly understood.

Sometimes diazomethane reacts without losing its nitrogen. Thus, with acetylene and ethylene it gives pyrazole and pyrazoline.



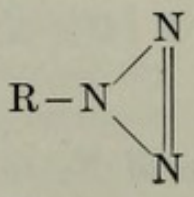
Similar reactions occur with substituted acetylenes and olefins especially those with the unsaturation $\alpha\beta$- to a C=O grouping.

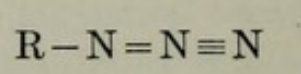
Polymerization of diazomethane gives C,C-dihydrotetrazine, $CH_2(N=N)_2CH_2$.

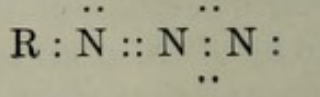
Diazoethane has been made from nitroso N-ethyl urethane.

Higher homologs are obtained by HgO oxidation of hydrazones of aldehydes and ketones. $Me_2CN_2$ is a red oil.

**Alkyl azides,** alkyl azimides, azido alkanes, $RN_3$, are obtainable from alkyl iodides or sulfates and sodium azide, $NaN_3$. They explode at high temperatures. $MeN_3$, b. about 20°. As with the diazo compounds there is doubt as to the structure of these triazo compounds.







**Cyanogen azide,** carbon pernitride, $CN.N_3$, is obtained from BrCN and $NaN_3$, as soluble crystals, m. 36°, unstable to heat and shock. Hydrolysis gives $CO_2$ and $HN_3$. Traces of bromine convert it to an insoluble polymer (Darzens 1912).

**Carbon subnitride, $C_3N_2$,** is obtained by heating tetraiodoglyoxaline to 420°. It resembles carbon in appearance. Heating with soda lime gives ammonia. Heating to higher temperatures gives dicyanogen (Rep. 1913, 127–9).

## X. ALKYL COMPOUNDS OF MEMBERS OF THE PHOSPHORUS FAMILY

**Alkyl compounds of phosphorus** resemble those of nitrogen in many ways but differ in being less basic and more subject to oxidation, properties which would be predicted from a comparison of the parent substances ammonia and phosphine, $PH_3$, the latter being very weakly basic and highly inflammable. There are primary, secondary, and tertiary phosphines and quaternary phosphonium compounds. Each additional alkyl group increases the basic properties from the primary phosphines $RPH_2$ whose hydrochlorides are decomposed by water to $R_4POH$ which is a strong base comparable with $R_4NOH$ and KOH.

The action of phosphine with alkyl halides does not give primary and secondary phosphines but gives directly the tertiary and quaternary compounds. This is because of the rapidly increasing basicity accompanying the introduction of the alkyl groups, the ease of addition of RX being strongly in the order $R_3P > R_2PH > RPH_2 > PH_3$. Treatment of the resulting mixture with alkali and distillation gives the volatile tertiary phosphine leaving the stable phosphonium salt in solution.

Phosphonium iodide, $PH_4I$, heated with an alkyl halide and zinc oxide, gives a mixture of primary and secondary phosphines. These can be converted to their hydrochlorides of which $R_2PH_2Cl$ is stable in water while $RPH_3Cl$ is hydrolyzed completely to $RPH_2$ by cold water.

Tertiary phosphines can be made from Grignard reagents or dialkyl zinc compounds and $PCl_3$.

Phosphorus, heated with alkyl iodides at 180°, gives a mixture

of polyiodides from which the quaternary phosphonium iodide can be prepared by treatment with hydrogen sulfides (Masson 1889). The reaction resembles the dismutation which takes place when phosphorus is heated with water under pressure

$$8\,P + 12\,H_2O \rightarrow 5\,PH_3 + 3\,H_3PO_4$$
$$2\,P + 7\,RI \rightarrow R_4PI_3 + R_3PI_4$$

Of the two organic products, the first is changed by $H_2S$ solution to $R_4PI$ and the latter to the phosphine oxide, $R_3PO$ which is more soluble than the phosphonium compound.

Phosphine with formaldehyde and HCl gives crystalline tetrahydroxymethyl phosphonium chloride $(HOCH_2)_4PCl$ (Rep. 1922, 67).

The boiling points of the methyl and ethyl phosphines (°C.) are −14, 25, 41 and 25, 85, 128 respectively.

Oxidation of primary phosphines gives monoalkyl phosphonic acids, $RPO(OH)_2$, (phosphinsäure), analogous to arsonic and sulfonic acids. Related monoalkyl phosphinous acids RPHO(OH) are obtained by the action of water with an alkyl phosphine dichloride, $RPCl_2$, obtainable from dialkyl mercury and $PCl_3$. The latter acids resemble phosphorous acid in being disproportionated by heat.

$$4\,H_3PO_3 \rightarrow PH_3 + 3\,H_3PO_4$$
$$3\,RPHO_2H \rightarrow RPH_2 + 2\,RPO_3H_2$$

$MePO_3H_2$, m. 105°.

Secondary phosphines on oxidation give dialkyl phosphinic acids, $R_2PO_2H$. $Me_2PO_2H$, m. 76°.

Tertiary phosphines give phosphine oxides, $R_3PO$, which differ from the corresponding nitrogen compounds in stability to heat and reducing agents. Thus they are formed when quaternary phosphonium hydroxides are heated

$$R_4POH \rightarrow R_3PO + RH$$

This is in marked contrast to the behavior of $R_4NOH$. Triethyl phosphine undergoes autoxidation in air much as phosphorus does. Thus a substance which can be oxidized but which does not ordinarily react rapidly with oxygen gas undergoes rapid

oxidation in the presence of such a substance. Probably a peroxide is first formed. Thus the process involved in the oxidation of indigo white by air in presence of $Et_3P$ are probably as follows:

$$Et_3P \rightarrow Et_3PO_2 \rightarrow \text{Indigo blue} + Et_3PO.$$

Characteristically, half of the oxygen goes to the readily oxidizable substance and half to the less readily oxidizable substance, the "acceptor." $Me_3PO$, m. 138°, b. 215°.

Tertiary phosphines react exothermally with sulfur giving $R_3PS$. They also add halogens to form $R_3PX_2$. $R_3P$ also reacts violently with $CS_2$.

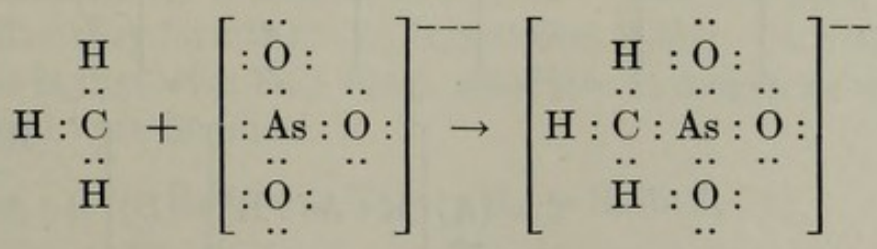
$Et_3PS$, m. 94°. $Et_3PSe$, m. 112°. $Et_3P.CS_2$, m. 95°.

**Alkyl compounds of arsenic.** These differ from the corresponding nitrogen compounds even more than do those of phosphorus. The primary, secondary and tertiary arsines have practically no basic properties. Like the phosphines they are readily oxidized. The quaternary compounds resemble those of nitrogen. The hydroxides are strong bases.

The arsines are prepared very differently from the amines. Thus the best preparations for *methyl arsine*, $MeAsH_2$, b. +2° are:

1. By reduction of methyl arsenic dichloride, b. 133°, obtained from $HgMe_2$ and $AsCl_3$.

2. By reduction of sodium methyl arsonate, $MeAsO_3Na_2$, prepared from MeI and sodium arsenite. A barely alkaline solution of $As_2O_3$ in NaOH is used in this reaction. NaI is formed and the methyl carbon with only six electrons attaches itself to the free electron pair of the arsenite ion



This is similar to the action of a sulfite to give a sulfonate with an alkyl halide. Sodium methyl arsonate is used medicinally as Arrhenal.

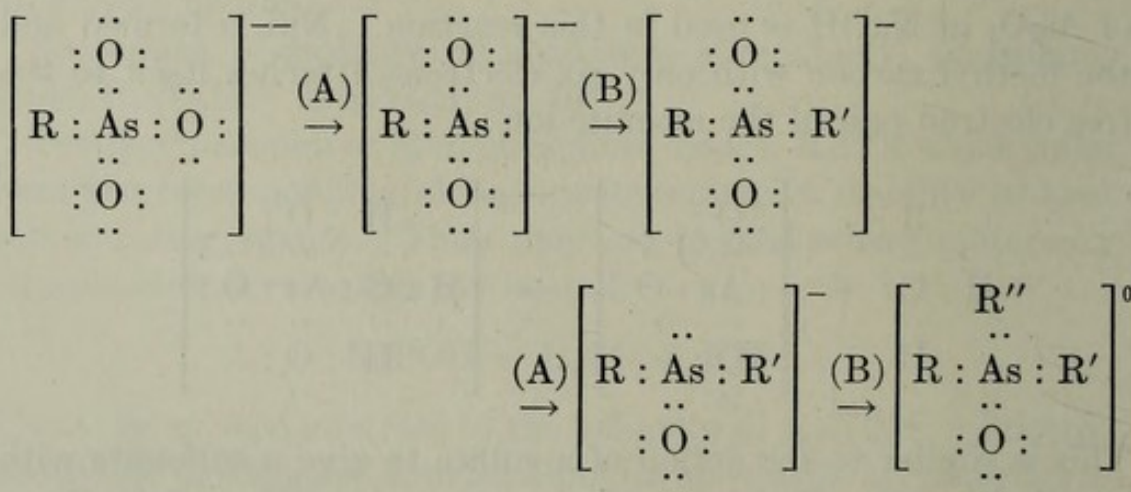
Like all arsenic compounds, especially the volatile ones, methyl arsine is poisonous.

**Dimethyl arsine,** cacodyl hydride, $Me_2AsH$, b. 37° is an extremely poisonous, spontaneously inflammable liquid of terrible odor. The corresponding oxide, cacodyl oxide, $(Me_2As)_2O$, is obtained by heating $As_2O_3$ and potassium acetate (Cadet 1760, Bunsen 1843). Many compounds of the cacodyl radical ($Me_2As-$) have been studied. Its chloride, with zinc, gives cacodyl, $Me_2AsAsMe_2$, b. 170°, spontaneously inflammable. It reacts with limited amounts of oxygen, sulfur and halogens to give cacodyl compounds. With MeI it gives cacodyl iodide and tetramethylarsonium iodide. Cacodylic acid is dimethylarsinic acid, $Me_2AsO_2H$.

Diethyl arsine is probably formed by moulds growing in material containing arsenic compounds. At a time when "aniline dyes" were made with arsenic acid (p. 848), wall papers printed with these dyes made possible this peculiar production of a volatile poisonous arsenic compound.

Tertiary arsines are made from $AsCl_3$ with Grignard reagents or alkyl zinc compounds.

The arsines are readily oxidized to arsonic acids, $RAsO_3H_2$, arsinic acids, $RR'AsO_2H$, and arsine oxides, $RR'R''AsO$. The acids can be reduced by $H_2SO_3$ (A) to the trivalent form of arsenic and converted to the related sodium salts which react with alkyl halides (B) in the same way as sodium arsenite.



The final product is the tertiary arsine oxide.

The arsines readily unite with oxygen, sulfur and halogens to give pentavalent compounds. When the pentavalent chlorides $R_nAsCl_{5-n}$ ($n=1$ to 4) are heated, RCl separates leaving $R_{n-1}AsCl_{4-n}$. This, with chlorine, gives $R_{n-1}AsCl_{6-n}$, etc., until all alkyl groups are removed and $AsCl_3$ is left. This is a remarkable difference from the behavior of nitrogen compounds. Another important difference is the reaction of the arsines with arsenic chloride.

$$R_3As + AsCl_3 \rightarrow R_2AsCl \text{ and } RAsCl_2$$

Methyl-dichloro-arsine, $CH_3AsCl_2$, was used as a war gas. It was ineffective compared with mustard gas. It can be prepared according to the last equation or by the action of an excess of HCl on $MeAsO_3Na_2$ obtained from sodium arsenite and $Me_2SO_4$ or MeCl.

A penta-alkyl compound of arsenic can be made, $Me_5As$, from zinc dimethyl and $Me_4AsI$. It is a volatile liquid.

The war gas, Lewisite, is chlorovinyl dichloro arsine,

$$ClCH=CHAsCl_2.$$

When prepared from $AsCl_3$ and acetylene, much of the secondary and tertiary arsines are obtained. These can be changed to Lewisite by heating with $AsCl_3$.

Organic Arsenical Compounds, Raiziss and Gavron, A.C.S. Monograph, Chemical Catalog Company, New York, 1923.

**Alkyl compounds of antimony, Stibines.** In these, the increasing metallic nature of antimony makes marked changes from the amines. $SbCl_3$ with zinc alkyls gives *trialkylstibines*. They are spontaneously inflammable liquids. With halogens, oxygen and sulfur they form $R_3SbX_2$, $R_3SbO$ and $R_3SbS$. A remarkable reaction is that with HCl which generates hydrogen as though a free metal were involved.

$$R_3Sb + 2\,HCl \rightarrow H_2 + R_3SbCl_2$$

Just as a free metal discharges hydrogen ions by means of its valence electrons the antimony, when attached to three alkyl groups acquires metallic properties in the sense that its free

electron pair acts like a free metal.

$$Ca: + 2\,H:\ddot{Cl}: \rightarrow Ca^{++} + 2\,Cl^{-} + H:H$$

$$R:\ddot{Sb}:(R) + 2\,H:\ddot{Cl}: \rightarrow \left[R:\ddot{Sb}:\ddot{Cl}:\right]^{+}(R) + Cl^{-} + H:H$$

Another example of the metallic tendencies of antimony is the existence of salts such as $R_3SbSO_4$. The electronic nature of such a substance offers an interesting field for speculation. It may be

$$\left[R:\ddot{Sb}:R\right]^{++}\left[:\ddot{O}:\ddot{S}:\ddot{O}:\ddot{O}:\right]^{--}$$

$Me_3Sb$, b. 81°. $Et_3Sb$, b. 159°. $Me_5Sb$, b. 100°.

Alkyl iodides add to tertiary stibines giving quarternary stibonium compounds of properties like the corresponding ammonium compounds. The hydroxide, $R_4SbOH$, is also a strong base.

Organic Derivatives of Antimony, Christiansen, A.C.S. Monograph, Chemical Catalog Company, New York, 1925.

**Alkyl compounds of bismuth.** These are true metallo-organic compounds in contrast to the compounds of N, P, As and Sb. They are prepared from $BiCl_3$ and Grignard reagents. The trialkyl bismuthines react with acids to give bismuth salts and hydrocarbons.

$$Me_3Bi + 3\,HCl \rightarrow BiCl_3 + 3\,CH_4$$

With halogens and sulfur they show no tendency to form pentavalent compounds but suffer a splitting of the C-metal linkage. Thus

$$Me_3Bi + 3\,I_2 \rightarrow BiI_3 + 3\,MeI$$
$$2\,Me_3Bi + 6\,S \rightarrow Bi_2S_3 + 3\,Me_2S$$

No quaternary compounds are formed.

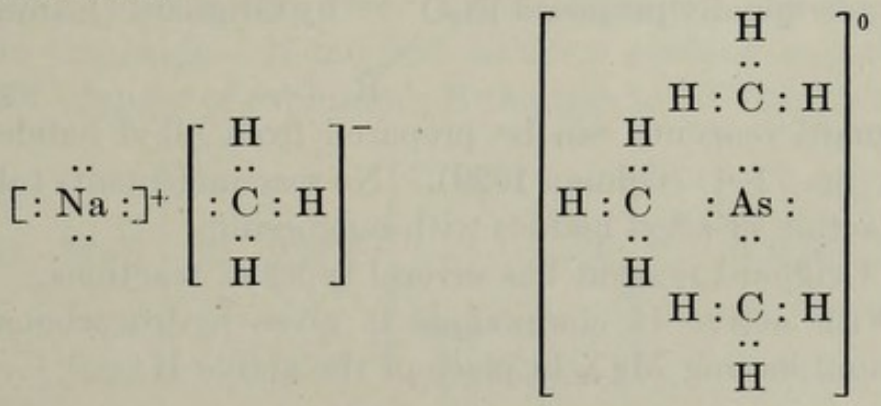
$Me_3Bi$, b. 110°. It explodes when heated in air.

## XI. METAL ALKYLS

**Alkyls of the alkali metals** are best obtained from the metals and mercury alkyls in the absence of air (Schlenk 1927). Sodium added to dimethylzinc precipitates metallic zinc. While the zinc compound does not act with $CO_2$ the resulting product gives sodium acetate.

$$MeNa + CO_2 \rightarrow MeCO_2Na$$

The alkali alkyls are non-volatile solids, insoluble in inert organic solvents. Their solutions in diethylzinc conduct electricity (Hein 1924). These properties are in sharp contrast to those of substances like the volatile, soluble, non-conducting arsines. One type of substance is polar and the other is non-polar (Carothers 1929).



Lithium alkyls can also be prepared from Li and RBr in $N_2$ atmosphere (Ziegler 1930, Gilman 1932). They are useful in certain synthetic processes in which Grignard reagents fail.

Sodium ethyl reacts with ether to give NaOEt, ethane and ethylene (Rep. 1923, 58). This reaction introduces complications into Wurtz reactions run in ether solution since RNa is probably an intermediate.

NaEt when heated below 150° gives ethane, ethylene, hydrogen and sodium acetylide. NaMe gives $CH_4$, sodium and $Na_2C_2$ (Carothers 1929, 1930).

Organo-alkali compounds, Wooster, Rev. 1932, II 1–92.

Organo-metals, Ahr. 1927, 320–428.

Organo-alkali compounds, Schlenk, Bergmann, A. *463*, 1; *464*, 1 (350 pp.).

**Alkyl derivatives of magnesium.** The Grignard reagent, RMgX, is the most important reagent ever introduced into organic chemistry (Hallwachs 1859, Lohr 1891, Fleck 1893, Barbier 1899, Grignard 1901). It is formed from the alkyl halides with metallic magnesium, usually in the presence of anhydrous ethyl ether but other solvents such as higher ethers (Marvel 1928), tertiary amines and even hydrocarbons may be used. In special cases no solvent is used. In the solution obtained there is an equilibrium $2\,RMgX \rightleftharpoons R_2Mg + MgX_2$ (Schlenk 1929, Gilman 1929, 1930). Of the three substances only $R_2Mg$ is soluble in dioxan (Schlenk 1932).

The nature of the oxonium complex of the Grignard reagent with ether has never been settled. It has been proved *not* to be of the type originally proposed $Et_2O\begin{matrix}\diagup\,MgX\\ \diagdown\,R\end{matrix}$ by Grignard (Kamm 1911).

Grignard reagents can be prepared from alkyl halides of all classes (pp. 71–4) (Gilman 1929). No rearrangements take place in the action of alkyl halides with magnesium.

The Grignard reagent has several types of reactions.

1. With active H compounds it gives hydrocarbons and a compound having MgX in place of the active H.

$$RMgX + HOH \rightarrow RH + HOMgX$$

Similarly ammonia, primary and secondary amines, all acids and $-C\equiv CH$ compounds give $NH_2MgX$, $RNHMgX$, $R_2NMgX$, $ClMgX$ and $-C\equiv C-MgX$. The last type of compound is a Grignard reagent and can be used as such in syntheses.

The action of methyl Grignard reagent in a high boiling ether is used as a quantitative test for active hydrogen compounds ($-OH$, $-NH$, $-SH$ etc.) by measuring the methane evolved (Zerewitinoff), (Kohler).

2. With multiple linkages between carbon and another element it adds with the MgX on the other element and the alkyl group on the carbon.

$$=C=O + RMgX \rightarrow =C(R)OMgX \rightarrow =C(R)OH$$

The last step is produced by treatment with acid or with solutions of ammonium salts if the final product is sensitive to acids.

$$=C=S \rightarrow =C(R)SMgX \rightarrow =C(R)SH$$
$$-C\equiv N + RMgX \rightarrow -C(R)=NMgX \rightarrow$$
$$-C(R)=NH \rightarrow -C(R)=O$$

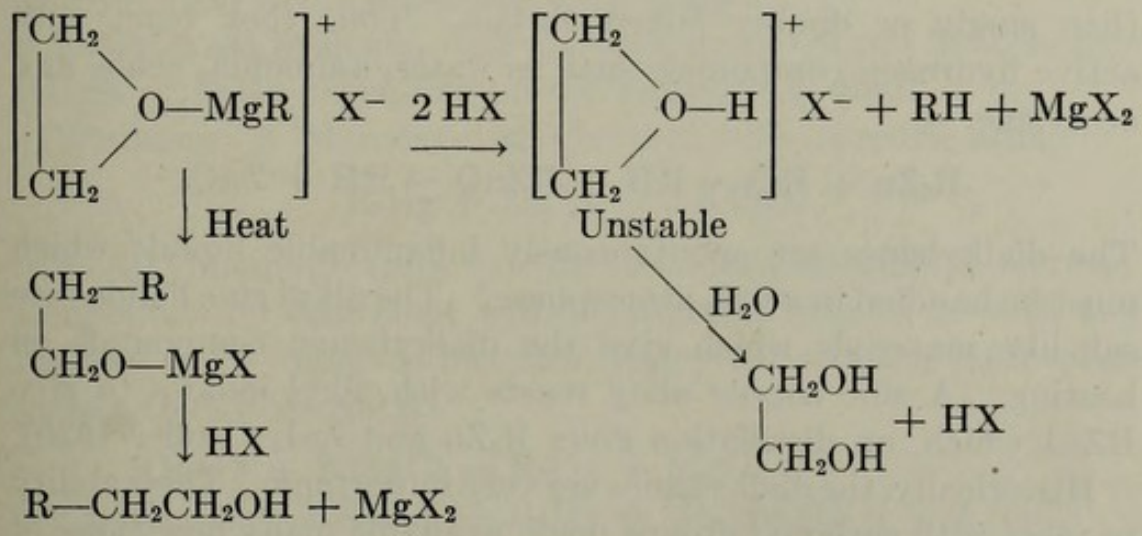
3. With elements such as the halogens, oxygen and sulfur, Grignard reagents form alkyl halides, alcohols and mercaptans.

$$2\,RMgX + O_2 \rightarrow RX + MgO + ROMgX \rightarrow ROH$$

These reactions have not been adequately studied (Marvel 1933). Hydrogen peroxide (30%) gives alcohols (Oddo).

4. With halides such as $PCl_3$ and $HgCl_2$, to introduce alkyl groups in place of halogen atoms.

5. With ethylene oxides. The first product is an oxonium salt which, when treated with water or acid, gives RH and the glycol related to the oxide. If the first addition product is heated to about 150° (danger of explosion), it changes to $RCH_2CH_2OMgX$:




6. With alkyl halides to give hydrocarbons.

$$RX + R'MgX \rightarrow MgX_2 + RR'$$

The yields are poor, especially so, with tertiary halides. A better modification involves the use of alkyl esters of aromatic sulfonic acids (Gilman)

$$Tol-SO_3R + R'MgX \rightarrow RR' + Tol-SO_3MgX$$

Esters of aliphatic sulfonic acids give sulfones

$$RSO_3R' + R''MgX \rightarrow RR''SO_2 + R'OMgX$$

7. Silver bromide produces a peculiar coupling to give hydrocarbon, R—R (Gardner 1929).

$$2\ RMgBr + 2\ AgBr \rightarrow R-R + 2\ MgBr_2 + 2\ Ag$$

8. Grignard Reagents give a characteristic color with iodine and Michler's ketone (Gilman, Schulze 1925; Gilman, Heck 1930).

Magnesium in Organic Chemistry, Courtot.

Grignard reagent, Ahr. 1905, 89 pp.; 1908, 90 pp.

West and Gilman, 1922.

Rep. 1932, 99–103.

**Alkyl compounds of beryllium and calcium** resembling the Grignard reagent have been prepared (Gilman 1927).

**Alkyl compounds of zinc** are typical metallo-organic compounds (Frankland 1849). They are completely decomposed by all compounds containing hydrogen attached to elements other than singly or doubly linked carbon. Thus they react with active hydrogen compounds such as water, ammonia, acids, and acetylene.

$$R_2Zn + HQ \rightarrow RH + RZnQ \rightarrow RH + ZnQ_2$$

The dialkylzincs are spontaneously inflammable liquids which must be handled in a $CO_2$ atmosphere. The alkyl zinc halides are salt-like materials which give the dialkyl zinc compounds on heating. A zinc copper alloy reacts with alkyl iodides to give RZnI which, on distillation gives $R_2Zn$ and $ZnI_2$ (Noller 1929).

Historically, the dialkylzincs are very important. Their ability to react with carbonyl groups made available many new types of compounds.

$$RCHO + R_2'Zn \rightarrow RR'CHOZnR' \rightarrow RR'CHOH$$

At present their most important use is in replacing a halogen by an alkyl group when the result cannot be achieved in any other way. Thus: $Me_3CCl + R_2Zn \rightarrow Me_3CR$ (Noller 1929). For this purpose they are better than Grignard reagents although the yields are still poor.

The zinc compounds are sometimes useful in making ketones from acid chlorides since they react only slowly with the products whereas Grignard reagents act rapidly with ketones.

Dialkyl zinc compounds react readily only with tertiary halides and with acid halides. Other types of halides are not sufficiently reactive to give the full yield.

Zinc diethyl in ether solution is a poor conductor but can be electrolyzed to give zinc at the cathode and ethyl radicals at the anode (Rodebush 1929).

$Me_2Zn$, b. 46°, $Et_2Zn$, b. 118°.

**Alkyl compounds of mercury.** These show properties of both the nonmetallic and metallic derivatives of organic compounds. They are not attacked by water but are split by acids. The dialkyl mercury compounds, $R_2Hg$, are poisonous liquids. The organomercuric salts, RHgX, are crystalline solids.

General methods of preparation.

1. Sodium amalgam with alkyl bromides in presence of a catalyst such as ethyl acetate, give $R_2Hg$.

2. Grignard reagents, with mercuric or mercurous halides, give RHgX or $R_2Hg$ depending on the proportions used.

Reactions: 1. Mercury dialkyls react with mercuric salts,

$$R_2Hg + HgX_2 \rightarrow 2\ RHgX$$

2. Alkylmercuric salts can be converted to dialkyl mercury compounds by treatment with a Grignard reagent or with any reagent which removes mercuric ions from solution more completely than does NaOH

$$RHgCl + RMgCl \rightarrow R_2Hg + MgCl_2$$
$$2\ RHgCl + 4\ NaCN \rightarrow R_2Hg + Na_2Hg(CN)_4 + 2\ NaCl$$

3. Both types of mercury compound react with acids, especially halogen acids, with splitting of the C—Hg linkage and formation of a hydrocarbon.

$$R_2Hg \rightarrow RH + RHgCl \rightarrow RH + HgCl_2$$

4. The C—Hg linkage is split by halogens.

$$R_2Hg + X_2 \rightarrow RX + RHgX \rightarrow RX + HgX_2$$

This method may be of preparative value as in the case of

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neopentyl bromide and iodide which cannot be made by the ordinary reactions.

5. It might be expected that alkyl mercury compounds would react with alkyl halides to give $HgX_2$ and higher paraffins. This is not possible. Either there is no reaction or the C—Hg compound merely removes HX from the halide, thus acting as a hydrocarbo base (Jones 1918). All metallo-organic compounds belong to this category in that they neutralize acids with the formation of hydrocarbons in the same way that an aquo base neutralizes an acid and forms water.

Alkylmercuric hydroxides, RHgOH, contrary to older reports, are very weak bases. They can be prepared from RHgCl by alcoholic KOH which precipitates KCl (Adams). The impression that MeHgOH was a strong base came from the fact that it liberates $NH_3$ from ammonium salts and has a caustic effect on the skin. It is actually a weaker base than aniline. It forms an insoluble carbonate and a soluble bicarbonate. Boiling either with water expels $CO_2$ *completely* leaving the free base. An aqueous solution of the base reacts quantitatively with NaCl solution precipitating RHgCl and leaving NaOH in the solution. Thus NaCl can be causticized by this peculiar base in the same way that sodium carbonate is converted to NaOH by lime. The compounds, RHgOH, are unique in being *weak, soluble, stable bases.* All other weak bases are either insoluble or unstable.

| | |
|---|---|
| $Me_2Hg$, b. 95°. | MeHgI, m. 143°. |
| $Et_2Hg$, b. 160°. | EtHgCl, m. 193°. |

Methylmercuric iodide can be made from MeI and Hg in sunlight. The change is catalyzed by mercurous iodide (Maynard 1923).

Ethylmercuric chloride is important industrially as a fungicide in treating seeds, lumber, etc. It is used in high dilution either in solution or in dusting powders. It is made from $HgCl_2$ and lead tetraethyl.

Mercuric salts react with olefins and acetylenes (pp. 34, 64).

It is possible to attach several mercury atoms to a carbon. Thus the organic compound containing the smallest percentage of carbon is the iodide of ethane hexamercarbide, $(IHg)_3CC(HgI)_3$.

Organic Compounds of Mercury, Whitmore, A.C.S. Monograph, Chemical Catalog Company, New York, 1921.

**Alkyl compounds of boron** are made from Grignard or zinc compounds with $BCl_3$ and with boric acid esters such as $(MeO)_3B$. *Trimethyl borine* is a gas, and $BEt_3$ boils at 95°. They are spontaneously inflammable and are decomposed by acids to give hydrocarbons. Alkyl boric acids, $R_2BOH$ and $RB(OH)_2$ are obtained by replacing part of the chlorine atoms in $BCl_3$ and hydrolyzing the products. They thus have properties of both metal and non-metal alkyl compounds.

**Aluminum trialkyls** can be made from the mercury alkyls with metallic aluminum. Aluminum powder with ethyl iodide gives $Et_2AlI$ and $EtAlI_2$, b. 120° and 160°. Both are spontaneously inflammable and are decomposed by water as are the trialkyl compounds.

$Me_3Al$, b. 130°.

**Gallium triethyl,** b. 142°, is made from gallium and $HgEt_2$. It is spontaneously inflammable (Dennis 1932). $GaMe_3$, b. 55.7°, is prepared from the chloride and $Me_2Zn$. The solid even at −76° catches fire spontaneously (Kraus 1933).

**Thallium triethyl,** b. 51° (1.5 mm.), is obtained from lithium ethyl and thallous chloride (Birch 1934).

**Alkyl compounds of silicon** are made like those of bismuth and boron. They are of special interest because the introduction of the silicon atom leaves the compounds as true organic substances in many respects.

Tetra-alkyl derivatives of silicane, $SiH_4$, silicopentane, $Me_4Si$, b. 28°, silicononane, $Et_4Si$, b. 153°.

In such compounds it is possible to replace hydrogen by chlorine without breaking the C—Si bond. The chlorine can be replaced by an acetate group which can be hydrolyzed to the corresponding alcohol, $Et_3SiCH_2CH_2OH$.

$Et_3SiSiEt_3$, b. 253°. $Et_3SiH$, b. 107°. $Et_3SiCl$, b. 143°.

$Et_3SiOH$, of camphor odor, b. 154°, gives tertiary alcohol reactions.

**Germanium alkyls** have been made and studied extensively (Dennis 1925, 1930, 1932). $Et_4Ge$, b. 163.5°, d. 0.99, pleasant odor.

**Alkyl compounds of tin** have been extensively studied. They are true metallo-organic compounds. They are made from alkyl iodides with alloys of tin with sodium or zinc. Mixed compounds $R_nSnI_{4-n}$ are obtainable. Stannous chloride, $SnCl_2$, with dialkylzincs or Grignard reagents gives the tetra-alkyl stannanes and metallic tin (Kraus).

Treatment of the alkyl tin compounds with halogen acids or halogens replaces alkyl groups by halogens forming paraffins or alkyl halides. They do not act with water.

The free radical, $Me_3Sn$, obtained from the corresponding halide with Na, absorbs oxygen, etc.

$Me_4Sn$, b. 78°, $Me_3SnI$, b. 170°, $Me_2SnI_2$, m. 30°, b. 228°.

$Et_4Sn$, b. 181°. $Et_3SnSnEt_3$, b. 270°.

Asymmetric tin compounds of the type MeEtPrSnI have been obtained in optically active forms (Pope 1903).

**Alkyl compounds of lead** have been studied very extensively especially in recent years because of the interest in lead tetraethyl as an anti-knock for gasoline. The lead tetra alkyls resemble the mercury dialkyls in general properties and reactions.

The lead dialkyls are unstable. Lead chloride heated with a Grignard reagent gives the tetra-alkyl.

$$2\ PbCl_2 + 4\ RMgCl \rightarrow R_4Pb + 4\ MgCl_2 + Pb$$

Free methyl and ethyl radicals were first prepared by heating the lead alkyls (Paneth 1929). Their half life is about 0.006 sec. Higher alkyl radicals decompose even more rapidly into olefins and methyl or ethyl radicals. The free radicals attack metallic mercury forming $Me_2Hg$ which can be identified as MeHgBr (Rice 1932).

Lead tetraethyl is made commercially by heating ethyl chloride under pressure with sodium lead alloy. The amount produced per year is in excess of twenty million pounds.

Many simple and mixed lead tetra-alkyls have been prepared (Grüttner 1918).

Mixed compounds $R_nPbCl_{4-n}$ and diplumbic compounds $R_3PbPbR_3$ are known. Trivalent and bivalent lead alkyls have been prepared.

$Me_3PbOH$ is a strong base.

Organic Compounds of Lead, Calingaert, Rev. 1925, 43–84.

The metallo-organic compounds of Cu, Ag, Au, Cr, Th, Fe, Pt etc. are very unstable (Kharasch 1931).

## XII. ALDEHYDES AND KETONES

Their relations as dehydrogenation products of the primary and secondary alcohols have been considered. Both contain the reactive grouping, C=O, carbonyl, a grouping characterized by extreme unsaturation or ability to add a great variety of reagents. This ability is modified by the attached groups. Thus the aldehydes which have H attached to the carbonyl group are considerably more reactive than the ketones which have two alkyl groups attached to it. In turn the methyl ketones containing the grouping, $CH_3CO$, are more reactive than those which contain two larger groups. Branching of the alkyl groups, especially near the carbonyl has a profound effect both on the activity of that group and on the production of such aldehydes and ketones. (Conant 1929).

Aldehydes and ketones are anhydrides of *gem*-dihydroxyl compounds. Such hydrates of carbonyl compounds can be isolated only in special cases such as chloral hydrate, $Cl_3CCH(OH)_2$. In water solution the lower aldehydes and ketones probably exist in equilibrium with their hydrates.

$$=C=O + H_2O \rightleftharpoons =C(OH)_2 \quad \text{(Perkin 1887).}$$

The aliphatic aldehydes range in volatility from gaseous formaldehyde through liquids to solids at the $C_{12}$ member and in odor from the very sharp smelling lower aldehydes through perfume materials to odorless solids. The ketones range from liquids to solids. They have sweet odors. The intermediate ones are valuable in perfumes.

### *A.* Saturated Aldehydes

These have the formula, $R—C(=O)H$, and are named from the acids which they give on oxidation.

**Formaldehyde,** methanal, HCHO, b. $-21°$, is prepared from methanol by oxidation or dehydrogenation. Because of its volatility, the first reaction is readily carried out although formaldehyde is much more readily oxidized than methanol. There is excellent evidence that the first step in the oxidation of a substance like methanol is the conversion of the H of the group, CHOH, to hydroxyl giving $C(OH)_2$. Two hydroxyl groups seldom remain attached to the same carbon. In most cases water is lost leaving a *carbonyl group*, $=C=O$. Thus the oxidation of methanol is as follows:

$$CH_3OH + [O] \rightarrow H_2C(OH)_2 \rightarrow H_2C=O + H_2O$$

The dehydrogenation is carried out in the presence of heated platinum, silver or copper. By admitting air with the methanol vapors, part of the hydrogen is oxidized to give the heat necessary for the reaction. Formaldehyde is available as *formalin*, a 35–40% solution in water and methanol. It also contains varying amounts of impurities such as *formal*, formaldehyde dimethyl acetal, $H_2C(OMe)_2$. Formaldehyde has a characteristic penetrating odor. Formaldehyde is also obtained in small yields by the partial oxidation of hydrocarbons, especially ethane and ethylene. The steps in the oxidation are possibly

$$CH_3CH_3 \rightarrow CH_2=CH_2 \rightarrow HOCH_2CH_2OH \rightarrow$$
$$HCOCHO \rightarrow H_2CO + CO$$

Since these substances are gaseous under the conditions of the oxidation and the formaldehyde is the most easily oxidized, it is not surprising that the yield is small. The first step represents what has been proved to be the first step in the "cracking" of ethane. The next step is based on the behavior of olefins with oxidizing agents in the presence of water. Apparently $H_2O+[O]$ add 2 $-OH$ groups to the ethylenic linkage to give a glycol. The third step represents the usual oxidation of a glycol. The last step includes a common decomposition of an aldehyde at high temperatures. It is also a case of "dismutation," this time, within a single molecule. Two adjacent carbons are oxidized and reduced by each other.

Formaldehyde is said to occur in air in minute amounts as a

result of its formation during combustion processes (Gautier 1904).

Formaldehyde is also produced by heating certain formates, $(HCO_2)_2Ca \rightarrow CaCO_3 + H_2CO$. This again is dismutation, half of the formate is oxidized to carbonate and the other half is reduced to formaldehyde.

There is excellent evidence that the first product formed from carbon dioxide by the chlorophyll of green plants is formaldehyde, $CO_2 + H_2O \rightarrow H_2CO + O_2$. (Rep. 1906, 83–88). The ratio of oxygen given off by the plant to the carbon dioxide absorbed has been found experimentally to be 1 : 1 (Willstätter). The formaldehyde, being extraordinarily reactive, undergoes a variety of changes. If the living plant needs an oxidizer or a reducer, the formaldehyde can serve in either capacity, changing to methanol and to formic acid or carbonic acid respectively. The first of these changes is indicated by the presence of methyl derivatives in many plant products. Most of the formaldehyde probably undergoes the *aldol condensation*, the H from one molecule adding to the carbonyl group of another, etc.

$$2\ H_2C{=}O \rightarrow HOCH_2CHO$$

This product is glycollic aldehyde, the simplest "carbohydrate." Another $H_2CO$ can add to this substance to form

$$HOCH_2CHOHCHO,$$

glyceric aldehyde, another simple carbohydrate. This process of building up the carbohydrate molecules may continue stepwise or two of the glyceric aldehyde molecules may condense to form a *hexose*. This has been accomplished in the laboratory with the formation of *formose* or $\alpha$-acrose, a mixture of hexoses very similar to the ordinary hexose sugars (E. Fischer).

The reactions of formaldehyde are partly typical of aldehyde reactions and partly peculiar to itself.

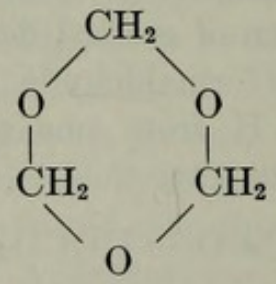
1. Oxidation is very easy.

$$H_2C{=}O \rightarrow HC(OH){=}O \rightarrow HO{-}C(OH){=}O \rightarrow CO_2 + H_2O$$

In this case the mechanism of oxidation through the change of C—H to C—OH is apparent. In common with other aliphatic aldehydes and in contrast to ketones, formaldehyde reduces ammoniacal silver solution and Fehling's solution (alkaline cupric tartrate solution). In alkaline solution hydrogen peroxide oxidizes it quantitatively to a formate.

2. Reduction is also easy, $CH_2O \rightarrow CH_3OH$.

3. Polymerization. Formaldehyde readily changes reversibly into solid polymers. *Paraformaldehyde*, paraform, $(CH_2O)_x$, is obtained as an amorphous white solid by evaporation of an aqueous solution of $CH_2O$. It is probably $HOCH_2(OCH_2)_nCHO$ (Staudinger 1932, Sauter 1933). Rapid condensation of $CH_2O$ vapors can give $\alpha$-trioxymethylene which is a definite 6-membered ring compound. It is crystalline and readily soluble in water, alcohol and ether.



Treatment of formaldehyde solution with sulfuric acid in various ways gives several different "trioxymethylenes" or, more properly, polyoxymethylenes of unknown molecular weight and structure. All these polymers are readily converted back to formaldehyde by heat. "Paraform" candles are used for fumigating, part of the paraformaldehyde burning and part being depolymerized to formaldehyde.

The change of formaldehyde to formose also agrees with every possible definition of polymerization, even to the probability that it is reversible to a certain degree.

4. With bases.

*a*. Concentrated strong bases cause dismutation (Cannizzaro) (Willstätter 1931, Fry 1931).

$$2\,H_2CO + KOH \rightarrow HCO_2K + CH_3OH$$

This reaction is characteristic of aldehydes which have no *alpha* hydrogen, that is, no hydrogen on the carbon *next* to the carbonyl

group. Thus it occurs with benzaldehyde, $C_6H_5CHO$, and pivalic aldehyde, $Me_3CCHO$. When two alpha hydrogens are present the strong base gives complex aldol condensation products or aldehyde resins.

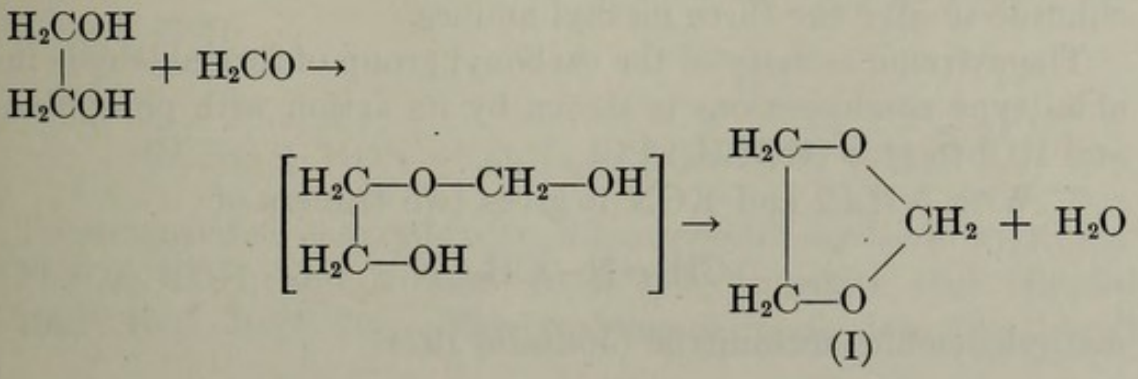
*b.* Dilute and weak bases cause aldol condensations as discussed under the behavior of formaldehyde in plants.

Formaldehyde supplies a very reactive carbonyl group for aldol condensations with $\alpha-H$ compounds such as acetaldehyde and isobutyraldehyde. With ketones and secondary amines it replaces the $\alpha-H$ atoms with the group $-CH_2NR_2$. Thus acetone with formalin and dimethylamine gives products from $Me_2NCH_2CH_2COCH_3$ to $(Me_2NCH_2)_3CCOC(CH_2NMe_2)_3$.

5. Alcohols in the presence of a trace of acid give "formals" ethers of the hypothetical hydrate of formaldehyde $H_2C(OH)_2$.

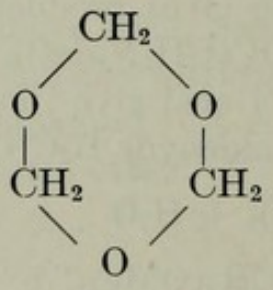
$$H_2CO + 2\,ROH \rightarrow H_2C(OR)_2 + H_2O$$

**Methylal,** methylene dimethyl ether, $CH_2(OMe)_2$, b. 42°, is obtained by the partial oxidation of methanol at low temperatures with acid oxidizing agents. It may also be made from a methylene halide and sodium methylate. Methylal with $Br_2$ gives $Br_2C(OMe)_2$, an active methylating agent which converts aniline to methyl aniline, sodium cinnamate to methyl cinnamate, naphthols to their ethers and sodiomalonic ester to the methyl compound (Rep. 1922, 73). The formals differ from ordinary ethers in being readily hydrolyzed by strong acids. Hemiformals, $CH_2(OH)OR$, are less stable. Glycols give cyclic formals, *dioxolanes*, the parent substance (I) being obtained from formaldehyde and ethylene glycol. The first product may be a hemiacetal with reactive groups in the 1,5-position, thus making ring closure easy.

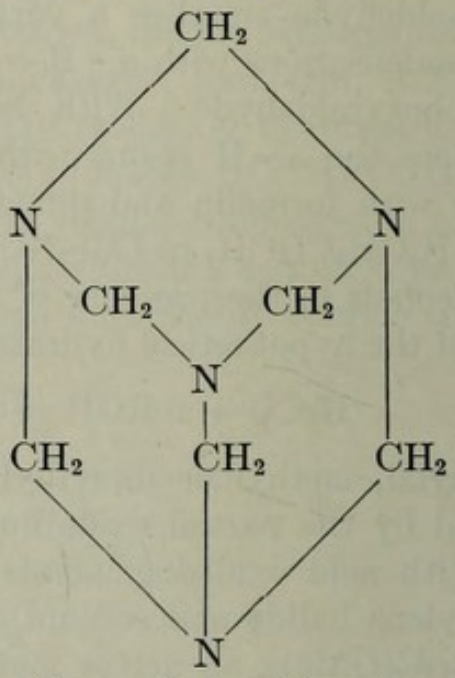



(I)

6. Ammonia forms hexamethylene tetramine, $(CH_2)_6N_4$. The first product undoubtedly results from the addition of $NH_3$ to the carbonyl group in the usual manner. This product loses water to form the imino analog of formaldehyde, $H_2C=NH$. This polymerizes much as formaldehyde does except that the higher valence of nitrogen makes possible a more complex polymer.



Trioxymethylene



Hexamethylene tetramine

The probability of the latter formula becomes very obvious when it is made from atomic models. It forms a very symmetrical structure containing four 6-membered rings. Hexamethylene tetramine is used in medicine as a urinary antiseptic (Urotropine). In acid solution it slowly gives ammonium salts and formaldehyde which acts as a disinfectant. It is also used with phenols to form resins. In the rubber industry it finds use as an accelerator (Hexa).

As has been seen, formaldehyde reacts with ammonium chloride to give the three methyl amines.

The extreme activity of the carbonyl group of formaldehyde in aldol type condensations is shown by its action with phosphine and HCl to give $(HOCH_2)_4PCl$.

7. With $NH_4Cl$ and KCN it gives two trimers of

$$CH_2=N—CH_2CN,$$

methyleneaminoacetonitrile (Johnson 1924).

8. Formaldehyde reacts with amines to give more or less complex products. Thus, with isobutyl amine, it forms triisobutyltrimethylene triamine, a substance having RN in place of each O of trioxymethylene. The intermediate $RN=CH_2$ evidently polymerizes readily. The reaction of formaldehyde with amino acids is of considerable practical importance in determining these substances. Since they contain both acid and basic groups they are amphoteric and cannot be titrated either with bases or acids. Glycine may be taken as an example. It exists mainly as an inner salt (like betaine).

$$\begin{array}{l} CH_2{-}NH_2 \\ | \\ CO{-}OH \end{array} \qquad \begin{array}{l} CH_2{-}NH_3 \\ | \quad | \\ CO-O \end{array} \quad \text{or} \quad \oplus NH_3CH_2CO_2\ominus$$

Treatment with formaldehyde eliminates the amino group so that the acid can be titrated with a base and indicator (*Formol titration*)

$$\begin{array}{l} CH_2NH_2 \\ | \\ CO_2H \end{array} \rightarrow \begin{array}{l} CH_2NH{-}CH_2OH \\ | \\ CO_2H \end{array} \rightarrow \begin{array}{l} CH_2N=CH_2 \\ | \\ CO_2H \end{array}$$

The action of formaldehyde with amino groups is undoubtedly related to its ability to harden and preserve biological specimens.

Dimethyl amine gives $HOCH_2NMe_2$ and $Me_2NCH_2NMe_2$ (Frdl. *11*, 783).

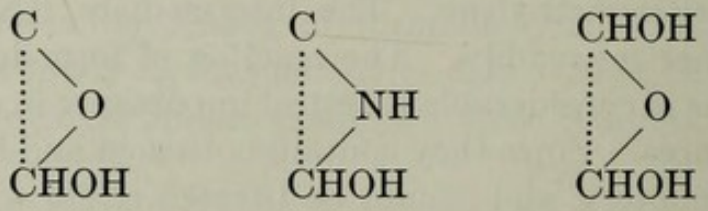
9. With primary and secondary amines and alcohols it gives ethers of the types $MeN(CH_2OR)_2$ and $Me_2NCH_2OR$ (Rep. 1921, 76; 1923, 87). Mercaptans give similar thio ethers.

10. Angeli-Rimini aldehyde reactions. When heated with the sodium salt of nitrohydroxylamine, aldehydes give hydroxamic acids which react with ferric chloride to form deep purplish colors (Angeli 1900)

$$RCHO + HON=NO_2Na \rightarrow RC(OH)=NOH + NaNO_2$$

Treatment of an aldehyde with N-benzenesulfonylhydroxylamine, $PhSO_2NHOH$, and a base gives a hydroxamic acid (Rimini 1901; Rep. 1909, 79). This reaction fails, as does the Angeli

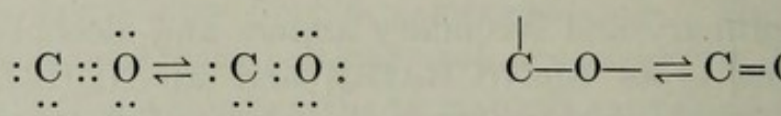
reaction, with aldehydes having OH, $NH_2$, or CO groups in the gamma or delta position. These evidently exist in cyclic structures and have no free aldehyde group.



11. Grignard reagents form primary alcohols. For example,

$$Me_3CMgCl + H_2CO \rightarrow Me_3C-CH_2OMgCl \rightarrow Me_3CCH_2OH$$

This is another case of addition to the carbonyl group, the $-MgCl$ adding to the O and the tertiary butyl group adding to the C. This type of addition to the carbonyl group is the basis of nearly all of the reactions of compounds containing it (aldehydes, ketones, ketenes and acids and their derivatives). It may be worthwhile to speculate as to the electronic mechanism of this important process. The electronic structure of the carbonyl group is undoubtedly $:\ddot{C}::\ddot{O}$ Parachor measurements on aldehydes and ketones indicate a true double linkage (p. 171) (Sidgwick, 127). The carbonyl group may be regarded as existing in equilibrium with an activated form which is the "opened double bond" often assumed in explaining organic reactions.

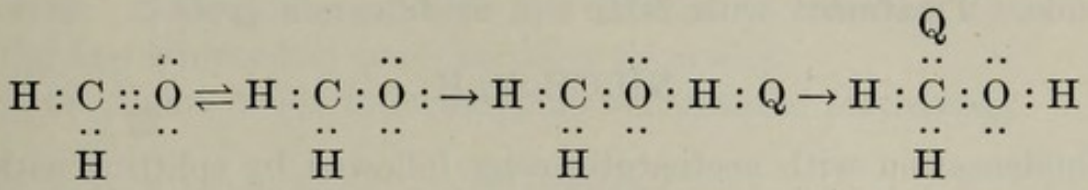


When a suitable substance H : Q or a suitable metal derivative M : Q reacts with a carbonyl group the process may be regarded in at least two ways.

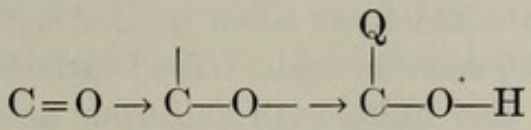
*a*. The addend ionizes and the $H^+$ or $M^+$ adds to one of the electron pairs of the activated carbonyl group. This leaves the carbon with only six electrons. This shortage is rectified by the addition to it of Q: , with its electron pair left by the ionization of the original compound.

*b*. The first step may be the formation of a *coordinate link* between the oxygen of the activated carbonyl group and the H

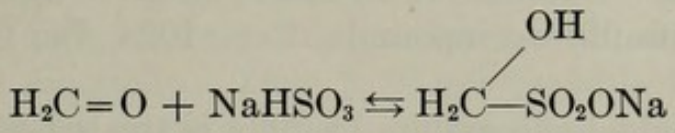
or M of the addend (Sidgwick, 73, 117, 147). The next step would be the transfer of Q: to the electronically deficient carbon.



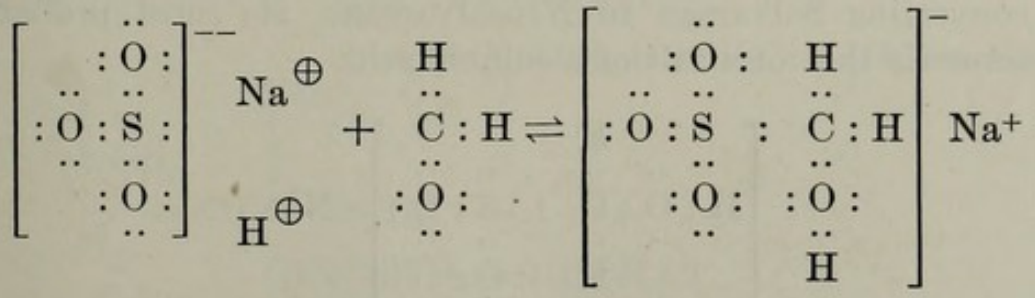
This is merely a restatement of the process known to organic chemists since long before the discovery of electrons and their application to valency problems



12. Sodium bisulfite forms an addition compound as with many carbonyl compounds.



Formerly this was believed to have the structure of a sulfite because of the ease with which acids reverse the reaction. The present tendency is to regard it as a sulfonic acid derivative with the S attached to C (Rep. 1927, 65; 1928, 74). This agrees with the modern conception of the "structure" of sulfites (p. 166).



The hydroxy sulfonic acid structure of the bisulfite products of carbonyl compounds involves the conception that the C—S linkage is weakened by an OH group on the same carbon; thus a *hydroxyl* and a *sulfonic acid group* on the *same carbon* form an unstable arrangement like the combination of two hydroxyl groups with one carbon. The structure of the bisulfite addition

product as a sulfonate, $HOCH_2SO_3Na$, rather than as a sulfurous ester is shown by many of its reactions to give known sulfonic acids. Treatment with $NH_3$ and acidification gives

$$NH_2CH_2SO_3H.$$

Condensation with acetoacetic ester followed by splitting with alkali or acid gives $HO_3SCH_2CH_2CO_2H$ or $CH_3COCH_2CH_2SO_3H$ (Rep. 1927, 65). The formation of a C—S linkage from a carbonyl compound and a bisulfite is entirely analogous to that from an alkyl halide and a sulfite (p. 166). The bisulfite compound reverts to the aldehyde when treated with reagents which react with $NaHSO_3$ such as acids, bases, carbonates, etc.

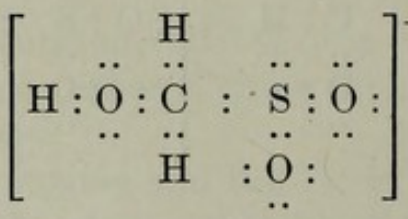
Aldehydes can also unite with sulfurous acid itself. This is the basis for Schiff's test to distinguish aldehydes from ketones. A solution of the dye fuchsin (magenta) is just decolorized with sulfurous acid. Addition of an aldehyde gives a pink color.

Aldehyde bisulfite compounds, Rep. 1928, 74; Gibson, Rev. 1934, I, 435.

When formaldehyde-sodium bisulfite is treated with zinc dust it is converted to "sodium formaldehyde sulfoxylate,"

$$HOCH_2SO_2Na,$$

or, less probably, $HOCH_2OSONa$. This is used as a bleaching agent (Rongalite C, Sulfoxite C, Formopon) with vat dyes and in converting Salvarsan to Neosalvarsan. Its most probable structure is that of a salt of a sulfinic acid.



A better method than that starting with sodium bisulfite is to treat $SO_2$ solution with zinc dust to get zinc hydrosulfite, $ZnS_2O_4$, which reacts with formaldehyde to give zinc formaldehyde sulfoxylate. Treatment with sodium carbonate gives the sodium derivative.

The formaldehyde sulfoxylates are important in discharge printing with azo dyes and in the general use of vat or indigoid dyes. Both classes of dyes are reduced to colorless materials, the first irreversibly and the latter reversibly.

13. Halide acids form unstable halogenated methanols,

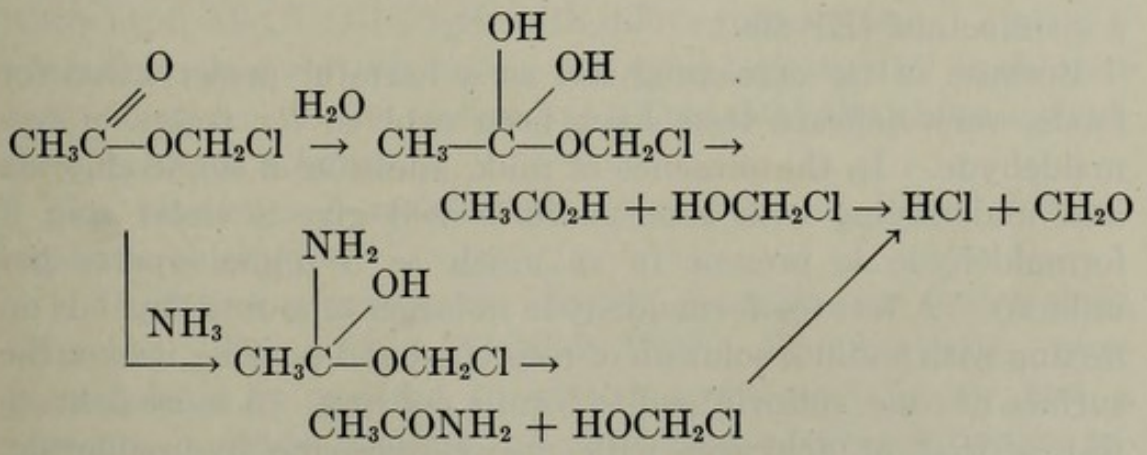
$$XCH_2OH,$$

and more stable ethers, $XCH_2OCH_2X$. In presence of alcohols, mixed ethers, $XCH_2OR$, are obtained. Higher aldehydes give similar $\alpha$-halogen ethers (Gebauer 1934). The halogens in all these ethers react metathetically with Grignard reagents.

14. Ammonium sulfide gives the 6-membered ring,

$$CH_2(SCH_2)_2NMe.$$

15. Acid chlorides form chloromethyl esters, for example $CH_3CO_2CH_2Cl$, b. 115° (Adams 1921). The reactions of this type of substance illustrate the greater ease of addition than of metathetical reactions. Thus it is not possible to *replace* the chlorine in these esters because *addition* takes place with the carbonyl group of the ester instead. This may be illustrated by the action with water and with ammonia.




16. With urea, it forms both simple and complex condensation products, $HOCH_2NHCONHCH_2OH$, dimethylol urea, etc., until the molecules become so complex that resins are formed. Thiourea gives resins even more readily, perhaps because of the polymerizing tendency of sulfur.

17. With casein, important plastic resins are obtained.

18. The formation of resins (Bakelite, Redmanol, Condensite) with phenols and related compounds starts with the usual addition to the carbonyl group of formaldehyde. The H atoms in the ortho and para positions in phenols are reactive. One of these adds to the O and the rest of the phenol molecule adds to the C.

$$C_6H_5OH + H_2CO \rightarrow HOCH_2C_6H_4OH$$

These molecules can condense with more phenol and more formaldehyde forming molecules with several reactive groups which continue to react until the final molecules are too large and complex to crystallize and consequently form resins (Wanscheidt 1936). In general any organic molecule which contains at least two reactive groups can produce a resin.

19. With other aromatic compounds, products are formed in which two aromatic nuclei are linked by a methylene group. These reactions take place with surprising ease and are of great value in making certain classes of dyes and syntans, as in the union of two dimethylaniline or two naphthalene sulfonic acid residues.

Formaldehyde is produced in very large amounts commercially for the manufacture of resins and other organic products and as a disinfectant (EP 860).

Because of its occasional use as a harmful preservative for foods, very delicate tests have been evolved for traces of formaldehyde. In the presence of milk, addition of ferric chloride and underlaying with conc. sulfuric acid give a violet ring if formaldehyde is present in as much as 5 p.p.m. (parts per million). A test for formaldehyde in larger amounts depends on mixing with a dilute solution of resorcinol and pouring it over the surface of conc. sulfuric acid to form a red ring. A more delicate test is that of Schryver with phenylhydrazine hydrochloride, potassium ferricyanide and conc. hydrochloric acid to give a red color.

Typical derivatives of formaldehyde are:

*a.* Oxime, $CH_2=NOH$, b. 84°; *b.* Phenylhydrazone, alpha and beta forms, m. 168° and 211°; *c.* p-Nitrophenylhydrazone, m. 182°.

**Acetaldehyde,** "Aldehyde," ethanal, $CH_3CHO$, b. 21°, is obtained by the oxidation of ethyl alcohol. Because of its volatility, the acetaldehyde escapes from the oxidizing mixture before it can be oxidized to acetic acid. It is also contained in the "first runnings" in the distillation of fermented liquids. As has been seen, it is undoubtedly an intermediate in fermentation (p. 107).

Acetaldehyde is made in large amounts from acetylene by catalytic hydration by means of an acid solution of mercuric sulfate. $HC{\equiv}CH \rightarrow H_2C{=}CHOH \rightarrow CH_3CHO$ (Rep. 1920, 53; EP 675). An intermediate organic mercury compound is formed which reacts with the acid to give acetaldehyde and regenerate the mercuric salt. The process is carried out by passing acetylene up through a packed tower down which the catalyst solution is flowing. Some of the mercuric salt is reduced to metallic mercury which collects at the bottom of the tower. This is periodically converted to mercuric sulfate by nitric and sulfuric acids. A modification of this process uses a suspension of HgO in dilute sulfuric acid. The mercury gradually accumulates in an organic sludge. This is electrolyzed in alkaline solution to regenerate the HgO.

Acetaldehyde is obtained along with formic acid by warming lactic acid, $MeCHOHCO_2H$, with dilute sulfuric acid. This is a general method for converting an *alpha hydroxy acid to the next lower aldehyde.* If the former has a branch at the alpha carbon, the product is a *ketone.*

The *reactions of acetaldehyde* are typical of those of most aliphatic aldehydes.

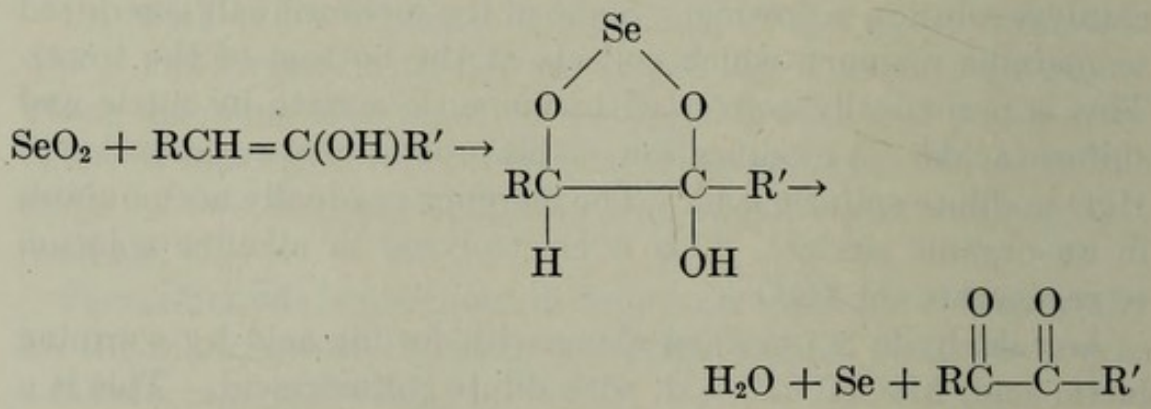
1. Oxidation is very easy. In air, peroxides are first formed (Hatcher 1931, 1932; Wieland 1932). Commercially, pure acetaldehyde is oxidized to glacial acetic acid by air and a manganous oxide catalyst. Ammoniacal silver solution is reduced to a silver mirror.

$$CH_3CHO + 2\,Ag(NH_3)_2OH + 2\,H_2O \rightarrow CH_3CO_2NH_4 + 2\,Ag + 3\,NH_4OH$$

Oxidation in water solution probably involves the dehydrogenation of the aldehyde hydrate (Wieland). Thus finely divided

palladium in the absence of oxygen converts a small amount of acetaldehyde in water solution into acetic acid. When the palladium is saturated with hydrogen the reaction stops until $O_2$ is admitted to oxidize the hydrogen in the palladium.

A most interesting oxidation of acetaldehyde is that by means of selenium dioxide, $SeO_2$, which gives a good yield of glyoxal, $(CHO)_2$ (Riley 1932). The attack on the alpha H atoms and the failure to attack the easily oxidized aldehyde H indicate that the $SeO_2$ attacks the enol form. This valuable reagent has been studied with a great variety of aldehydes and ketones. Its specificity for the conversion of an alpha $CH_2$ to carbonyl is remarkable. It suggests the specificity of enzyme reactions. Just as an enzyme adds to a specific configuration, the $SeO_2$ may add to the enolic double bond




in which R and R′ may be H, alkyl or aryl. Propionaldehyde and butyraldehyde give 30 and 45% yields of MeCOCHO and EtCOCHO by this process.

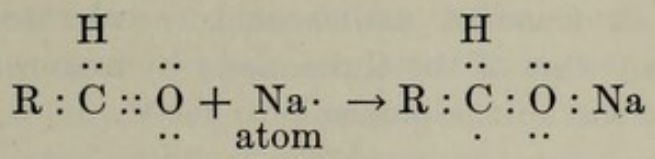
The above mechanism fails to explain the conversion of $C=CH-CH_2-$ to $C=CH-CO-$ by $SeO_2$ as in the change of $\alpha$-pinene to verbenone.

2. Reduction is also easy. There is always a possibility that ethyl alcohol may be produced commercially this way. It is largely a matter of cheap acetylene. In addition to reduction to a primary alcohol, there is some product of a bimolecular reduction to give a substituted glycol.

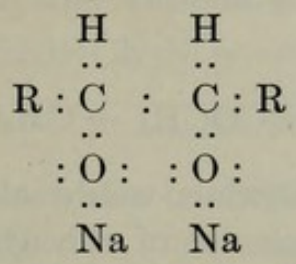
$$2\,CH_3CHO \rightarrow CH_3CHOHCHOHCH_3$$

This may be the source of the $\beta$-butylene glycol formed in some fermentation processes. The reductions which give a maximum

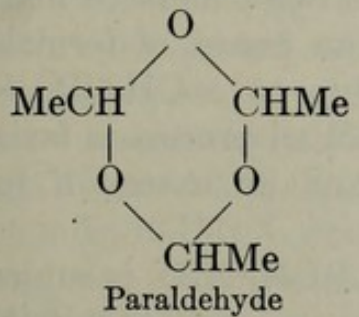
of the bimolecular product are usually by means of metals. The processes involved may be as follows:



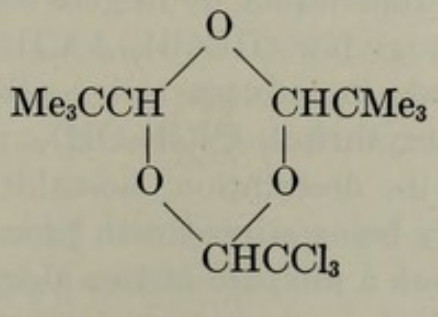
The resulting intermediate product is a free radical (with an odd electron). With some aromatic compounds another Na atom can unite to give a metal ketyl. Ordinarily an H atom adds to the free radical giving the primary alcohol. It is also possible for two of the free radicals to combine to give



3. It polymerizes reversibly. A trace of sulfuric acid converts it to *paraldehyde*, b. 124°, a trimer, $Me_3$-trioxymethylene. It is used as a soporific in cases where all others fail, as in delirium tremens. It reverts to acetaldehyde on heating with dilute acid. It is used in many reactions in place of acetaldehyde itself. The polymerization of acetaldehyde is increased by very high pressures (Conant). Heating paraldehyde with a trace of acid gives acetaldehyde. *Mixed paraldehydes* are obtainable from mixtures of aldehydes (Hibbert 1928).



Paraldehyde



In presence of a trace of HCl or $SO_2$ below 0° crystals of *metaldehyde* separate which sublime above 150°. Its molecular weight shows it to be a tetramer (Hantzsch, Rep. 1907, 80). Heating with sulfuric acid depolymerizes it.

4. Bases. *a.* Dilute or weak bases produce the true *aldol condensation* (Wurtz 1872) from which all other similar processes are named. A trace of amino acids accelerates many aldol condensations. One of the three *alpha* hydrogen atoms adds to the O and the rest of the molecule to the C.

$$CH_3C(H)=O + HCH_2CHO \rightarrow \underset{\text{"aldol"}}{CH_3CHOH—CH_2CHO}$$

Acetaldehyde may be used to supply the *carbonyl group* for an aldol condensation with another substance which supplies the *alpha hydrogen*. Thus

$$CH_3CHO + HCH_2COCH_3 \rightarrow CH_3CHOHCH_2COCH_3$$

Each of the initial materials would also condense with itself. Such aldol combinations are of the utmost value in synthetic chemistry. The $\beta$-hydroxy carbonyl compounds obtained in this way are readily dehydrated to give $\alpha\beta$-unsaturated carbonyl compounds. Thus the two compounds listed above give $CH_3CH=CHCHO$, crotonaldehyde, and $CH_3CH=CHCOCH_3$, penten-3-one-2.

Acetaldehyde may also supply the *alpha hydrogen* for condensation with the *carbonyl group* of another compound. Thus

$$H_2C=O + HCH_2CHO \rightarrow HOCH_2CH_2CHO$$

The other alpha hydrogens can react with more formaldehyde finally giving $(HOCH_2)_3CCHO$. If an excess of formaldehyde is used, it reduces the $-CHO$ group to $-CH_2OH$, forming pentaerythritol, $C(CH_2OH)_4$. The actual process is far simpler than its description, acetaldehyde and an excess of formalin merely being stirred with lime.

When a mixture of two aldehydes, $RCH_2CHO$, is subjected to the aldol condensation three products are possible but the chief reaction generally consists in the union of the carbonyl of the smaller one with an alpha H from the larger one. In general the ease of supplying the $\alpha$-H for the condensation is in the order $R_2CHCHO > RCH_2CHO > CH_3CHO$ (Lieben 1901).

The aldol condensation is given by certain $\alpha$-H compounds other than aldehydes and ketones. In general any C—H compound which will give a sodium derivative, such as malonic ester, acetoacetic ester, cyanoacetic ester and nitromethane will condense with aldehydes in the presence of a trace of base or acid. As many molecules of aldehyde can react as there are $\alpha$-H atoms. The "aldols" formed lose water readily if they contain $\alpha$-H. This gives important preparations for $\alpha\beta$-unsaturated compounds

$$RCHO + H_2C(CO_2Et) \rightarrow RCHOHCH(CO_2Et)_2 \rightarrow RCH=C(CO_2Et)_2 \rightarrow RCH=CHCO_2H$$

$$RCHO + CH_3NO_2 \rightarrow RCHOHCH_2NO_2 \rightarrow RCH=CHNO_2$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad (RCHOH)_2CHNO_2 \text{ etc.}$$

The aldol condensation can also be obtained with the H which is "alpha" to a conjugatedly unsaturated aldehyde system. $CH_3(CH=CH)_nCHO$ (Rep. 1907, 80; 1932, 115). This gives an important method for making aldehydes with several ethylenic linkages in conjugated relation. This may be illustrated as follows:

$$2\ Me_2C=CHCHO \rightarrow Me_2C=CHCH=CHC(Me)=CHCHO$$

This transmittal of the "alpha effect" through a conjugated system is responsible for the reactivity of the methyl group in piperitone (Simonsen, I, 325). It also explains the older observation that acetaldehyde in presence of $K_2CO_3$ gives a product from which *n*-octoic acid can be obtained (Neuki 1900). It also gives a preparation for *n*-hexyl alcohol and *n*-octyl alcohol either from acetaldehyde directly or through crotonic aldehyde (Vinylogy, Fuson 1936).

Compounds, ROMgX, cause the aldol condensation and at the same time give ester formation by dismutation (see 5 below) (Rep. 1928, 96).

*b*. Concentrated strong bases give *aldehyde resins* (Rep. 1912, 81). As in the case of all resins these are simply molecules too large and complex to be true crystalline solids. Resins result from combinations of organic compounds which have a number

of points of reactivity. Acetaldehyde answers this description admirably. It has three alpha hydrogen atoms which can react with the carbonyl groups of three other molecules of acetaldehyde. The resulting molecule will still have a carbonyl group which can react with an alpha hydrogen of another acetaldehyde molecule, etc., etc. Moreover, the resulting products are secondary alcohols and secondary alcohols may condense with each other in the presence of strong bases to give higher secondary alcohols. Finally some of the products contain no H atoms alpha to the $-CHO$ group and, consequently, can give the Cannizzaro reaction with the strong base used.

Apparently an aldehyde must have at least two $\alpha$-H atoms to give resins as isobutyraldehyde, $Me_2CHCHO$, gives none but undergoes the aldol condensation and Cannizzaro reaction.

5. Aluminum ethylate. Although the reactivity of its $\alpha$-H atoms prevents acetaldehyde from giving the Cannizzaro reaction, a similar dismutation may be achieved by means of aluminum ethylate which converts it to ethyl acetate catalytically (Tischtschenko 1906) $2\ MeCHO \rightarrow MeCO_2CH_2Me$. This reaction takes place with higher aldehydes as well. Addition compounds such as $AlCl_3.3Al(OEt)_3$ and $HgCl_2.2Al(OEt)_3$ are even more effective (Rep. 1925, 72).

Aluminum ethylate in absolute ethyl alcohol reduces higher aldehydes smoothly to primary alcohols (Meerwein, Rep. 1925, 71).

$$3\ RCHO + Al(OEt)_3 \rightarrow (RCH_2O)_3Al + 3\ CH_3CHO$$

The reaction apparently goes through the stage

$$RCH(OEt)OAl(OEt)_2$$

which loses acetaldehyde and forms $RCH_2OAl(OEt)_2$, etc. EtOMgCl acts like $Al(OEt)_3$. Aluminum isopropoxide is an even better special reducing agent for aldehydes (Young 1935)

$$3\ RCHO + Al(OCHMe_2)_3 \rightarrow (RCH_2O)_3Al + 3\ Me_2CO$$

6. With alcohols and a trace of acid, *acetals* are formed.

$$CH_3CHO + 2\ RCH_2OH \rightarrow CH_3CH(OCH_2R)_2 + H_2O$$

"Acetal," $CH_3CH(OC_2H_5)_2$, b. 104°, is also obtained by the partial oxidation of ethyl alcohol with acid oxidizers. A study of the rate of acetal formation with a variety of alcohols in presence of HCl gives surprising results (Adkins, Rep. 1925, 69; 1928). Methyl alcohol acts most slowly and tertiary alcohols more rapidly. Heptaldehyde reacts several hundred times as rapidly as butyraldehyde. Calcium chloride is a better catalyst for acetal formation than zinc or ferric chlorides. Boron trifluoride is an excellent catalyst (Nieuwland).

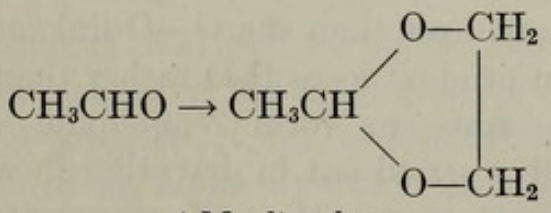
One of the best catalysts for acetal formation is $NH_4Cl$. Before isolating the product the mixture is exactly neutralized with NaOEt (Rep. 1922, 68).

The term *acetal* is applied not only to the compounds

$$CH_3CH(OR)_2$$

but also to all similar compounds formed from aldehydes, $RCH(OR')_2$. The aldehydes are regenerated by boiling with an excess of dilute acid. They are stable to bases. $H^+$ ions apparently add to an O atom giving an oxonium salt whereas $OH^-$ ion has no point of attachment as it has in esters.

Cyclic acetals, *dioxolanes*, are given by glycols.




4-Me-dioxolane

Acetal formation between a variety of aldehydes and dipropenylglycol, 4,5-dihydroxyoctadiene-2,6, has shown that *n*-aldehydes to $C_7$ show little difference (85–90% yield) (Burt 1930). Strangely chloral, benzaldehyde, cinnamaldehyde and crotonaldehyde give no acetal although acetone gives 70% yield. Dioxolanes have been obtained from aldehydes and aromatic substituted glycols (Read 1927).

The union of one mol of alcohol with a carbonyl group gives a *hemiacetal*, RCH(OH)OR'. These are usually very unstable (Adkins 1928).

Mercaptans form mercaptals, $CH_3CH(SR)_2$. The aldehyde can be regenerated by treatment with HgO or $HgCl_2$ and water.

7. Aldehydes with alcohols and an excess of HCl or HBr give $\alpha$-halogen ethers of great value in synthetic work because they react nearly quantitatively with the Grignard reagent.

$$RCHO + R'OH + HX \rightarrow RCHX—OR'$$

8. Acid anhydrides give esters of the hydrated aldehydes, such as $CH_3CH(OCOMe)_2$, acetaldehyde diacetate, ethylidene diacetate. These are hydrolyzed by dilute acids. Ethylidene diacetate is obtained commercially from acetylene and acetic acid with a Hg catalyst. On heating, it gives acetic anhydride and MeCHO (Coffin 1931). The esters of the aldehydes are readily decomposed by acids and bases.

Aldehydes boiled with acetic anhydride give acetates of their enol forms, RCH=CHOAc (Rep. 1909, 79).

9. Hydrogen sulfide forms thioacetaldehyde which polymerizes readily.

$$CH_3CHO + H_2S \rightarrow CH_3CH(OH)SH \rightarrow$$
$$H_2O + CH_3CHS \rightarrow (CH_3CHS)_3$$

The formation of the thioaldehyde depends on the fact that the C—S linkage is stronger than the C—O linkage. Consequently the first addition product loses $H_2O$ rather than $H_2S$.

10. Ammonia adds to form "aldehyde ammonia." The reaction is usually carried out in dry ether in which the product is insoluble. Treatment with acid regenerates the aldehyde. Thus the process is sometimes used for isolating acetaldehyde from a mixture. The first step is the usual addition to the carbonyl group to give $MeCH(OH)NH_2$. This grouping is unstable and loses $NH_3$ to give back acetaldehyde or changes to a trimer. The cyclic formula analogous to that of paraldehyde (Delepine) has been questioned because of the easy change of the trimer to a dimer in solution (Rep. 1915, 83). Either of these substances reacts with acids to give ammonium salts and aldehyde.

11. Various nitrogen bases related to ammonia give simpler condensation products than ammonia. Typical examples are

hydroxylamine, $NH_2OH$, phenyl hydrazine, $C_6H_5NHNH_2$, and semicarbazide, $NH_2NHCONH_2$. The reactions consist of an addition to the carbonyl group followed by the loss of water to leave a C=N linkage. Thus

$CH_3CHO + NH_2OH \rightarrow CH_3CH{=}NOH$, acetaldehyde oxime, acetaldoxime.

$C_6H_5NHNH_2 \rightarrow CH_3CH{=}NNHC_6H_5$, acetaldehyde phenylhydrazone.

$NH_2NHCONH_2 \rightarrow CH_3CH{=}NNHCONH_2$, acetaldehyde semicarbazone.

The last two substances are useful for identifying acetaldehyde because they are easily purified and give definite melting points. Acetaldehyde phenylhydrazone exists in $\alpha$- and $\beta$-forms, m. 100° and 57° respectively (Rep. 1911, 98).

12. Primary amines form Schiff's bases, MeCH=NR. Treatment with acids gives back the original substances. Reduction in alkaline solution gives secondary amines, EtNHR. Secondary amines give resinous products with aldehydes.

13. Sodium bisulfite forms the addition compound,

$$MeCH(OH)SO_3Na.$$

The rate of addition of $NaHSO_3$ to higher aldehydes decreases with length and branching of the alkyl group.

14. Hydrocyanic acid, HCN, forms MeCH(OH)CN, a cyanohydrin, the nitrile of an alpha hydroxy acid (Lapworth 1931). Traces of $NH_3$ or amines catalyze the addition. Hydrolysis gives the $\alpha$-OH-acid.

$$MeCHOHCN + 2\,H_2O + H_2SO_4 \rightarrow NH_4HSO_4 + MeCHOHCO_2H$$

Treatment with ethyl alcohol and $H_2SO_4$ gives ethyl lactate directly. This is used in lacquer solvents since it has the solvent properties of an alcohol and an ester in the same substance.

A better preparation of the cyanohydrin is to make the bisulfite addition compound and treat it with a soluble cyanide, $MeCH(OH)SO_3Na + NaCN \rightarrow Na_2SO_3 + MeCHOHCN$. This

might either throw doubt on the sulfonic acid structure of the bisulfite compound or be a further indication of the lability of the C—S linkage in the presence of OH on the same carbon. The formation of a cyanide from a sulfonic acid is common in the aromatic series but requires fusion of the sodium salt with NaCN.

15. An ammonium salt and an alkali cyanide give an alpha amino nitrile from which an alpha amino acid (alanine) can be prepared. This is the *Strecker amino acid synthesis.*

$$RCHO + NH_4Cl + KCN \rightarrow RCH(NH_2)CN + KCl$$

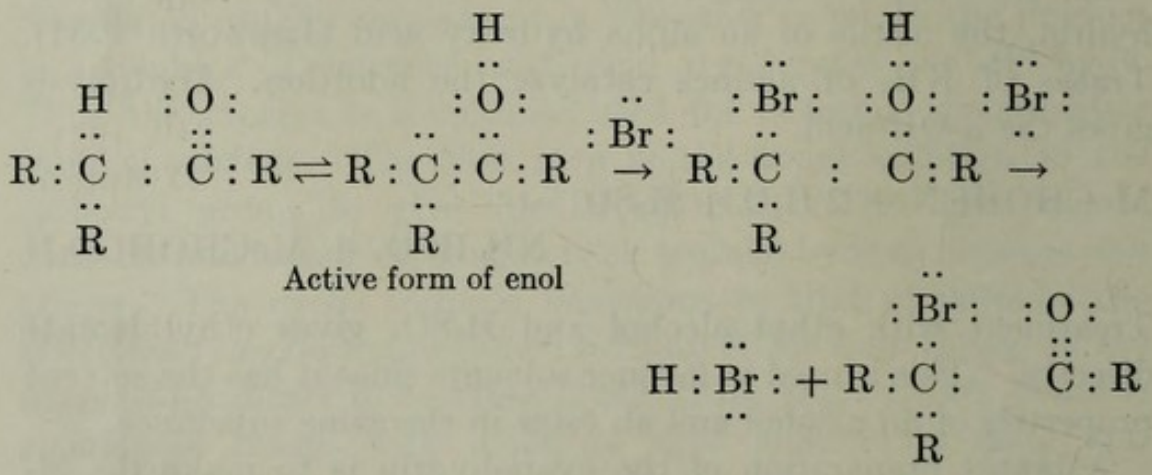
16. Grignard reagents give secondary alcohols, MeCHOHR.

17. Reactive aromatic compounds such as phenols and naphthalene compounds condense to give substances $CH_3CHOHAr$ and $CH_3CHAr_2$.

18. Halogens replace the alpha hydrogens much more easily than in hydrocarbons. This is presumably because the *enol* form reacts

$$CH_3CHO \rightleftharpoons CH_2{=}CHOH \rightarrow BrCH_2CH(OH)Br \rightarrow BrCH_2CHO$$

Since halogen and hydroxyl cannot exist on the same carbon, HX is lost leaving bromoacetaldehyde, $BrCH_2CHO$. It is not necessary to assume that the bromine atom adds to the aldehyde carbon and then splits off. The process of the easy halogenation of all substances containing H alpha to a CO group may proceed as follows (R = H or an organic group):




After the first bromine (positive) has added, the carbonyl carbon is left with only six electrons. It can overcome this deficiency by

expelling a proton ($H^+$) and forming a double bond with the oxygen. The $H^+$ and the second bromine (negative) form HBr. This is entirely analogous to the action of halogens with certain olefins to give unsaturated monohalides instead of the expected saturated dihalides (p. 42). The other alpha H atoms in acetaldehyde can also be replaced to give bromal, $Br_3CCHO$.

The best preparation for $\alpha$-bromoaldehydes is the action of the trimers such as paraldehyde with bromine in the cold (Rep. 1927, 63). Chlorine reacts with paraldehyde in the cold to give *butyl chloral*, 2,2,3-trichlorobutanal, $CH_3CHClCCl_2CHO$.

19. Phosphorus pentachloride replaces the O by $Cl_2$ giving 1,1-dichloroethane, ethylidene chloride, $CH_3CHCl_2$. This reaction is important with higher aldehydes as a source of intermediates for making 1-acetylenes, $RC{\equiv}CH$. $PBr_5$ tends to replace the alpha H atoms by bromine because of its easy dissociation to give $Br_2$ and $PBr_3$.

*Important Derivatives of Acetaldehyde*

*a*. Acetaldoxime, $CH_3CH{=}NOH$, m. 47°, b. 115°;
*b*. Phenylhydrazone, alpha and beta forms, m. 100° and 57°;
*c*. *p*-$NO_2$-phenylhydrazone, m. 128°.

**Propionaldehyde,** propanal, $CH_3CH_2CHO$, is prepared in the usual way by the oxidation of *n*-propyl alcohol. It can also be prepared by dehydrogenating the alcohol by passing the vapors over a heated copper or brass catalyst. This avoids the danger of further oxidation to propionic acid.

The reactions of propionaldehyde are practically like those of acetaldehyde. It must be remembered that only the two alpha hydrogen atoms are active in replacement and condensation reactions. Thus

$$CH_3CH_2CHO + \underset{\displaystyle CH_3}{\overset{\displaystyle |}{HCHCHO}} \rightarrow \underset{\displaystyle CH_3}{\overset{\displaystyle |}{CH_3CH_2CHOHCHCHO}}$$

In this case the remaining alpha H is also tertiary. The product is, therefore, very easily dehydrated to 2-methylpenten-2-al.

**Butyraldehyde,** butanal, "Butalyde," $CH_3CH_2CH_2CHO$, is commercially available as an oxidation product of *n*-butyl alcohol

or by the partial reduction of crotonaldehyde obtained from acetaldehyde.

$$2\ MeCHO \rightarrow MeCHOHCH_2CHO \rightarrow MeCH{=}CHCHO \rightarrow MeCH_2CH_2CHO$$

Its reactions are like those of acetaldehyde. Condensation of a mixture of it with acetaldehyde and reduction of the resulting unsaturated aldehydes would give three products besides *n*-BuOH.

$$2\ C_4 \rightarrow \text{2-Et-hexanol-1}$$
$$C_2 + C_4 \rightarrow \text{2-Et-butanol-1}$$
$$C_4 + C_2 \rightarrow \textit{n}\text{-hexyl alcohol}$$

In the last two reactions, the first aldehyde supplies the CO group and the second the H. The three alcohols listed are commercially available (C. and C.).

**Isobutyraldehyde,** methylpropanal, dimethylacetaldehyde, $(CH_3)_2CHCHO$, is obtained by oxidizing isobutyl alcohol or by dehydrogenating it. The presence of the fork in the alpha position presents slight complications in both cases, cutting down the yields as compared with the normal compound. It can also be obtained by hydrolysis (with rearrangement) of isobutylene bromide, $Me_2CBrCH_2Br$, obtained by direct bromination of *t*-BuOH.

The reactions of isobutyraldehyde are like those of its lower homologs except that the forked chain introduces variations. Thus it is possible to oxidize the tertiary H rather than the aldehyde group, by ceric sulfate, $Ce(SO_4)_2$, to give $Me_2CHOHCHO$ (Conant 1928). It gives an aldol condensation with formaldehyde.

$$Me_2CHCHO + H_2CO \rightarrow HOCH_2CMe_2CHO$$

An excess of formaldehyde gives 2,2-dimethylpropandiol-1,3. Isobutyraldehyde with concentrations of alkali which would give aldehyde resins with most aldehydes undergoes an aldol condensation to give $Me_2CHCHOHC(Me)_2CHO$. This can undergo a Cannizzaro reaction with excess of base to form the corresponding primary alcohol and a salt of isobutyric acid (Rep. 1927, 92). Reactions of isobutyraldehyde with primary Grignard reagents give the expected products but more complex Grignard reagents

give a side reaction which is not noticeable with simpler ones. This consists in the *reduction* of a portion of the aldehyde to the primary alcohol. Thus

$$2\ Me_2CHCHO + 2\ Me_3CMgCl \rightarrow Me_2CHCHOHCMe_3 + Me_2CHCH_2OH + Me_2C{=}CH_2$$

The yields of the normal and abnormal products are about 40 and 20 percent (Conant 1929). With *n*-butyraldehyde the yield of normal product becomes 60%.

Aldehydes, RR'CHCHO, can be made by treating the ketone RR'CO with $ClCH_2CO_2Et$ and solid NaOEt. The intermediate glycidic acid loses $CO_2$ and gives the aldehyde (Rep. 1904, 62).

**Methylethylacetaldehyde,** 2-Me-butanal,

$$(CH_3CH_2)(CH_3)CHCHO,$$

with alcoholic KOH to give

$$MeEtCHCHOHC(Me)(Et)CH_2OH$$

and $MeEtCHCO_2K$. The first is the result of an aldol condensation followed by reduction of the aldehyde group at the expense of a mol of the initial aldehyde. This type of reduction is like that in fermentation processes (p. 107).

***n*-Valeraldehyde,** pentanal, $CH_3(CH_2)_3CHO$, and isovaleraldehyde, 3-methylbutanal, $(CH_3)_2CHCH_2CHO$, are made from the corresponding primary alcohols in the usual way. The oxidation of the corresponding primary alcohol offers complications because of the ease of oxidation of the aldehyde which stays in the reaction medium because of its high boiling point. Use of insufficient oxidizing agent merely leads to ester formation, $2\ RCH_2OH \rightarrow RCO_2CH_2R$. Dehydrogenation with copper catalysts gives better results but complications are caused by the temperatures required. Before *n*-amyl alcohol was available, *n*-valeraldehyde could be made by the destructive distillation of a mixture of calcium *n*-valerate, made from *n*-butyl bromide through the cyanide, and calcium formate (Piria 1856).

$$(BuCO_2)_2Ca + (HCO_2)_2Ca \rightarrow 2\ BuCHO + 2\ CaCO_3$$

Other products would be dibutyl ketone and formaldehyde. A

similar result is obtained by passing the vapors of *n*-valeric acid and formic acid over heated manganous oxide as a catalyst (Sabatier 1914). This changes to the salts which decompose as do the calcium salts. At the temperature used the manganous carbonate decomposes as fast as formed to give MnO again. $TiO_2$ has also been used.

**Trimethylacetaldehyde,** pivalic aldehyde, neovaleraldehyde, 2,2-$Me_2$-propanal, $(CH_3)_3CCHO$, can be made by oxidizing or dehydrogenating the corresponding alcohol $Me_3CCH_2OH$ (Conant). Since this does not involve breaking the C—O linkage in neopentyl alcohol, no rearrangement takes place. A better method of preparation is from a tertiary butyl Grignard reagent and an excess of ethyl or methyl formate at a low temperature.

$$Me_3CMgCl + HCO_2R \rightarrow Me_3C—CH(OMgCl)OR \rightarrow Me_3CCHO + RMgCl$$

Although an aldehyde normally reacts with a Grignard reagent, this is prevented in this case by the following factors:

(1) The low temperature retards the decomposition of the first addition product. (2) The excess of formate is in competition with the less active aldehyde. (3) The highly branched Grignard reagent reacts more slowly with the highly branched aldehyde. Any of the former which does react, reduces the aldehyde to alcohol instead of adding to it.

Since neovaleraldehyde has no alpha hydrogen atoms it fails to give many of the ordinary aldehyde reactions such as resin formation and aldol condensation with carbonyl groups. It gives the Cannizzaro reaction with alkalies. It gives the ordinary carbonyl reactions except that it reacts smoothly only with normal Grignard reagents. With branched Grignard reagents it is reduced to the alcohol. With light of about 3000 Å it gives CO and isobutane (Conant).

$Me_3CCHO$ and isovaleraldehyde have been isolated from the "ketone oil" from wood distillation (Rep. 1923, 67).

**Higher aldehydes** have similar preparations and reactions to the ones described with like groupings around the alpha carbon.

**Heptaldehyde,** oenanthol, $CH_3(CH_2)_5CHO$, is formed in about

60% yield by the destructive distillation of castor oil under reduced pressure (Perkins 1927, Bruson 1933). The catalytic hydrogenation of heptaldehyde gives heptyl alcohol, *n*-heptane, *n*-hexane and other products depending on the catalyst and the conditions.

**Caprylic aldehyde** ($C_8$) and **pelargonic aldehyde** ($C_9$) are found in the essential oils of many plants.

Many *higher aldehydes*, including the $C_6$, $C_9$, $C_{12}$, $C_{14}$, $C_{16}$ and $C_{17}$ members, have been made by heating the lactides from α-hydroxy acids (Blaise, Rep. 1904, 62).

$$2\ RCHOHCO_2H \rightarrow \begin{matrix} RCH{-}CO{-}O \\ \diagdown \quad\quad | \\ O{-}CO{-}CHR \end{matrix} \rightarrow 2\ CO + 2\ RCHO$$

α-Hydroxy acids are also converted to aldehydes by treatment with $PbO_2$ and sulfuric acid.

α-Amino acids with NaOCl give N-chloro amino acids which lose HCl to form imino acids. Hydrolysis of the latter gives aldehydes.

α-Bromo acid amides in the Hofmann reaction ($Br_2$ and KOH) give aldehydes. Thus stearic acid is readily converted to margaric aldehyde, $C_{16}H_{33}CHO$ (Rep. 1922, 69). This resembles the degradation of gluconic amide to arabinose. In these cases the rearrangement step gives RCHBrNCO and RCH(OH)NCO which on hydrolysis give compounds having a Br or an OH on the same carbon as the $NH_2$ group. These form aldehydes readily.

More difficultly obtainable aldehydes may be made by the action of an acid chloride with hydrogen and a palladium catalyst (Rosenmund, Rep. 1918, 52; 1922, 68; 1928, 74).

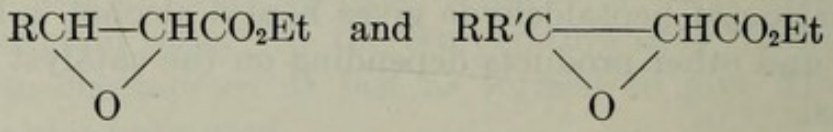
Aldehydes may be obtained from ethyl orthoformate and Grignard reagents, the acetal formed being hydrolyzed by an excess of dilute sulfonic acid (Tschitschibabin 1904).

$$RMgX + HC(OEt)_3 \rightarrow EtOMgX + RCH(OEt)_2 \rightarrow RCHO$$

A similar preparation is from N-dialkyl formamides (Bouveault 1904).

$$HCONR_2 + RMgX \rightarrow RCH(OMgX)NR_2 \rightarrow R_2NMgX + RCHO$$

Aldehydes and ketones react with $ClCH_2CO_2Et$ and NaOEt to give ethylene oxidic esters (glycidic esters)



The free acids lose $CO_2$ and rearrange to give $RCH_2CHO$ and RR′CHCHO (Erlenmeyer, Jr. 1892).

*n*-Octylic, myristic, and stearic aldehydes have been obtained in nearly quantitative yields from the corresponding nitriles (Stephen, Rep. 1925, 70).

$$RCN \xrightarrow{HCl} \xrightarrow{SnCl_2} RCH{=}NH.HCl \rightarrow RCHO$$

Ether containing a minute trace of water is used.

Some aldehydes are obtainable by decomposition of ozonides of olefinic compounds (Harries 1903). Thus oleic ester gives pelargonic aldehyde and the half aldehyde of azelaic acid (Adams).

Higher aldehydes give the reactions of the lower ones according to their structures as $RCH_2CHO$, RR′CHCHO, and RR′R″CCHO. They all give the Angeli-Rimini hydroxamic acid reaction (p. 227).

Aldehydes and ketones can be converted to the corresponding hydrocarbons by heating their hydrazones, phenylhydrazones or semicarbazones with dry NaOEt (Wolff, Rep. 1927, 121). The same result can be achieved by heating the carbonyl compound with hydrazine sulfate and excess NaOEt (Kishner).

**Chloral,** trichloroethanal, $Cl_3CCHO$, b. 97°, is obtained by the chlorination of ethyl alcohol or acetaldehyde with dry chlorine. It differs from most carbonyl compounds in adding water and alcohols to its carbonyl group to form stable compounds, chloral hydrate, $Cl_3CCH(OH)_2$, m. 57°, and chloral alcoholate,

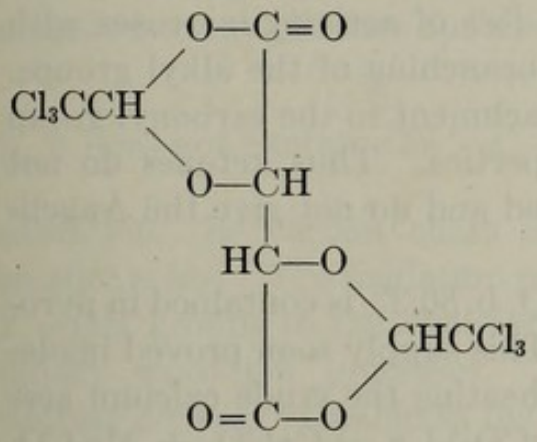
$$Cl_3CH(OH)OC_2H_5,$$

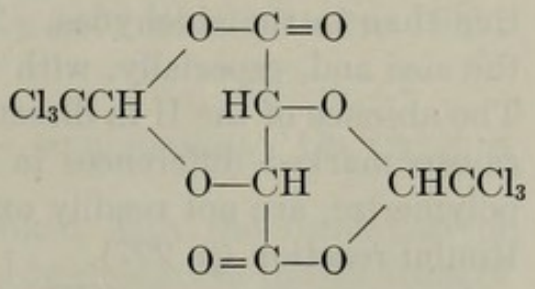
a hemi-acetal. It also forms acetals, $Cl_3CCH(OR)_2$. With glycols it gives cyclic acetals readily.

Chloral gives the usual aldehyde reactions with oxidizing agents, ammonia, bisulfites, hydrocyanic acid, acetic anhydride, etc. With acetaldehyde and $Al(OEt)_3$ it gives $Cl_3CCH_2OH$

(Rep. 1925, 72). Tribromoethanol, $Br_3CCH_2OH$ (Avertin, an anesthetic), is made similarly.

Chloral hydrate reacts with hydroxy acids in presence of sulfuric acid to give chloralides (Rep. 1927, 84). Lactic acid gives $MeCH(-O-CHCCl_3)-CO-O$. Salicylic acid reacts with chloral hydrate even without sulfuric acid. The product has a 6-membered ring. *d*-Tartaric acid gives two isomeric di-chloralides, m. 118° and 161°. These may have the structures:





**Chloral** on oxidation with fuming sulfuric acid gives *chloralide*, (I), m. 115°, b. 273°, a peculiar compound involving the combination of a molecule of $Cl_3$-lactic acid through its hydroxyl and carboxyl groups with a molecule of chloral.

$$3\,Cl_3CCHO + H_2S_2O_7 \rightarrow Cl_3CCH(-O-CHCCl_3)-CO-O + CO + 2\,HSO_3Cl + HCl$$

(I)

Chloralide, with KOH, gives $CHCl_3 + HCO_2K$. With EtOH at 150°, it gives $Cl_3CCH(OH)OEt$ and $Cl_3CCHOHCO_2Et$.

Chloral gives the *haloform reaction* characteristic of the grouping $X_3CC=O$.

$$Cl_3CCHO + NaOH \rightarrow CHCl_3 + HCO_2Na$$

**Butyrchloral,** "butylchloral," 2,2,3-$Cl_3$-butanal,

$$CH_3CHClCCl_2CHO,$$

is obtained as the hydrate from the reaction mixture from paraldehyde and chlorine.

$$CH_3CHO \rightarrow ClCH_2CHO \rightarrow [CH_3CHOHCHClCHO] \rightarrow$$
$$[CH_3CH{=}CClCHO] \rightarrow CH_3CHClCCl_2CHO$$

### *B.* Saturated Ketones

Aliphatic ketones, $R_2CO$ and $RR'CO$, have much the same reactions as the aldehydes, namely, those of the carbonyl group and of alpha hydrogen atoms. The carbonyl group is less reactive than in the aldehydes. This loss of activity increases with the size and, especially, with the branching of the alkyl groups. The absence of the H in direct attachment to the carbonyl group causes marked differences in properties. Thus ketones do not polymerize, are not readily oxidized and do not give the Angeli-Rimini reaction (p. 227).

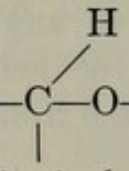
**Acetone,** propanone, $(CH_3)_2C{=}O$, b. 56.3°, is contained in pyroligneous acid in small amounts. This supply soon proved inadequate and more was obtained by heating the crude calcium acetate obtained from the acid. $(MeCO_2)_2Ca \rightarrow CaCO_3 + Me_2CO$. Heating acetic anhydride with $CaC_2$ gives acetone more readily than heating calcium acetate (Rep. 1906, 81). During the World War the demand for acetone for the manufacture of explosives and for "dopes" for cloth airplane wings increased so that new sources were necessary. Acetaldehyde made from acetylene was oxidized catalytically to glacial acetic acid which was then converted to acetone by passing over hot lime, or better, MnO. $2\ MeCO_2H \rightarrow Me_2CO + CO_2 + H_2O$. Thorium oxide, $ThO_2$, at 400° converts acids (Rep. 1912, 80) and acid anhydrides (Rep. 1928, 79) to ketones. Iron filings at 600° give a quantitative yield of acetone (Curme 1919). $Fe_2O_3$ at 480° gives similar results (Rep. 1914, 113).

Another source developed to meet the war demand for acetone was the special fermentation of starch from corn to give acetone and *n*-butyl alcohol in the ratio 1 : 2. This process is more used than ever but the acetone is now a by-product and molasses is used in place of corn (Peterson, Fred, 1932). More recently still acetone has been produced commercially starting with

propylene from cracked gases (EP 404). It can also be prepared catalytically from ethanol (Meerwein 1933).

Acetone is formed in small amounts in animal metabolism by the decomposition of acetoacetic acid, $CH_3COCH_2CO_2H$, formed by the "beta oxidation" of fats. In diabetics the amounts of this acid and acetone increase greatly.

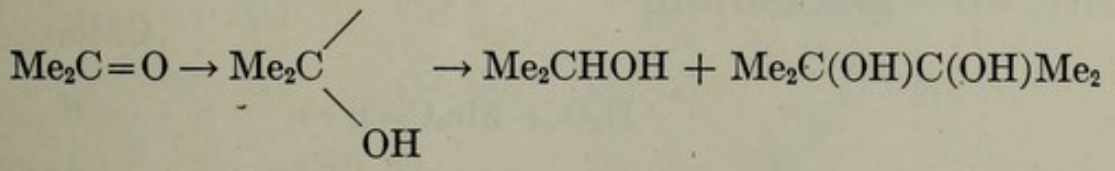
**The reactions of acetone are** largely those due to the activity of alpha H atoms and the carbonyl group. In these respects its reactions resemble closely those of the aldehydes.

1. Oxidizing agents do not act readily because the carbon attached to oxygen does not also have an H attached to it. That is, it does not contain the  combination. On vigorous oxidation, the carbon chain is broken with the formation of smaller acids. The oxidation probably consists in the addition of 2 $-OH$ groups to the enol form of the ketone, followed by ordinary oxidation processes. The splitting of a ketone into simpler acids is valuable in determining the structures of higher ketones. Thus a ketone which gives $C_2$ and $C_9$ acids on oxidation is a methyl nonyl ketone. The structure of the nonyl group is determined by identification of the $C_9$ acid.

Ketones do not reduce Fehling's solution nor ammoniacal silver solution.

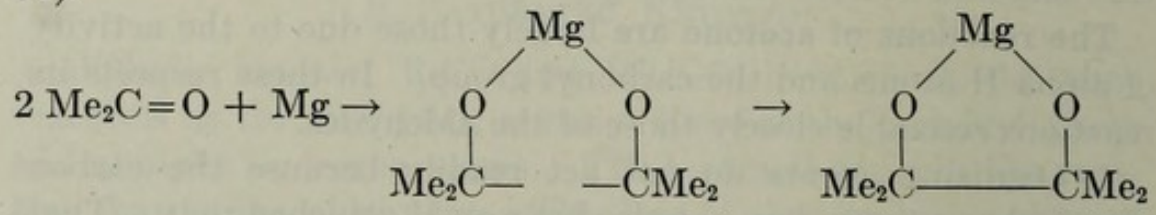
Oxidation with selenium dioxide converts an alpha $CH_2$ to CO forming pyruvic aldehyde, $CH_3COCHO$. This process works with any compound containing the grouping $COCH_2$ (p. 234).

2. Reducing agents change acetone to isopropyl alcohol. This process was formerly of commercial importance. Most reducing agents give as a by-product a bimolecular reduction product, pinacol ("pinacone"), b. 174° (p. 369).



Amalgamated magnesium gives pinacol as the chief product (OS). This reaction was important in Germany during the World War

because pinacol was the intermediate for "methyl rubber." A perhaps fanciful picture of the reaction with Mg involves the action of the latter with two molecules of acetone followed by a closing of a 5-membered ring through the free valences (single electrons) of the carbonyl carbon atoms (Couturier, Rep. 1906, 81).




The name *pinacol* is applied to any tetrasubstituted ethylene glycol. Under the influence of acids, pinacols undergo the *pinacolone rearrangement* so-called from the name of the substance obtained from pinacol itself.

$$Me_2C(OH)C(OH)Me_2 \rightarrow Me_3CCOMe + H_2O$$

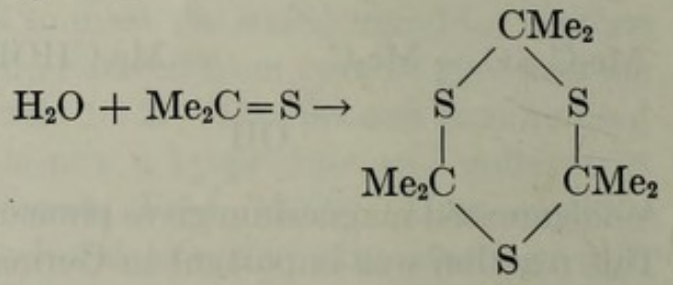
Pinacolone (pinacoline)

Vigorous reduction of ketones by amalgamated zinc and conc. hydrochloric acid gives the corresponding hydrocarbon (Clemmensen, Rep. 1914, 123). This process is most successful with higher ketones.

3. Pyrolysis of acetone vapor at 700° gives ketene, $H_2C=C=O$ and $CH_4$ (Hurd).

4. Acetone does not polymerize like aldehydes. This is apparently because of the lesser activity of the carbonyl group in acetone. Thioketones, however, polymerize to such an extent that the monomeric forms are unknown. The conversion of acetone to its sulfur analog is accomplished by the addition of hydrogen sulfide to its carbonyl group, in presence of a trace of HCl.

$$Me_2C=O \rightarrow Me_2C(SH)OH \rightarrow$$

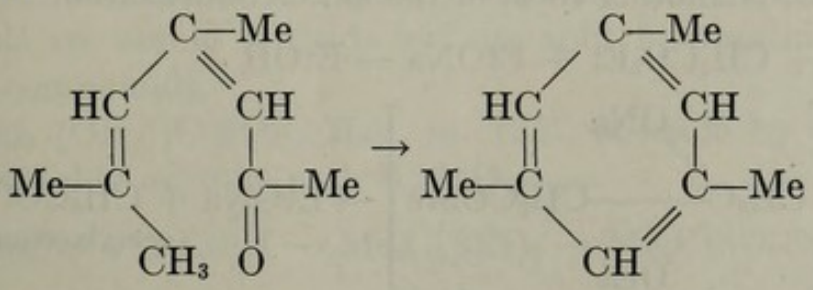


This complete polymerization of the thioacetone is further evidence of the peculiar reactivity of the C=S linkage.

5. Acetone gives the *aldol condensation* readily. Contact with solid barium hydroxide converts it to diacetone alcohol, $MeCOCH_2C(OH)Me_2$, 2-methylpentanol-2-one-4. The reverse change of diacetone alcohol to acetone has been studied in great detail (Akerlöf 1927, 1928, Kilpatrick). Dehydration of diacetone alcohol by refluxing with iodine converts it to mesityl oxide, $MeCOCH=CMe_2$, 2-methylpenten-2-one-4.

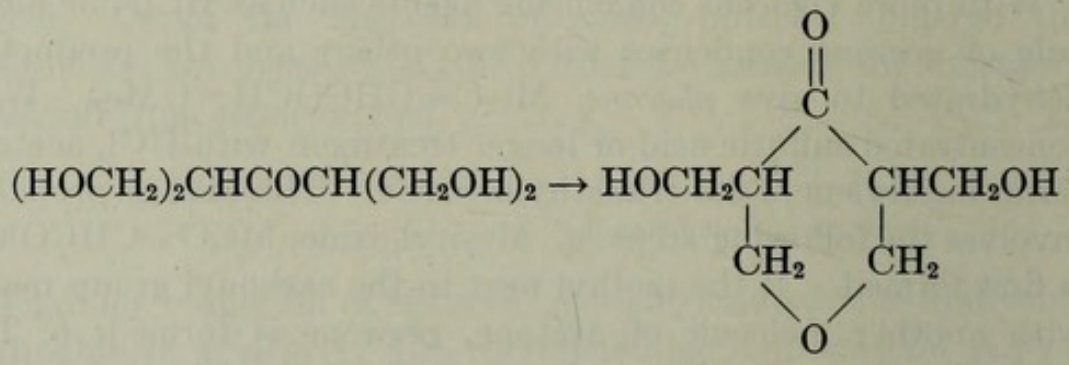
$CaC_2$ and $CaH_2$ also cause the aldol condensation with acetone and with methyl ketones in general but not with other ketones such as diethyl ketone (Rep. 1925, 73).

With more vigorous condensing agents such as HCl, one molecule of acetone condenses with two others and the product is dehydrated to give *phorone*, $Me_2C=CHCOCH=CMe_2$. With concentrated sulfuric acid or longer treatment with HCl, acetone forms mesitylene, 1,3,5-trimethylbenzene. This change probably involves the following steps: *a*. Mesityl oxide, $Me_2C=CHCOMe$, is first formed. If the methyl next to the carbonyl group reacts with another molecule of acetone, phorone is formed; *b*. The methyl at the end of the conjugated system (p. 270) can supply the "$\alpha$−H" for condensation with another carbonyl to give $Me_2C=CHC(Me)=CHCOMe$. If the alpha methyl group condenses, a product is obtained which will not give mesitylene; *c*. The carbonyl group and the methyl at the other end of the molecule are however in the 1 : 6 position and can approach each other in space. The methyl group being at the end of the conjugated system can supply an H atom for condensation with the carbonyl group. Loss of water gives mesitylene. The last step may be illustrated:




In view of the varied possibilities at each step, it is not surprising that the yield of mesitylene is small (30%) (Ipatieff 1930).

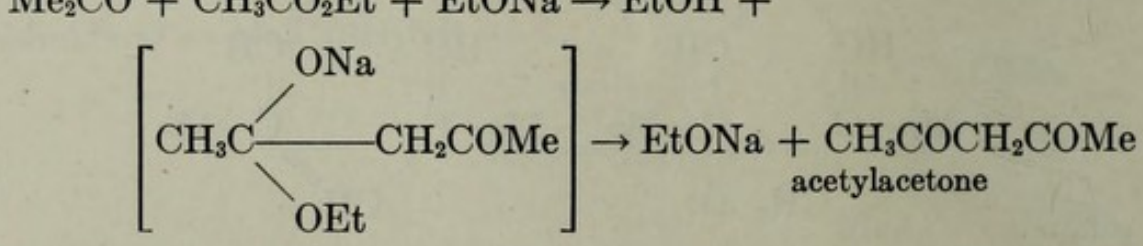
Acetone also gives aldol condensations with other ketones and with aldehydes. With the latter, the aldehyde supplies the more reactive carbonyl group and the acetone supplies the $\alpha-H$ atom. Thus a mixture of acetaldehyde and acetone treated with dilute bases gives aldol and $MeCHOHCH_2COMe$ but no $Me_2C(OH)CH_2CHO$. Formaldehyde and acetone give $MeCOCH_2CH_2OH$ and more complex products due to the reaction of more $\alpha-H$ atoms with $CH_2O$. Under ordinary conditions 90% of the product consists of resins. Under carefully controlled conditions di-hydroxymethyl-tetrahydropyrone is a product. This is formed by inner ether formation between OH groups in the 1 : 5 position in sym-tetra-hydroxymethyl acetone.



In contrast to acetone, MeEt ketone and $Et_2$ ketone, with formaldehyde, give 5% and less than 1% resin respectively.

6. One of the best-known "aldol" condensations of acetone is that with chloroform in presence of a solid base to give *Chloretone*, $Cl_3CMe_2COH$, used as an antispasmodic and in Mothersills Seasick Remedy. Although chloroform will add similarly to methyl ethyl ketone it will not add to the aliphatic aldehydes (Howard 1925).

7. The Claisen condensation of ketones with esters in presence of NaOEt is another form of the aldol condensation.



8. A reaction related to the aldol condensation is that of a

ketone with chloroacetic ester in presence of NaOEt to give a glycidic ester. The latter decomposes readily to give a disubstituted acetaldehyde.

$$Me_2CO + ClCH_2CO_2Et \rightarrow Me_2C(OH)—CH(Cl)CO_2Et \rightarrow$$

$$Me_2C\text{—}CHCO_2Et \rightarrow Me_2CHCHO$$
(O)

The last step is a common rearrangement of ethylene oxides to related carbonyl compounds.

9. A peculiar condensation involving $\alpha$—H atoms is that with $R_2NCH_2OH$, from formaldehyde and a secondary amine. From one to six of the H atoms in acetone can be replaced by the group $-CH_2NR_2$.

10. Although water and alcohols do not add to the carbonyl group of acetone, "acetals" can be obtained by heating with orthoformates.

$$Me_2CO + HC(OR)_3 \rightarrow Me_2C(OR)_2 + HCO_2R$$

This reaction is deeply influenced by the size and branching of the alkyl groups. While acetone gives a 90% yield, Me-*t*-Bu ketone gives only a 12% yield (Adkins, Rep. 1928, 75).

11. Mercaptans add readily to ketones in the presence of dilute acids, to give *hemimercaptols*, $Me_2C(SR)OH$. There is no tendency for ROH to split off with formation of a thioketone. Instead, another molecule of mercaptan reacts to form a *mercaptol*, $Me_2C(SR)_2$, analogous to the acetals. They are intermediates in the formation of sulfonal and related soporifics. The acetals of ketones are readily split by dilute acids. The mercaptols are stable to acids but are split by treatment with mercuric compounds.

**Sulfonal,** $(CH_3)_2C(SO_2C_2H_5)_2$, m. 125°, is made by oxidizing the mercaptol of acetone with $KMnO_4$.

$$Me_2CO + 2\ EtSH \rightarrow Me_2C(SEt)_2 \rightarrow Me_2C(SO_2Et)_2$$

It is a soporific. Many modifications are known. The best known are *trional* and *tetronal* which contain three and four Et

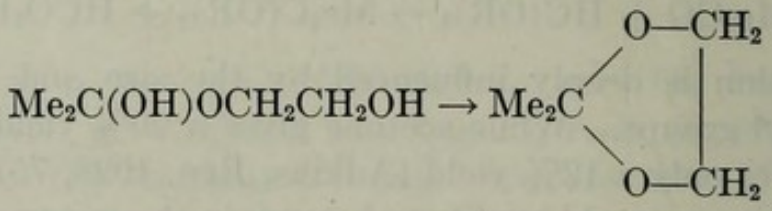
groups. They can be made from MeEt-ketone and $Et_2$-ketone but are more readily prepared from acetaldehyde and propionaldehyde.

$$RCHO \rightarrow RCH(SEt)_2 \rightarrow RCH(SO_2Et)_2 \xrightarrow[EtBr]{Na} REtC(SO_2Et)_2$$

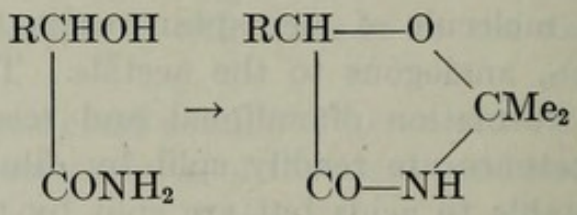
12. While acetone does not form acetals with ordinary alcohols, it forms *cyclic acetals* with 1,2-glycols such as ethylene glycol, glycerol, and the various carbohydrates. This is an example of the stabilizing effect of ring formation of 5 or 6 atoms. Thus with an ordinary alcohol, the equilibrium is so far on the side of the acetone that there is no opportunity to react with another molecule of alcohol to give the stable acetal.

$$Me_2C{=}O + ROH \rightleftharpoons Me_2C(OH)OR$$

On the other hand, when a glycol is used, the second OH may assume a favorable position in respect to the OH of the hemiacetal. Water is lost and the stable cyclic acetal results.



A related reaction is that with $\alpha$-hydroxy acid amides to give keto-tetrahydro-oxazoles.



13. **Sodium bisulfite** forms a crystalline addition compound with acetone. This can be recrystallized and then treated with sodium carbonate to regenerate the acetone. Methyl ketones, MeCOR, form such compounds with decreasing yields as the alkyl group increases in length. If both groups in the ketone are ethyl or higher the reaction with sodium bisulfite is too slow to be of any practical value (Stewart 1905). Acetone slowly

restores the color to Schiff's reagent (p. 230). Higher ketones act more slowly or not at all.

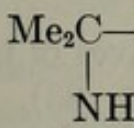
14. Hydrocyanic acid gives a *cyanohydrin*, which on hydrolysis gives alpha hydroxyisobutyric acid, and on alcoholysis gives the corresponding ethyl ester, which is used as a lacquer solvent. $Me_2C(OH)CN \rightarrow Me_2C(OH)CO_2Et$. As with the aldehydes, the best way to make these compounds is from the bisulfite addition products and a soluble cyanide. Ketones react with $NH_4$ salts and cyanides to give $RR'C(NH_2)CN$ which on hydrolysis forms the corresponding amino acids.

15. Grignard reagents react with acetone to give tertiary alcohols of the type $(CH_3)_2C(OH)R$. Complications appear here because of the basic nature of the Grignard reagent, and of the primary product, $RMe_2COMgX$. Both cause the acetone to undergo the aldol condensation. Thus the best way to make an alcohol, $RMe_2COH$, is not from acetone but from $RCO_2Et$ and an excess of MeMgCl. A good example is the preparation of dimethylisobutylcarbinol (deGraef 1931). Ethyl isovalerate with excess MeMgBr gives an 86% yield whereas acetone and isoBuMgBr gives only a 40% yield with the following by-products: mesityl oxide, phorone, isophorone, di-isobutyl, diacetone alcohol and the compounds $Me_2C(OH)CH_2COCH=CMe_2$, $Me_2C(OH)CH_2C(OH)(Me)CH_2CMe_2$, and

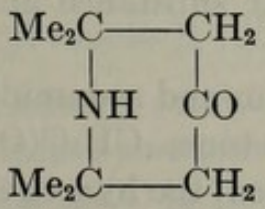
$$Me_2C=CHC(Me)=CHCMe_2.$$

Ketones with zinc and $\alpha$-bromo esters give beta hydroxy esters (Reformatzky). The simplest case is that of acetone and bromoacetic ester giving $Me_2C(OH)CH_2CO_2Et$.

16. With ammonia, acetone gives even more complicated products than do aldehydes. The ammonia first acts as a base inducing aldol condensations of two and three molecules of acetone to form mesityl oxide and phorone, respectively. These react with a molecule of ammonia to form diacetone amine (I) and triacetone amine (II).



(I)



(II)

While ammonia does not add to an ordinary olefinic linkage, it adds when that linkage is alpha beta to a carbonyl group. The mechanism is probably 1 : 4 addition followed by "ketonization,"

$$C{=}C{-}C{=}O \xrightarrow{NH_3} H_2N{-}C{-}C{=}C{-}OH \rightarrow H_2N{-}C{-}CH{-}C{=}O.$$

In the case of phorone, the addition of $NH_3$ would give

$$Me_2C(NH_2)CH_2COCH{=}CMe_2$$

in which the $NH_2$ and the farther olefinic carbon are in the 1 : 6 position. Intramolecular addition takes place to form triacetone amine. Triacetonamine is an intermediate for various drugs. Thus the benzoate of the corresponding secondary alcohol is Beta Eucaine, a cocaine substitute.

17. Hydroxylamine, phenyl hydrazine and semicarbazide act with acetone as with aldehydes, giving oximes, phenylhydrazones and semicarbazones.

Acetone oxime, acetoxime, $Me_2C{=}NOH$, m. 69°.
Acetone 2,4-dinitrophenylhydrazone, m. 128°.

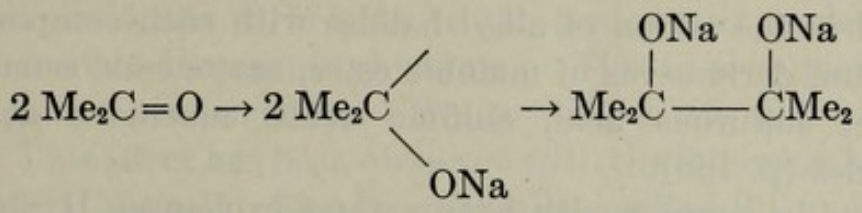
18. Nitrous acid, RONO + HCl, reacts with acetone to give isonitrosoacetone. The reaction probably resembles an aldol condensation with the N=O group serving the part of the carbonyl group.

$$Me_2CO + HON{=}O \rightarrow MeCOCH_2N(OH)_2 \rightarrow [MeCOCH_2N{=}O] \rightarrow MeCOCH{=}NOH$$

As has been seen the grouping $=CHNO$ changes to $=C{=}NOH$. It is interesting that formyl acetone, $HCOCH_2COMe$, exists only as the Na derivative of the enol, $NaOCH{=}CHCOMe$. Acidification gives complex products including triacetylbenzene. Isonitrosoacetone is the mono oxime of pyruvic aldehyde, MeCOCHO. It gives that substance and hydroxylamine on hydrolysis with dilute acids.

19. Sodium and sodamide form sodium derivatives of the enol form of acetone, $CH_3C(ONa){=}CH_2$ (Rep. 1907, 83). When sodium is used, the hydrogen evolved reduces some of the acetone

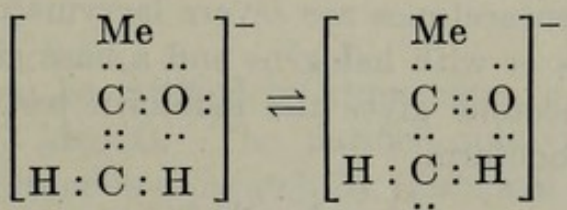
to isopropyl alcohol. Moreover there is a tendency to form the disodium derivative of pinacol.



Sodamide is the better reagent for making the sodium derivative of acetone. This sodium derivative reacts with alkyl halides or alkyl sulfates to give ketones of the form $CH_3COCH_2R$ (Rep. 1913, 61). If the treatment with $NaNH_2$ and alkyl halides is repeated, the final product will be $R_3CCOCR_3$, all the alpha H atoms having been replaced. With larger or forked groups the reaction fails before this point is reached. When a ketone containing no alpha H is heated with sodamide and the products are treated with water, the carbon chain is split.

$$R_3C-CO-CR_3 \rightarrow R_3CONH_2 + R_3CH$$

The reaction of the sodium acetone compound with RX might be expected to give $CH_3C(OR)=CH_2$, an unsaturated ether. The fact that $CH_3COCH_2R$ is obtained has been used as an argument that the sodium compound has the structure $CH_3COCH_2Na$, the metal being attached to carbon. Both these conceptions are at fault because they are based on the assumption that the reaction is a simple metathesis like the action of solutions of sodium chloride and silver nitrate. The negative ion of the sodium-acetone may be represented by the following equilibrium



A. B.

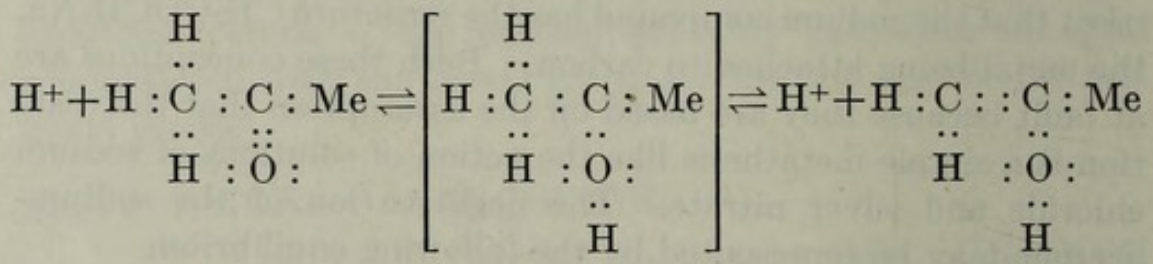
In the course of the reaction the alkyl halide $R:\ddot{\underset{\cdot\cdot}{X}}:$ parts with the halogen, the latter taking the electron octet. The R left with two electrons less than an octet is in a position to unite with a free electron pair on the O in A or on the C in B. The energy

relations are such that a new C—C linkage is formed instead of a C—O linkage. This is the same type of process as that involved in the action of alkyl halides with such compounds as the sodium derivatives of malonic ester, acetoacetic ester, nitromethane, sulfurous acid, sulfinic acids, arsenious acid and arsinoxides (p. 166).

Acetone in contact with heavy water exchanges H atoms for deuterium atoms (Halford 1934).

$$CH_3COCH_3 \rightleftharpoons CH_3C(OH)=CH_2 \overset{D_2O}{\rightleftharpoons} CH_3C(OD)=CH_2 \rightleftharpoons CH_3COCH_2D$$

20. Halogens replace the alpha hydrogens in acetone much as in aldehydes (Watson, Rev. 1930, 173). This process presumably takes place through the enol form. The conception that enolization is a bimolecular rather than a monomolecular process (p. 144) is strengthened by the fact that the rate of halogenation of ketones in solution is independent of the concentration of halogen but is proportional to the hydrogen ion concentration. The electronic system in the case of acetone and its enol would be as follows:



The monohalogen acetones are severe lacrymators. Treatment with hypohalites or with halogens and a base gives a haloform, $CHX_3$. Thus acetone gives the iodoform test and is used in manufacturing iodoform.

$$Me_2CO \rightarrow MeCOCX_3 \xrightarrow{NaOH} MeCO_2Na + CHX_3$$

21. Phosphorus pentachloride reacts with acetone to give a poor yield of "acetone dichloride," $CH_3CCl_2CH_3$. A large amount of $CH_3CCl=CH_2$ is obtained. Similar complications appear with higher ketones. In addition *sym*-$Me_4$ acetone and

$Me_5$- acetone give $\alpha-Cl$ ketones. Oxalyl chloride, ClCOCOCl, gives the dichloride (Staudinger, Rep. 1909, 79). Phosphorus pentabromide tends to brominate the acetone by replacing an $\alpha-H$ instead of the carbonyl oxygen. This is presumably due to the greater tendency for $PBr_5$ to dissociate. $PBr_5 \rightleftharpoons PBr_3 + Br_2$. This effect has been observed with the following ketones: $Me_2$, MeEt, Me*iso*Pr, Et-*t*-Bu, di-*iso*Pr, *iso*Pr-*t*-Bu and *iso*Pr-*iso*Bu. Pinacolone, Me-*t*-butyl ketone, gives some of the ketone dibromide but, in addition, the surprising products

$$Me_2CBrCOCH_2Me$$

and $Me_2CBrCOCHBrMe$ (Favorsky 1913).

22. Sunlight causes several peculiar reactions with acetone (Ciamician and Silber).

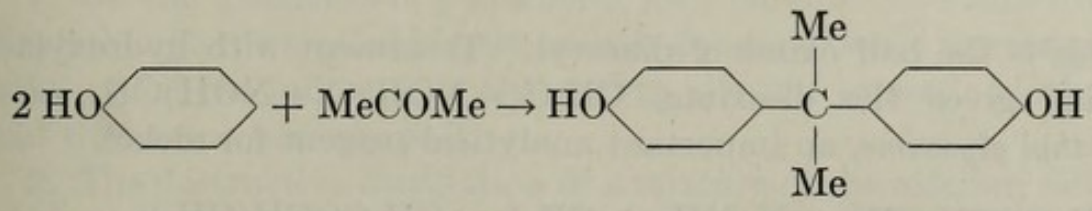
*a*. Water gives methane and acetic acid.

*b*. Methanol gives isobutylene glycol, isopropyl alcohol and ethylene glycol.

*c*. Ethanol gives $Me_3$-ethylene glycol, butandiol-2,3, and isopropyl alcohol.

*d*. Isopropyl alcohol gives pinacol ($Me_4$-ethylene glycol).

23. Acetone condenses with reactive aromatic compounds in the presence of acids, bridging together two aromatic radicals by the group $(CH_3)_2C$. Thus




24. Acetone can be purified by conversion to the crystalline compound $NaI.3\,Me_2CO$. The purified solid is treated with water and the acetone is separated by fractional distillation and drying with anhydrous sodium sulfate. Acetone forms compounds with $CaCl_2$ (Rep. 1917, 68).

25. Acetone can be identified by conversion to dibenzalacetone, $(C_6H_5CH=CH)_2CO$, m. 112°.

**Methyl ethyl ketone,** butanone, $CH_3COCH_2CH_3$, b. 79.6° is obtained from pyroligneous acid in even smaller amounts than

acetone. It is manufactured by catalytic dehydrogenation of butanol-2 from cracked gases (Shell) (EP 415).

During the World War, when *n*-BuOH was without uses and there was not enough acetone, methyl ethyl ketone was prepared from the former to supplement the supply of the latter. Dehydration was followed by hydration and then by dehydrogenation (all catalytic).

$$EtCH_2CH_2OH \rightarrow EtCH=CH_2 \rightarrow EtCHOHCH_3 \rightarrow EtCOMe$$

Its reactions are practically identical with those of acetone.

Vigorous oxidation gives mainly acetic acid. Very little propionic acid and $CO_2$ are obtained. This is probably because the enolization takes place mainly with the methylene group rather than with the methyl group.

$$\underset{\text{Very little}}{CH_2=C(OH)CH_2Me} \rightleftharpoons CH_3COCH_2Me \rightleftharpoons \underset{\text{Mainly}}{CH_3C(OH)=CHMe}$$

The last product formed before the breaking of the carbon chain is probably diacetyl, $CH_3COCOCH_3$. This is readily oxidized to acetic acid. Of the five alpha hydrogens, the two in the methylene group are generally more reactive with nitrous acid, in enolization as with $NaNH_2$, and with halogens. Thus

$$CH_3COCH_2CH_3 + HONO \rightarrow CH_3COC(=NOH)CH_3$$

This is the half oxime of diacetyl. Treatment with hydroxylamine gives the di-oxime, $CH_3C(=NOH)C(=NOH)CH_3$, *dimethyl glyoxime*, an important analytical reagent for nickel.

$$CH_3COCH_2CH_3 + NaNH_2 + CH_3I \rightarrow CH_3COCH(CH_3)_2$$
$$CH_3COCH_2CH_3 + Br_2 \rightarrow CH_3COCHBrCH_3 \quad \text{(mainly)}$$

In the aldol condensation with HCl, the methylene group is reactive giving mainly MeEtC=C(Me)COMe while with NaOMe, the alpha methyl group reacts to give MeEtC=CHCOEt (Colonge 1931, Powell 1931). Butyl Grignard reagent acts like NaOMe giving a good yield of the product from the action of the methyl group. $CaH_2$ and $CaC_2$ cause condensation of the $CH_3$ group. This is in keeping with the fact that they cause aldol

condensations of methyl ketones but are without effect on diethyl ketone (Rep. 1925, 73).

Sodium bisulfite adds, but less rapidly than with acetone (Stewart 1905). Hydrocyanic acid adds normally. The reactions with ammonia and related compounds are like those of acetone. Phosphorus pentachloride gives an even poorer yield of the dichloride than with acetone. This is probably because of the greater tendency to split HX out with a secondary H atom than with a primary one, $CH_3CCl_2CH_2CH_3 \rightarrow CH_3CCl=CHCH_3$.

Bromination in water in presence of $CaCO_3$ gives

MeCOCHBrMe,

b. 37° (12 mm.), and $BrCH_2COEt$, b. 90° (12 mm.).

Methyl ethyl ketone condenses with normal aldehydes up to $C_7$ to give RCHOHCHMeCOMe, the $CH_2$ group entering the condensation. With a fork at the alpha carbon of the aldehyde as with isobutyraldehyde, MeEt-acetaldehyde, $Et_2$-acetaldehyde and EtBu-acetaldehyde the $CH_3$ group reacts giving

RRCHCHOHCH$_2$COEt

(Powell 1935).

**Methyl *n*-propyl ketone,** pentanone-2, $CH_3COCH_2CH_2CH_3$, can be obtained in a variety of ways typical for the preparation of higher ketones.

1. By the oxidation of pentanol-2 with chromic acid mixture. Even though the alcohol is pure there is danger of some rearrangement under the influence of the acid to give the isomeric alcohol and then some pentanone-3.

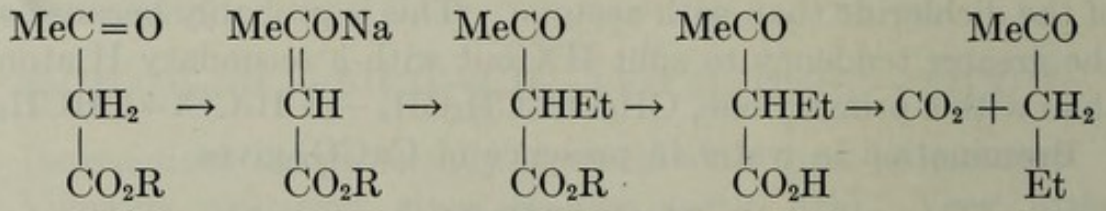
2. The destructive distillation of a mixture of the calcium salts of acetic and propionic acids gives methyl ethyl ketone along with acetone and dipropyl ketone. A similar result is obtained by passing the vapors of the acids over heated MnO.

3. From a *n*-propyl Grignard reagent and acetonitrile or acetamide

$$MeCN + RMgX \rightarrow RMeC=NMgX \rightarrow RMeC=NH \rightarrow RMeC=O$$

$$MeCO(NH_2) + 2\,RMgX \rightarrow RMeC(OMgX)(NHMgX) \rightarrow RMeC(OH)NH_2 \rightarrow RMeCO$$

4. From sodium acetoacetic ester and ethyl bromide, followed by treatment with *dilute* alkali and acid. The first steps of this process duplicate those of alkylating acetone by sodamide and alkyl halides. The last step depends on the instability of acids containing the grouping, $-COCH_2CO_2H$, beta-keto acids which lose $CO_2$ readily to give $-COCH_3$.



By similar reactions monosubstituted acetones, $CH_3COCH_2R$, may be prepared from alkyl halides of Class 1 (p. 71) and a few others such as isopropyl and isobutyl. After one alkyl group has been introduced, another can be put in by treatment with NaOEt and the proper alkyl halide. The second alkyl group to enter can usually belong only to Class 1.

(5) From sodium oxalyl acetone formed from acetone and diethyl oxalate and NaOEt (Rep. 1913, 61).

$$Me_2CO + EtOCOCO_2Et \rightarrow MeCOCH_2COCO_2Et$$

This is converted to the sodium derivative, treated with ethyl halide and then split by bases and acid. This method is not limited to methyl ketones.

**Methyl isopropyl ketone,** 3-methylbutanone-2,

$$CH_3COCH(CH_3)_2,$$

can be made as follows:

(1) By oxidation of methyl isopropyl carbinol prepared by the Grignard reaction.

(2) From acetoacetic ester by converting it to the sodium derivative and treating with methyl iodide; converting again to the sodium derivative and again treating with methyl iodide; finally saponifying with dilute alkali and acidifying. The last step is

$$CH_3COC(CH_3)_2CO_2H \rightarrow CO_2 + CH_3COCH(CH_3)_2$$

(3) Best, by hydrolyzing and rearranging trimethylethylene

dibromide or dichloride obtained directly from tertiary amyl alcohol and bromine or chlorine or from $Me_3$-ethylene (Sharples).

$$Me_2CBrCHBrMe + H_2O \rightarrow Me_2CHCOMe + 2\,HBr$$

The reactions of methyl isopropyl ketone are like those of the other methyl ketones except that they are complicated by the presence of the forked chain and the tertiary H atom in the alpha position. The replacement of this H by Br or NO is very easy indeed. Thus slightly less than 1 mol of $Br_2$ at 0° gives a 90% yield of $MeCOCBrMe_2$ (Favorski 1913). $PBr_5$ gives a similar result. Phosphorus pentachloride would probably give none of the dichloride. Because of the activity of the tertiary H atom, the product would probably be $MeCCl{=}CMe_2$. Ethyl nitrite and HCl give the bimolecular form of the tertiary nitroso compound, $[MeCOC(NO)Me_2]_2$. This is colorless but on heating turns blue, due to the formation of the monomolecular true nitroso compound. Reduction gives first an azoxy compound, R : N :: N : R, and then hydrazine, $H_2NNH_2$, and Me isoPr

: O :

ketone (Aston 1932). Nitrous acid reacts to give only

$$[MeCOC(NO)Me_2]_2$$

(Aston 1932).

The tertiary H does not take part in aldol condensations, apparently because of the difficulty for a relatively large group to add to such a "crowded" atom (so-called *steric hindrance*). It gives an aldol condensation involving an alpha H atom in the methyl group

$$2\,Me_2CHCOCH_3 \rightarrow Me_2CHC(OH)(CH_3)CH_2COCHMe_2 \rightarrow Me_2CHC(Me){=}CHCOCHMe_2$$

2,3,6-$Me_3$-hepten-3-one-5

This change is also brought about by treatment with a tertiary butyl Grignard reagent. No evidence of reduction of the ketone to methyl isopropyl carbinol by the Grignard reagent is obtained. The action of methyl isopropyl ketone with *t*-butyl magnesium chloride is a good example of the influence of branching on an

addition reaction. Depending on the branched structures of the Grignard reagent and the ketone, their action may give: (*a*) A tertiary alcohol by their union; (*b*) A secondary alcohol by reduction of the ketone; (*c*) A mesityl oxide homolog by aldol condensation and dehydration; (*d*) An MgX derivative of the enol form of the ketone with evolution of RH (Conant, Blatt 1929).

**Diethyl ketone,** propionone, pentanone-3,

$$CH_3CH_2COCH_2CH_3,$$

may be made as follows:

(1) By the destructive distillation of calcium propionate or by passing the vapors of propionic acid over hot MnO. This preparation gives the name propionone. Similar names derived from the corresponding acids are applied to the symmetrical ketones obtained by this oldest preparation for ketones. Thus:

| Acid | Ketone | |
|---|---|---|
| Acetic | acetone | $Me_2CO$ |
| Propionic | propionone | $Et_2CO$ |
| Butyric | butyrone | $Pr_2CO$ |
| Isobutyric | isobutyrone | $(Me_2CH)_2CO$ |
| Pivalic | pivalone | $(Me_3C)_2CO$ |
| Stearic | stearone | $(C_{17}H_{35})_2CO$ |

Symmetrical ketones can be prepared by heating the compounds, $RCO_2MgX$, obtained from the Grignard reagent and $CO_2$.

(2) By oxidation of pentanol-3 obtained from the chlorination of pentane or by the action of an excess of ethyl Grignard reagent with an ester of formic acid.

Its reactions are typical ketone reactions except that its carbonyl group is less reactive than in the methyl ketones. It is one of the few ketones, other than methyl ketones, which react even slowly with sodium bisulfite (Stewart 1905). With ethyl acetate and NaOEt at room temperature diethyl ketone gives the expected product, MeCOCHMeCOEt, but at higher temperatures $MeCOCH_2COEt$ is also formed (Rep. 1925, 73). The latter indicates the formation of MeEt ketone in the mixture. This is due to the ordinary alkaline splitting of a 1,3-diketone, especially one substituted in the 2 position. This is familiar in

substituted acetoacetic esters. The split can occur in the 1 : 2 or 2 : 3 position.

$$\mathrm{MeC(=O)CH(Me)C(=O)Et} \xrightarrow{\mathrm{NaOEt}} \mathrm{MeCO_2Et} + \mathrm{MeCH{=}C(ONa)Et}$$

$$+ \mathrm{EtCO_2Et} + \mathrm{MeCH{=}C(ONa)Me}$$

The last product is the Na derivative of MeEt ketone.

Diethyl ketone with $NaNH_2$ and MeI gives Et isoPr ketone and di-isoPr ketone (Haller and Bauer, Rep. 1913, 61).

Diethyl ketone, condensed with ethyl oxalate and EtONa, treated with RX and then split with bases gives ketones EtCOCHMeR (Rep. 1913, 61).

**Methyl *n*-butyl ketone,** hexanone-2, $CH_3CO(CH_2)_3CH_3$, can be made (1) from sodium acetoacetic ester and *n*-propyl halide, (2) by oxidation of hexanol-2, (3) from acetic and *n*-valeric acids. Its reactions are those of methyl ketones retarded by the increased size of the molecule.

**Ethyl *n*-propyl ketone,** hexanone-3, $CH_3CH_2COCH_2CH_2CH_3$, can be made by the usual methods except the acetoacetic ester synthesis. Its carbonyl group is even more sluggish than that in its methyl isomer.

**Methyl isobutyl ketone,** 4-methylpentanone-2,

$$CH_3COCH_2CH(CH_3)_2,$$

can be made by the usual reactions including the sodium acetoacetic ester synthesis although the action of isopropyl halides with that substance gives poorer yields than do the halides of Class 1. A better preparation is by a special method, the reduction of mesityl oxide by an acid reducing agent or by a catalytic method which does not act on the carbonyl group.

$$\mathrm{MeCOCH{=}CMe_2} \rightarrow \mathrm{MeCOCH_2CHMe_2}$$

Another preparation would be the oxidation of the corresponding alcohol obtained by heating isopropyl alcohol with bases (Guerbet). This ketone is sold as Hexone (C and C).

**Ethyl isopropyl ketone,** 2-methylpentanone-3,

$$CH_3CH_2COCH(CH_3)_2,$$

can be made from isobutyronitrile and ethyl Grignard reagent or by the oxidation of the corresponding secondary alcohol. The preparation from two acids, always unsatisfactory because of the three products, would be especially so because in this case both of the acids are rather expensive.

Treatment with nitrous acid gives the surprising result that the replacement of secondary and tertiary H takes place in the ratio 4 : 1 giving $MeC(=NOH)COCHMe_2$ and

$$[MeCH_2COC(NO)Me_2]_2.$$

Reduction of the latter compound gives hydrazine, $H_2NNH_2$, indicating the linkage of N—N in the bimolecular form of the nitroso ketone (Aston 1932).

A peculiar formation of ethyl isopropyl ketone is from *n*- or *iso*-pentane and CO in presence of $AlCl_3$ (EP 418).

**Methyl sec-butyl ketone,** 3-methylpentanone-2,

$$CH_3COCH(CH_3)CH_2CH_3,$$

can be made by the acetoacetic ester synthesis by use of methyl and ethyl halides in succession. The ethyl group should be introduced first because it is easier to purify $MeCOCHEtCO_2R$ than $MeCOCHMeCO_2R$.

The best preparation would probably be from a *sec*-Bu Grignard reagent and acetonitrile.

**Methyl *tert*-butyl ketone, pinacolone,** " pinacoline," 3,3-$Me_2$-butanone, $CH_3COC(CH_3)_3$, b. 106°, is best obtained by the rearrangement of pinacol by acids (OS). It can also be made by the action of *t*-BuMgCl on an excess of acetyl chloride. If a smaller group is to be introduced in place of the Cl of an acid chloride, the zinc alkyls give better results.

**Methyl *n*-amyl ketone** is obtained by the dehydration and partial reduction of the condensation product of acetone with *n*-butyraldehyde.

$$PrCHO + CH_3COMe \rightarrow PrCHOHCH_2COMe \rightarrow PrCH=CHCOMe \rightarrow PrCH_2CH_2COMe$$

**Dipropyl ketone,** butyrone, $(CH_3CH_2CH_2)_2CO$, is obtained in the usual ways and gives the reactions of a higher ketone.

**Diisopropyl ketone,** isobutyrone, $(CH_3)_2CHCOCH(CH_3)_2$, is

obtained by oxidation of the corresponding secondary carbinol which is an important by-product of synthetic methanol (p. 103). It can also be made from isobutyric acid and by the action of $NaNH_2$ and MeI with acetone, methyl ethyl ketone, diethyl ketone and methyl isopropyl ketone (Haller and Bauer).

Treatment with $PCl_5$ replaces one of the $\alpha$-tertiary H atoms instead of giving the expected dichloride (Favorsky 1913).

**Hexamethylacetone,** pivalone, $Me_3CCOCMe_3$, b. 151°, is obtained by exhaustive methylation of methyl isopropyl ketone or diisopropyl ketone with $NaNH_2$ and MeI or $Me_2SO_4$ (Haller, Bauer 1909). It can be made in small yield from pivalyl chloride, $Me_3CCOCl$ and *t*-BuMgCl. It gives no derivatives with hydroxylamine, hydrazines, etc. It is best identified by treatment with MeMgX to give $Me_7$-isopropyl alcohol, m. 42°.

**Methyl neopentyl ketone,** $MeCOCH_2CMe_3$, b. 124°, is available from the oxidation of the lower boiling diisobutylene,

$$Me_3CCH_2C(Me)=CH_2.$$

Its reactions are those of an ordinary methyl ketone.

**Higher ketones** have been made in large numbers by the reactions outlined above and by other special reactions.

Higher methyl ketones may be obtained by the destructive distillation of the barium salt of a higher acid with Ba acetate (Rep. 1925, 81). In this way Me $C_{18}$ and Me $C_{19}$ ketones have been made. It will be recalled that margaric acid ($C_{17}$) for intarvin manufacture is made from the Me $C_{17}$ ketone prepared in a similar way (Krafft) (p. 306). Thus methyl heneicosyl ketone, $MeCOC_{21}H_{43}$, has been made from behenic acid obtained by the hydrogenation of erucic acid (Rep. 1925, 81).

Ketones of the type $RCOCH_2R$ can be made from *acyloins*, RCOCHOHR, obtained by the action of Na on esters in ether solution. Reduction of the acyloin by Na and absolute alcohol gives RCHOHCHOHR and $RCH_2CHOHR$. Treatment with dilute sulfuric acid rearranges the glycol to the desired ketone and oxidation gives the same product from the alcohol (Rep. 1906, 82).

The ketones are readily reduced to alcohols by heating with sodium isopropylate. Thus Me *n*-nonyl ketone gives a quantita-

tive yield of undecanol-2 and acetone (Rep. 1925, 72). Heating a ketone with hydrazine sulfate and an excess of NaOEt reduces it to the hydrocarbon by converting CO to $CH_2$ (Wolff, Kishner).

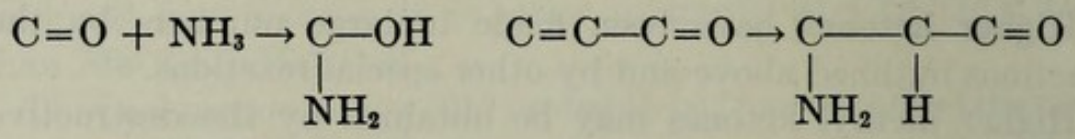
### *C.* Unsaturated Aldehydes and Ketones

These give the reactions of the saturated carbonyl compounds and of olefins and, in addition, give other reactions if the unsaturation is conjugated with the carbonyl giving groupings,

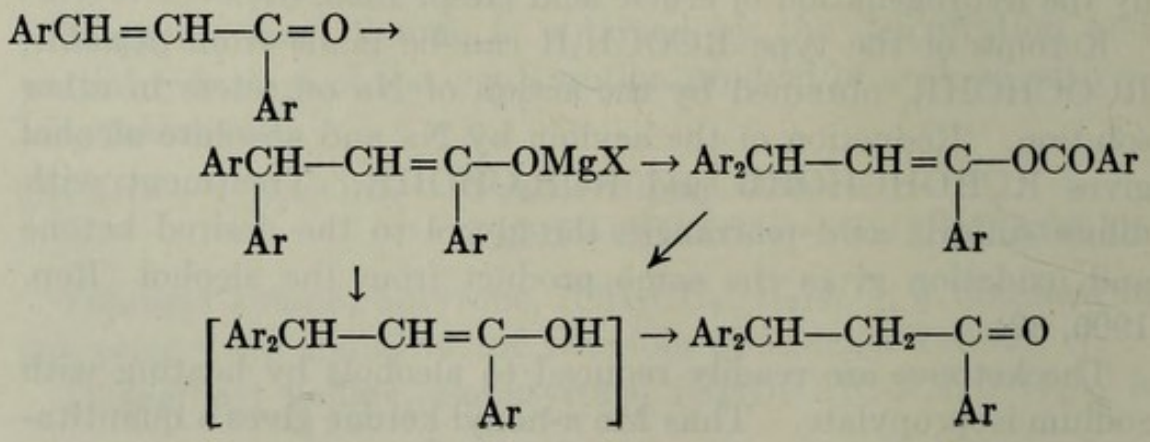
$$C=C-C=O,\ C=C-C=C-C=O,$$

etc. These conjugated groupings result in the transfer of some of the properties of the carbonyl carbon and the $\alpha$-carbon to the end carbon in the conjugated system and to the one just beyond it (Vinylogy, Fuson 1935).

1. Certain groups which ordinarily add to the carbonyl carbon add to the carbon at the end of the conjugated system probably by a process of 1 : 4 addition. The net result is the addition to the $\alpha\beta$-double bond of groups which do not ordinarily add to an olefinic linkage.

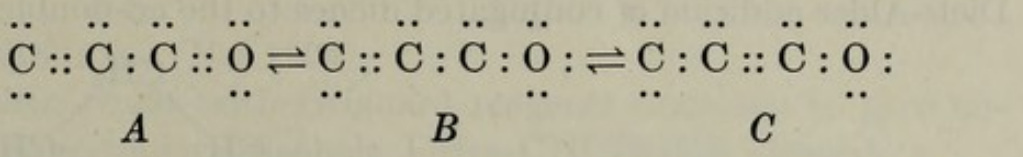


Some believe that such processes are due to an activation of the double bond by the adjacent carbonyl group. In some cases, such as the addition of Grignard reagents to certain alpha-beta unsaturated compounds, the addition has been proved to go through 1 : 4-addition to the ends of the conjugated system (Kohler, Rep. 1905, 113).



Thus the net result is the addition of ArH to the $\alpha\beta$-double bond.

The electronic mechanism for addition to a conjugated system involving a carbonyl group may include the following steps:



*A* *B* *C*

Phase *A* is the stable arrangement. *B* and *C* are formed by combination with $H^+$ or a group like MgX. In *B* the carbon of the carbonyl group is in a position to add an atom or group having a complete octet such as $Br^-$ or $NH_2$. In *C* the carbon at the end of the conjugated system can add such a group. In the addition of HBr or $NH_3$ to the unsaturated carbonyl compound, reaction with *B* would give products containing the unstable groupings C(OH)Br and $C(OH)NH_2$ which can lose HBr and $NH_3$. On the other hand, addition to *C* is irreversible. Hence the 1 : 4 addition product is obtained. With the Grignard reagent, the 1 : 2 addition product on the carbonyl group is stable and is the only product unless the steric relations are such as to favor the addition of the organic radical in the 4 rather than the 2 position (Kohler). The electronic shifts in such a system are often indicated as $C=\overset{\frown}{C}-C=\overset{\frown}{O}$ (Rep. 1927, etc.).

A similar process is the addition of beta keto esters and related compounds under the influence of NaOEt and similar catalysts (Michael). Thus sodiomalonic ester is represented as adding to methylene acetone as follows:

$$CH_2=CHCOCH_3 \rightarrow (EtO_2C)_2CHCH_2CH=C(ONa)CH_3 \rightarrow (EtO_2C)_2CHCH_2CH_2COCH_3$$

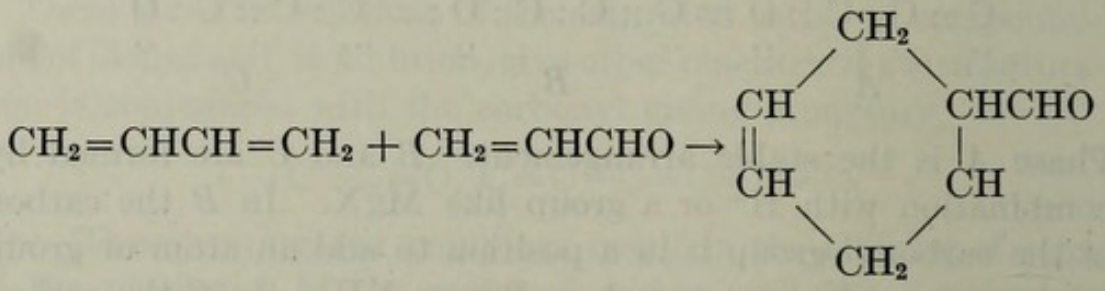
Only a small amount of NaOEt is needed since the malonic ester is more "acidic" than the enol. The net result is the addition of malonic ester to the olefinic double bond. Acetoacetic ester, cyanoacetic ester, acetylacetone and such compounds give this reaction.

2. The carbon "alpha" to the end of the conjugated system has the properties of an ordinary alpha carbon in that its H

atom can take part in an aldol condensation.

$$MeCHO + CH_3CH{=}CHCHO \rightarrow MeCHOHCH_2CH{=}CHCHO$$

3. Another peculiarity of the conjugated carbonyl system is the Diels-Alder addition of conjugated dienes to the $\alpha\beta$-double bond.



Cumulative double bonds, as found in the *ketene* grouping, C=C=O, give even more unusual mutual effects between the olefinic and carbonyl linkages than those shown by conjugated compounds.

**Acrolein,** acrylic aldehyde, propenal, $CH_2{=}CHCHO$, b. 52°, is formed in the thermal decomposition of fats. Its odor is very irritating. It is best prepared by heating glycerol with a mild dehydrating agent such as $KHSO_4$ or $MgSO_4$ (Rep. 1912, 81). The process involves dehydration and rearrangement, perhaps including the following steps:

$$HOCH_2CHOHCH_2OH \rightarrow HOCH_2CH{=}CHOH \rightarrow HOCH_2CH_2CHO \rightarrow CH_2{=}CHCHO$$

Acrolein polymerizes to resins unless stabilized by various "anti-oxidants" such as hydroquinone (Moureu). It gives resins with phenols (Maksorow 1932).

Acrolein gives both the reactions of olefins and of aldehydes. Its conjugated system of double bonds modifies its addition reactions somewhat. The ethylenic bond is more easily reduced due to 1 : 4 addition of hydrogen (Robinson 1932).

$$C{=}C{-}C{=}O \rightarrow HC{-}C{=}C{-}OH \rightarrow HC{-}CH{-}C{=}O$$

Reduction also gives a 25% yield of the dimolecular product, divinyl glycol, $CH_2{=}CHCHOHCHOHCH{=}CH_2$. Halide acids add entirely contrary to Markownikoff's Rule which would predict that the halogen would take the alpha position. This

also may be explained on the basis of 1 : 4 addition, the H adding first to the O.

Acrolein with $H_2O$ at 100° gives hydracrylic aldehyde,

$$HOCH_2CH_2CHO,$$

b. 90° (18 mm.) (Nef 1904).

Acrolein reacts with Grignard reagents normally to give unsaturated secondary alcohols, $CH_2=CHCHOHR$ (Bouis).

Both the olefinic and aldehyde groups are sensitive to oxidation. Thus mild oxidation gives glyceric acid,

$$CH_2OHCHOHCO_2H,$$

and more vigorous oxidation breaks the chain. Silver oxide does not attack olefinic linkages and thus oxidizes it to acrylic acid. If ordinary oxidizing agents are to be used to oxidize only one of the reactive groups the other must be "protected." The C=C can be protected by adding bromine.

$$CH_2BrCHBrCHO \rightarrow CH_2BrCHBrCO_2H \xrightarrow{Zn} CH_2=CHCO_2H$$

The CO can be protected by making the acetal with EtOH and HCl gas. Thus

$$CH_2=CHCHO \rightarrow ClCH_2CH_2CH(OEt)_2 \xrightarrow{KOH} CH_2=CHCH(OEt)_2 \rightarrow CH_2OHCHOHCH(OEt)_2$$

The acetal groups can be removed by boiling with excess of dilute acid, thus giving glyceric aldehyde.

**Crotonaldehyde,** crotonic aldehyde, buten-2-al,

$$CH_3CH=CHCHO,$$

b. 104°, is obtained by heating aldol alone at 140° or by warming it with a trace of a dehydrating agent. The yield is usually not over 50% but can be increased to 80% by using iodine as the catalyst (Hibbert 1915). The product consists entirely of the *trans* form (Young 1932).

Its reactions are practically identical with those of acrolein except that the $CH_3$ next to the conjugated system can take part in aldol condensations. Thus crotonaldehyde can be con-

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densed to an aldol which on dehydration gives octatrienal, $Me(CH=CH)_3CHO$ (Rep. 1932, 115). With acetaldehyde, crotonaldehyde gives hexadienal, $Me(CH=CH)_2CHO$ (Kuhn 1931).

The autoxidation of crotonaldehyde is stopped by 10 p.p.m. of hydroquinone (Rep. 1922, 69).

The reduction of crotonaldehyde by the Zn—Cu couple gives *n*-BuOH, crotonyl alcohol, $MeCH=CHCH_2OH$, but mainly the bimolecular reduction product, dipropenyl glycol,

$$MeCH=CHCHOHCHOHCH=CHMe.$$

**Vinyl acetaldehyde,** buten-3-al, $CH_2=CHCH_2CHO$, is unknown probably because of its easy rearrangement to the conjugated compound crotonic aldehyde. The tendency to form a conjugated system resembles the tendency for an enol form to change to a keto form.

$$-CH=CH-CH_2-C=O \rightarrow -CH_2-CH=CH-C=O$$
$$C=C-OH \rightarrow CH-C=O$$

In each case a 1 : 3 shift of H occurs. In both cases this is probably the net result of a bimolecular reaction with hydrogen ion (p. 260). The C=C—C=O and C=O groups resemble each other in stability as compared with the non-conjugated and enolic forms. They confer a similar reactivity on H atoms attached to a carbon *alpha* to them.

**Tiglic aldehyde,** $\alpha$-methylcrotonic aldehyde, $\alpha\beta$-dimethylacrolein, 2-methylbuten-2-al, $CH_3CH=C(CH_3)CHO$, b. 118°, is obtained from a mixture of acetaldehyde and propionaldehyde through the aldol condensation. The other product of the "mixed" condensation, $EtCH=CHCHO$, is formed in only small amounts. Thus the lower aldehyde tends to supply the carbonyl group rather than the alpha H for the aldol condensation.

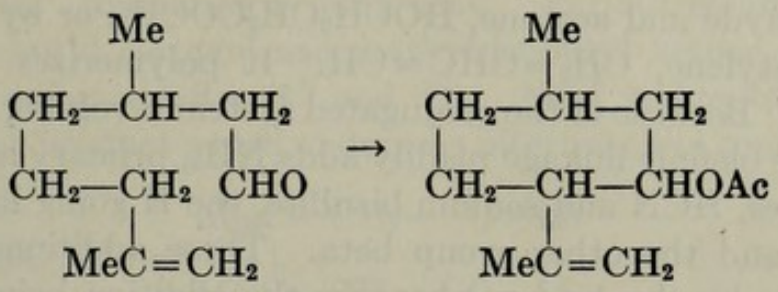
**$\beta$-Methylcrotonaldehyde,** $(CH_3)_2C=CHCHO$, b. 133°, is made by brominating the acetal of isovaleraldehyde, removing HBr by alkali and hydrolyzing the unsaturated acetal. It gives the reactions of crotonaldehyde including the ability of the $\beta$-methyl groups to take part in aldol condensations. Thus it gives an

aldol which can be dehydrated to 3,7-$Me_2$-octatrien-2,4,6-al (Rep. 1932, 115).

**$\alpha\gamma$-Dimethylcrotonic aldehyde,** $\alpha$-methyl-$\beta$-ethylacrolein, 2-methylpenten-2-al, $CH_3CH_2CH=C(CH_3)CHO$, is obtained by aldol condensation of propionaldehyde. Similarly *$\alpha$-ethyl-$\beta$-propylacrolein* is obtained from *n*-butyraldehyde. It is related to 2-Et-hexanol-1 (C and C).

**Higher alpha-beta unsaturated aldehydes** and **ketones** are readily obtained from the corresponding aldol condensation products.

**Citronellal,** (Rhodinal) 3,7-$Me_2$-octen-7 or 6-al, b. 202°, 82° (2 mm.), is found in *d*- and *l*-forms in various essential oils. Treatment with acetic anhydride gives *isopulegol acetate,* a ring formation typical of the terpene series.




This change involves an *intramolecular* aldol condensation of an H which is alpha to an ethylenic linkage. Such an aldol condensation would be most improbable *intermolecularly* because the more reactive H alpha to carbonyl would react by preference.

The essential oil of *Eryngium foetidum* is mainly dodecen-2-al (Koolhaas 1932).

**Citral** (Geranial, Neral), 3,7-$Me_2$-octadien-2,6-al (*cis* and *trans* forms), b. 228°, occurs in many essential oils. When heated with mild alkaline reagents it is split at the 2-double bond to give acetaldehyde and *methylheptenone* (6-Me-hepten-5-one-2). This is a reversal of the aldol condensation. It is apparently dependent on the fork at the $\beta$-position. Treatment with dilute sulfuric acid closes a 6-membered ring and dehydrates it to give cymene, 1,4-methylisopropylbenzene. Citral is used in making $\alpha$- and $\beta$-ionones for perfumery.

Violet leaves contain a perfume oil which consists largely of nonadien-2,6-al (Späth 1934).

**Propargylic aldehyde,** propynal, $CH{\equiv}CCHO$, can be made by adding bromine to acrolein acetal, treating with excess of alkali and hydrolyzing the propargylic acetal with excess of dilute acid.

Higher $\alpha\beta$-acetylenic aldehydes can be made from acetylenic Grignard reagents and orthoformic ester.

$$RC{\equiv}CH \xrightarrow{MeMgCl} RC{\equiv}CMgCl \xrightarrow{HC(OEt)_3} RC{\equiv}CCH(OEt)_2 \rightarrow RC{\equiv}CCHO$$

They can also be made from $RC{\equiv}CNa$ and formic esters (Moureu 1901).

**Vinyl methyl ketone,** methylene acetone, $CH_2{=}CHCOCH_3$, can be made by dehydrating the first condensation product of formaldehyde and acetone, $HOCH_2CH_2COCH_3$, or by hydrating vinyl acetylene, $CH_2{=}CHC{\equiv}CH$. It polymerizes much like acrolein. Because of the conjugated system involving a carbonyl group the olefinic linkage readily adds $NH_3$, primary and secondary amines, HCN and sodium bisulfite, the H going in the alpha position and the other group beta. These additions probably take place by the 1 : 4-mechanism, the addition being initiated by addition of H to the oxygen of the reactive carbonyl group.

$$CH_3COCH{=}CH_2 \rightarrow CH_3COCH_2CH_2NH_2 \quad \text{(Frdl. } 11\text{, 785)}$$
$$\rightarrow CH_3COCH_2CH_2CN \quad \text{(Lapworth 1904)}$$
$$\rightarrow CH_3COCH_2CH_2SO_3Na$$

Heat causes a peculiar addition to the olefinic linkage (probably 1 : 4) giving $MeCOCH_2CH_2CH_2COCH{=}CH_2$. Further evidence of the activity of the conjugated system is given by the action of dilute potassium carbonate solution with the latter to add $H_2O$ giving octadion-3,7-ol-1 (Rep. 1911, 106). Grignard reagents react normally with the CO group whereas the related phenyl substituted compound $PhCOCH{=}CHPh$ adds PhMgBr in the 1 : 4 position (Kohler).

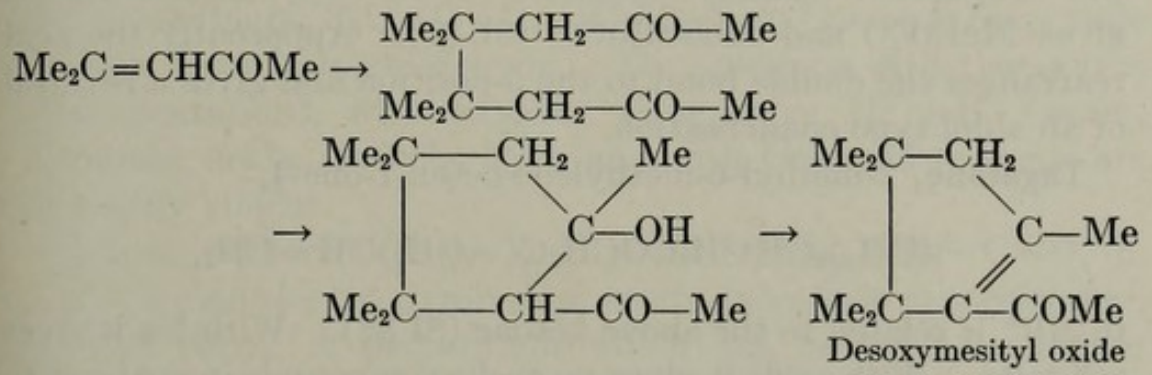
**Vinyl** alkyl ketones can be made from $\beta$-chloropropionyl chloride with RZnI (Blaise).

$$ClCH_2CH_2COCl \rightarrow ClCH_2CH_2COR \rightarrow CH_2{=}CHCOR$$

Hexen-3-one-2 has been found in acetone oil from wood distillation (Rep. 1923, 67).

Methyl unsaturated ketones of the type $CH_3COCH=CHR$, can be made by dehydrating the aldol condensation product of acetone and an aldehyde. Many aldehydes, however, condense with themselves much more readily than with acetone.

**Mesityl oxide,** 2-Me-penten-2-one-4, b. 130°, is readily available by the dehydration of diacetone alcohol. It is a typical $\alpha\beta$-unsaturated ketone. It gives the reactions of the conjugated system as given by methyl vinyl ketone. With HOCl it gives $Me_2C(OH)CHClCOMe$, which with alkali gives the $\alpha\beta$-ethylene oxide (Rep. 1918, 54). A peculiar reaction is that with MeOH and KOH to give the methyl ether of diacetone alcohol. This addition of MeOH to the double bond also probably follows the 1 : 4 course. Reduction is very easy. Various conditions give methyl isobutyl carbinol and methyl isobutyl ketone which are available commercially (C and C). Mild reduction gives a bimolecular product which undergoes internal aldol condensation.



Desoxymesityl oxide

**Phorone,** 2,6-$Me_2$-heptadien-2,5-one-4, b. 197°, is also obtained by aldol condensation of acetone. It gives the same reactions as mesityl oxide with the added possibility of internal condensation to form a 6-ring as in triacetonamine. Mild reduction gives a dimolecular condensation product analogous to that from mesityl oxide. Vigorous reduction gives 2,6-$Me_2$-heptanol-4, diisobutyl carbinol. Reduction by $H_2$ and Pt gives diisobutyl ketone, diisobutylcarbinol or methylisobutylcarbinol depending on the pressure used (Rep. 1911, 92).

$\alpha\beta$-Unsaturated ketones with $H_2$ and Pd give saturated ketones (Rep. 1909, 77).

**Methylheptenone,** 2-Me-hepten-2-one-6,

$$Me_2C=CHCH_2CH_2COCH_3,$$

b. 171°, is obtained from citral and dilute bases. It gives reactions of the carbonyl and olefinic groups. With sulfuric acid it condenses to a 6-membered ring forming 5,6-dihydro-*m*-xylene. $\alpha$-Methylheptenone with the grouping $CH_2=C(Me)-$ instead of $Me_2C=$ has been prepared, b. 168° (SI 35). Its oxidation does not give acetone as does that of ordinary methylheptenone. In the terpene and related series there is much confusion between these groupings probably because one can be converted into the other in the presence of acid catalysts as in the case of the isomeric diisobutylenes.

**2,6-Dimethylocten-7-one-4,** dihydrotagatone,

$$(CH_3)_2CHCH_2COCH_2CH(CH_3)CH=CH_2,$$

b. 186°, does not react with 20% sulfuric acid or with $NaHSO_3$ (no conjugated carbonyl system). With 70% sulfuric acid it gives MeEtCO and MeisoBuCO (SI 87). Apparently the acid rearranges the double bond to the 5-position and gives a reversal of an aldol type condensation.

**Tagatone,** 2-methyl-6-methylene-octen-7-one-4,

$$(CH_3)_2CHCH_2COCH_2C(=CH_2)CH=CH_2,$$

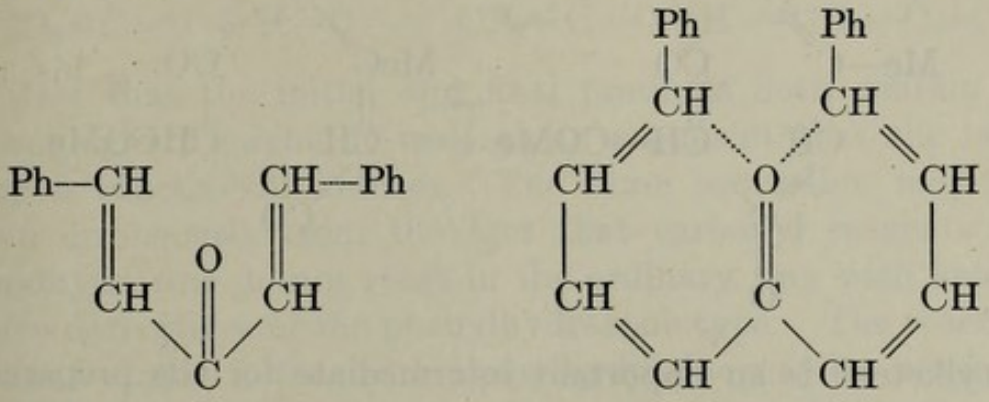
b. 210°, is related to the above ketone (SI 88). With Na it gives red salts. With acids it gives no cyclic compounds in contrast to methylheptenone and related compounds. The latter usually have a double bond in the $\gamma\delta$-position with a fork at the $\delta$-carbon.

**Artemesia ketone,** $Me_2C=CHCOC(Me_2)CH=CH_2$ (SI 90) is one of the few naturally occurring substances containing a *neo* carbon.

**Pseudoionone,** 2,6-$Me_2$-undecatriene-2,6,8-one-10, is obtained by aldol condensation of citral and acetone. By ring closure it gives $\alpha$- and $\beta$-ionone. Other ketones have been used instead of acetone (Hibbert 1924).

**Chelation of unsaturated ketones.** The fact that acetoacetic ester in presence of NaOEt will add to dibenzalacetone but not

to dicinnamalacetone can be explained on the basis of residual affinities at the ends of conjugated systems (*chelate ring* formation) (Rep. 1910, 70).



$\alpha\beta$-Acetylenic ketones, $RC{\equiv}CCOR'$, are obtained from acyl halides, $R'COX$, and $RC{\equiv}CNa$ or $RC{\equiv}CMgX$ (Moureu 1900).

### *D.* Ketenes

Ketenes of two types are known, aldoketenes, $RCH=C=O$, and ketoketenes, $R_2C=C=O$. The carbonyl group is even more reactive than in formaldehyde. The reactions with themselves (polymerization), with oxygen, with active H cpds. (water, ammonia, acids, alcohols, etc.), and with Grignard reagents are unusually violent.

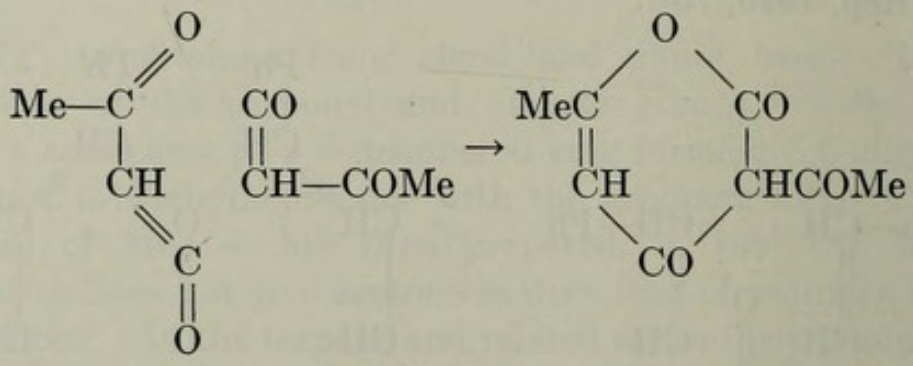
*Ketene*, carbomethylene, methylene ketone, $CH_2=C=O$, b. $-56°$, is made by the pyrolysis of acetic anhydride or, preferably, acetone (OS). A preparation which can be used for higher ketenes is the action of zinc with bromoacetyl bromide. This preparation also throws light on the structure of the ketenes.

$$\begin{matrix} CH_2{-}C{=}O \\ | \quad\ | \\ Br \quad Br \end{matrix} + Zn \rightarrow ZnBr_2 + CH_2{=}C{=}O$$

Ketene polymerizes very rapidly. Its dimer is acetyl ketene, $CH_3COCH=C=O$, b. 127°, instead of a cyclobutane derivative analogous to the dimers of $R_2C=C=O$ (Angus 1935, Hurd 1936). The polymerization can be regarded as an aldol condensation

$$2\,H_2C{=}C{=}O \rightarrow H_2C{=}C(OH)CH{=}C{=}O \rightarrow CH_3COCH{=}C{=}O$$

Further polymerization gives dehydroacetic acid. This may involve a Diels-Alder reaction.



Acetylketene is an important intermediate for the preparation of methyl and ethyl acetoacetates by the action of MeOH and EtOH and of acetoacetanilide by the action of aniline (C and C).

The addition reactions of ketenes are of two types, those which involve the olefinic linkage directly and those which involve it only indirectly, addition taking place first at the carbonyl linkage and being followed by rearrangement of the resulting enol to a keto form. To the first type belongs the action of halogens and of oxygen. The former give the alpha halogen acyl halides from which the ketenes can be made by the action of zinc. Oxygen gives very explosive peroxides which decompose to form $CO_2$ and aldehydes or ketones. Grignard reagents and active H cpds. add to the carbonyl group in the usual way.

$$CH_2{=}C{=}O + RMgX \rightarrow CH_2{=}\overset{\displaystyle R}{\overset{|}{C}}{-}OMgX \rightarrow$$

$$CH_2{=}\overset{\displaystyle R}{\overset{|}{C}}{-}OH \rightarrow CH_3{-}\overset{\displaystyle R}{\overset{|}{C}}{=}O$$

The net result is the addition of R—H to the olefinic bond much as in the 1,4-addition of a Grignard reagent to benzalacetophenone. Similarly $H_2O$, ROH, $NH_3$, $RNH_2$, $R_2NH$, HCl, etc., add to the carbonyl group with great readiness. Ketonization gives acetic acid, esters, acid amides, acid chloride, etc. Again,

the net result is the addition of H—Q to the olefinic bond.

$$CH_2{=}C{=}O + H{-}Q \rightarrow CH_2{=}\overset{\overset{Q}{|}}{C}{-}O{-}H \rightarrow CH_3{-}\overset{\overset{Q}{|}}{C}{=}O$$

The fact that the initial and final products both contain the carbonyl group might be used as an argument that the latter group is inactive in ketenes. The same conclusion might be drawn erroneously from the fact that carbonyl reagents like phenylhydrazine do not react in the ordinary way with ketenes to give derivatives of the phenylhydrazone type. The reactions of acetone and of ketene with phenylhydrazine may be compared.

$$Me_2CO + PhNHNH_2 \rightarrow Me_2C(OH)NHNHPh \rightarrow H_2O + Me_2C{=}NNHPh$$

$$CH_2{=}CO + PhNHNH_2 \rightarrow CH_2{=}C(OH)NHNHPh \rightarrow CH_3CO{-}NHNHPh \rightleftharpoons CH_3C(OH){=}NNHPh$$

The product from ketene is simply acetyl phenylhydrazine.

Glacial acetic acid and ketene form acetic anhydride.

As would be expected of such a reactive substance, ketene is very poisonous. Attempts to find adequate commercial uses for ketene are being pushed vigorously.

Higher ketenes are made by the action of zinc with alpha bromo acid bromides. The *aldoketenes* are colorless, are not auto-oxidizable, and are polymerized by pyridine probably to give homologs of acetylketene, $RCH_2COC(R){=}C{=}O$. The *ketoketenes* are colored, are easily auto-oxidized to give peroxides, and form addition cpds. with cyclic tertiary bases like pyridine, quinoline, and acridine. These are definite compounds formed by a peculiar co-polymerization involving two mols of the ketoketene and the N=C linkage of the cyclic base. The dimers of the ketoketenes are tetra-substituted 1,3-cyclo-butandiones.

**Carbon suboxide,** $C_3O_2$, $O{=}C{=}C{=}C{=}O$, b. 7°, is obtained by the action of phosphoric anhydride with malonic acid or of zinc with dibromomalonyl bromide. Probably the best preparation is by the pyrolysis of diacetyltartaric anhydride (Hurd 1933). It gives the typical ketene reactions to give malonic acid and its derivatives. A cyclic structure containing a triple bond was proposed and abandoned (Michael).

### *E.* Oximes

Aldoximes, RCH=NOH, and ketoximes, RR′C=NOH, are obtained from aldehydes and ketones with hydroxylamine, $H_2NOH$ (V. Meyer 1882).

$$=C=O + H_2NOH \rightarrow [=C(OH)NHOH] \rightarrow =C=NOH$$

The velocity of formation of oximes depends on the length and branching of the groups attached to the carbonyl groups (Petrenko-Kritschenko 1903–1907, Stewart 1905). In many cases the oximes are crystalline compounds of value in *identifying* the *carbonyl compounds.* By the *Beckmann rearrangement* (1887) the ketoximes give a method of degrading ketones to simpler products. The oximes can exist in several *isomeric forms.*

$$RCH_2CH=NOH \rightleftharpoons RCH=CH—NHOH \rightleftharpoons RCH_2—\underset{\diagdown\,\diagup\ O}{CH}—NH$$

*A* *B* *C*

Forms *A* and *B* can each exist in geometrically isomeric forms *cis* and *trans* or *syn* and *anti.*

$$RCH_2—C(=N—OH)—H \qquad RCH_2—C(=N—HO)—H \qquad R—C(=C(—H)—NHOH)—H$$

$$HONH—C(=C(—H)—R)—H$$

In the aliphatic series, with primary and secondary groups, it is not possible to isolate the individual compounds because of the lability of $\alpha-H$ atoms. In the aromatic series, however, it is possible in a few cases to isolate individual isomers, of all four of the above types. Those of type B add HCN while the others do not. Type *C* represents the *isoximes.*

*Reactions.*

1. Hydrolysis regenerates the carbonyl compound and $H_2NOH$.
2. Bases give soluble compounds such as RCH=NONa.
3. HCl gives hydrochlorides.
4. Reduction gives primary amines, $RNH_2$. This is valuable in cases where the corresponding bromide is either unobtainable

or reacts abnormally. Examples are $Me_3CCH_2NH_2$ and

$$Me_3CCH(NH_2)Me.$$

5. Aldoximes with acetic anhydride give nitriles while ketoximes gives acetates.

$$RCH{=}NOH \rightarrow RC{\equiv}N \qquad RR'C{=}NOH \rightarrow RR'C{=}NOCOMe$$

6. Ketoximes, with acetyl chloride, $PCl_5$, HCl, conc. sulfuric acid in glacial acetic acid, and other acid reagents, give the Beckman rearrangement, resulting in a monosubstituted acid amide. $BF_3$ causes the same change (Meerwein 1933)

$$RR'C{=}NOH \rightarrow RCONHR' + R'CONHR$$

In general the larger group migrates to the greater extent. This is like the behavior in 1 : 2-carbon rearrangements such as the pinacolone rearrangement. Thus the Beckmann rearrangement of the oximes of methyl *t*-amyl ketone and methyl pinacolyl ketone (2,2,3-$Me_3$-pentanone-4) gives as the chief products N-*t*-amylacetamide, $MeCONHCMe_2Et$, and N-pinacolylacetamide, $MeCONHCH(Me)CMe_3$ (Drake 1934). Similarly the oximes of methyl cyclohexyl ketone and methyl undecyl ketone give only N-substituted acetamides. Hydrolysis of the substituted amides gives acids and primary amines which can be identified in the usual ways.

The Beckmann rearrangement involves essentially the same type of change as the Hofmann rearrangement of N-bromoamides, RCONHBr, the Lossen rearrangement of hydroxamic acids, RCONHOH, and the Curtius rearrangement of acid azides, $RCON_3$. These processes have been exhaustively studied by Julius Stieglitz and Lauder W. Jones and their students.

7. Oxidation of aldoximes with monopersulfuric acid forms *hydroxamic acids*, $RC(=NOH)OH$ which give color reactions with ferric chloride.

8. With bromine water, the ketoximes give bromonitroso compounds, RR'C(NO)Br.

9. Alkylation may take place on the N or on the O giving derivatives which, on hydrolysis, form RNHOH or $H_2NOR$. Thus alkylation of acetoxime, $Me_2C=NOH$, with MeI gives exclusively the N—Me compound while MeI in the presence of NaOMe gives the O—Me compound as well.

10. An exceptional reaction is that of acetaldoxime with chlorine to give MeCHCl(NO) which exists as a blue liquid above 85°. Below that temperature, it forms a colorless dimer (p. 182). Long heating changes the blue liquid colorless by conversion to the oxime of acetyl chloride.

$$MeCH=NOH \rightarrow MeCHCl-N=O \rightarrow MeCCl=N-OH$$

The first change is like that of isobutylene with chlorine to give a "substitution" product (p. 42).

**Formaldoxime,** $CH_2=NOH$, b. 85°, tends to polymerize to a trimer.

**Acetoxime,** m. 59°, b. 135°.

The melting points of the aldoximes, RCH=NOH, for ethyl to hexadecyl (°C.) are 21, liq., 51, 52, 58, 59, 63, 69, 72, 73, 80, 82, 86, 88, 89. Those for the ketoximes, RR′C=NOH for combinations of alkyl groups are di-isopropyl, 7, di-*n*-heptyl, 20, di-*n*-octyl, 12, di-*n*-undecyl, 40, di-*n*-tridecyl, 51, di-*n*-pentadecyl, 59, and di-*n*-heptadecyl, 63.

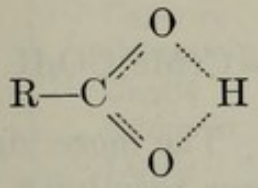
## XIII. ALIPHATIC MONOBASIC ACIDS

### *A.* Saturated Acids, $C_nH_{2n+1}CO_2H$

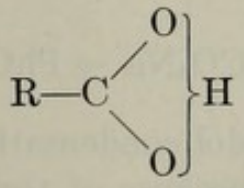
These acids are oxidation products of the primary alcohols, $RCH_2OH$, and the aldehydes, RCHO; hydrolysis products of the alkyl cyanides, RCN; and reaction products of the Grignard reagents, RMgX with $CO_2$. The name fatty acids is due to the occurrence of higher homologs such as palmitic, $C_{16}$, and stearic, $C_{18}$, acids in natural fats in the form of glycerides.

The carboxyl group, $-C(=O)OH$, is represented as a combination of a carbonyl group and a hydroxyl group. Many properties of

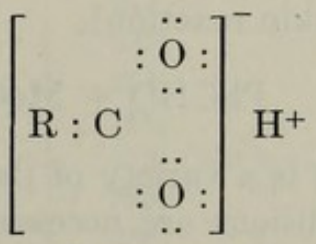
acids indicate that this is not an accurate picture. The absorption spectra of carboxylic acids and their esters differ radically. The acids are *associated* while the esters are not. The parachor is less than would be expected. Alpha ketonic acids and esters are colorless instead of being yellow as would be expected from compounds having adjacent carbonyl groups as in diacetyl. MeCOCOMe, and benzil, PhCOCOPh. The peculiar nature of the carbonyl group in the carboxylic acids has been indicated in various ways.



Mesohydric form (Oddo 1906, 1932)



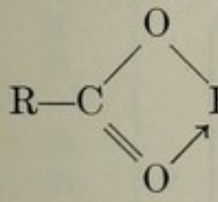
(Hantzsch, Rep. 1918, 55)



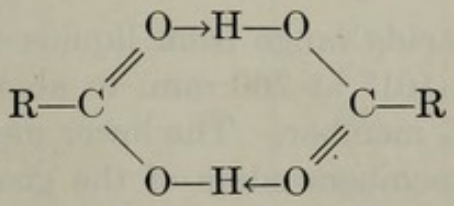
(Lewis 1916)

Bülow, Ahr. 1919, 189. Rep. 1912, 191.

In more modern terms this might be thought of as involving a coordinate link between the H and the carbonyl oxygen;



Many facts about the carboxylic acids and their esters make this improbable (Sidgwick 252–5). Coordinate links are possibly formed between two molecules, thus causing the well-known association of acetic acid and its homologs (Smith 1932).



In view of the uncertainty as to the exact nature of linkages within the carboxy group, the formula, $R-CO_2H$, is perhaps better than the older formula, R−CO(OH) or R−COOH. In aqueous solution the carboxyl group is at least partially hydrated.

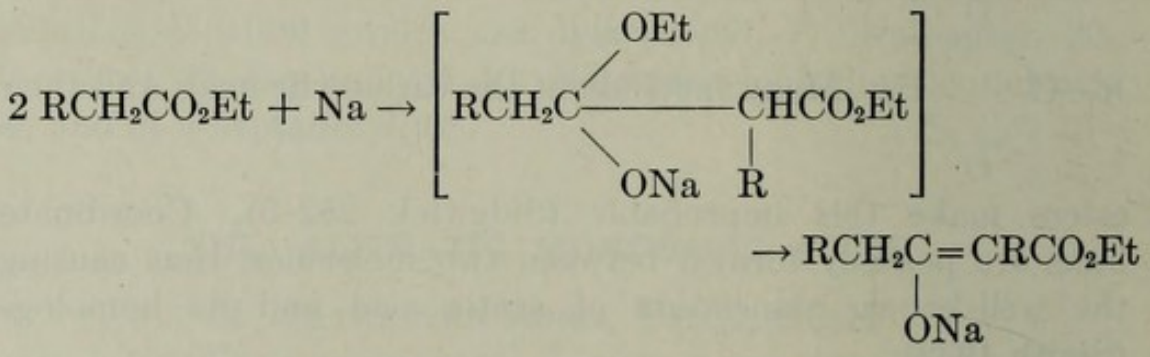
$$R-CO_2H + H_2O \rightleftharpoons R-C(OH)_3$$

The hydrogen atoms on the alpha carbon atom (next the carboxyl group) are reactive as are the alpha H atoms of aldehydes and ketones. The degree of activity is slightly less, however. As in other alpha H compounds the activity is explained partly on the basis of enolization as in the ready replacement by halogens and in the racemization of compounds having an asymmetric alpha carbon and partly as the effect of the adjacent group as in the condensation of sodium salts of carboxylic acids with aldehydes in presence of acid anhydrides (Perkin reaction).

$$PhCHO + MeCH_2CO_2Na \rightarrow PhCH{=}C(Me)CO_2H$$

This is a variety of the aldol condensation. The more vigorous conditions are necessary because of the lower reactivity of the alpha H atoms in the acid. When the hydrogen atoms are alpha to two carboxyl groups as in malonic acid and its derivatives the reaction takes place much more readily (Knoevenagel 1893, 1904).

A related reaction is that of the esters of carboxylic acids with Na to give sodioketoesters (Claisen).




The carboxylic acids range from liquids to solids varying in boiling point from 101° at 760 mm. to about 300° at 100 mm. pressure for the $C_{19}$ member. The lower members have a sharp odor, the middle members odors of the goat-like type and the higher members practically no odor. The melting points fall into two series for the odd and even members, the former being slightly lower than the latter. This alternation in melting points is found in various homologous series and is an indication of the slightly greater symmetry of the even numbered molecules (Rep. 1927, 95–6).

NORMAL FATTY ACIDS

| C atoms | Name | m.p. °C. | b.p. °C. |
|---|---|---|---|
| 1. | Formic | 8.3 | 101. |
| 2. | Acetic | 16.67 | 119. |
| 3. | Propionic | −36. | 141. |
| 4. | Butyric | −2. | 163. |
| 5. | Valeric | −58. | 186. |
| 6. | Caproic | −1.5 | 205. |
| 7. | Oenanthic | −10.5 | 223. |
| 8. | Caprylic | 16.5 | 237. |
| 9. | Pelargonic | 12.5 | 254. |
| 10. | Capric | 31.4 | 269. |
| 11. | Undecoic | 28. | 212 (100 mm.) |
| 12. | Lauric | 43.6 | 225. " |
| 13. | Tridecoic | 40.5 | 236. " |
| 14. | Myristic | 54. | 248. " |
| 15. | Pentadecoic | 52.1 | 257. " |
| 16. | Palmitic | 63.1 | 268. " |
| 17. | Margaric | 62. | 277. " |
| 18. | Stearic | 70.1 | 287. " |
| 19. | Nondecoic | 69.3 | 298. " |
| 20. | Arachidic | 76.2 | 328. |
| 21. | Heneicosoic(Heneicosanoic) | 75.2 | |
| | Cluytinic | — | |
| 22. | Behenic | 80.5 | |
| 23. | Tricosoic | 79.6 | |
| 24. | Lignoceric (Carnaubic) | 84.7 | |
| 25. | Pentacosoic | 83.2 | |
| 26. | Cerotic | 87.8 | |
| | Hexacosoic | 79. | (Rep. 1926, 100) |
| 27. | Carboceric | — | |
| 28. | Octacosoic | 90.4 | |
| 29. | Montanic | 85. | |
| 30. | Melissic | 94. | |
| 31. | Myricinic (?) | — | |
| 32. | Psyllaic | 94. | |
| 33. | Psyllostearic | — | |

The first three members are completely soluble in water. The solubilities from *n*-butyric to *n*-heptoic acid drop from 6 to 0.2 g. per 100 cc. of water. The acids to $C_6$ are readily volatile with steam, those from $C_{16}$ up are not volatile at all with steam.

The volatility with steam of the acids from various fats is useful in detecting adulteration. Thus butter fat gives a larger amount of volatile acids than does oleomargarine.

Formic acid appears about 5% ionized in 0.1 N solution while its homologs are only about 1% ionized.

**Formic acid,** methanoic acid, $HCO_2H$, b. 100.5, m. 8.3°, has been made in ways which are of interest as bearing on its structure and its relation to its homologs.

1. Hydrolysis of HCN by dilute acid

$$HCN + 2\,H_2O + HCl \rightarrow HCO_2H + NH_4Cl$$

2. Saponification of methine halides.

$$CHCl_3 + 4\,NaOH \rightarrow HCO_2Na + 3\,NaCl + 2\,H_2O$$

3. Hydrogen and carbon dioxide in the corona discharge (silent electric discharge).

$$H_2 + CO_2 \rightarrow HCO_2H$$

Formic acid is prepared *commercially* by special processes.

1. By the action of carbon monoxide with soda lime at 210° under pressure.

$$CO + NaOH \rightarrow HCO_2Na$$

2. From oxalic acid, by heating with glycerol. Heated alone, oxalic acid gives very little formic acid but mainly CO and $CO_2$. The glycerol presumably forms an oxalic ester (I) which loses $CO_2$ leaving a formic ester which then reacts with more oxalic acid to give formic acid and regenerate the oxalic ester.

$$Q-OH \rightarrow \underset{\text{(I)}}{Q-OCOCO_2H} \rightarrow CO_2 + Q-OCHO \rightarrow$$

$$HCO_2H + \underset{\text{(I)}}{Q-OCOCO_2H}$$

A more volatile alcohol would give esters which would distill instead of decomposing. The formic acid distills over with the water formed. Since the glycerol oxalate (I) is constantly regenerated, only a small amount of glycerol is needed unless too high a temperature is reached and allyl alcohol is formed. Obviously this process is available only when oxalic acid is

much cheaper than formic acid. Since one of the commonest ways of making oxalic acid is from formates, this is not usually the case. In the laboratory, cellulose (cotton) has been used in place of glycerol (Montgomery 1931).

3. A potential source is from methyl formate obtained as a by-product in methanol manufacture.

$$2\,H_2 + 2\,CO \rightarrow HCO_2CH_3 \xrightarrow{NaOH} HCO_2Na + CH_3OH$$

In many of its *reactions*, formic acid differs from its homologs.

1. It is a stronger acid. Its ionization constant is $21 \times 10^{-5}$ whereas those for its homologs are of the order of $1 \times 10^{-5}$.

It esterifies alcohols readily, serving as its own catalyst.

2. Containing an aldehyde group, it is a reducing agent.

$$HCO_2H + [O] \rightarrow H_2O + CO_2$$

It reduces a solution of mercuric chloride to a precipitate of calomel.

$$2\,HgCl_2 + HCO_2H \rightarrow Hg_2Cl_2 + CO_2 + 2\,HCl$$

Its reducing power is utilized in a process for separating Cu and Cd analytically (Fulmer 1931). The solution is treated with potassium formate, evaporated and heated at 160°. The copper salt is reduced to the metal while the Cd salt is not.

3. It reacts with dehydrating agents.

$$HCO_2H \rightarrow H_2O + CO$$

This is the best way to make pure carbon monoxide on a laboratory scale (Schierz 1929).

4. It decomposes on heating at a relatively low temperature (160°).

$$HCO_2H \rightarrow H_2 + CO_2$$

This is a case of oxidation and reduction within the molecule, the carbon being oxidized from the valence in CO to that in $CO_2$ and the hydrogen being reduced to the elementary state.

Alkali formates, heated under reduced pressure, give oxalates and $H_2$. This is an important preparation of oxalic acid.

The vapor of formic acid is a mixture of single and double molecules (Coolidge 1928).

The azeotrope with 22.5% water is unusual in that it boils higher than either component, namely at 107°.

The photochemical decomposition of formic acid gives CO and $CO_2$ (Allmand 1926, Herr 1928).

Anhydrous formic acid has been used as a solvent for the study of the action of acids. In it, sulfuric acid acts as a strong monobasic acid and Na formate and aniline act as strong bases (Hammett 1932).

**Acetic acid,** ethanoic acid, $CH_3CO_2H$, b. 119°, m. 16.67°, is obtained in a great variety of ways.

1. By oxidation of many organic compounds since it is more resistant to oxidation than most such compounds and their primary oxidation products.

2. By the hydrolysis of methyl cyanide obtained from methyl halides.

3. By the action of carbon dioxide on sodium methyl obtained from mercury dimethyl (Wanklyn 1858).

$$CH_3Na + CO_2 \rightarrow CH_3CO_2Na$$

A more practical form of this method utilizes the Grignard reaction (1901).

$$CH_3MgCl + CO_2 \rightarrow CH_3CO_2MgCl$$

The best results are obtained at low temperatures.

Another modification is the use of ethyl carbonate with the Grignard reagent (Tschitschibabin).

$$MeMgCl + (EtO)_2C{=}O \rightarrow (EtO)_2C(Me)OMgCl \rightarrow MeCO_2Et + EtOMgCl$$

The reaction is carried out rapidly at a low temperature to prevent the further action of the Grignard reagent to form acetone and tertiary butyl alcohol.

4. By the action of carbon monoxide on sodium methylate at 160°.

$$CH_3ONa + CO \rightarrow CH_3CO_2Na$$

A modification of this reaction is the catalytic action of carbon monoxide under high pressure with methanol to give acetic acid directly (Krase) (Singh 1935).

5. By the action of alkalies on trihalogenated acetone.

$$CH_3COCX_3 + NaOH \rightarrow CH_3CO_2Na + CHX_3$$

6. By the splitting of acetoacetic ester by concentrated alcoholic potash.

$$CH_3COCH_2CO_2Et + 2\,KOH \rightarrow 2\,CH_3CO_2K + EtOH$$

With $\alpha$-substituted acetoacetic esters this gives mono- and di-substituted acetic acids.

7. By the thermal decomposition of malonic acid.

$$CH_2(CO_2H)_2 \rightarrow CO_2 + CH_3CO_2H$$

Substituted malonic acids give $RCH_2CO_2H$ and $RR'CHCO_2H$.

These methods of formation combine to settle definitely the structure of acetic acid and, consequently, throw light on the structure of the many organic substances related to it. They are also applicable to the preparation of certain of its *higher homologs*.

Three methods are used for the *commercial preparation of acetic acid*.

1. Until recently the chief source has been pyroligneous acid from wood distillation. This liquid contains about 10 per cent acetic acid.

(*a*) The older method consists in neutralizing the liquid with lime and distilling off the volatile materials including methyl alcohol, acetone, higher ketones, etc. The residue is "brown" or "gray" acetate of lime depending on the amount of tarry impurities. It is distilled with dilute sulfuric acid to give dilute acetic acid (28 per cent).

(*b*) Because of the competition of newer processes, modifications have been made in the separation of acetic acid from pyroligneous acid. This is now accomplished by a continuous extraction process using solvents such as ethyl ether or, more recently, isopropyl ether. The latter is less soluble in the aqueous layer and is more readily recovered by distillation.

The Suida process uses an oil distilled from the pyroligneous acid itself as an extractant for the acetic acid (Poste 1932).

2. The oldest method of producing acetic acid is the acetic fermentation of dilute ethyl alcohol. This process has been known since early times in the souring of alcoholic liquors and in the making of vinegar. This method is not suitable for making acetic acid itself because of the large amount of water involved. By recent developments, the dilute acetic acid (about 10%) so obtained can be converted directly into alkyl acetates, the chief form in which acetic acid is used.

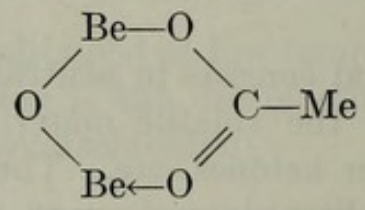
3. The best method for pure acetic acid (*glacial acetic acid*) is the catalytic oxidation of acetaldehyde obtained from acetylene. Air and manganese acetate wet with acetic acid are used at 70° to absorb the acetaldehyde. Yields of better than 80% from acetylene to acetic acid are obtained (Rep. 1920, 53).

The *reactions of acetic acid* are typical of the saturated aliphatic acids.

1. It forms soluble salts of all the metals. With many of the heavy metals it forms "basic salts." Some of these are very complex such as the blood red basic ferric acetate,

$$[Fe_3(OH)_2(OAc)_6]OAc.$$

These compounds probably contain chelate rings as in basic beryllium acetate (Sidgwick 255).

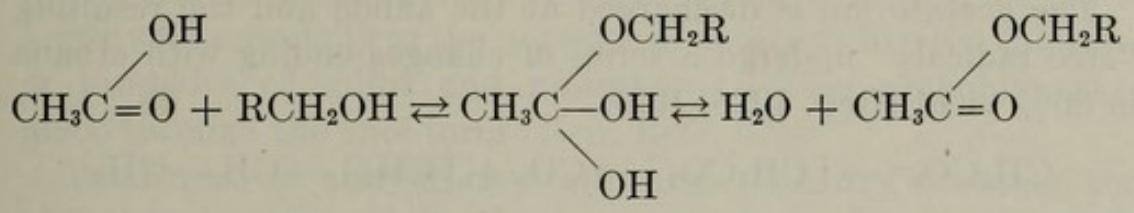



*Sugar of lead* is $Pb(OAc)_2.3H_2O$. *Verdigris* is basic copper acetate. *Paris Green* contains copper acetate and arsenite. Acetates of various heavy metals such as Al, Cr and Fe are used as mordants with dyes like alizarin.

Lead tetraacetate is a valuable oxidizing agent for converting reactive CH to COAc, and C=C to the diacetate of the corresponding glycol (Rep. 1923, 90).

2. With alcohols it forms esters. This reaction results in an

equilibrium. The first step probably consists in the usual addition to a carbonyl group (Wegscheider) (p. 228)



The attainment of the equilibrium is catalyzed by hydrogen ions. The final equilibrium reached follows the Law of Mass Action.

Secondary alcohols react much less rapidly to form esters.

When tertiary alcohols are heated with acetic acid, the chief result is catalytic dehydration of the alcohol.

The *acetylation* of a hydroxyl group by means of acetic acid or one of its derivatives is an important means of *protecting* the hydroxyl. The protecting acetate group can be removed by basic or acid hydrolysis.

3. Sodium acetate heated with soda lime gives methane.

$$CH_3CO_2Na + NaOH \rightarrow CH_4 + Na_2CO_3$$

4. When calcium acetate is heated, acetone is obtained. This process has had considerable commercial value.

$$(CH_3CO_2)_2Ca \rightarrow CH_3COCH_3 + CaCO_3$$

When a mixture of calcium acetate and another calcium salt is heated, a mixed ketone, $CH_3COR$, is obtained along with acetone and the ketone RCOR.

The same result is achieved by passing the vaporized acid or a mixture of acids over heated manganous oxide and other catalysts.

$$2\,CH_3CO_2H \rightarrow CH_3COCH_3 + CO_2 + H_2O$$

Another method is to pass acetic acid or, better, acetic anhydride over hot calcium carbide (Rep. 1906, 81).

5. When it is heated alone to 500°, ketene is obtained (Hurd)

$$CH_3CO_2H \rightarrow H_2O + CH_2{=}C{=}O$$

6. When a solution of its sodium salt is electrolyzed, ethane is obtained (Kolbe 1848).

The acetate ion is discharged at the anode and the resulting "free radicals" undergo a series of changes ending with ethane in 80% yield (Rep. 1926, 102).

$$CH_3CO_2^- \rightarrow [CH_3CO_2] \rightarrow CO_2 + [CH_3] \rightarrow CH_3-CH_3$$

Salts of the $C_3$ and $C_4$ acids on electrolysis give poor yields of the saturated hydrocarbons but the normal acids from $C_5$ to $C_{18}$ give 75–90% yields. A branch at the $\alpha$-position causes the production of olefin (Petersen 1900).

7. Distillation of a concentrated solution of ammonium acetate gives acetamide.

$$CH_3C(=O)ONH_4 \rightarrow H_2O + CH_3C(=O)NH_2$$

The mechanism of this dehydration may resemble the mechanism suggested for esterification, involving addition to the carbonyl group.

$$CH_3C(=O)ONH_4 \rightleftharpoons NH_3 + CH_3C(=O)OH \rightleftharpoons CH_3C(OH)(OH)NH_2 \rightleftharpoons H_2O + CH_3C(=O)NH_2$$

8. With acid chlorides, acetyl chloride is formed.

$$\begin{aligned} CH_3CO_2H + PCl_5 &\rightarrow CH_3C(=O)Cl + HCl + POCl_3 \\ 3\,CH_3CO_2H + PCl_3 &\rightarrow 3\,CH_3COCl + H_3PO_3 \\ CH_3CO_2H + SOCl_2 &\rightarrow CH_3COCl + SO_2 + HCl \\ CH_3CO_2H + COCl_2 &\rightarrow CH_3COCl + CO_2 + HCl \end{aligned}$$

9. When sodium acetate is treated with half the amount of acid chloride needed to form the acyl chloride, acetic anhydride is obtained.

$$6\,CH_3CO_2Na + POCl_3 \rightarrow 3\,(CH_3CO)_2O + 3\,NaCl + Na_3PO_4$$

Sulfur monochloride, $S_2Cl_2$, has been used more recently in place of the more expensive acid chlorides.

10. Chlorine and bromine replace alpha hydrogen atoms in acetic acid especially in the presence of catalysts like the chlorides or bromides of sulfur and phosphorus. This probably takes place through the enol form (Rep. 1923, 67).

Treatment of anhydrous acetic acid with dry bromine and phosphorus gives alpha bromoacetyl bromide, $BrCH_2COBr$ (Hell-Volhard-Zelinsky). Di- and tri-halogen acetic acids are best prepared by indirect means.

11. When its sodium salt and its anhydride are heated with an aldehyde, an alpha-beta unsaturated acid results (Perkin).

Glacial acetic acid is finding wide use as a non-aqueous solvent for studying problems of solutions (Hall 1928). Solutions of acids in it show "super-acid properties." For instance they can be used to titrate extremely weak "bases" such as acetamide (Hall 1930). The purest acid has a specific conductance of $0.7 \times 10^{-8}$ mho. A pH scale has been worked out for solutions in glacial acetic acid (Conant 1928).

Addition of water to glacial acetic acid at first increases its density. A maximum is reached corresponding to the ortho acid $CH_3C(OH)_3$ (Bassett).

While pure acetic acid freezes at 16.67° small amounts of water depress the freezing point greatly. Thus 99% and 87% acids freeze at 14.8° and − 0.2°.

Much study has been devoted to the dissociation constant of acetic acid, $1.75 \times 10^{-5}$ at 25° (MacInnes 1932, Harned 1932).

Acetic acid is sold in various concentrations. The official acetic acid is 36%, glacial acetic acid contains at least 99%. Commercial glacial acid contains about 80%. A technical grade containing 28% acid is also known as No. 8 acetic acid because it can be diluted with water to give eight volumes of official 4% vinegar (British Excise system).

**Peracetic acid,** $CH_3C(=O)(O—OH)$, is best obtained by the action of hydrogen peroxide with acetic anhydride. It is a powerful

oxidizing agent, being capable of converting manganese salts to permanganates (Rep. 1912, 91).

**Propionic acid,** propanoic acid, methylacetic acid,

$$CH_3CH_2CO_2H,$$

is prepared by oxidation of *n*-propyl alcohol. During the World War it was available as a by-product in the extraction of potash from kelp. The mixture of aliphatic acids obtained by the fermentation of the kelp was separated by the distillation of the ethyl esters. It can be salted out of its water solution as an oil. Hence its name as the "first" fatty acid.

Carbon monoxide with alcohols and suitable catalysts gives acids. Ethyl alcohol gives propionic acid, isopropyl alcohol gives isobutyric acid and the butyl alcohols give mixtures of $C_5$ acids consisting largely of $Me_3$-acetic acid (Hardy 1936). The process presumably takes place through the olefins.

The reactions of propionic acid are like those of acetic acid. It is a weaker acid than the latter. Only its two alpha H atoms are readily replaced by halogens and take part in the Perkin reaction.

$$CH_3CH_2CO_2H \rightarrow CH_3CHBrCO_2H \rightarrow CH_3CBr_2CO_2H$$

$$RCHO + CH_3CH_2CO_2Na + (CH_3CH_2CO)_2O \rightarrow RCH{=}C(Me)CO_2H$$

With certain higher carboxylic acids and nitriles, the following apparently metathetical reaction takes place

$$R{-}CN + R'{-}CO_2H \rightarrow R{-}CO_2H + R'{-}CN$$

This peculiar reaction has been explained on the basis of the following equilibria (Rep. 1904, 86).

$$RCN + R'CO_2H \rightleftharpoons RC(OH){=}NCOR' \rightleftharpoons RCONHCOR'$$

$$\rightleftharpoons RCON{=}CR'(OH) \rightleftharpoons RCO_2H + R'CN$$

***n*-Butyric acid,** butanoic acid, ethylacetic acid,

$$CH_3CH_2CH_2CO_2H,$$

occurs in butter (2–3%). It is made by the butyric fermentation of carbohydrates and by the oxidation of *n*-butyl alcohol. In the former process, acetaldehyde probably goes to aldol which undergoes a dismutation to the acid. Certain microorganisms convert lactic acid to *n*-butyric acid by similar changes. Its reactions are like those of propionic acid. In addition it shows the phenomenon of "beta oxidation." Thus, with hydrogen peroxide it goes through the following steps (Dakin).

$$CH_3CH_2CH_2CO_2H \rightarrow CH_3CHOHCH_2CO_2H \rightarrow CH_3COCH_2CO_2H \rightarrow CO_2 + CH_3COCH_3$$

A similar oxidation of fatty acids occurs in living organisms. Its mechanism has never been satisfactorily explained (Marvel 1932). Alpha oxidation is also possible (Witzemann 1926).

Electrolysis of potassium butyrate solution gives mainly propylene together with isopropyl butyrate. Presumably the *n*-propyl radical forms propylene which combines with butyric acid to form isopropyl butyrate.

***iso*-Butyric acid,** methylpropanoic acid, dimethylacetic acid, $(CH_3)_2CHCO_2H$, b. 155°, occurs in carob beans (St. John's Bread). It is best prepared by oxidation of isobutyl alcohol or from isopropyl alcohol through the chloride and cyanide. Its reactions are complicated by the fork in the chain in the alpha position. Thus it is much more sensitive to oxidation than any of its lower homologs except formic acid.

$$Me_2CHCO_2H \rightarrow Me_2C(OH)CO_2H \rightarrow Me_2CO + CO_2 + H_2O$$

Sodium isobutyrate, on electrolysis, gives large amounts of propylene and isopropyl isobutyrate. This is in contrast to the *n*-butyrate which gives mainly propylene and very little ester.

Ethyl isobutyrate does not condense with itself under the influence of NaOEt (Hurd).

While Ca isobutyrate is more soluble in hot water than in cold,

Ca *n*-butyrate is more soluble in cold than in hot water. One salt crystallizes with 5 $H_2O$ and the other with 1 $H_2O$.

***n*-Valeric acid,** *n*-valerianic acid, pentanoic acid, *n*-propylacetic acid, $CH_3CH_2CH_2CH_2CO_2H$, is made by the oxidation of *n*-amyl alcohol or from *n*-butyl alcohol through the bromide and the cyanide. An 80% yield has been obtained from BuMgBr and $CO_2$ at −20°. At higher temperatures considerable $Bu_2CO$ results (Gilman 1925). It is also obtained by the vigorous reduction of levulinic acid obtained from sucrose and hydrochloric acid,

$$MeCOCH_2CH_2CO_2H \rightarrow MeCH_2CH_2CH_2CO_2H$$

***iso*-Valeric acid,** *iso*-valerianic acid, 3-methylbutanoic acid, *iso*-propylacetic acid, $(CH_3)_2CHCH_2CO_2H$, b. 174°, is obtained by oxidation and hydrolysis of the corresponding alcohol and cyanide respectively. It is available in reasonable amounts from pyroligneous acid.

Electrolysis of its sodium salt gives 60% of diisobutyl and 29% of isobutylene.

Heating calcium isovalerate gives mainly isovaleraldehyde instead of isovalerone (Rep. 1906, 81).

**Active valeric acid,** methylethylacetic acid, 2-methylbutanoic acid, $C_2H_5(CH_3)CHCO_2H$, b. 177° is obtained by the oxidation of "active" amyl alcohol. If *d*-amyl alcohol (levorotatory) from fusel alcohol is used, the product is dextrorotatory. If secondary butyl carbinol from the chlorination of isopentane is used, the product is a "racemic mixture" of the two optically active isomers. A similar optically inactive mixture is obtained if the acid is made by the malonic ester synthesis or the acetoacetic ester synthesis.

Such a mixture of enantiomorphic forms cannot be separated by any ordinary means because the physical properties of the *d*- and *l*-isomers are identical except for the action on plane polarized light. Such a mixture of optically active acids can be resolved into the optical isomers by forming salts with an optically active base such as *d*-brucine. Two salts will be formed which are no longer enantiomorphic and which differ enough in solubilities to make their separation by fractional crystallization possible.

These two salts may be represented as

*d*-Acid.*d*-Brucine and *l*-Acid.*d*-Brucine

After they have been crystallized into two fractions the optical rotations of which do not change on further crystallization, the optically active acids can be liberated by treatment with hydrochloric acid.

$$d\text{-Acid}.d\text{-Brucine} + HCl \rightarrow d\text{-Brucine}.HCl + d\text{-Acid}$$
$$l\text{-Acid}.d\text{-Brucine} + HCl \rightarrow d\text{-Brucine}.HCl + l\text{-Acid}$$

The wide occurrence of isovaleric and active valeric acids in nature is due to their formation by enzymes from the amino acids, leucine and isoleucine. Many higher optically active acids have been obtained (Levene 1932).

**Trimethylacetic acid,** pivalic acid, 2, 2-dimethylpropanoic acid, $(CH_3)_3CCO_2H$, b. 163°, m. 35°, has been made:

(*a*) From tertiary butyl cyanide made from the chloride and the double salt $KCN.Hg(CN)_2$; (*b*) From the Grignard reagent and $CO_2$; (*c*) From acetone through pinacol and pinacolone (OS). It gives the usual acid reactions except that the accumulated groups on the alpha carbon and the absence of $\alpha-H$ atoms modify them. Thus its velocity of esterification is much less than that of isobutyric acid which, in turn, esterifies much more slowly than *n*-butyric acid. (Menschutkin). These facts have sometimes been improperly generalized in a statement that primary, secondary and tertiary acids, can be distinguished by their speeds of esterification. This is a safe method only if acids of the same molecular weight are compared.

With phosphorus pentoxide, $Me_3$-acetic acid, gives a 60% yield of CO and no $CO_2$ (Laughlin 1932).

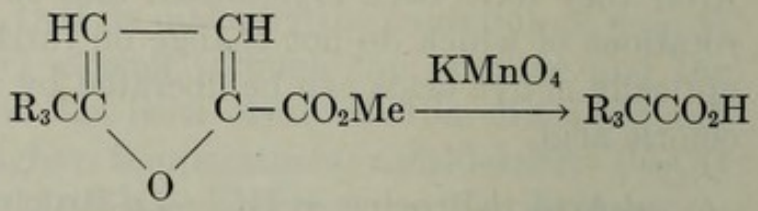
$$Me_3CCO_2H + P_2O_5 \rightarrow 2\,HPO_3 + CO + (Me_2C{=}CH_2)_n$$

Under similar conditions isobutyric and *n*-butyric acids give small yields of mixtures of CO and $CO_2$ in the ratios 5 : 1 and 1 : 5 respectively.

Trisubstituted acetic acids are difficultly obtainable by ordinary reactions if the groups are at all complicated. A solution of this difficulty has been achieved by introducing the tertiary group

into a furan nucleus and then oxidizing the latter to leave only a carboxyl group (Reichstein 1935).

$$R_3CCl + \text{Me furoate} + AlCl_3 \rightarrow$$

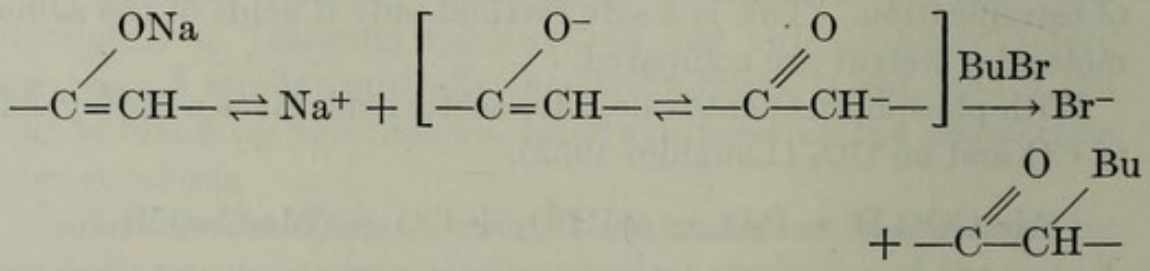



**Caproic acid,** *n*-hexylic acid, *n*-butylacetic acid, hexanoic acid, $CH_3(CH_2)_4CO_2H$.

At the time caproic acid was first needed for the production of hexyl resorcinol, *n*-butyl alcohol was readily available. The acid was made by the acetoacetic acid synthesis (Drake 1930). The entire process starting with ethylacetate is as follows:

$$2\ CH_3CO_2Et + Na + \text{trace } NaOEt \rightarrow CH_3C(ONa) = CHCO_2Et + EtOH$$

The trace of sodium ethylate causes an aldol condensation between an alpha H of one ester molecule with the carbonyl group of another. The resulting product loses alcohol, enolizes and forms the sodio derivative. This is treated with absolute alcohol and *n*-butyl bromide forming *n*-butyl acetoacetic ester or, more properly, ethyl *n*-butylacetoacetate. As usual the new C—C linkage is not formed where the Na was attached. A consideration of only the reacting portions of the molecules gives




The butyl acetoacetic ester is then split by heating with alcoholic potash to give the potassium salts of acetic acid and of *n*-butyl acetic acid.

$$MeCOCH(Bu)CO_2Et + 2\ KOH \rightarrow MeCO_2K + BuCH_2CO_2K + EtOH$$

The mixture is acidified and the caproic acid floats as an oily layer. A similar treatment gives any substituted acetic acid $RCH_2CO_2H$ in which R corresponds to a halide of Class 1 (p. 71) and a few members of the other classes (*not* tertiary). A similar process has been used starting with octadecyl bromide and sodiomalonic ester to synthesize the even-numbered normal acids from $C_{20}$ to $C_{30}$. The $C_{13}$ and $C_{24}$ acids have been made similarly from the $C_{11}$ and $C_{22}$ halides (Levene 1914).

When *n*-amyl alcohol became available, the process for caproic acid was changed to go through the corresponding bromide or chloride and cyanide.

If *n*-hexyl alcohol (C and C) becomes cheap enough, it may be practical to oxidize it to caproic acid.

The making of caproic acid for hexyl resorcinol is typical of the development of organic chemical processes. If it had been needed before the World War, it would have been very difficult to obtain. Since that time $C_4$, $C_5$ and $C_6$ compounds have been developed which can be used in its preparation.

Another preparation of caproic acid is by the oxidation of capryl alcohol, methylhexylcarbinol obtained from castor oil. Other products are obtained.

A potential source of caproic acid is the aldol condensation product of three molecules of acetaldehyde,

$$MeCH=CHCH=CHCHO.$$

This is closely related to the *n*-hexyl alcohol preparation.

***iso*-Caproic acid,** isobutylacetic acid, 4-methylpentanoic acid, $(CH_3)_2CHCH_2CH_2CO_2H$, can be obtained by the acetoacetic ester synthesis using isobutyl bromide. The yield is cut because of the alkaline nature of the sodium acetoacetic ester, much of the bromide being changed to olefin. Better methods of preparation are from the corresponding cyanide and from an isoamyl Grignard reagent and carbon dioxide.

**Methyl-*n*-propylacetic acid,** 2-methylpentanoic acid,

$$CH_3CH_2CH_2CH(CH_3)CO_2H,$$

is best made by the acetoacetic ester synthesis. Acetoacetic ester in absolute alcohol is treated with one equivalent each of

NaOEt and MeI and refluxed until a test sample mixed with water is neutral. The solution then contains methyl acetoacetic ester, $MeCOCH(Me)CO_2Et$. Then another equivalent of NaOEt and one of *n*-PrBr are added. The final product is methyl-*n*-propylacetoacetic ester. A better yield of the ester is obtained this way than if the *n*-propyl group is introduced first. The product is split by alcoholic KOH as usual.

$$MeCOC(Me)(Pr)CO_2Et + 2\,KOH \rightarrow MeCO_2K + MePrCHCO_2K$$

The splitting effect of concentrated alcoholic KOH on the groupings

$$-CO-CH_2-CO- \quad -CO-CHR-CO- \quad -CO-CRR'-CO-$$

is analogous to the splitting of the grouping $Cl_3C-CO-$ even by dilute alkali.

The *malonic ester synthesis of this acid* is entirely similar to this process. Treatment with NaOEt, MeI and again with NaOEt and finally with PrBr gives methyl-*n*-propylmalonic ester, $MePrC(CO_2Et)_2$. When this is saponified with alcoholic KOH and acidified, the corresponding disubstituted malonic acid is obtained. On heating, this loses $CO_2$ giving the desired disubstituted acetic acid.

Another preparation of MePr-acetic acid is by the oxidation of the alcohol obtained by heating *n*-propyl alcohol with its sodium derivative (Guerbet).

$$PrONa + MeCH_2CH_2OH \rightarrow PrMeCHCH_2OH \rightarrow PrMeCHCO_2H$$

This acid has been obtained in optically active form, $[\alpha]_D = +8.9°$.

**Diethylacetic acid,** 2-ethylbutanoic acid, $(CH_3CH_2)_2CHCO_2H$, was formerly prepared by introducing two ethyl groups into acetoacetic ester or malonic ester and splitting in the usual manner. It can now be prepared by oxidation of the commercially available alcohol, $Et_2CHCH_2OH$ (C and C).

***sec*-Butylacetic acid,** 3-methylpentanoic acid,

$$CH_3CH_2(CH_3)CHCH_2CO_2H,$$

would be obtained in poor yield by either the malonic ester or

the acetoacetic ester synthesis. It is best made through the cyanide from sec-butyl carbinol.

**Dimethylethylacetic acid,** 2,2-dimethylbutanoic acid,

$$CH_3CH_2(CH_3)_2CCO_2H,$$

cannot be made by the acetoacetic ester or malonic ester synthesis. It is made by the action of carbon dioxide on a *ter*-amyl Grignard reagent.

***tert*-Butylacetic acid,** 3,3-dimethylbutanoic acid,

$$(CH_3)_3CCH_2CO_2H,$$

cannot be made by the acetoacetic ester or malonic ester synthesis. It cannot be made by the cyanide method because the necessary halide is inactive. It is best made by the action of $Br_2$ and NaOH on methyl neopentyl ketone, $MeCOCH_2CMe_3$, from the oxidation of the lower isomer of diisobutylene.

**Methyl-*iso*-propylacetic acid,** 2,3-dimethylbutanoic acid, $(CH_3)_2CH(CH_3)CHCO_2H$, can be made in poor yields by the malonic ester or acetoacetic ester synthesis. The isopropyl group must be introduced first and followed by the methyl group.

***n*-Heptoic acid,** *n*-heptylic acid, oenanthic acid, heptanoic acid, $CH_3(CH_2)_5CO_2H$, is readily available by the oxidation of heptaldehyde obtained by the destructive distillation of castor oil (mainly glyceryl triricinoleate).

***n*-Octoic acid,** caprylic acid, $CH_3(CH_2)_6CO_2H$, has been obtained from natural fats and by the oxidation and reduction of the aldol condensation product of two molecules of aldol, $Me(CH=CH)_3CHO$ (Rep. 1907, 80).

***n*-Nonoic acid,** pelargonic acid, $CH_3(CH_2)_7CO_2H$, is obtained by the oxidation of oleic acid. A preparation useful in making many complex acids is by the reduction of the corresponding $\alpha\beta$-unsaturated acids with sodium amalgam. The unsaturated acids can be made from malonic acid or ester and aldehydes by a modification of the aldol condensation (Knoevenagel 1894, 1904).

$$C_6H_{13}CHO + CH_2(CO_2H)_2 \xrightarrow{Et_2NH} C_6H_{13}CH=C(CO_2H)_2 \rightarrow C_6H_{13}CH=CHCO_2H \rightarrow C_6H_{13}CH_2CH_2CO_2H$$

It can also be obtained by fusion of the potassium salt of unde-

cylenic acid with KOH. This represents a shift of the double bond from one end of the chain to the $\alpha\beta$-position at the other end. The $\alpha\beta$-unsaturated acid is split by the fused alkali.

$$CH_2{=}CH(CH_2)_8CO_2K + KOH + H_2O \rightarrow CH_3(CH_2)_7CO_2K + CH_3CO_2K + H_2$$

A similar process changes oleic acid to palmitic acid. Before the possibilities in the shift of a double bond were understood, this reaction was believed to indicate oleic acid as an $\alpha\beta$-unsaturated acid.

***n*-Decoic acid,** capric acid, $CH_3(CH_2)_8CO_2H$, is obtained from lauric acid by oxidation of the $\alpha\beta$-unsaturated acid obtained from the $\alpha$-bromo acid. This is a general method of removing two carbons from an acid.

$$RCH_2CH_2CO_2H \rightarrow RCH_2CHBrCO_2H \rightarrow RCH{=}CHCO_2H \rightarrow RCO_2H$$

It is readily available from the seed fat of the California bay tree (Noller 1933).

***n*-Undecoic acid,** $CH_3(CH_2)_9CO_2H$, is best prepared by hydrogenation of undecylenic acid, $CH_2{=}CH(CH_2)_8CO_2H$, obtained by the destructive distillation of castor oil.

**Lauric acid,** *n*-dodecanoic acid, $CH_3(CH_2)_{10}CO_2H$, is readily obtained from cocoanut oil which contains glycerides of lower acids than most oils and fats. Conversion of the glycerides to methyl esters and the fractionation of 130 kg of these esters gave the following % values for the acids: caproic, $C_6$, 0.4; caprylic, $C_8$, 8.7; capric, $C_{10}$, 5.6; *lauric, $C_{12}$, 45.0;* myristic, $C_{14}$, 17; $C_{16}$ and higher 23 (Taylor 1927). The catalytic reduction of lauric acid or its ester gives lauryl alcohol which is valuable in detergents containing sodium lauryl sulfate (S.L.S.).

Electrolysis of sodium laurate gives a 90% yield of $n$-$C_{22}H_{46}$ (Petersen 1900).

**Butlerow's Acids,** $C_{11}H_{23}CO_2H$, **dineopentylacetic acid,**

$$(Me_3CCH_2)_2CHCO_2H$$

and **methyl-*t*-butylneopentylacetic acid,**

$$(Me_3CCH_2)(Me_3C)MeCCO_2H,$$

are obtained by the acid oxidation of triisobutylene ($C_{12}H_{24}$). (Conant 1933, Whitmore 1934). Such a formation of an acid from an olefin *without loss of carbon* involves a rearrangement similar to those observed with the more complex alcohols. The structure of these acids was determined by use of the reaction of hydrazoic acid (v. Braun 1930).

$$RCO_2H + HN_3 \rightarrow RNH_2 + CO_2 + N_2$$

The process actually goes through the acid azide and the isocyanate.

**Myristic acid,** $CH_3(CH_2)_{12}CO_2H$, is best prepared from its glyceride found in nutmegs (OS).

**Palmitic acid,** hexadecanoic acid, $C_{15}H_{31}CO_2H$, and **stearic acid,** octadecanoic acid, $C_{17}H_{35}CO_2H$, occur as glycerides in animal and vegetable fats and oils. In general the higher the melting point of the fat the larger the proportion of the glycerides of these saturated acids. Similarly the "hardening" of liquid fats and oils by catalytic hydrogenation increases the proportion of these acids in the fats.

They are prepared from the glycerides by hydrolysis in presence of a base (lime) or with an acid catalyst (Twitchell's reagent, a complex product from the action of naphthalene, oleic acid and sulfuric acid). The free acids are allowed to crystallize and the liquid acids such as oleic acid are pressed out. The resulting mixture of solid acids is *stearin,* used for candle making. It is also converted to the sodium salts (soap). If the pure acids are desired, the mixture can be fractionated at about 5 mm. pressure. Separation is more readily obtained in the laboratory by distillation of the Me or Et esters (Rep. 1925, 78).

Hydrogenation with a Cu−Cr oxide catalyst gives the $C_{16}$ and $C_{18}$ alcohols whose sulfates are valuable as detergents (Dreft, etc.). Until the development of this catalytic method, acids could be reduced only by conversion to the esters and treatment with Na and absolute EtOH (Bouveault and Blanc).

Silver salts of the fatty acids undergo a peculiar reaction to form the ester of the acid with the next lower alcohol.

$$2\,RCH_2CO_2Ag + I_2 \rightarrow 2\,AgI + CO_2 + RCH_2CO_2CH_2R$$

Hydrolysis of the ester gives the lower alcohol $RCH_2OH$. This is a special way of going down the series.

$$RCH_2CO_2H \rightarrow RCH_2OH$$

An isomer of stearic acid, 3,5,7-$Me_3$-pentadecanoic acid has been made starting with methyl *n*-octyl ketone and applying the Reformatzky reaction, dehydration, hydrogenation, conversion to the acid chloride and treatment with dimethylzinc to give a methyl ketone on which the cycle of changes is twice repeated (Rupe 1932).

$$RCOMe + BrCH_2CO_2Et + Zn \rightarrow RMeC(OH)CH_2CO_2Et \rightarrow RMeC{=}CHCO_2Et \rightarrow RMeCHCH_2CO_2Et \rightarrow RMeCHCH_2COCl \rightarrow RMeCHCH_2COMe \rightarrow$$

A very important series of isomers of $C_{16}$ and $C_{18}$ acids has been made by means of the malonic ester synthesis. Hexadecanoic and octadecanoic acids $RR'CHCO_2H$ in which R is one of the first eight *n*-alkyls or isopropyl, isobutyl, *sec*-butyl or *sec*-amyl have been studied as to their bactericidal action (Stanley 1929).

Other high molecular weight fatty acids have been made by the malonic ester synethesis (Bleyberg 1932).

Alpha methyl derivatives of the normal $C_{15}$ to $C_{18}$ acids have been made by treating the $\alpha$-bromo acids in ether solution with an excess of MeMgX (Morgan 1927).

**Margaric acid,** daturic acid, $C_{16}H_{33}CO_2H$, differs from the naturally occurring fatty acids which contain an even number of carbon atoms. The latter are probably built up in the organism by some such process as the aldol condensation which would give products containing $2n$ carbons. The natural fats on digestion undergo beta oxidation and lose two carbon atoms at a time thus eventually giving $CH_3COCH_2CO_2H$ and $CH_3COCH_3$. In diabetic conditions these products accumulate. Hence margaric acid, an odd-numbered acid which cannot give these products, has been made as a source of artificial fats for the use of diabetics (Intarvin). Its preparation is by the method devised by Krafft (1882) for making higher acids. The Ba or Ca salts of stearic acid and acetic acid are destructively distilled to give acetone and

methyl heptadecyl ketone, $MeCOC_{17}H_{35}$, which on oxidation gives acetic acid and margaric acid.

The method of degrading the naturally occurring fatty acids by conversion to methyl ketones and oxidation has been performed from stearic acid to capric acid, $C_{10}$, which was proved by synthesis to have a normal chain. This is the evidence for the normal chain in the natural acids (Krafft 1882). A fork in the chain would produce a ketone instead of an acid.

$$RR'CHCOMe \rightarrow MeCO_2H + RR'CO$$

Various *higher fatty acids* are obtained by the oxidation of paraffin wax and other petroleum products by air or oxygen (Penniman, James, Burwell, EP 930–960). These processes are rapidly becoming important commercially. Much of this work had its origin in a war-time effort to increase the supply of fats (Rep. 1920, 52).

**Dicetylacetic acid,** $(C_{16}H_{33})_2CHCO_2H$, m. 70°, has been made by the malonic ester synthesis.

Tricosanoic ($C_{23}$) and tetracosanoic ($C_{24}$) acids have been synthesized by the Clemmensen reduction of the 13-keto acids from the action of the chlorides of undecanoic and lauric acids on the sodium derivative of an ester obtained from sodium aceto-acetic ester and ethyl 11-Br-undecoate (Robinson 1936). While the melting points of the acids are 79° and 84° respectively, mixtures containing up to 40% of the second melt 78.5–79°.

*n*-Triacontanoic acid ($C_{30}$) has been synthesized by a method which involves ω-bromo esters, sodio acetoacetate and acyl chlorides, in this case ω-bromoundecylenic acid and stearyl chloride (G. M. Robinson 1934)

$$Br(CH_2)_nCO_2Et \xrightarrow[NaOEt]{MeCOCH_2CO_2Et} MeCOCH(CO_2Et)(CH_2)_nCO_2Et$$

$$\xrightarrow[Me(CH_2)_mCOCl]{NaOEt} Me(CH_2)_mCOC(COMe)(CO_2Et)(CH_2)_nCO_2Et \rightarrow$$

$$Me(CH_2)_mCO(CH_2)_{n+1}CO_2H$$

$$\xrightarrow[HCl]{Zn\times Hg} Me(CH_2)_mCH_2(CH_2)_{n+1}CO_2H.$$

The last step (Clemmensen reduction) is best done with amalgamated zinc prepared by powdering pure zinc, treating with mercury and then treating the amalgam three times with hot HCl before adding the keto compound.

*Identification of Acids*

This may be achieved by conversion to a variety of solid derivatives of definite melting points such as: *a.* amides, $RCONH_2$; *b.* anilides, $RCONHC_6H_5$; *c.* para halogen phenacyl esters, $RCO_2CH_2COC_6H_4X$, obtained from the sodium salts and $BrCH_2COC_6H_4X$ (Moses, Reid 1932; Lund 1932); *d.* *p*-phenylphenacyl esters, $RCO_2CH_2COC_6H_4C_6H_5$ (Snell 1930, Drake 1932). Even the formic ester of the latter melts at 74°; *e.* *p*-nitrobenzyl esters, $RCO_2CH_2C_6H_4NO_2$ (Reid 1917); *f.* a method valuable in special cases is the reaction of the sodium salts with chloroacetone and formation of the semicarbazone of the resulting ester, $RCO_2CH_2C(Me)=NNHCONH_2$ (Locquin 1904, Freylon 1910).

## *B.* Olefinic Acids, $C_nH_{2n-1}CO_2H$

1. **Acrylic acid,** propenoic acid, $CH_2=CHCO_2H$, m. 12°, b.142°.

*Preparation* (Staudinger 1931). 1. Oxidation of acrolein by silver oxide.

$$CH_2=CHCHO + Ag_2O \rightarrow CH_2=CHCO_2H + 2\,Ag$$

More powerful oxidizers attack the double bond as well as the aldehyde hydrogen.

2. By oxidation of allyl alcohol after protecting the double bond.

$$CH_2=CHCH_2OH \rightarrow CH_2BrCHBrCH_2OH \rightarrow CH_2BrCHBrCO_2H \rightarrow CH_2=CHCO_2H$$

3. By dehydration of hydracrylic acid, beta hydroxypropionic acid. It is not obtained from lactic acid or its esters which give a lactide instead.

4. From $\alpha$- or $\beta$-halogen propionic acids and alcoholic KOH.

5. It is reported that acrylic acid can be made from ethylene and $CO_2$ (EP 586).

*Reactions.* 1. Acrylic acid gives the reactions of carboxylic acids, sometimes complicated by the alpha beta unsaturation (conjugated with the unsaturation of the carbonyl group).

2. It gives olefin reactions with unusual ease. It is readily reduced by $Na_xHg$, whereas ordinary olefins are not. It does not follow Markownikoff's Rule but adds HX with X in the beta position. These peculiarities are due to the conjugated system of double bonds which as usual gives addition reactions more readily than does one double bond. Under suitable conditions substances like ammonia, HCN, and alcohols add to such an unsaturated system although they do not add to an ordinary olefinic bond. In these cases the amino, CN, and alkoxyl groups enter the beta position. Similarly sodium derivatives of 1,3-diketo compounds such as malonic and acetoacetic esters add to the $\alpha\beta$-unsaturated esters. All these processes probably involve 1,4-addition with the H or Na adding to the carbonyl O and the other group adding to the beta C (p. 270). This type of addition is general with $\alpha\beta$-unsaturated esters and acids (Rep. 1932, 107). With a substance like hypochlorous acid which adds to olefins and contains no group which can add to oxygen, a mixture of the two possible isomers is obtained.

$$CH_2{=}CHCO_2H \rightarrow HOCH_2CHClCO_2H + ClCH_2CHOHCO_2H$$

A study of the addition of HOCl to the hexenoic acids shows the influence of the position of the double bond on the direction of the addition (Rep. 1932, 106). With the $\alpha\beta$-compound the Cl adds 100% $\alpha$, with the $\beta\gamma$-compound 90% $\beta$ and with the $\gamma\delta$-compound 95% $\delta$.

3. It polymerizes readily (Staudinger 1932). This tendency can be overcome by adding a trace of an inhibitor such as hydroquinone (Moureu). The polymerization of ethyl acrylate gives valuable colorless resins (Neher 1936).

4. When heated with very concentrated alkali it is split at the double bond.

$$CH_2{=}CHCO_2K + KOH + H_2O \rightarrow HCO_2K + CH_3CO_2K + H_2$$

This is characteristic of all alpha beta unsaturated acids.

5. Acrylic esters react with Na and alcohols to give $\beta$-alkoxy propionic esters, and with diazomethane and diazoacetic ester to give pyrazolin-3-carboxylic ester and pyrazolin-3,5-dicarboxylic ester respectively. With pure NaOMe, methyl acrylate gives $\alpha$-methylene glutaric ester. With conjugated dienes, substituted tetrahydrobenzoic acids are obtained (Diels, Alder) (p. 54). This is general for $\alpha\beta$-unsaturated compounds.

6. Acrylic acid is about twice as much ionized as propionic acid.

**Crotonic acid,** *trans*-buten-2-oic acid, *trans*-$\Delta^2$-butenoic acid, $CH_3CH=CHCO_2H$, is available commercially as a product from acetaldehyde obtained from acetylene (Niacet).

*Preparation.* 1. By oxidation of crotonaldehyde from aldol with silver oxide or catalytically (Young 1932).

2. From alpha bromo *n*-butyric ester and alcoholic KOH or a tertiary amine like diethylaniline.

3. From malonic ester with paraldehyde in acetic anhydride or with acetaldehyde and secondary amines (Knoevenagel).

$$MeCHO + CH_2(CO_2R)_2 \rightarrow MeCHOHCH(CO_2R)_2 \rightarrow MeCH=C(CO_2R)_2 \rightarrow MeCH=C(CO_2H)_2 \rightarrow MeCH=CHCO_2H$$

4. From allyl cyanide by hydrolysis and rearrangement. The cyanide is made from allyl bromide and cuprous cyanide (OS).

$$CH_2=CHCH_2CN \rightarrow [CH_2=CHCH_2CO_2H] \rightarrow CH_3CH=CHCO_2H$$

This shift of a double bond to the alpha beta position in which it is conjugated with the carbonyl group is general. The reverse shift is favored only in presence of a branch in the beta or gamma position (Rep. 1927, 111; 1932, 136–144).

*Reactions.* The reactions of crotonic acid closely resemble those of acrylic acid except that it has less tendency to polymerize. With concentrated alkali it gives two molecules of acetate.

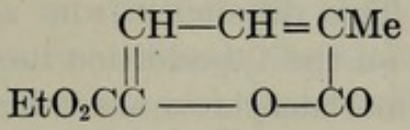
*The gamma H atoms in such an unsaturated acid have some of the properties of ordinary alpha H.* Thus the esters of $\alpha$-Me- and

$\beta$-Me-crotonic acids react with oxalic ester and KOEt the same as ethyl acetate does (Rep. 1923, 73).

$$EtO_2CCO_2Et + CH_3CO_2Et \rightarrow \underset{\text{oxalacetic ester}}{EtO_2CCOCH_2CO_2Et}$$

$$EtO_2CCO_2Et + CH_3CH{=}CMeCO_2Et \rightarrow EtO_2CCOCH_2CH{=}CMeCO_2Et$$

The product is stable as the enol containing an 8-atom conjugated system, $O{=}C(OEt){-}C(OH){=}CH{-}CH{=}C(Me){-}C{=}O$. Treatment with HCl gives the $\alpha$-pyrone,



On the other hand, the $\gamma-H$ atoms will not take part in the Perkin reaction with benzaldehyde. Benzaldehyde and crotonic anhydride react in the presence of tertiary bases but the $\alpha-H$ is involved instead of the $\gamma-H$ to give $C_6H_5CH{=}C(CO_2H)CH{=}CH_2$ (Rep. 1932, 115).

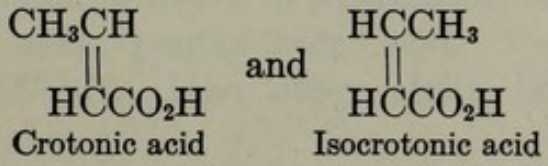
**Isocrotonic acid,** *cis*-buten-2-oic acid, *cis*-$\Delta^2$-butenoic acid, $CH_3CH{=}CHCO_2H$, is obtained by the reduction of chloro-isocrotonic ester with sodium amalgam.

$$CH_3COCH_2CO_2Et \rightarrow CH_3CCl_2CH_2CO_2Et \rightarrow CH_3CCl{=}CHCO_2Et \rightarrow CH_3CH{=}CHCO_2Et$$

This replacement of a halogen by hydrogen under conditions which would be expected to hydrogenate the double bond is common with acids containing the grouping $C{=}CX$.

Isocrotonic and crotonic acids are identical *structurally* since both give *n*-butyric acid on hydrogenation, potassium acetate on heating with conc. KOH, and acetic and oxalic acids on oxidation. Isocrotonic acid melts at 15° and boils at 172° whereas crotonic acid melts at 72° and boils at 189°. Isocrotonic acid slowly changes to crotonic acid at temperatures above 100°.

The two acids are *stereoisomers* of the *cis-trans* or "geometric" type characteristic of olefins of the type $abC{=}Cac$. The formulas assigned to the two acids are:




Crotonic acid Isocrotonic acid

Of these the labile form is isocrotonic acid which is converted to the stable form, crotonic acid, by action of various catalysts such as nitrous acid and also by traces of $I_2$ or $Br_2$ in sunlight. This type of change is general for geometric isomers in this series.

**α-Methylacrylic acid,** methacrylic acid, methylpropenoic acid, $CH_2=C(CH_3)CO_2H$, is prepared by removing halogen acid from α-bromoisobutyric acid or by dehydrating ethyl α-hydroxyisobutyrate. In reactions, it resembles acrylic acid closely except that it adds HX to give an *alpha* substituted product thus following Markownikoff's Rule. This addition cannot take place in the 1,4-manner. This difference from acrylic acid has been used to throw doubt on the 1,4-addition mechanism in all cases.

Polymers of alkyl methacrylates are valuable as resins (Neher 1936).

**Vinylacetic acid,** buten-3-oic acid, $\Delta^3$-butenoic acid,

$$CH_2=CH-CH_2CO_2H.$$

*Preparation.* 1. From allyl magnesium bromide (Gilman) and $CO_2$.

2. From allyl cyanide after protecting the double bond.

$$CH_2=CHCH_2CN \rightarrow BrCH_2CHBrCH_2CN \rightarrow BrCH_2CHBrCH_2CO_2H \rightarrow CH_2=CHCH_2CO_2H$$

*Reactions.* Vinylacetic acid gives the reactions of a carboxyl compound and of an olefin practically independent of each other because there is no conjugation of the unsaturation in the two groups. It adds $Br_2$ more rapidly than does the αβ-unsaturated acid (Rep. 1910, 70; Muskat 1930). Thus the greater activity of the αβ-acids with substances of the type HQ is due to the initiation of the reaction by addition of the H to the O of the conjugated system. Bromine cannot add to O in this way. It must add to C directly. The βγ-double bond is thus more unsaturated than the αβ-double bond when the latter acts independently of the carboxyl.

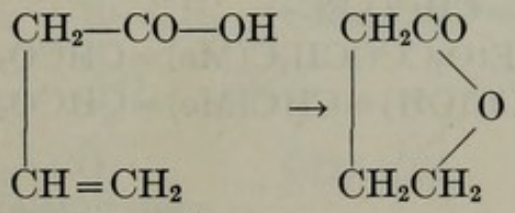
On boiling with dilute acids or alkalies, it changes to crotonic acid. Gaseous HBr even at 0° causes this change. This is

another indication of the activity of its double bond.

$$H^+ + CH_2{=}CH{-}CH_2CO_2H \rightarrow$$
$$CH_3{-}\overset{*}{C}H{-}CH_2CO_2H \rightleftarrows H^+ + CH_3CH{=}CHCO_2H$$

Concentrated alkalies give two molecules of acetate by shifting the double bond and splitting the alpha beta unsaturated compound as it is formed. The change from an unsubstituted beta gamma to an alpha beta unsaturated acid is not reversible because an alpha H atom is so much more reactive than a gamma H atom that a beta substituted compound which can form an olefin by loss of HQ always selects the alpha H atom. This fact is of importance in the biological "beta oxidation" of fats and in the action of higher olefinic acids with strong alkalies which always results in the removal of two C atoms. The presence of a fork in the gamma position makes possible an equilibrium between the $\beta\gamma$- and $\alpha\beta$-acids (Rep. 1927, 111). The older conception that the shift of the double bond took place by the addition and removal of water is probably incorrect (Rep. 1927, 108).

In one reaction, vinylacetic acid shows a complication between its two reactive groups. It readily changes to butyrolactone because the carboxyl and ethylene linkages can approach each other closely in space (Rep. 1932, 108).




This is the "inner ester" of gamma hydroxy *n*-butyric acid. This is apparently an addition contrary to Markownikoff's Rule, the H adding to the C with the fewest H atoms. In order for the H to add to the end C, a *four* membered ring would have to form. Looked at in another way, as the molecule of vinylacetic acid bends around in space, the O of the carboxyl group is very near to the end carbon. Since that carbon is unsaturated, addition takes place and the H has to add to the next carbon. Lactone formation is a general property of $\beta\gamma$-unsaturated acids.

**β-Ethylacrylic acid,** penten-2-oic acid, $\Delta^2$-pentenoic acid, $CH_3CH_2CH{=}CHCO_2H$. Like other alpha beta unsaturated

acids, it can be made (1) by removing HX from the alpha halogen acid, (2) by the condensation of an aldehyde with sodium acetate and acetic anhydride, and (3) through the condensation of an aldehyde with malonic ester in the presence of secondary amines (Knoevenagel). Because of the availability of *n*-amyl alcohol the first method would be the best. Its reactions are like those of crotonic acid.

**ββ-Dimethylacrylic acid,** 3-methylbuten-2-oic acid,

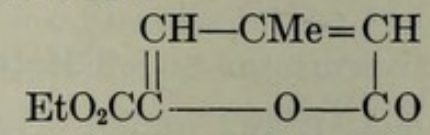
$$(CH_3)_2C=CHCO_2H,$$

is made (1) from acetone and malonic acid, (2) from the corresponding $\alpha$-bromoisovaleric acid and (3) by dehydrating $\beta$-hydroxyisovaleric acid obtained from acetone, bromoacetic ester and zinc (Reformatzky). This is a general method for $\alpha\beta$-unsaturated acids of the types $RR'C=CHCO_2H$ and

$$RR'C=CR''CO_2H.$$

The *reactions* of dimethyl acrylic acid are like those of its lower homologs. It also shows the peculiar activity of the $\gamma-H$ atoms due to their relation to the conjugated system (Rep. 1923, 73). Ethyl oxalate reacts as follows:

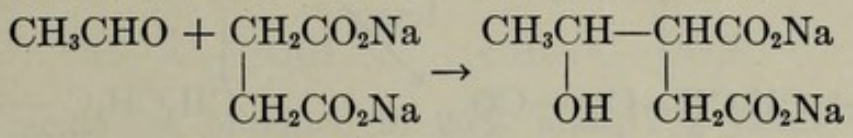
$$(CO_2Et)_2 + Me_2C=CHCO_2Et \rightarrow$$
$$EtO_2CCOCH_2C(Me)=CHCO_2Et \rightarrow$$
$$EtO_2CC(OH)=CHC(Me)=CHCO_2Et \rightarrow$$



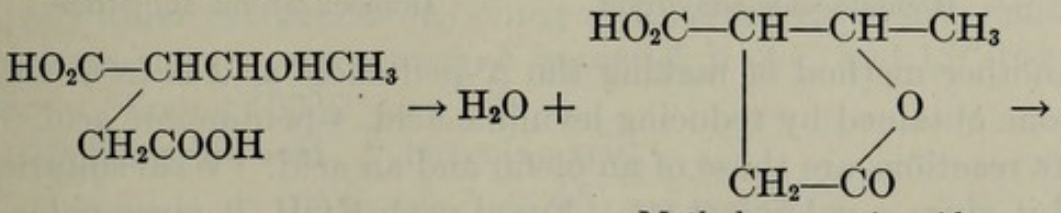
The formation of the $\alpha$-pyrone from the 8-atom conjugated system takes place spontaneously.

**β-Pentenoic acid,** $CH_3CH=CHCH_2CO_2H$, is not available by any of the ordinary methods. A beta halogen acid loses HX entirely with an alpha H atom. A gamma halogen acid when treated with alkali gives a gamma lactone instead of the desired unsaturated acid. This is another example of the ease of formation of a five membered ring. When the alkali has removed the halogen, the end of the reactive fragment is very near the O of

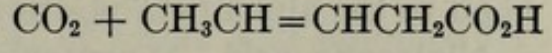
the carboxyl group and the result is ring closure instead of the formation of a double bond. In common with other *beta gamma unsaturated acids*, it can be made by distilling the proper alkyl paraconic acid obtained by a modification of the Perkin reaction from an aldehyde, sodium succinate and acetic anhydride.



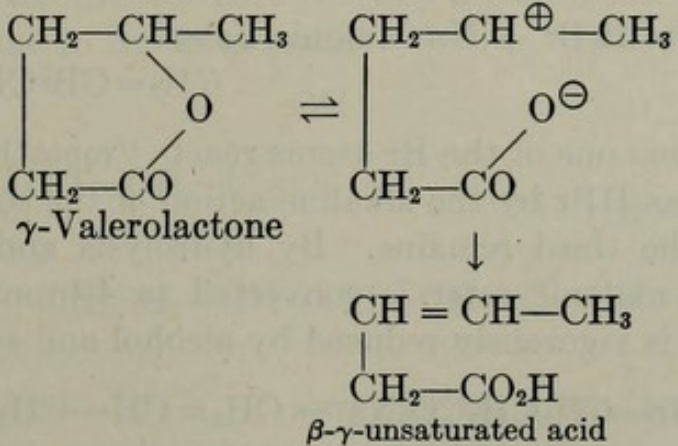
When this intermediate product reacts with acid, one of the carboxyl groups is very near the hydroxyl group in space and a lactonic acid results.



Methyl paraconic acid
(β-carboxy-γ-methylbutryolactone)



Three other products are obtained in smaller amounts. Of the four products, two involve the loss of the carboxyl group. The next steps may be as follows:

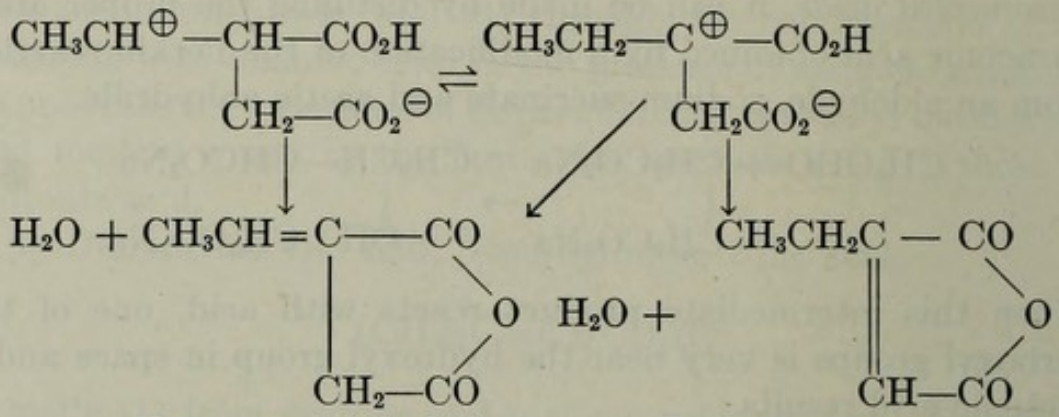


γ-Valerolactone

β-γ-unsaturated acid

The other two products are anhydrides of dibasic acids, homoitaconic and homocitraconic acids (the prefix homo-indicates the next higher homolog with no other change in structure). Re-

writing the formula for methyl paraconic acid with the lactone opened, gives:



Homoitaconic anhydride Homocitraconic anhydride

Another method of making the $\Delta^3$-pentenoic acid is from the lactone obtained by reducing levulinic acid, 4-pentanonic acid.

Its reactions are those of an olefin and an acid. With sulfuric acid it gives $\gamma$-valerolactone. Fused with KOH, it gives potassium acetate and propionate, showing the shift of the double bond to the alpha beta position.

**Allylacetic acid,** $\Delta^4$-pentenoic acid, $CH_2=CHCH_2CH_2CO_2H$, may be prepared readily by the malonic ester or acetoacetic ester synthesis for acids using allyl bromide. Another preparation is from tribromopropane. (Perkin.)

$$BrCH_2CHBrCH_2Br + Na\ Malonic\ Ester \rightarrow CH_2=CBrCH_2CH(CO_2R)_2$$

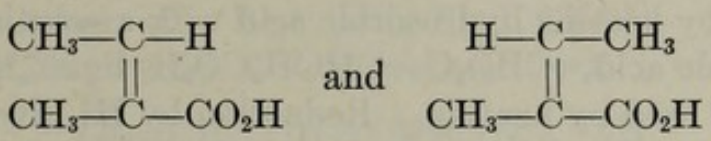
In this process one of the Br atoms reacts "metathetically," one is removed as HBr by the alkaline action of the sodium malonic ester and the third remains. By hydrolysis and heating, the substituted malonic ester is converted to 4-bromopenten-4-oic acid. This is vigorously reduced by alcohol and sodium.

$$CH_2=CBr—CH_2CH_2CO_2Na \rightarrow CH_2=CH—CH_2CH_2CO_2Na$$

The reactions of allyl acetic acid are like those of its lower homologs which have no conjugated system. With sulfuric acid, it forms methyl butyrolactone ($\gamma$-valerolactone). This reaction is in accord both with Markownikoff's Rule and Baeyer's Strain Theory. The tendency to form a six-membered ring is not enough to make the addition go contrary to Markownikoff's Rule with the formation of $\delta$-valerolactone.

**Angelic** and **tiglic acids,** *cis-trans* isomers of 2-methyl-$\Delta^2$-

butenoic acid, $CH_3CH=C(CH_3)CO_2H$, are found in the roots of *Angelica archangelica* and in *Croton tiglium* respectively. Their melting points are 45° and 64.5° and their boiling points 185° and 198° respectively.

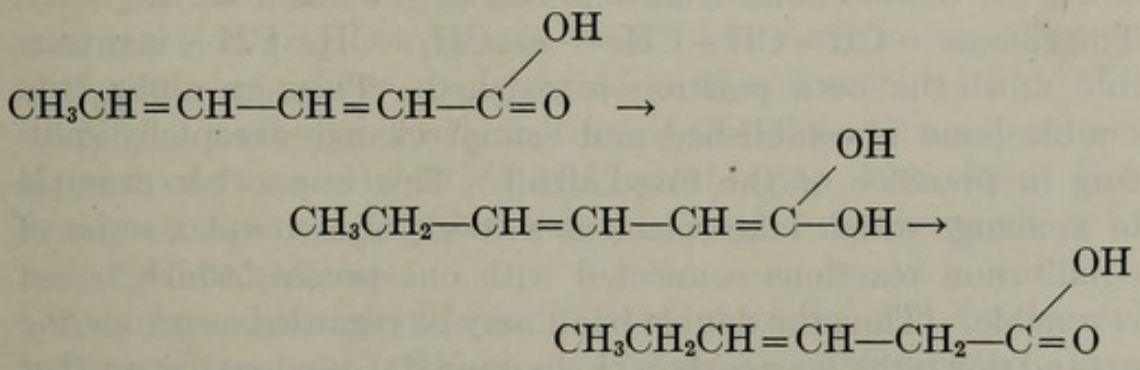


The two acids are obtained in 25% and 17% yields by the dehydration of α-hydroxy-α-methylbutyric acid obtained from methylethyl ketone by the cyanohydrin synthesis. They add HI giving the β-iodo-α-methylbutyric acids, m. 58° and 86° respectively which decompose on boiling with sodium carbonate solution to form the two stereomers of butene-2, b. 3.7° and 1.0° respectively (Young 1929).

**Hydrosorbic acid,** $\Delta^3$-hexenoic acid,

$$CH_3CH_2CH=CHCH_2CO_2H,$$

is obtained by the distillation of ethyl paraconic acid (p. 315) and by the partial reduction (1 : 4) of sorbic acid obtained by the condensation of crotonaldehyde with malonic acid. This reduction takes place more easily than with a similar 4-carbon system not adjacent to a carbonyl group. Thus it is highly probable that the process here is really 1,6-addition followed by the usual change to the keto form.



The partial reduction of similar diolefinic acids is a general method for making βγ-unsaturated acids.

Hydrosorbic acid gives the usual reactions of a βγ-unsaturated acid, including rearrangement and splitting by alkalies and lactone formation when treated with sulfuric acid.

**Isohydrosorbic acid,** $\Delta^2$-hexenoic acid,

$$CH_3CH_2CH_2-CH=CHCO_2H,$$

is obtained from *n*-caproic acid through the alpha bromo compound and by heating hydrosorbic acid with a solution of alkali.

**Pyroterebic acid,** $(CH_3)_2C=CHCH_2CO_2H$, b. 207°, is obtained from terebic acid by heating. Reduction by HI gives isocaproic acid.

**Teracrylic acid,** $(CH_3)_2C=C(CH_3)CH_2CO_2H$, b. 218°, is obtained by heating terpenylic acid.

A **decenoic acid** having a branched chain has been obtained from Capsaicin (Rep. 1920, 85).

**Undecylenic acid,** $\Delta^{10}$-undecenoic acid, $CH_2=CH(CH_2)_8CO_2H$, is obtained by the destructive distillation of castor oil under reduced pressure (15% yield). The yield can be increased by heating the castor oil with rosin (Bruson 1933). Its constitution is proved by its conversion to sebacic acid, $HO_2C(CH_2)_8CO_2H$, by oxidation. Its dibromide, on treatment with alcoholic KOH gives 10-undecynoic acid, $HC\equiv C(CH_2)_8CO_2H$, which on fusion with KOH at 180° rearranges to 9-undecynoic acid,

$$CH_3C\equiv C(CH_2)_7CO_2H.$$

When undecylenic acid is fused with KOH it gives potassium acetate and nonylate in the usual way. Thus the action of alkali shifts the double bond from one end of the chain to the other. The change $-CH=CH-CH_2-\rightarrow-CH_2-CH=CH-$ is reversible until the beta position is reached. Then an alpha beta double bond is established and cannot change except by splitting in presence of the fused alkali. This is another example of a change which takes place as a result of a complex series of equilibrium reactions connected with one process which is not reversible. Thus the double bond may be regarded as wandering up and down the long carbon chain purely at random except that each molecule in which the double bond reaches the alpha beta position can not longer change except by splitting.

The addition of HBr to undecylenic acid in ether follows Markownikoff's Rule while in toluene the $\omega$-bromo acid is obtained (Rep. 1932, 107).

$\omega$-Olefinic acids of $C_{12}$ and $C_{13}$ have been synthesized (Adams, Rep. 1927, 87).

**Myristolenic** ($C_{14}$) and **palmitolenic (zoomaric)**($C_{16}$) **acids** with the double bond mainly in the 9-position have been obtained from certain whale oils (Rep. 1925, 79; 1928, 84).

**Oleic acid,** rapic acid, $\Delta^9$-octadecenoic acid,

$$CH_3(CH_2)_7CH=CH(CH_2)_7CO_2H,$$

m. 13–14°, occurs as glyceride in most fats and oils. Its constitution is proved by its hydrogenation to stearic acid and its ozonation to pelargonic aldehyde,

$$CH_3(CH_2)_7CHO$$

and the half aldehyde of azelaic acid, $OCH(CH_2)_7CO_2H$. At 100° it reacts with oxygen to give a very complex mixture of acids including 15% 9,10-dihydroxystearic acid, 35% nonylic acid and 1% acetic acid and 0.5% formic acid.

Fusion with KOH converts oleic acid to the $\alpha\beta$-unsaturated salt and splits that into the acetate and palmitate ($C_{16}$). Oxidation with nitric acid gives all the lower fatty acids from $C_{10}$ to $C_2$ with the corresponding dibasic acids. This indicates shifts of the double bond under the influence of the acid. It is noteworthy that the shift takes place in either direction from the normal position in the middle of the chain.

Very dilute $KMnO_4$ solution adds two hydroxyl groups to produce 9,10-dihydroxystearic acid. More vigorous oxidation with permanganate gives pelargonic acid and azelaic acid. The oxidation of ethyl oleate in acetone or glacial acetic acid solution gives the two acids in 59 and 95% yields (Rep. 1925, 79). Evidently there is no shift of the double bond as in the presence of acids or fused alkalies.

The formation of oleic acid from stearolic acid by careful hydrogenation with nickel indicates its *cis* configuration (Rep. 1926, 100).

Addition of sulfuric acid followed by hydrolysis gives mainly 10-hydroxystearic acid (de Groote 1931). Benzene adds to oleic acid under the influence of sulfuric acid to give equal amounts of 9- and 10-phenylstearic acids (Marvel 1932).

Treatment with a trace of nitrous acid converts the liquid oleic acid, m. 14°, into its solid *trans* stereoisomer, *elaidic acid*, m. 51°. The structural identity of elaidic acid and oleic acid is proved by the identity of the products obtained by hydrogenation and by vigorous oxidation. Mild oxidation by hydrogen peroxide converts methyl oleate and methyl elaidate into the two dihydroxystearic acids of m.p. 95° and 132° respectively (Rep. 1928, 83).

Oleic acid with zinc chloride gives stearolactone (Rep. 1926, 100).

Lead oleate differs from the lead salts of stearic and palmitic acids in being soluble in ether. Pure oleic acid can be prepared from this salt or from the lithium salt or from the product of addition of mercuric acetate (Rep. 1927, 86). Crude oleic acid is sometimes called Red Oil.

Reduction of oleic esters with Na and EtOH gives oleyl alcohol without changing the double bond.

Oleic acid has been synthesized (Rep. 1925, 80).

**Iso-oleic acid,** m. 45°, with $\Delta^{10}$ is obtained by hydrating oleic acid and dehydrating the hydroxystearic acid formed.

**Petroselic acid,** m. 34°, is an isomer of oleic acid having the double bond in the 6,7-position. It is thus related to lactarinic acid (6-keto-) and tariric acid (6,7-acetylenic). Petroselic acid is changed by a trace of nitrous acid to its *trans* isomer, m. 54° (Rep. 1927, 89). Oxidation gives lauric and adipic acids. The $\Delta^{11}$, liquid, and $\Delta^{12}$, m. 35°, isomers of oleic acid are obtained from the bromide of 12-hydroxystearic acid formed by the catalytic hydrogenation of ricinoleic acid (Rep. 1912, 84).

**Erucic** and **brassidic acids,** *cis-trans* isomers of $\Delta^{13}$-docosenoic acid, $CH_3(CH_2)_7CH=CH(CH_2)_{11}CO_2H$ (Rep. 1922, 72). Erucic acid is present as a glyceride in the oils from rape-seed and grape-seed. It melts at 34°. Oxidation gives nonylic and brassylic acids. Nitrous acid converts erucic acid to brassidic acid, m. 65°. The *cis* form, erucic acid, is hydrogenated more rapidly than the *trans* form (Rep. 1930, 84). Isoerucic acid is a mixture of the $\Delta^{12}$ and $\Delta^{14}$ isomers (Rep. 1927, 87).

**Cetoleic acid,** an isomer of erucic acid having $\Delta^{11}$, is found in certain animal oils (Rep. 1928, 84).

**Nervonic acid,** erucylacetic acid,

$$Me(CH_2)_7CH=CH(CH_2)_{13}CO_2H,$$

has been isolated from a cerebroside from human brains. It has been synthesized from erucyl alcohol through the bromide and the malonic ester synthesis (Rep. 1926, 100; Adams 1930). It exists in *cis* and *trans* forms, m. 39° and 61°.

### *C.* Diolefinic Acids, $C_nH_{2n-3}CO_2H$

**β-Vinylacrylic acid,** pentadien-2,4-oic acid,

$$CH_2=\overset{4}{C}HCH=\overset{2}{C}HCO_2H,$$

m. 80°, is made from acrolein and malonic acid in presence of pyridine. This is a general method for making 2,4-diolefinic acids.

Vinylacrylic acid with $H_2$ and $PtO_2$ (Adams) (OS) gives ethylacrylic acid (Muskat 1931) while reduction by $Na_xHg$ gives 1,4-addition to form penten-3-oic acid with a lesser amount of 1,2-addition to give vinylpropionic acid (Burton 1929).

Thus catalytic hydrogenation apparently initiates at the terminal carbon while reduction starts at the carbonyl oxygen as part of the 1,6-conjugated system (Muskat 1931)

$$C=C-C=C-C=O \xrightarrow[PtO_2]{H_2} HC-\underset{|}{C}-C=C-C=O \rightarrow$$

$$\begin{array}{l} \\ \\ \\

vinylacrylic acid gives formic and tartaric acids. The influence of the 6-atom conjugated system is seen in the addition of two mols of $NH_3$ to give diaminovaleric acid when vinyl acrylic acid is heated with ammonium hydroxide solution. Since ammonia does not add to ordinary olefinic linkage, to butadiene, or to $\beta\gamma$-unsaturated acids, the process probably includes the following steps.

$$\begin{aligned} CH_2{=}CHCH{=}CHC{=}O(OH) &\rightarrow NH_2CH_2CH{=}CHCH{=}C(OH)_2 \\ &\rightarrow NH_2CH_2CH{=}CHCH_2C{=}O(OH) \\ &\rightarrow NH_2CH_2CH_2CH{=}CHC{=}O(OH) \\ &\rightarrow NH_2CH_2CH_2CH(NH_2)CH{=}C(OH_2) \\ &\rightarrow NH_2CH_2CH_2CH(NH_2)CH_2CO_2H \end{aligned}$$

The change from the $\beta\gamma$- to the $\alpha\beta$-unsaturated acid takes place as usual in the alkaline medium.

The addition of hypochlorous acid takes place exclusively at the terminal olefinic linkage forming $ClCH_2CHOHCH{=}CHCO_2H$, thus following Markownkoff's Rule. The $\alpha\beta$-unsaturation remains as part of the conjugated system with the carbonyl group (Rep. 1932, 109).

Vinylacrylic acid and other 2,4-diolefinic acids polymerize on heating probably by the Diels-Alder reaction, the butadiene system of one molecule reacting with the $\alpha\beta$-double bond of another. Vinylacrylic acid gives ethyl benzene on vigorous heating.

Vinylacrylic ester with sodiomalonic ester gives less than 2% addition at the $\alpha\beta$-bond but mainly

$$(MeO_2C)_2CHCH_2CH{=}CHCH_2CO_2Me$$

due to either $\alpha\delta$- or 1 : 6-addition (Kohler 1926, Ingold 1931).

A related substance, cinnamalmalonic ester,

$$PhCH{=}CHCH{=}C(CO_2Et)_2,$$

adds HBr, HCN and cyanoacetic ester in the $\alpha\beta$-position but malonic ester in the $\alpha\delta$-position (Ingold).

**Sorbic acid,** hexadien-2,4-oic acid, $CH_3CH{=}CHCH{=}CHCO_2H$, m. 134°, occurs in unripe sorb apples. It is best prepared from crotonic aldehyde and malonic acid in pyridine. It gives reac-

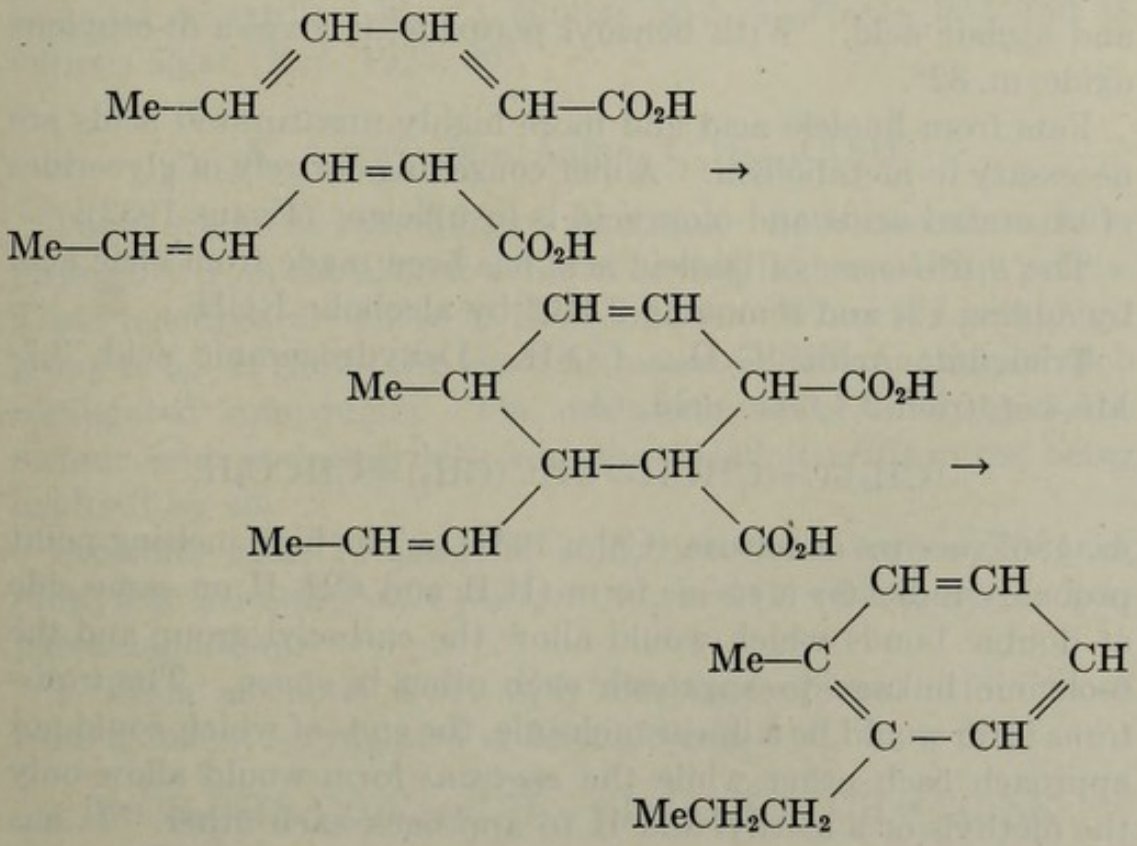
tions like those of vinylacrylic acid. Partial hydrogenation gives hydrosorbic acid (hexen-3-oic acid) and, to a lesser extent, the $\alpha\beta$- and $\gamma\delta$-addition products (Rep. 1932, 110). Thus the chief addition is 1 : 6, initiated at the carbonyl oxygen. Hypochlorous acid which cannot initiate such a reaction adds to the 4-ethylenic linkage, the Cl adding to the 5—C (Rep. 1932, 109).

Cyanoacetic ester adds to sorbic ester mainly in the $\alpha\delta$-position and only about 10% in the $\alpha\beta$-position (Ingold 1931). This may be assumed to be due to 1 : 6- and 1 : 4-addition initiated at the carbonyl oxygen or to 1 : 4- and 1 : 2-addition to the conjugated four carbon system adjacent to the carboxyl group.

The H atoms of the methyl at the end of the 6-atom conjugated system show some properties of $\alpha$—H atoms. Thus sorbic ester condenses with oxalic ester to give the remarkably conjugated compound,

$$O{=}C(OEt)C(OH){=}CHCH{=}CHCH{=}CHC{=}O(OR)$$

(Rep. 1932, 114–15). Sorbic acid heated with barium hydroxide gives *o*-propyltoluene, the first step being undoubtedly a Diels-Alder addition (Rep. 1932, 112).



Alcoholic KOH at 170° converts sorbic acid to hexyn-3-oic acid which on oxidation gives malonic, propionic and oxalic acids.

**Geranic acid,** 3,7-$Me_2$-octadien-2,6-oic acid,

$$(CH_3)_2C=CH(CH_2)_2C(CH_3)=CHCO_2H,$$

b. 153° (13 mm.), is obtained by oxidation of the corresponding aldehyde (citral) by silver oxide or by the hydrolysis of the nitrile obtained from the oxime of citral and acetic anhydride. Under the action of 70% sulfuric acid a 6-membered ring is closed to form α-cyclogeranic acid, 2,2,6-$Me_3$-1,2,3,4-tetrahydrobenzoic acid.

**Linoleic acid,** linolic acid, octadecadien-9,12-oic acid,

$$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7CO_2H,$$

occurs as glycerides in almost all oils and fats, especially in drying oils such as linseed oil. It exists in the four possible stereoisomeric forms, *transtrans*, *trans-cis*, *cis-cis* and *cis-trans* (Nicolet 1922). Oxidation with alkaline permanganate gives *sativic acid*, tetrahydroxystearic acid, which can be reduced to stearic acid by HI. More vigorous oxidation gives caproic acid, oxalic acid and azelaic acid. With benzoyl peroxide, it gives a di-ethylene oxide, m. 32°.

Fats from linoleic acid and more highly unsaturated acids are necessary in metabolism. A diet consisting entirely of glycerides of saturated acids and oleic acid is insufficient (Evans 1932).

The *8,10-isomer* of linoleic acid has been made from oleic acid by adding $Cl_2$ and removing 2 HCl by alcoholic KOH.

**Triolefinic Acids,** $C_nH_{2n-5}CO_2H$. Dehydrogeranic acid, 3,7-$Me_2$-octatrien-2,4,6-oic acid, (A),

$$(CH_3)_2C=CHCH=CHC(CH_3)=CHCO_2H,$$

m. 186°, occurs in nature (Cahn 1931). The high melting point probably indicates a *cis-cis* form (H,H and $CH_3$,H on same side of double bond) which would allow the carboxyl group and the 6-olefinic linkage to approach each other in space. The *trans-trans* form would be a linear molecule, the ends of which could not approach each other while the *cis-trans* form would allow only the methyls or a methyl and H to approach each other. It has

been found in essential oils as an ester with geraniol. It has been synthesized (Kuhn 1932, Fischer 1932).

$$Me_2C{=}CHCHO + Me_2CO \rightarrow Me_2C{=}CHCH{=}COMe$$

$$BrCH_2CO_2R + Zn \longrightarrow Me_2C{=}CHCH{=}CHC(OH)(Me)CH_2CO_2R \rightarrow (A)$$

**Linolenic acid,** octadecatrien-9,12,15-oic acid,

$$CH_3(CH_2CH{=}CH)_3(CH_2)_7CO_2H,$$

is present in large amounts in the glycerides of linseed oil. It has also been found in Cassava starch. It is usually isolated as the hexabromide (Stanfield 1932). *Isolinolenic* and *pecorinic acids* are isomers of linolenic acid.

**Elaeostearic acid** ("eleomargaric acid"), m. 44°, formerly regarded as a stereoisomer of linoleic acid, is the 9,11,13-isomer (Rep. 1925, 79). $\alpha$-form, m. 47°; $\beta$-form, m. 67°. In the form of glycerides, it constitutes over 90% of Chinese wood oil (Rep. 1925, 79; Rhodes 1927). It exists in several stereo forms.

**Clupanodonic acid,** $C_{18}H_{28}O_2$, contains four double bonds. It is found in sardine oil. A similar acid, $C_{22}H_{36}O_2$, is found in various algae (Rep. 1925, 80).

### *E.* Acetylenic Acids, $C_nH_{2n-3}CO_2H$

These are made by standard reactions. Some members differ physically from the olefinic acids in having higher melting points. Their reactions are those of their groups. When the acetylenic group is $\alpha\beta$- it shows the usual increased additive power of such conjugated compounds. The acetylenic acids differ from the olefinic acids and especially from the diolefinic acids in not being oxidized by air.

**Propiolic acid,** propargylic acid, acetylene carboxylic acid, propynoic acid, $HC{\equiv}CCO_2H$, m. 9°, b. 144° (dec.), can be prepared as follows:

1. From alcoholic KOH with dibromopropionic acid formed from acrolein, acrylic acid or allyl alcohol.

$$BrCH_2CHBrCO_2K \rightarrow CH_2{=}CBrCO_2K \rightarrow CH{\equiv}CCO_2K$$

2. From the monosodium derivative of acetylene (Rep. 1926, 98) or the mono-Grignard derivative (Oddo 1908), with $CO_2$.

3. Probably best, from maleic acid by addition of $Br_2$, removal of 2 HBr and loss of $CO_2$ on heating the acid potassium salt of acetylene dicarboxylic acid.

$$HO_2CC{\equiv}CCO_2K \rightarrow CO_2 + HC{\equiv}CCO_2K$$

The effect on physical properties of the triple bond as compared with a double or single bond is interesting. For the three acids, propionic, acrylic and propiolic, the melting points are $-19°$, $+12°$, $+9°$; the boiling points are 141°, 142° and 144° (dec.); the densities are 0.987, 1.06 and 1.33; while the boiling points of the ethyl esters are 99°, 100° and 120°.

Propiolic acid shows the properties of acetylene and of a carboxylic acid. The two groups influence each other as is shown by the easy reduction of the triple bond to form acrylic acid and then propionic acid. The esters and salts of $\alpha\beta$-acetylenic acids also add one or two mols of sodium bisulfite or ammonia or primary or secondary amines, the H going to the $\alpha$-carbon and the rest of the addend to the $\beta$-carbon. Thus the mechanism probably involves 1,4-addition initiated at the carbonyl group.

Sodium propiolate reacts with ammoniacal cuprous solution to give $(NaO_2CC{\equiv}CCu)_2$. Oxidation of this compound with potassium ferricyanide gives the sodium salt of diacetylenedicarboxylic acid.

Polymerization of propiolic acid in sunlight gives a small yield of trimesic acid, benzene-1,3,5-tricarboxylic acid.

**Tetrolic acid,** methylpropiolic acid, butyn-2-oic-acid,

$$CH_3C{\equiv}CCO_2H,$$

m. 76°, b. 203°, is prepared from crotonic acid through the dibromide or from allylene through its Na or Grignard derivative. It gives the expected reactions. Hydrogenation with Pd at 20° gives isocrotonic acid (the *cis* form) (Rep. 1925, 75). Many homologs of the type $RC{\equiv}CCO_2H$ have been prepared. The best known one is made from heptaldehyde from castor oil and is used in the form of its methyl ester as methyl heptine

carbonate, an artificial violet perfume. The steps are as follows (Moureu 1900):

$$C_6H_{13}CHO \xrightarrow{PCl_5} \xrightarrow{NaOH} \xrightarrow{NaNH_2} \xrightarrow{Na} \xrightarrow{CO_2} \xrightarrow{acid} \xrightarrow{MeOH} C_5H_{11}C{\equiv}CCO_2Me$$

Similarly, methyl octyne carbonate can be made from capryl alcohol (MeHex-carbinol) from castor oil by first oxidizing it to the ketone and then using a similar set of changes.

**Pentyn-4-oic acid,** $CH{\equiv}CCH_2CH_2CO_2H$, is made from 1,2,3-tribromopropane (tribromohydrin) and sodiomalonic ester (Rep. 1907, 92). A more efficient way would be to convert the tribromide to 2-bromoallyl bromide by alkali and use that with the malonic ester to give $CH_2{=}CBrCH_2CH(CO_2Et)_2$ which gives the desired product on treatment with alcoholic KOH and decarboxylation.

**Dehydro-undecylenic acid,** undecyn-10-oic acid,

$$CH{\equiv}C(CH_2)_8CO_2H,$$

b. 175° (15 mm.), m. 43°, can be made from the dibromide of undecylenic acid by careful treatment with alkali (Rep. 1927, 88). Its structure is proved by oxidation to sebacic acid and by the formation of typical acetylenic silver compounds by its esters. When heated with bases to 180° it is converted to *undecolic acid*, m. 59°, undecyn-9-oic acid. This is converted by oxidation to azelaic acid. Its esters form no Ag or Cu compounds.

**Stearolic acid,** octadecyn-9-oic acid,

$$CH_3(CH_2)_7C{\equiv}C(CH_2)_7CO_2H,$$

m. 48°, is made from oleic or elaidic acid through their dibromides. It reacts with conc. sulfuric acid to give 9- and 10-ketostearic acids (Rep. 1926, 99). Reduction by $H_2$ and Ni gives oleic acid (*cis*) while zinc and acetic acid give elaidic acid (*trans*). Oxidation by $HNO_3$ or $KMnO_4$ gives first stearoxylic acid, a 9,10-diketo acid and then pelargonic and azelaic acids.

**Tariric acid,** m. 50°, the 6-isomer of stearolic acid, is found in nature. Its reactions are entirely analogous to those of stearolic acid. Its final oxidation products are lauric and adipic acids.

**Behenolic acid,** docosyn-13-oic acid,

$$CH_3(CH_2)_7C{\equiv}C(CH_2)_{11}CO_2H,$$

m. 57°, is made from the dibromides of erucic and brassidic acids. It resembles stearolic acid in its reactions. Mild reduction gives erucic acid (*cis*) and more vigorous reduction gives brassidic acid (*trans*) (Rep. 1926, 99).

### *F.* Halogenated Aliphatic Acids

In general the preparations and reactions of the halogenated carboxylic acids resemble those of alkyl halides of analogous structure. An exception is that the alpha hydrogen atoms in an acid are more easily replaced by chlorine and bromine than are those of hydrocarbons. The properties of the halogen acids vary with the position of the halogen in relation to the carboxyl group. Halogen in the alpha position increases the dissociation of an acid greatly. Thus trichloroacetic acid is nearly as strong as the inorganic acids. Halogen atoms introduced farther away from the carboxyl group have little effect on its strength.

The action of bases on halogenated acids varies greatly with the position of the halogen.

1. Alpha halogen acids give alpha hydroxy acids and alpha beta unsaturated acids

$$RCH_2CHXCO_2H \rightarrow RCH_2CHOHCO_2H + RCH{=}CHCO_2H$$

2. Beta halogen acids, if there is no substitution at the alpha carbon, give mainly $\alpha\beta$-unsaturated acids with lesser amounts of $\beta-$OH-acids.

$$RCHXCH_2CO_2H \rightarrow RCH{=}CHCO_2H + RCHOHCH_2CO_2H$$

With an $\alpha$-substituted acid, carbon dioxide is lost and an olefin formed

$$RCHXCHQCO_2H + NaOH \rightarrow NaBr + CO_2 + RCH{=}CHQ$$

This reaction occurs whether Q is an alkyl group or a halogen. Thus it is given by $\alpha$-Me-$\beta$-Br-butyric acid, $\alpha\alpha$-$Me_2$-$\beta$-Br-butyric acid and by $\alpha\beta$-$Br_2$-butyric acid.

3. Gamma and delta halogen acids form the corresponding lactones.

4. When the halogen is farther away than the delta position, it acts like that in an alkyl halide. It can react intermolecularly with the carboxyl of another molecule. Thus highly polymeric esters can be formed (Carothers).

*Halogenated Fatty Acids*

**Chloroformic acid,** chlorocarbonic acid, chloromethanoic acid, $ClCO_2H$, and the other halogen analogs are unknown in the free state since they decompose to HX and $CO_2$ as soon as formed. Its esters and amide can be prepared from phosgene.

$$COCl_2 \rightarrow ClCO_2R,\ ClCONH_2$$

**Monochloroacetic acid,** chloroethanoic acid, $ClCH_2CO_2H$, m. 63°.

*Preparation.* 1. Chlorination of acetic acid in sunlight or with halogen carriers like sulfur and phosphorus. 2. Hydrolysis of trichloroethylene obtained from acetylene (Rep. 1922, 73).

$$ClCH{=}CCl_2 \rightarrow ClCH_2{-}CCl_2(OH) \rightarrow ClCH_2COCl \rightarrow ClCH_2CO_2H$$

*Reactions.* 1. As an acid, it is stronger than acetic acid but gives similar reactions. 2. As an alpha halogen compound it gives the reactions of alkyl halides but is even more reactive. With the free acid or one of its salts, the Cl can be replaced by (1) iodine by NaI in alcohol, (2) CN by NaCN, (3) OH by water or alkali, (4) sulfonic acid group by sodium sulfite, (5) amino by ammonia or Gabriel's phthalimide reaction, and (6) nitro by $AgNO_2$. If $NaNO_2$ is used, the resulting sodium nitroacetate decomposes to nitromethane.

Chloroacetic acid is used in making indigo from aniline.

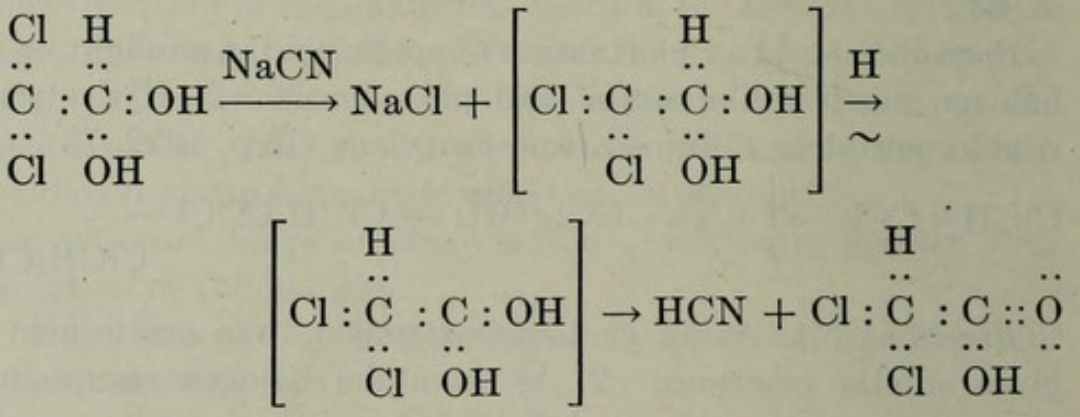
**Bromoacetic acid** can be prepared like chloroacetic acid. **Iodoacetic acid** is best prepared from chloroacetic acid with sodium iodide in alcohol or acetone. The resulting sodium chloride is insoluble in the organic solvent. Esters of bromoacetic acid, in

common with other alpha bromo esters, give the *Reformatzky reaction* with ketones and zinc.

$$RR'CO + R''CHBrCO_2Et \rightarrow RR'C(OH)CH(R'')CO_2Et$$

This is a modified Grignard reaction. It is valuable in preparing complex $\beta$-hydroxy acids.

**Dichloroacetic acid,** $Cl_2CHCO_2H$, can be prepared by chlorination but is more readily obtained from chloral hydrate and NaCN (Pucher 1920, Doughty 1925). The action of the cyanide is not understood since the change is entirely within the molecule. It is another example of the removal of a group from one carbon and the entry of the new group on the adjacent carbon. In this case the change involves a rearrangement of the aldehyde H atom. The processes involved may include the following electronic changes:



If this mechanism is correct, it should be possible to produce the change by other reagents.

A still better method for making dichloroacetic acid is from trichloroacetic acid and copper in water solution (Doughty 1931).

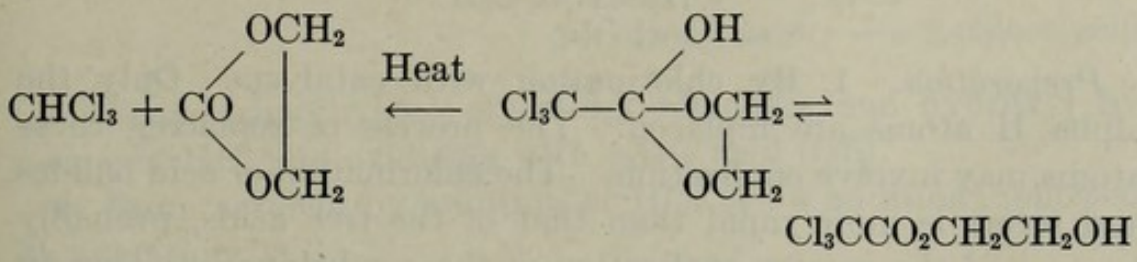
The reactions of dichloroacetic acid are like those of an acid and methylene chloride. Boiling with alkalies gives oxalates and acetates. This reaction represents an extreme case of dismutation. The process is surprising since the related glyoxylic acid gives the normal dismutation with alkalies, forming oxalic acid and glycollic acid.

**Trifluoroacetic acid,** $F_3CCO_2H$, is prepared by a method which illustrates the stability and inactivity of the C—F linkage. Benzotrichloride is treated with Ag or Sb fluoride and the resulting benzotrifluoride is vigorously oxidized, the benzene ring being destroyed.

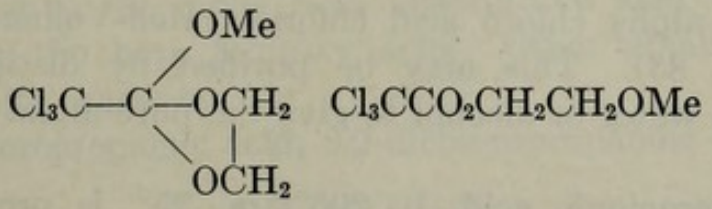
$$F_3CC_6H_5 \rightarrow F_3CCO_2H$$

The benzene ring is more easily destroyed if it is first nitrated and the resulting nitro compound reduced. This is because of the greater ease of oxidation of an aromatic amine as compared with the hydrocarbon.

**Trichloroacetic acid,** $Cl_3CCO_2H$, b. 195°, m. 55°, is best prepared by the oxidation of chloral hydrate with nitric acid (Kolbe). It is a much stronger acid than any other organic acid. It is dangerously corrosive on the skin. Hot alkalies split it to give chloroform and carbonates. Analogous to the effect of the trichloromethyl group on the carbonyl group in chloral, the latter group in trichloroacetic acid shows unusual reactions. Thus, with ethylene oxide, it gives the following: (Meerwein 1931).

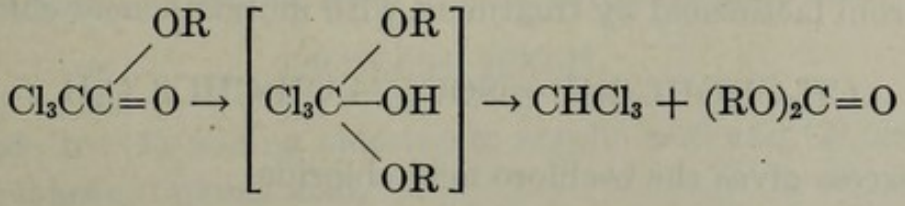



The ethylene acetal of the acid can be methylated with diazomethane to give a product of camphor odor which is stable to bases but is easily split by acids. This is isomeric with the trichloroacetic ester of β-methoxyethyl alcohol which has a true ester odor and is split by both dilute alkalies and acids.




Thus, when the carbonyl group is lacking, bases have no point of attack on the molecule but acids can attack it through oxonium salt formation.

Esters of trichloroacetic acid heated with alcohols give $CHCl_3$ and alkyl carbonates.



Trichloroacetic acid gives peculiar types of esters. Thus with ethylene glycol the product is related to the ortho acid. The benzyl ester decomposes on heating to give an apparent reversal of the Cannizzaro reaction (Rep. 1931, 96).

$$Cl_3CCO_2H + HOCH_2CH_2OH \rightarrow Cl_3C{-}C(HO){-}O{-}CH_2{-}CH_2{-}O$$

$$Cl_3CCO_2CH_2Ph \rightarrow Cl_3CCHO + PhCHO$$

**Alpha-chloropropionic acid,** 2-chloropropanoic acid,

$$CH_3CHClCO_2H.$$

*Preparation.* 1. By chlorination with catalysts. Only the alpha H atoms are replaced. The process of replacing these atoms may involve enolization. The chlorination of acid halides and esters is more rapid than that of the free acids, probably because of the greater enolization of these substances. This, in turn, depends on the fact that the carbonyl group in these substances is more reactive than the corresponding group in the acids.

One of the best methods of alpha chlorination is the use of anhydrous acid with chlorine (dried with $H_2SO_4$) and phosphorus to give the alpha chloro acid chloride (Hell-Volhard-Zelinsky) (Rep. 1912, 83). This may be purified by distillation and treated with water or alcohol to give the pure alpha chloro acid or ester.

**α-Bromopropionic acid,** b. 205°, m. 25°, is prepared in a similar way. For preparation of the acid bromide, all materials must be dried with sulfuric acid or phosphorus pentoxide (a given amount of water will convert eleven times its weight of the bromo acid bromide to the bromo acid).

The *iodo acid* is made from the chloro acid and NaI.

2. From lactic acid by treatment with inorganic acid chlorides.

$$CH_3CHOHCO_2H + SOCl_2 \rightarrow CH_2CHClCO_2H$$

An excess gives the α-chloro acid chloride.

*Reactions.* 1. With suitable reagents the alpha halogen is readily replaced as in chloroacetic acid. Hydrogen and palladium remove the $\alpha$-chlorine but not a $\beta$-chlorine.

2. With aqueous alkalies the main product is lactic acid with some acrylic acid, $CH_2=CHCO_2H$. With alcoholic KOH the latter is the chief product.

**Beta-chloropropionic acid,** 3-chloropropanoic acid,

$$ClCH_2CH_2CO_2H.$$

*Preparation.* 1. From ethylene by the following steps:

Ethylene $\rightarrow$ chlorohydrin $\rightarrow$ cyanide $\rightarrow$

$$\beta\text{-hydroxy acid} \xrightarrow{HCl} \beta\text{-chloro acid}$$

2. From trimethylene glycol by replacing one hydroxyl by means of HCl and oxidizing with nitric acid (OS).

3. From acrolein by addition of HCl (1 : 4 addition) followed by oxidation (OS).

4. From acrylic acid and HCl.

5. Propionyl chloride in $CCl_4$ solution reacts with chlorine in sunlight to give beta substitution, $ClCH_2CH_2COCl$ (Michael).

*Reactions.* 1. Replacement of the beta halogen by other groups is not as easy as with the alpha cpd.

2. Bases give the alpha beta unsaturated acid with smaller amounts of the beta hydroxy acid. Other alkaline reagents have a similar tendency.

**$\alpha\alpha$-Dichloropropionic acid,** 2,2-dichloropropanoic acid,

$$CH_3CCl_2CO_2H,$$

can be prepared by direct chlorination with catalysts. Its silver salt, on boiling with water, gives pyruvic acid, $CH_3COCO_2H$.

**$\alpha\alpha$-$Br_2$-propionic acid** with bases gives pyruvic acid, $\alpha$-Br-acrylic acid and a polymer $(C_3H_4O_3)_x$.

**$\alpha\beta$-Dichloropropionic acid,** 2,3-dichloropropanoic acid,

$$ClCH_2CHClCO_2H,$$

is made by (1) adding chlorine to acrylic acid and (2) chlorinating $\beta$-chloropropionic acid.

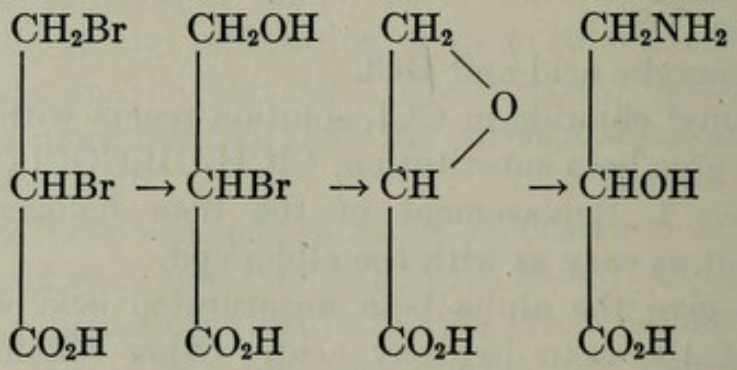
Boiling aqueous alkalies give carbonates and vinyl chloride. This is a general reaction of $\alpha\beta$-dihalogen acids. Surprisingly, the beta halogen reacts rather than the alpha.

$$RCHXCHXCO_2Na \rightarrow NaX + RCH{=}CHX$$

Milder treatment of $\alpha\beta$-$Br_2$-propionic acid with bases gives glyceric acid, $\alpha$-Br-$\beta$-OH-propionic acid and a small amount of pyruvic acid. It is to be noted that the beta halogen reacts more readily. Moreover the $\alpha\beta$-dibromo compound reacts more readily than the $\alpha\alpha$-(Lossen, Rep. 1906, 98).

Alcoholic KOH gives propiolic acid, $HC{\equiv}CCO_2H$. Zinc or inorganic iodides remove both halogens giving acrylic acid.

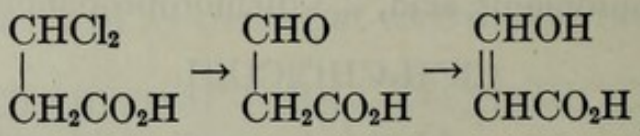
$\alpha\beta$-$Br_2$-propionic acid with silver carbonate gives $\alpha$-Br-$\beta$-OH-propionic acid. This, with ammonia under pressure, gives $\alpha$-OH-$\beta$-$NH_2$-propionic acid (isoserine) (Rep. 1907, 104). The changes involved are probably as follows:




**ββ-Dichloropropionic acid,** 3,3-dichloropropanoic acid,

$$Cl_2CHCH_2CO_2H,$$

is obtained from the $\alpha\beta$-compound by removing one HCl by alcoholic KOH and then adding HCl to the resulting $\beta$-chloro-acrylic acid, $ClCH{=}CHCO_2H$. Boiling with water gives the half aldehyde of malonic acid which is stable as the enol form.



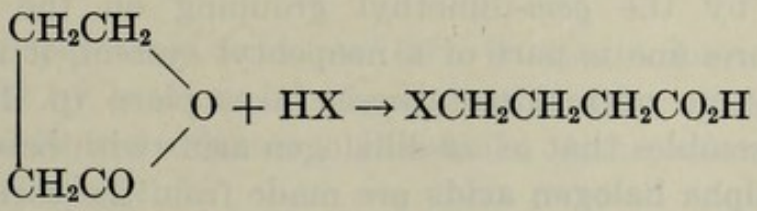

Alcoholic KOH gives propiolic acid.

**Halogenated Butyric Acids.**

*a.* The alpha halogenated *n*-butyric acids resemble the corresponding compounds of propionic acid in preparation and properties.

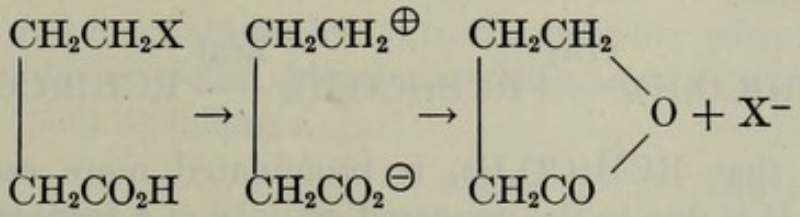
*b.* The beta acids are best prepared by adding HX to the alpha beta unsaturated acid. Their reactions are like those of the $\beta$-halogenated propionic acids. Loss of HX always takes place with an alpha H rather than with a gamma H.

*c.* Gamma halogen *n*-butyric acids are best obtained by treating butyrolactone with HX



$$CH_2CH_2 \quad O + HX \rightarrow XCH_2CH_2CH_2CO_2H$$
$$CH_2CO$$

The lactone is made by hydrolyzing the cyanide from 3-chloropropanol-1. It is not possible to replace the gamma halogen by any other group because of the tendency for lactone formation.



$$CH_2CH_2X \rightarrow CH_2CH_2^{\oplus} \rightarrow CH_2CH_2 \quad O + X^-$$
$$CH_2CO_2H \qquad CH_2CO_2^{\ominus} \qquad CH_2CO$$

The O of the carboxyl can approach the gamma carbon so closely that it is easier for the reaction to take place *inside* the molecule than with an *outside* atom or ion.

*d.* Alpha halogen isobutyric acids are formed with unusual ease because the alpha H in isobutyric acid is also tertiary. The reactions are like those of the other alpha halogen acids except for an increased tendency to lose HX instead of replacement of X by other groups. All reagents of alkaline nature give mainly $\alpha$-methylacrylic acid or its reaction products. Thus sodiomalonic ester with $\alpha$-Br-isobutyric ester gives

$$(EtO_2C)_2CHCH_2CMeCO_2Et,$$

the product which would be obtained from methacrylic ester.

**Halogenated valeric acids** resemble the corresponding butyric

compounds. δ-Halogen-valeric acids, on heating alone or with alkalies, give delta valerolactone (6-membered ring). In higher acids, having the halogen farther away from the carboxyl group than the delta position, the halogen acts independently of the carboxyl.

**Halogenated caproic acids** follow the usual reactions. 3-Bromo-2,2-dimethylbutyric acid, converted to its sodium salt, decomposes to give trimethylethylene. A beta halogen acid would be expected to give mainly an αβ-unsaturated acid and a lesser amount of a β-hydroxyl compound. In this case the first is prevented by the *gem*-dimethyl grouping on the α-carbon. Since the bromine is part of a neopentyl system, it is not surprising that no normal metathesis takes place (p. 128). The reaction resembles that of αβ-dihalogen acids with bases.

**Higher alpha halogen acids** are made from the corresponding fatty acids. If the acid is a monosubstituted acetic acid and has to be synthesized, it is best to use the malonic ester synthesis and brominate the resulting malonic acid before decomposing it (OS).

$$RCH(CO_2H)_2 \xrightarrow{Br_2} RCBr(CO_2H)_2 \xrightarrow{heat} RCHBrCO_2H$$

The fact that $RCH(CO_2H)_2$ is brominated more easily than $RCH_2CO_2H$ is due to the increased activity of a tertiary H atom and to the greater enolization in the malonic acid derivative.

**Higher omega (ω) halogen acids** are made from the polymethylene glycols which are available by the reduction of esters of dibasic acids with sodium and absolute alcohol. (Bouveault and Blanc.) One carbinol group is converted to a halide and the other is then oxidized to a carboxyl. When the ester salts of the dibasic acids are available they can be reduced to the ω-hydroxy acids. The fact that the ester group is reduced while the salt group remains unchanged is due to the presence of a carbonyl group in the former and, perhaps, none at all in the latter (p. 285).

Many higher halogenated fatty acids are obtained by adding $Br_2$, HBr, or HI to olefinic acids or $I_2$ to acetylenic acids. *Sabromin* and *Sajodin* are thus obtained by adding $Br_2$ and HI respectively to behenic acid.

*Halogen-substituted Unsaturated Acids*

**α-Chloroacrylic acid,** $CH_2=CClCO_2H$, m. 65°, is obtained from dichloropropionic acid (2,3 or 2,2) with alcoholic KOH. HCl adds to give the 2,3-compound (1 : 4-addition).

**β-Chloroacrylic acid,** $ClCH=CHCO_2H$, m. 85°, is obtained by reducing chloralide with Zn and aqueous-alcoholic HCl. HCl gives the 3,3-compound.

**α-Chlorocrotonic acid,** $CH_3CH=CClCO_2H$, m. 99°, b. 212°, is made from butyrchloral and potassium ferrocyanide.

$$CH_3CHClCCl_2CO_2H \rightarrow CH_3CH=CClCO_2H$$

**α-Chloroisocrotonic acid,** m. 66°, is obtained from 2,3-$Cl_2$-butyric acid by cautious treatment with bases. Heat converts it partly to its stereoisomer. Reduction with sodium amalgam gives isocrotonic acid.

**β-Chlorocrotonic acid,** $CH_3CCl=CHCO_2H$, m. 94°, b. 211°, is obtained from its chloride formed by $PCl_5$ with acetoacetic ester. It is less volatile with steam than its stereomer.

**β-Chloroisocrotonic acid,** m. 60°, b. 195°, is obtained like its stereomer and is separated by its ready volatility with steam.

The solubilities of the chlorobuten-2-oic acids in parts of cold water are about as follows:

| | crotonic | isocrotonic |
|---|---|---|
| Alpha Cl | 47. | 15 |
| Beta Cl | 35. | 52 |

*Iodostarin* is the product from 1 mol of $I_2$ and tariric acid, $Me(CH_2)_{10}C\equiv C(CH_2)_4CO_2H$.

## XIV. DERIVATIVES OF ALIPHATIC ACIDS

### *A.* Carboxylic Esters, $RCO_2R'$

While the formulas of the esters resemble those of the salts, $RCO_2M$, their properties are radically different. In general they are volatile non-ionized sweet-smelling liquids which are insoluble in water but soluble in organic liquids. They are good solvents for a variety of materials including lacquers.

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Boiling Points of Typical Esters, °C.

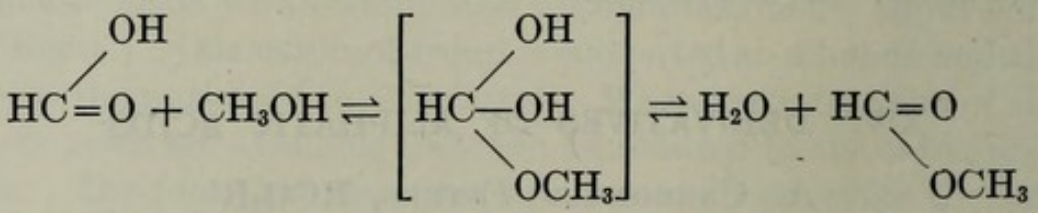
| *n*-alkyls | Formates | Acetates | Propionates | *n*-Butyrates | *n*-Valerates | *n*-Caproates | *n*-Heptoates | *n*-Octoates |
|---|---|---|---|---|---|---|---|---|
| Methyl | 32 | 57 | 80 | 102 | 127 | 149 | 172 | 193 |
| Ethyl | 54 | 77 | 99 | 121 | 145 | 167 | 187 | 206 |
| Propyl | 81 | 102 | 123 | 143 | 167 | 185 | 206 | 225 |
| Butyl | 107 | 126 | 145 | 164 | 186 | 204 | 225 | 240 |
| Amyl | 130 | 148 | | 185 | 204 | 222 | | |
| Hexyl | 154 | 169 | | 205 | 224 | | | |
| Heptyl | 177 | 191 | 208 | 225 | 244 | 259 | 274 | 289 |
| Octyl | 198 | 210 | 226 | 244 | 260 | 268 | 290 | 306 |

**Formates** are readily prepared by refluxing formic acid with primary or secondary alcohols. Tertiary alcohols are dehydrated.

$$HCO_2H + CH_3OH \rightleftharpoons HCO_2CH_3 + H_2O$$

The reaction is reversible and consequently reaches a condition of equilibrium if none of the products is allowed to escape. Because of its low boiling point (32°), the methyl formate is easily distilled out of the mixture as rapidly as formed. Hydrogen ions catalyze both the esterification and the hydrolysis reactions. Since formic acid is a relatively strong acid no other catalyst need be added.

The reaction takes place through an addition to the carbonyl group (Henry; Rep. 1910, 66).



Thus esterification and hydrolysis proceed through the same intermediate (p. 128). The reaction can be forced in either direction by taking advantage of the Mass Action Law and increasing or decreasing the concentrations in a suitable way.

Much study has been devoted to the mechanism of the forma-

tion and hydrolysis of esters under the influence of catalysts (Hückel 1930, Ingold 1932).

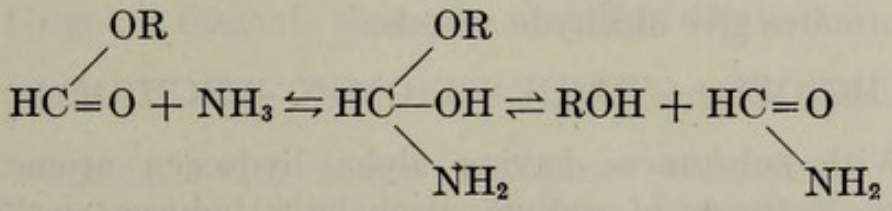
When the hydrolysis of the ester is assisted by the presence of a base and the ester is completely converted to a salt, the process is called *saponification* because it is the process used for soap making. The term saponification is incorrectly used as synonymous with the term hydrolysis.

Ethyl formate is made in a similar way but cannot be distilled from the mixture because its boiling point is too near that of ethanol.

*Reactions.* 1. Hydrolysis and saponification. In addition to the usual methods involving acid and basic reagents, esters can be split in neutral ether solution by $MgI_2$ (Rep. 1916, 82).

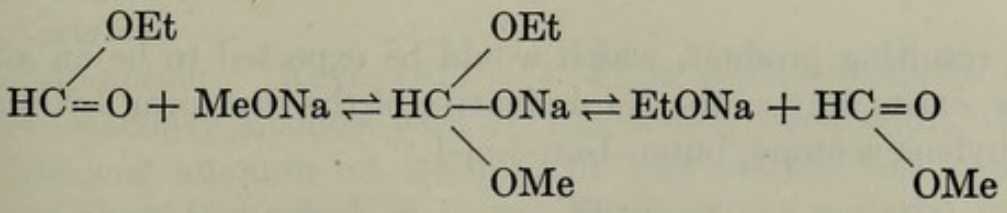
$$RCO_2R' + MgI_2 \rightarrow RCO_2MgI + R'I$$

2. Ammonolysis resembles hydrolysis



With higher esters this process may become very slow. Thus ethyl isobutyrate reacts at room temperature only after about eight weeks (Hurd).

3. Alcoholysis. (Rep. 1917, 73; 1921, 63–4.) The ester of one alcohol can be transformed into that of another alcohol by refluxing with an excess of the second alcohol in the presence of a trace of a catalyst such as an alcoholate or an acid.



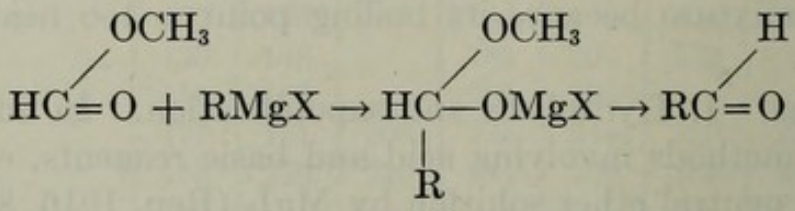
$$MeONa + EtOH \rightleftharpoons EtONa + MeOH$$

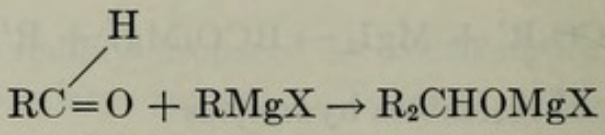
This change can be produced even with a trace of NaOH as catalyst. In general it is easier to replace a higher alcohol by a lower one (Bellet 1932). This reaction is valuable in cases

where ordinary hydrolysis or saponification would give undesirable side reactions. Thus $MeCHClCH_2OAc$ on refluxing with an excess of MeOH gives MeOAc and $MeCHClCH_2OH$ whereas treatment with water or bases would have involved the chlorine atom as well as the acetate group.

4. Other carbonyl reactions.

(*a*) With Grignard reagents, formic esters give aldehydes and secondary alcohols depending on the conditions used.

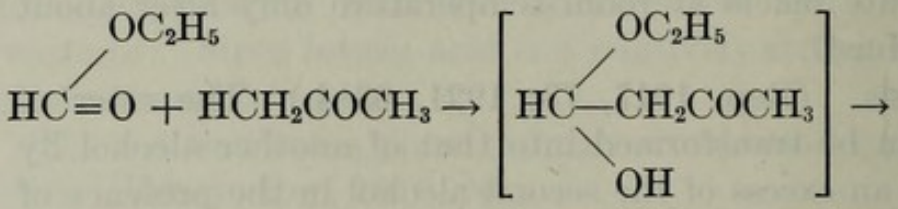




Orthoformates give aldehyde acetals.

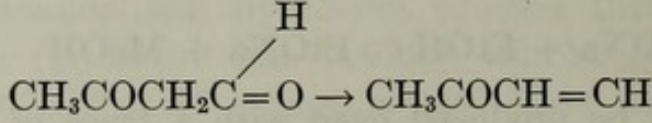
$$HC(OEt)_3 + RMgX \rightarrow EtOMgX + RCH(OEt)_2$$

(*b*) With substances having alpha hydrogen atoms. The presence of traces of sodium alcoholates induces an "aldol" condensation



$$[HCOCH_2COCH_3]$$

The resulting product, which would be expected to be an aldehyde, exists only as the Na derivative of the *enol* form, hydroxymethylene acetone, buten-1-on-3-ol-1.



On liberation from the Na compound, the product undergoes condensation to triacetylbenzene.

Similarly,

$$HCO_2Et + CH_3CO_2Et \rightarrow NaOCH{=}CHCO_2Et$$
$$HCO_2Et + CH_2(CO_2Et)_2 \rightarrow NaOCH{=}C(CO_2Et)_2$$

The resulting products behave as salts of fairly strong acids.

**Orthoformates,** $HC(OR)_3$, are made from chloroform, ROH and Na.

The hydrolysis of *ethyl orthoformate* has been studied in relation to catalysts (Harned 1932). The effective catalyst is the hydronium ion, $(H_3O)^+$. The hydrolysis is less rapid than that of ordinary formates. This is probably because the grouping $C{=}O$ is much more reactive with hydrogen ions than the grouping $C{-}O{-}C$.

Orthoformates react with carbonyl compounds to give acetals.

$$R_2CO + HC(OEt)_3 \rightarrow R_2C(OEt)_2 + HCO_2Et$$

With Grignard reagents they give acetals of aldehydes.

$$RMgX + HC(OEt)_3 \rightarrow RCH(OEt)_2 + EtOMgX$$

They condense with active methylene compounds to give $EtOCH{=}CQ_2$ in which the Q groups are combinations of $CH_3CO$, CN, $CO_2R$, etc.

$HC(OMe)_3$, b. 102°; $HC(OEt)_3$, b. 145°. Orthoformic esters of Pr, isoPr, Bu, isoBu and isoAm have been made (Sah 1932).

**Ortho esters** of higher acids can be made from the imido ethers obtained from the nitriles, HCl and EtOH.

$$RC(OEt){=}NH.HCl + 2\ EtOH \rightarrow RC(OEt)_3 + NH_4Cl$$

**Acetates.**

*Preparation.* (Keyes 1932.) 1. From acetic acid and primary and secondary alcohols with HCl or $H_2SO_4$ as catalyst. When equivalent amounts of acetic acid and ethanol are used an equilibrium is reached when two-thirds of the material is converted to ester and water. Thus the intermediate $MeC(OH)_2OEt$ tends to lose $H_2O$ rather than EtOH.

The per cent esterification of acetic acid by various alcohols in one hour at 155° is as follows: Me, 56; Et, 47; Bu, 47; Octyl, 47;

isoPr, 26; MeHexCHOH, 21; $Et_2CHOH$, 17, *t*-But, 1.4; *t*-Am, 0.8. It is not safe to assume from these results that all alcohols can be separated into their three classes by the difference in their speeds of esterification. In the higher alcohols, branching of the carbon chain has a profound effect.

2. Commercially, ethyl acetate is made from 10% acetic acid (quick "vinegar" process) and 50% alcohol ("high wines") by a distillation process. A ternary mixture of ethyl acetate, water and ethyl alcohol distills first. This is diluted with water to give two layers, nearly pure ethyl acetate and dilute alcohol. The latter is returned to the process. The "bottoms" are practically pure water and are discarded.

3. Acetic acid and ethanol passed over a silica gel catalyst at 150° give an equilibrium mixture containing 85% ethyl acetate (Reid 1931).

4. Still another commercial process for ethyl acetate is the dismutation of acetaldehyde by catalysts such as Al ethylate and its compounds with $AlCl_3$ and $HgCl_2$ (Rep. 1925, 72).

$$2\ MeCHO \rightarrow MeCO-OCH_2Me$$

Similarly ethanol with a dehydrogenating catalyst gives ethyl acetate (Greenawalt 1932).

5. Acetates of some secondary alcohols are made by adding olefins from cracked gases to acetic acid in the presence of sulfuric acid.

$$CH_3CO_2H + CH_3CH=CHCH_3 \rightarrow CH_3CO_2CH(CH_3)CH_2CH_3$$

6. Higher acetates may be made from acetyl chloride or acetic anhydride.

Acetic anhydride is used for making cellulose acetate for non-explosive photographic film and for artificial silk (Celanese).

Ketene, $CH_2=C=O$, acts as an anhydride of acetic acid and forms *acetates with alcohols.*

These methods ordinarily fail with tertiary alcohols, the products being tertiary chlorides and olefins respectively. In the presence of pyridine to combine with the liberated acid, tertiary acetates are obtained (Norris).

7. In extreme cases, acetates are sometimes prepared from

silver acetate and alkyl halides, preferably the iodides. This reaction is practically limited to halides of Class 1 (p. 71).

$$MeCO_2Ag + RI \rightarrow AgI + MeCO_2R$$

The use of thallous salts in place of the silver salts is recommended (Rep. 1926, 99).

*Reactions.* The esters of acetic acid give the same reactions as the corresponding formates. In addition, an acetate can act as both components in an aldol condensation (Claisen).

$$MeC(=O)OR + HCH_2CO_2R \xrightarrow[\text{NaOR}]{\text{Trace}} MeC(OH)(OR)CH_2CO_2R \rightarrow$$

$$ROH + \underset{\text{Keto form}}{MeCOCH_2CO_2R} \xrightarrow{Na} MeC(ONa)=CHCO_2R$$

Much work has been done on the mechanism of this condensation but the above conception seems as good as any (Rep. 1927, 90–92; Scheibler 1932; Adickes 1932; McElvain 1932–). The reaction is carried out by treating purified ethyl acetate with clean sodium. If the ethyl acetate has been purified to the point at which it contains no ethyl alcohol, a trace has to be added to start the reaction (Nef). Ethyl acetate will react similarly with other alpha hydrogen compounds. For instance, acetone gives acetyl acetone, $MeCOCH_2COMe$.

With higher esters, only the $\alpha$—H atoms take part in the Claisen reaction. Thus propionic ester gives $EtCOCHMeCO_2Et$.

Butyl and amyl acetates are of the utmost importance as lacquer solvents. "Pentacetate" is a mixture of amyl acetates (Sharples). Esters of secondary as well as primary alcohols are used (Park 1930).

**Esters of higher acids** may be made like those of acetic acid. With less reactive acids such as stearic, good yields are obtained by heating with an excess of alcohol and a little sulfuric acid and aluminum sulfate at 100°. Studies on the speed of esterification of acids of the types, $RCH_2CO_2H$, $R_2CHCO_2H$ and

$R_3CCO_2H$, show that the velocity decreases with the complexity of the acid (Menschutkin). The per cent esterification of isobutyl alcohol by various acids in one hour at 155° follows: formic, 62; acetic, 44; caprylic, 31; isobutyric, 29; $Bu_2$-acetic, 3; $Me_3$-acetic, 8; $Me_2Et$-acetic, 3; $Et_3$-acetic, 1.4; dineopentylacetic, 1.4; Me-*t*-Bu-neopentylacetic, 0.8. It is not correct to assume that the primary, secondary or tertiary nature of a complex acid can be determined with certainty by its speed of esterification. This is possible only in comparing acids of the same molecular weight.

In case the acid is to be synthesized through the *cyanide*, the latter can be *changed directly to the ester by alcoholysis* instead of being hydrolyzed to the acid and then esterified.

$$RCN + EtOH + H_2O + H_2SO_4 \rightarrow RCO_2Et + NH_4HSO_4$$

This reaction is important in making malonic ester, the steps being

$$\begin{array}{l} CH_2Cl \\ | \\ CO_2Na \end{array} \xrightarrow{NaCN} \begin{array}{l} CH_2CN \\ | \\ CO_2Na \end{array} \xrightarrow[H_2SO_4]{EtOH} CH_2(CO_2Et)_2$$

It is also used in making ethyl lactate and ethyl $\alpha$-hydroxyisobutyrate as solvents from the cyanohydrins of acetaldehyde and acetone respectively. Thus these esters are cheaper than the corresponding acids.

Methyl esters of expensive acids are available by the action of diazomethane (poison).

$$RCO_2H + CH_2N_2 \rightarrow N_2 + RCO_2CH_3$$

A cheaper but less effective reagent is $Me_2SO_4$ (poison) (Rep. 1904, 85).

*Esters of higher acids are reduced to the corresponding higher alcohols* by sodium and absolute alcohol (Bouveault and Blanc). Thus ethyl laurate gives lauryl alcohol.

$$RCO_2Et + 4\,Na + 2\,EtOH \rightarrow RCH_2ONa + 3\,EtONa$$

A modification of this process involves the addition of sodium

and acetic acid to an ether solution of the ester in contact with sodium acetate solution (Rep. 1924, 63).

Reduction of esters by sodium has become less important since the development of Cu—Cr oxide catalysts for direct hydrogenation (Folkers 1932).

*Sodium acts with esters* in ether solution to give *acyloins.* The first step is like that in the formation of a pinacol from a ketone and a metal. A free radical (having the odd electron due to the Na atom) is formed and then gives a dimolecular product.

$$2\,\mathrm{RCO(OEt)} + 2\,\mathrm{Na} \rightarrow 2\,\mathrm{RC(ONa)(OEt)} \rightarrow \begin{matrix}\mathrm{RC(ONa)(OEt)}\\ |\\ \mathrm{RC(ONa)(OEt)}\end{matrix} \rightarrow$$

$$2\,\mathrm{NaOEt} + \begin{matrix}\mathrm{RCO}\\ |\\ \mathrm{RCO}\end{matrix} \xrightarrow{2\,\mathrm{Na}} \begin{matrix}\mathrm{RCONa}\\ \|\\ \mathrm{RCONa}\end{matrix} \xrightarrow{\text{acid}} \begin{matrix}\mathrm{RCOH}\\ \|\\ \mathrm{RCOH}\end{matrix} \rightarrow \begin{matrix}\mathrm{RCO}\\ |\\ \mathrm{RCHOH}\end{matrix}$$

The disodium derivatives formed by the 1,4-addition of Na to the diketone can be obtained and changed to a diacetate. The free enediol is unstable and ketonizes to the acyloin at once.

**Esters of halogenated acids.**

*Preparation.* 1. Chlorination or bromination of the esters in sunlight to give alpha substitution.

2. Esterification of the halogen acids. This is easier than with the unsubstituted acids because the halogen increases the strength of the acids.

3. Treatment with absolute alcohol of the alpha halogen acyl halides prepared from the dry acids, bromine and phosphorus (Hell-Volhard-Zelinsky).

4. Iodo esters from the chloro esters and sodium iodide in alcohol.

*Reactions.* 1. The usual reactions of the corresponding acids except that the ester grouping prevents lactone formation except under conditions which would hydrolyze the ester.

2. Alpha halogen esters react with ketones and esters in the presence of zinc by a reaction resembling the Grignard reaction except that the intermediate organic zinc compound has never

been prepared (Reformatzky).

$$RR'CO + BrCH_2CO_2C_2H_5 + Zn \rightarrow RR'C(OH)CH_2CO_2C_2H_5$$

Esters such as ethyl oxalate and ethyl acetate will supply the reactive carbonyl group as well as the ketones originally used. Oxalic ester and bromoacetic ester give oxaloacetic ester,

$$EtO_2CCOCH_2CO_2Et.$$

The esters may also be of the types

$$RCHBrCO_2Et \text{ and } RR'CBrCO_2Et.$$

Thus $\alpha$-bromoisobutyric ester and acetoacetic ester react to give hydroxytrimethylglutaric acid.

$$Me_2CBrCO_2Et + MeCOCH_2CO_2Et \rightarrow EtO_2CC(Me_2)C(OH)(Me)CH_2COEt$$

Esters of higher acids and higher alcohols are *waxes*. These occur widely distributed in nature both in animal and vegetable products. Spermaceti contains the palmitates of cetyl ($C_{16}$) and octadecyl alcohols. Wool fat contains esters of carnaubyl alcohol ($C_{24}$). Carnauba wax and beeswax contain myricyl ($C_{30}$) cerotate ($C_{26}$) and palmitate. Chinese wax is largely ceryl cerotate. Artificial waxes have been made from a variety of higher alcohols and acids (Rep. 1926, 102). The oil of the "castor oil fish" consists mainly of liquid waxes, esters of cetyl and oleyl alcohols with oleic and hydroxyoleic acid (Cox 1932).

Vinyl esters, $RCO_2CH=CH_2$, are obtained by heating an ethylene dihalide with the corresponding sodium salt under pressure. A better method is the addition of an acid to acetylene in presence of a Hg catalyst (EP 679). The ethylidene diester is also formed. Vinyl acetate is an important intermediate for Vinylite resins.

Many esters are used in perfumes (Bogert).

Hydroxyacids give esters of various kinds. The internal esters from $\gamma$- and $\delta$-hydroxy acids are lactones. The product of two molecules of an $\alpha$-hydroxy acid is a *lactide*. When the hydroxyl and carboxyl are farther separated the product consists of cyclic or linear esters of high molecular weight. The smaller

molecules can be removed by means of a molecular still. The polymerization of these esters is reversible (Carothers 1932).

Esters of unsaturated acids are valuable in reactions in which it is desirable to mask the carboxyl group. Thus $\alpha\beta$-unsaturated esters react with esters having active methylene groups in the presence of sodium ethylate (Michael) (Rep. 1922, 71). The net result is the addition of the active ester to the double bond with H in the alpha position. Probably the reaction consists in the 1,4-addition of the sodium derivative to the conjugated system in the unsaturated ester.

$$RCH{=}CHCO_2Et + Na[CH(Q)CO_2Et] \rightarrow$$
$$RCH(CHQCO_2Et)CH{=}C(ONa)OEt \rightarrow$$
$$RCH(CHQCO_2Et)CH_2CO_2Et$$

Q may be $CH_3CO-$, CN, $CO_2Et$, etc.

$\alpha\beta$-Unsaturated esters add $NH_3$ and HCN similarly.

### *B.* Acid Halides

An acid halide, either organic or inorganic, is derived from an acid by replacing the "OH groups" in the acid by halogens. The halogen atoms do not ionize but are readily removed by hydrolysis.

| Acid | Acid Chloride |
|---|---|
| $H_3PO_3$ | $PCl_3$ |
| $H_3PO_4$ | $POCl_3$ |
| $[H_5PO_5]$ | $PCl_5$ |
| $H_2SO_4$ | $SO_2Cl_2$ |
| $H_2SO_3$ | $SOCl_2$ |
| $H_2CO_3$ | $COCl_2$ |
| $HNO_2$ | NOCl |

The hydrolysis of an acid chloride differs from that of a chloride salt of a weak base in that it is not reversed by HCl. Thus

$$POCl_3 + 3\ H_2O \rightarrow H_3PO_4 + 3\ HCl$$
$$AlCl_3 + 3\ H_2O \rightleftharpoons Al(OH)_3 + 3\ HCl$$

Organic acid halides of the type $RC(=O)X$ are *acyl halides.*

*Preparation.* 1. An acid or its salt is treated with a suitable inorganic acid halide.

Inorganic acid halide + organic acid → Organic acid halide + inorganic acid (or its anhydride)

For acids which are at all costly, thionyl chloride is the best reagent.

$$RCO_2H + SOCl_2 \rightarrow HCl + SO_2 + RCOCl$$

$PCl_3$, the most commonly used reagent, does not react quantitatively according to the equation.

$$3\ CH_3CO_2H + PCl_3 \rightarrow H_3PO_3 + 3\ CH_3COCl$$

Much HCl is evolved due to side reactions (Brooks 1912). A better yield is obtained from $PCl_3$ and a mixture of the acid and its anhydride.

2. The chlorination of aldehydes in the absence of water, catalysts and sunlight gives acyl chlorides.

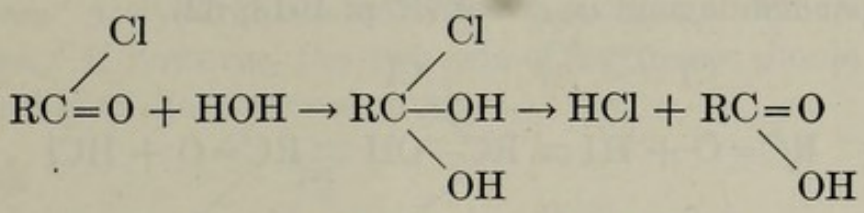
$$CH_3C(H)=O + Cl_2 \rightarrow CH_3C(Cl)=O + HCl$$

*Reactions.* 1. Acyl halides react readily and completely with all "active hydrogen compounds," that is, those in which the H is attached to an element other than carbon.

*a.* Water reacts instantly to give HX and the organic acid. This instantaneous reaction between water and a non-ionized halide is surprising and in sharp contrast to the general inactivity of alkyl halides with water even on heating. The most reasonable explanation of this reactivity is that it does not involve metathesis but a primary addition to the reactive carbonyl group. Thus reactions which cannot take place in this way are not rapid. An example is the action with AgCN to give RCOCN

$$RCOCl + HOH \rightarrow HCl + RCO_2H \quad \text{rapid}$$
$$RCOCl + AgCN \rightarrow AgCl + RCOCN \quad \text{slow}$$

The rapid reaction probably goes through the steps:



*b*. Ammonia gives acid amides, $RCONH_2$, by a similar mechanism.

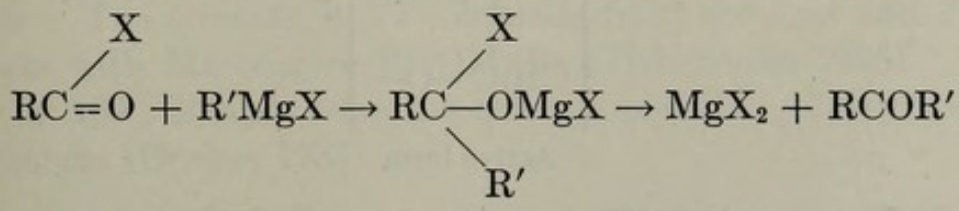
*c*. Primary and secondary alcohols give esters, $RCO_2R'$. When a tertiary alcohol is treated with acid chlorides without any precaution, the chief product is a tertiary chloride. That this is due to the ready action of HCl with tertiary alcohols and their esters is shown by the formation of the tertiary ester from the alcohol and acyl halide in presence of a basic substance like pyridine or dimethylaniline which can combine with the HX as rapidly as it is formed.

2. With sodium salts of organic acids they yield anhydrides.

$$CH_3COCl + CH_3CO_2Na \rightarrow NaCl + (CH_3CO)_2O$$

3. With silver cyanide, mercurous cyanide or cuprous cyanide, they give acyl cyanides, RCOCN which can be hydrolyzed to alpha keto acids, $RCOCO_2H$.

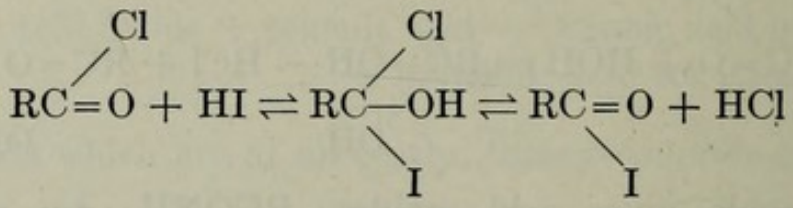
4. With Grignard reagents they give ketones and then tertiary alcohols. Earlier, a similar result was achieved with organic zinc compounds. In the latter case the reaction does not go beyond the ketone, if propyl or higher compounds of zinc are used. These reactions have been ordinarily regarded as purely metathetical in the step which gives the ketone. The reaction is probably an ordinary carbonyl addition.



5. Acyl halides may be reduced to aldehydes with $H_2$ and a palladium catalyst (Rosenmund 1922). Palladium is considerably cheaper than platinum. Again, the reaction probably proceeds through the carbonyl group.

6. Acyl halides react with other halide acids. For instance one

acid halide can be converted to a different one by passing through the proper halide acid *in excess* (Rep. 1913, 62).



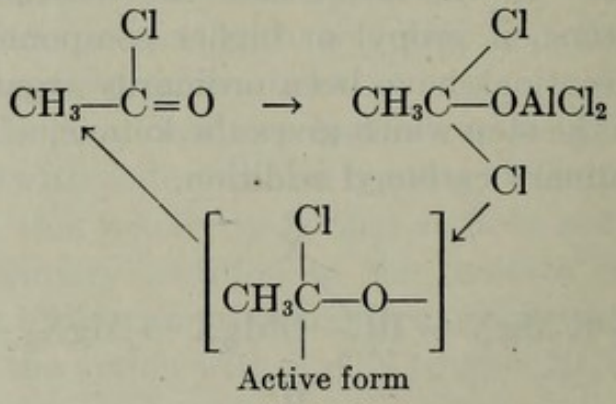
The reaction can be run to completion in either direction.

7. Acyl halides react with aromatic hydrocarbons and some of their derivatives in the presence of equimolar amounts of anhydrous aluminum chloride to give mixed aliphatic-aromatic ketones (Friedel and Crafts). For instance:

$$CH_3COCl + C_6H_6 \xrightarrow{AlCl_3} CH_3COC_6H_5 + HCl$$

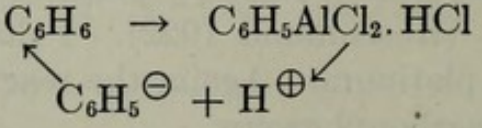
Methyl phenyl ketone

The mechanism of such processes has never been worked out. Definite compounds are known between all of the materials involved in the reaction, $RCOCl(AlCl_3)_n$, $RCOAr(AlCl_3)_m$, $ArH\text{-}(AlCl_3)_p$. The function of these compounds in the reaction is not known except that if the compound with the final product is more stable than those with the initial substances as in this case, molar amounts of aluminum chloride must be used. It may be that the aluminum chloride "activates" the carbonyl group of the acid chloride.

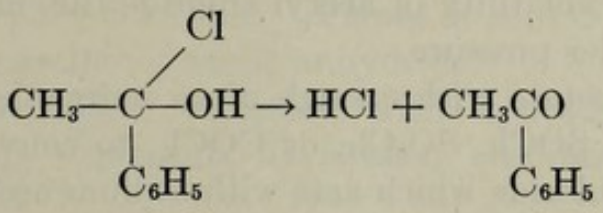


Active form

In a similar way the $AlCl_3$ may "activate" the benzene.



In each case the decomposition of the aluminum chloride complexes gives "active fragments" which can change to the original substances. If however, the two sets of fragments should unite, they would give the observed product.



In most catalytic reactions, it is necessary to *assume* the formation of intermediate unstable addition compounds. In the Friedel and Crafts reaction such compounds can be proved to exist.

8. Surprisingly, acyl halides do not react with metals like Na nor with MgI ($MgI_2$ + Mg, Gomberg).

**Formyl chloride,** HCOCl, is unknown. A mixture of HCl and CO acts with aromatic hydrocarbons as formyl chloride.

$$C_6H_6 + CO + HCl \xrightarrow{AlCl_3} C_6H_5CHO + HCl$$

**Acetyl chloride,** $CH_3COCl$, b. 50.9°, is a very important acetylating agent for converting $-OH$, $-NH_2$, and $=NH$ compounds to their acetyl derivatives. Commercially it is prepared from sodium acetate and a mixture of $SO_2$ and $Cl_2$. If ketene ever becomes cheap enough it can be used with HCl gas to give acetyl chloride

$$CH_2=C=O+HCl \rightarrow CH_2=C(OH)Cl \rightarrow CH_3COCl$$

**Acetyl fluoride,** b. 20°, is made from the chloride and zinc fluoride. The *bromide,* b. 77°, is made from the acid and $PBr_3$. It reacts with Mg to give RCOMgBr (Tishchenko 1925). The *iodide,* b. 108°, is made from the chloride and HI. Acetyl iodide splits ethers (Gustus 1933).

$$ROR + CH_3COI \rightarrow RI + CH_3CO_2R$$

The boiling points of the *n*-acid chlorides from $C_3$ to $C_7$ are (°C.), 80, 102, 128, 153, 175.

### *C.* Acid Anhydrides

**Formic anhydride,** $(HCO)_2O$, is unknown.

**Acetic anhydride,** $(CH_3CO)_2O$, b. 139°.

*Preparation.* 1. Acetyl chloride heated with sodium acetate. Because of the volatility of acetyl chloride this method must be carried out under pressure.

2. Sodium acetate with enough of an inorganic acid chloride, such as $POCl_3$, $SOCl_2$, $SO_2Cl_2$, or $COCl_2$, to convert half of the salt to acetyl chloride which acts with sodium acetate as rapidly as formed. Sulfur monochloride, $S_2Cl_2$, is used commercially (Rep. 1909, 79).

3. Heating acetaldehyde diacetate obtained from acetylene and acetic acid.

$$HC{\equiv}CH \rightarrow \underset{\text{vinyl acetate}}{CH_3C(=O)-OCH=CH_2} \rightarrow \underset{\text{acetaldehyde diacetate}}{(CH_3CO_2)_2CHCH_3} \rightarrow (CH_3CO)_2O + CH_3CHO$$

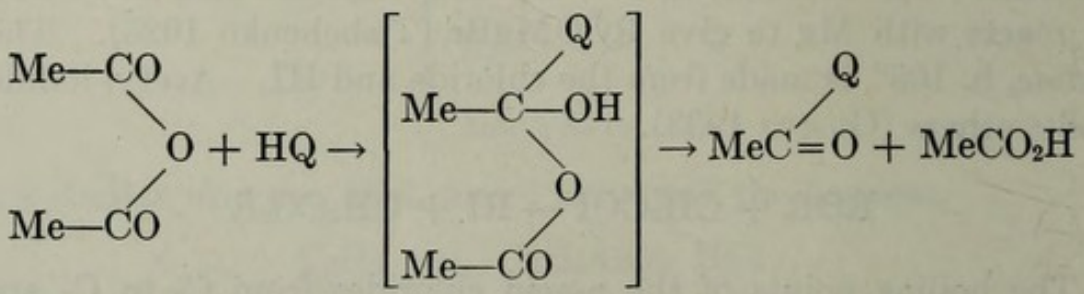
4. Ketene and acetic acid

$$CH_2=C=O + CH_3CO_2H \rightarrow (CH_3CO)_2O$$

With other acids mixed anhydrides, RCO−O−COMe, are obtained (Hurd 1932). When distilled, these form the simple anhydrides, $(MeCO)_2O$ and $(RCO)_2O$.

5. Acetic acid heated with various catalysts.

*Reactions.* Acetic anhydride resembles acetyl chloride in its reactions. With any active hydrogen compound, HQ, it forms a molecule of acid and an acid derivative, $CH_3C(=O)Q$. The initial step involves the usual addition compound.

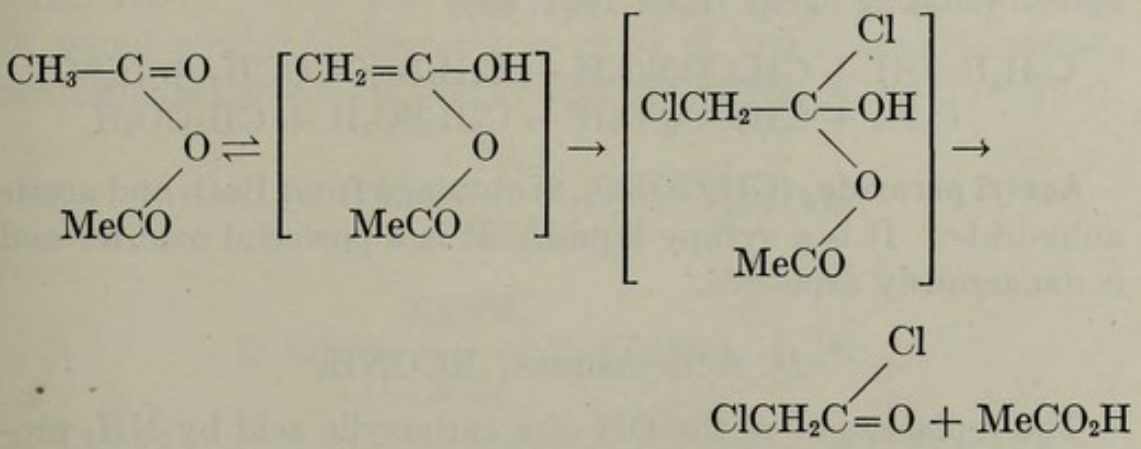


In this way it acts with (1) water, (2) halide acids, (3) ammonia,

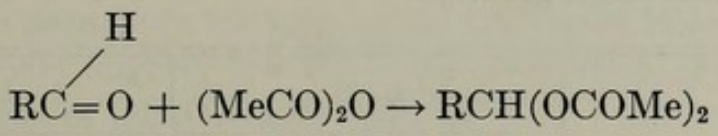
(4) amino compounds, (5) imino compounds, $-NH-$, (6) hydroxyl compounds. Acetic anhydride is the most important *acetylating agent* both for laboratory and commercial use. The largest amount of it is used in acetylating cotton for use in photographic film and artificial silk. A trace of sulfuric acid catalyzes the acetylating action of acetic anhydride.

Sometimes it reacts violently with hydroxyl compounds. Thus dangerous explosions have been obtained with it and ethylene glycol.

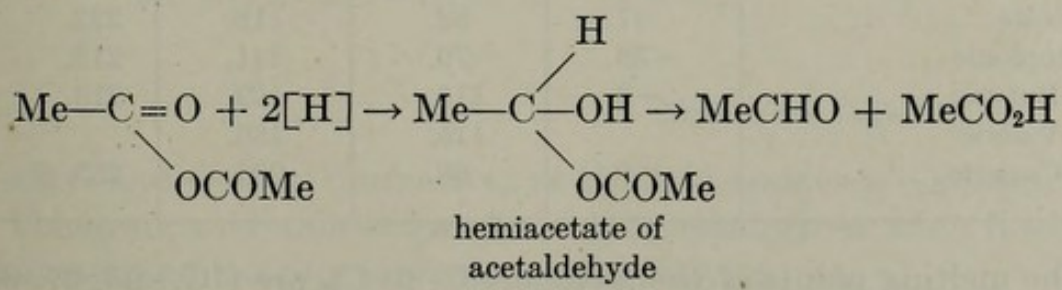
Chlorine reacts with acetic anhydride to give chloroacetyl chloride (Rep. 1923, 68).



Acetic anhydride reacts with aldehydes to give their diacetates.



Although sodium amalgam will not reduce acids, it reduces anhydrides to aldehydes and alcohols.



hemiacetate of acetaldehyde

Because of its ability to combine with water, acetic anhydride is much used as a dehydrating reagent, for example in the Perkin reaction.

**Higher anhydrides** may be obtained by the same methods and also by treating the acid or its salt with acetyl chloride or acetic anhydride in the presence of a catalytic trace of $H_2SO_4$. The reactions of the higher anhydrides are like those of acetic anhydride but are progressively slower as the molecular weight increases. Propionic anhydride is used in making *cellulose propionate* which is rapidly becoming commercially important.

Mixed organic and inorganic anhydrides are known.

**Acetyl nitrate,** $CH_3CO(ONO_2)$, is a powerful nitrating agent. It is dangerously explosive.

**Acetyl sulfuric acid,** $CH_3CO-OSO_3H$, is both an acetylating and sulfonating agent (Rep. 1921, 63).

$$C_6H_2Br_3OH + CH_3CO_2SO_3H \rightarrow C_6H_2Br_3OCOCH_3 + H_2SO_4$$
$$C_6H_6 + CH_3CO_2SO_3H \rightarrow C_6H_5SO_3H + CH_3CO_2H$$

**Acetyl peroxide,** $(CH_3CO)_2O_2$, is obtained from $BaO_2$ and acetic anhydride. It is a syrupy liquid. It is a powerful oxidizer and is dangerously explosive.

### *D.* Acid Amides, $RCONH_2$

The replacement of the OH of a carboxylic acid by $NH_2$ produces a surprising change in properties. The melting and boiling points are increased greatly.

| | m. °C. | | b. °C. | |
|---|---|---|---|---|
| | Acid | Amide | Acid | Amide |
| Formic | 8. | 2.5 | 101. | 200. dec. |
| Acetic | 17. | 82. | 118. | 222. |
| Propionic | −36. | 79. | 141. | 213. |
| *n*-Butyric | −8. | 115. | 162. | 216. |
| *n*-Valeric | | 115. | 186. | |
| *n*-Caproic | +8. | 98. | 205. | 255. |

The melting points of the members $C_7$ to $C_{12}$ are (°C.) 95, 97, 99, 108, 103 and 110; the even members $C_{14}$ to $C_{20}$ are 102, 104, 109 and 108.

The $NH_2$ group has an entirely different effect when attached

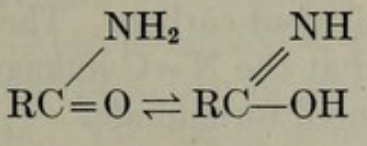
to acyl than when attached to alkyl. This can be seen from the boiling points of the $C_2$ compounds, ethanol 78°, ethyl amine 19°, acetic acid 118°, and acetamide 222°. In the first pair the boiling point is *lowered* and in the second *raised* by the substitution of $NH_2$ for OH. The replacement of the amino H atoms by methyl has the same effect as the replacement of the hydroxyl H in acetic acid. The boiling points of N-dimethyl acetamide and methyl acetate are 167° and 57°.

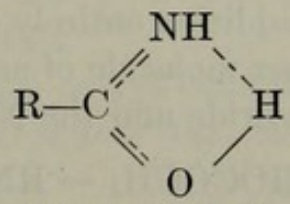
The basic properties of the nitrogen atom are practically neutralized by the "acid" properties of the acyl group, RCO. In glacial acetic acid, acid amides can be titrated with HCl (Hall 1930). They are also very weak acids (Branch 1928). In liquid ammonia they act as acids of the ammonia system, neutralizing the bases of that system, the metal amides (Franklin).

$$RCONH_2 \xrightarrow[HOAc]{HCl} RCONH_2.HCl$$

$$RCONH_2 \xrightarrow[NH_3]{NaNH_2} RCONHNa + NH_3$$

The amides react in tautomeric forms. The mesohydric form (Oddo) may cause the high melting and boiling points. The values of the parachors for formamide and acetamide have been found to be only slightly low for those calculated for one double bond in molecules $CH_3ON$ and $C_2H_5ON$





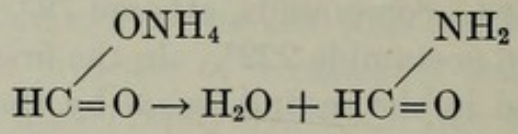
Mesohydric form

N-alkyl and O-alkyl derivatives of the acid amides are known.

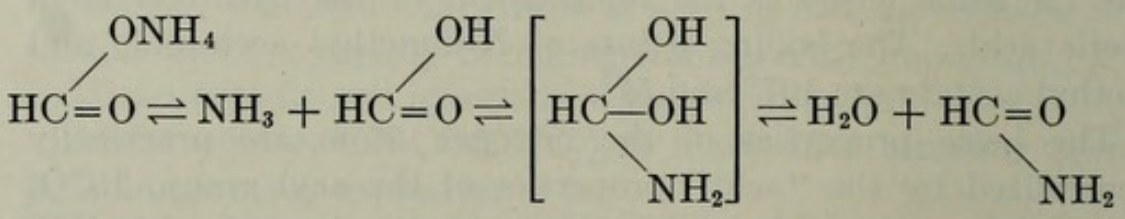
The lower acid amides are electrolytic conductors when fused. They are also ionizing solvents for electrolytes.

**Formamide,** HC=O, b. 200°.

*Preparation.* 1. Heating ammonium formate.

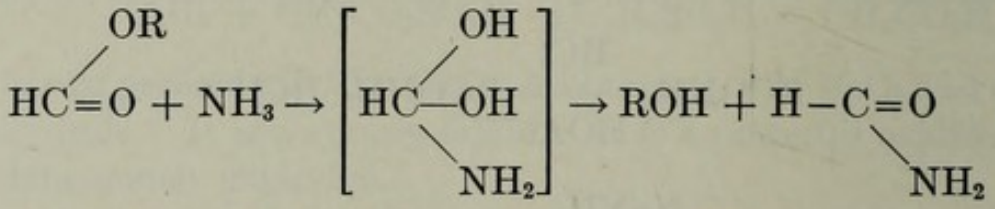


The equilibria involved are



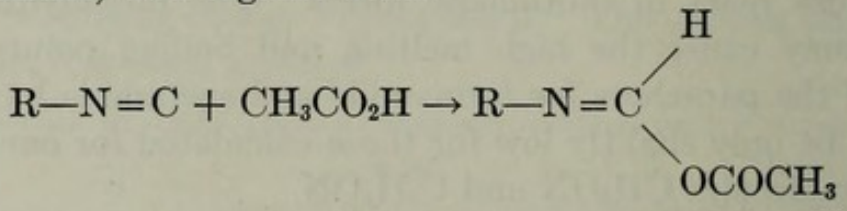
At the temperature used, the water is removed as steam and the process goes to completion.

2. Formic esters with ammonia.

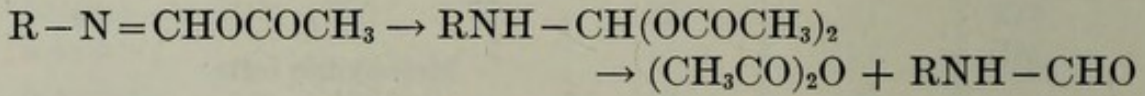


The methyl and ethyl esters react most rapidly.

3. N-Substituted formamides are obtained from isonitriles (carbylamines) and organic acids.

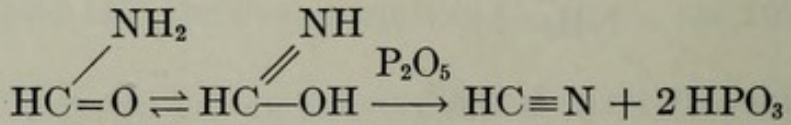


This is an addition entirely on the bivalent carbon. The product adds another molecule of acetic acid at the N=C linkage to give acetic anhydride and the N-substituted formamide.



*Reactions.* 1. Hydrolysis is the reverse of the first preparation.

2. Vigorous dehydrating agents like phosphorus pentoxide give hydrocyanic acid.



3. It dissolves mercuric oxide.

$$2\,HCONH_2 + HgO \rightarrow H_2O + (HCONH)_2Hg$$

There is good evidence that the Hg is attached to N in this compound.

4. It reacts with sodium giving a derivative of the "enol form"

$$HCONH_2 \rightleftharpoons HC(OH)=NH \rightarrow HC(ONa)=NH$$

5. With nitrous acid, the $NH_2$ is first replaced by OH and the formic acid is then oxidized. The net result is:

$$3\,HCONH_2 + 5\,HNO_2 \rightarrow 3\,CO_2 + 4\,N_2 + 7\,H_2O$$

6. Hypohalites or the calculated amount of halogen and base give an N-halogen amide, HCONHX. These react with water to give the amide and HOX. With excess base they give ammonia and a carbonate by the Hofmann rearrangement (1882).

With higher amides, $RCONH_2$, alkyl isocyanates, RNCO, and primary amines, $RNH_2$, are produced. In addition to its practical importance this reaction has been the incentive for many theoretical studies (Tiemann 1891, Stieglitz 1896, Manguin 1909, Jones 1913, Wallis 1931).

7. Unstable "salts" are formed with strong acids like HCl or $HNO_3$.

**Acetamide,** $CH_3CONH_2$, m. 82°, b. 222°.

*Preparation.* 1. Similarly to formamide, (a) from ammonium acetate, (b) from methyl or ethyl acetate.

2. From the action of ammonia with acetyl chloride or acetic anhydride. The use of primary or secondary amines in place of $NH_3$ gives N-substituted acetamides.

3. By the partial hydration of methyl cyanide by means of conc. $H_2SO_4$ or of alkaline hydrogen peroxide.

$$CH_3C{\equiv}N + H_2O \rightarrow CH_3C(OH)=NH \rightleftharpoons CH_3C(NH_2)=O$$

*Reactions.* 1. Similar to those of formamide except that (a) acetonitrile, $CH_3CN$, (b) acetic acid, and (c) methyl amine are

obtained by dehydration, by nitrous acid and by bromine and KOH (Hofmann).

2. With $PCl_5$ to give acetonitrile.

$$CH_3CONH_2 \rightarrow \underset{\text{Acetamido chloride}}{CH_3CCl_2NH_2} \rightarrow \underset{\text{Acetimido chloride}}{CH_3CCl{=}NH} \rightarrow CH_3CN$$

The intermediate chlorides are very unstable.

3. Nitrous acid forms $N_2$ and acetic acid. This reaction proceeds quantitatively even with highly branched compounds like $Me_3$-acetamide (Whitmore 1932).

**Diacetamide** and **triacetamide** are made from acetonitrile

$$CH_3CN + CH_3CO_2H \rightarrow (CH_3CO)_2NH, \text{ m. } 78°, \text{ b. } 223°$$
$$CH_3CN + (CH_3CO)_2O \rightarrow (CH_3CO)_3N, \text{ m. } 79°$$

Acetamide is finding wide uses because of its unusual solvent properties (Stafford 1933) (Niacet).

**N-Bromoacetamide** (acetbromoamide), is a brominating agent (Rep. 1922, 101).

$$C_6H_5NMe_2 + MeCONHBr \rightarrow BrC_6H_4NMe_2 + MeCONH_2$$

With silver carbonate or mercury alkyls or aryls, it gives methyl isocyanate, MeNCO, an intermediate in the Hofmann conversion of $RCONH_2$ to $RNH_2$.

**Higher acid amides** resemble acetamide in preparation and properties. Their preparation from esters becomes more difficult with increase in complexity. Thus ethyl isobutyrate and ammonium hydroxide react very slowly (Hurd 1932) and methyl trimethylacetate does not react at all (Rep. 1906, 107).

Acids above acetic when heated in a stream of dry $NH_3$ give good yields of amides (Mitchell 1931).

The most important reaction of acid amides is that with hypohalites (Hofmann). As has been seen, the product is a primary amine with one less carbon atom. With higher members, the amine may be oxidized by the hypohalite to the corresponding cyanide.

$$RCH_2NH_2 \rightarrow [RCH_2NX_2] \rightarrow RC{\equiv}N$$

It is important to note that while the Hofmann reaction involves the transfer of an organic group from carbon to nitrogen, it involves no rearrangement within the migrating group. Thus a neopentyl group migrates unchanged (Whitmore 1932) as does an optically active group (Wallis 1931, 1933).

Steps for converting stearic acid to the next lower acid, margaric acid, are:

$$C_{17}H_{35}CO_2H \rightarrow RCOCl \rightarrow RCONH_2 \rightarrow RNH_2 \rightarrow C_{16}H_{33}CN \rightarrow C_{16}H_{33}CO_2H$$

The Hofmann reaction with $\alpha$-halogen acid amides gives aldehydes or ketones

$$Me_2CBrCONH_2 + Br_2 + KOH \rightarrow Me_2C{=}O + KBr + K_2CO_3$$

A curious method of going down the series is the action of $\alpha$-bromo acid amides with bases to give aldehydes.

$$RCHBrCONH_2 + 2\,NaOH \rightarrow RCHO + NaBr + NaCN + 2\,H_2O$$

The crystalline character and definite melting points of the amides make them useful in *identifying* the related *acids.*

### *E.* Hydrazides, $RCONHNH_2$, and Azides, $RCON_3$

Hydrazine, $H_2N-NH_2$, reacts with esters and acid chlorides just as $NH_3$ does.

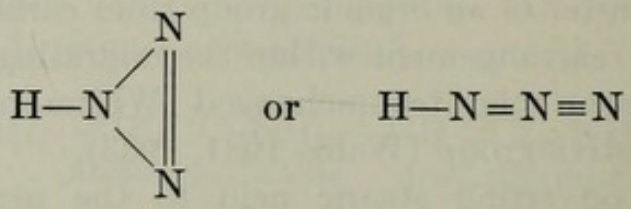
$$CH_3C(OCH_3){=}O + NH_2NH_2 \rightarrow \underset{\text{Acethydrazide}}{CH_3C(NHNH_2){=}O} + MeOH$$

The reactions of hydrazides are similar to those of the amides except that they (1) are more easily hydrolyzed, (2) have reducing properties, (3) have basic properties and form stable salts with strong acids, and (4) react with nitrous acid to give acid azides (Curtius 1917).

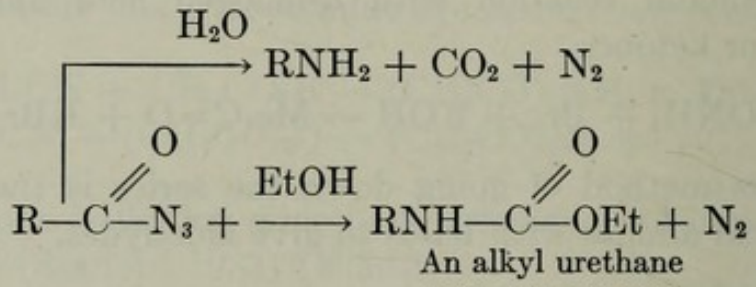
$$CH_3CONHNH_2 + HNO_2 \rightarrow 2\,H_2O + CH_3CON_3$$

The acid azides are acyl derivatives of hydrazoic acid, $HN_3$.

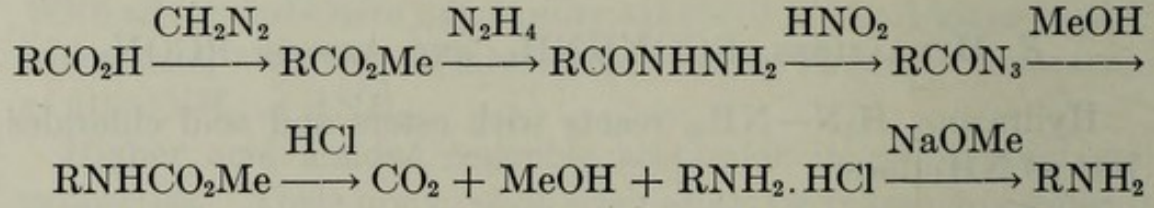
This acid can be "proved" to have either of two structures




Acid halides with sodium azide, $NaN_3$, give acid azides. On heating with water or alcohols, the acid azides undergo a rearrangement (Curtius) like the Hofmann rearrangement of acid amides with bromine and bases.

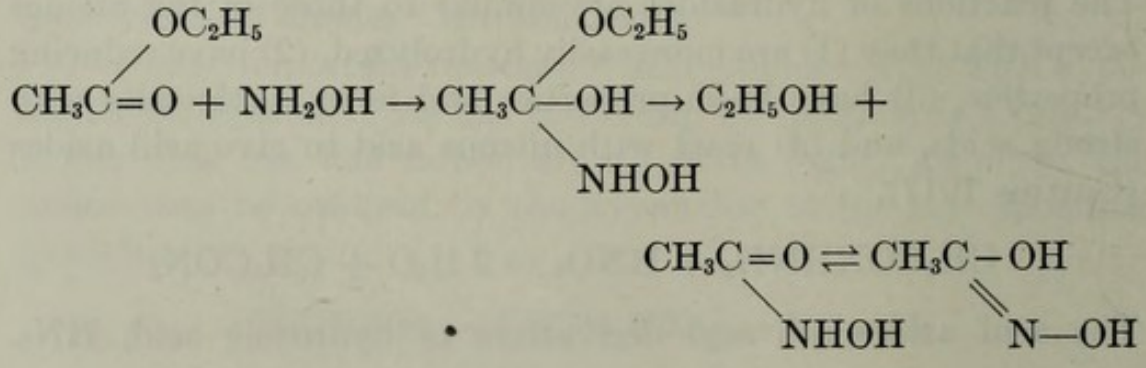



The series of changes, ester to hydrazide to azide to amine is valuable in going down the series with compounds which are sensitive to more violent reactions as in the polypeptides and proteins (Curtius, Rep. 1915, 83).




### *F.* Hydroxamic Acids

Hydroxylamine, $NH_2OH$, reacts with esters, acid chlorides, and acid amides.



A solution of sodium nitro hydroxylamine sulfonate obtained from sodium sulfite and nitrite solutions, converts aldehydes to hydroxamic acids (Angeli)

$$RCHO + NaO_3SNHOH \rightarrow RC(OH)=NOH + NaHSO_3$$

The hydroxamic acids give a distinctive red coloration with ferric chloride.

With strong acids they undergo a rearrangement (Lossen).

$$RC(OH)=NOH \rightleftharpoons RC(=O)-NHOH \rightarrow \left[RC(=O)-N\right] \rightarrow RNCO \rightarrow RNH_2$$

### *G.* Imino Ethers and Acid Amidines

The unstable acid imido chlorides, $RCCl=NH$, obtained from acid amides and $PCl_5$ or from nitriles and HCl, react readily with alcohols to give imino ethers $RC(OEt)=NH.HCl$. The best preparation is by passing dry HCl gas into a solution of nitrile in the anhydrous alcohol. The imino ethers are readily hydrolyzed to esters. With excess alcohol they give ortho esters. With $NH_3$ they give acid amidines (Rep. 1918, 71)

$$CH_3C(OC_2H_5)=NH.HCl + 2\,NH_3 \rightarrow CH_3C(NH_2)=NH + C_2H_5OH + NH_4Cl$$

Acetamidine

The free amidines are readily hydrolyzed to acid amides and decompose to nitriles. They are strong bases and their salts with strong acids are stable. They are not decomposed by nitrous acid.

### *H.* Thioacids

1. The introduction of one sulfur into a carboxyl group might be expected to give two different products.

$$R-C(SH)=O \quad \text{and} \quad R-C(OH)=S$$

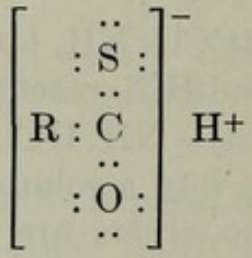
One of these would be called a *thiolic* acid and the other a *thionic*

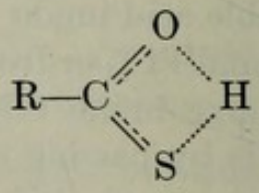
acid. As a matter of fact there is no evidence for the existence of such isomers. Several explanations might be given for this fact:

(1) The system $HS-\underset{|}{C}=O \rightleftharpoons S=\underset{|}{C}-OH$ is a typical tautomeric system.

(2) If it is true that sulfur cannot form part of a "double bond," the thiolic form, $HS-\underset{|}{C}=O$ would be the only one to exist.

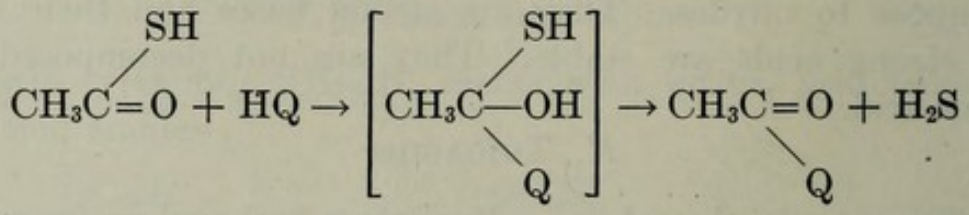
(3) Most probably there is no "double bond" in most of the molecules and the sulfur and oxygen occupy equivalent places in the ion. This may be a "tetragonal mesohydric nucleus" (Oddo 1932).





Thio acids are prepared (1) by treating the acid with a sulfide of phosphorus and (2) by reacting an acyl halide with NaSH.

**Thioacetic acid** is an unstable colorless, evil-smelling liquid boiling about 90°. It may be regarded as a "mixed anhydride" of acetic acid and $H_2S$. It gives the typical reactions of acetic anhydride with water, alcohols and ammonia, producing an acyl derivative and hydrogen sulfide.



This reaction is not appreciably reversible. Sodium thioacetate has been suggested for use in qualitative analysis. Acidification liberates $H_2S$ directly in the solution.

Thiol esters, RCO(SR′), are readily obtained from mercaptans, acid anhydrides and the corresponding salt (Reid). $CH_3COSH$, b. 93°.

2. Carboxyl derivatives having two sulfur atoms in place of the two oxygens are obtained from carbon disulfide and Grignard reagents (Rep. 1907, 99).

$$CH_3MgCl + CS_2 \rightarrow CH_3{-}C(SMgCl){=}S \rightarrow CH_3C(SH){=}S$$

Methyl carbithionic acid
Dithioacetic acid

The $-CS_2H$ group is more strongly acidic than the $-CO_2H$ group. The dithio acids are very sensitive to hydrolysis and oxidation.

## XV. POLYHYDRIC ALCOHOLS

### *A.* Glycols, Dihydric Alcohols

Usually an organic compound cannot have two hydroxyls on the same carbon. Occasionally this arrangement is stable as in the case of chloral hydrate, $Cl_3CCH(OH)_2$. In water solution the hydrated form of the carbonyl group probably exists in varying amounts. Aldehydes and ketones give derivatives of the dihydroxyl form, namely, hemiacetals, acetals, and diacetates.

$$=C{=}O + H_2O \rightleftharpoons =C(OH)_2, \qquad =C(OH)OR, \qquad =C(OR)_2, \qquad =C(OAc)_2.$$

The commonest glycols have the two hydroxyl groups on adjacent carbon atoms because of their easy preparation from olefins and by bimolecular reduction of carbonyl compounds.

1,4- and 1,5-glycols readily form inner ethers with 5- and 6-rings.

$\alpha\omega$-Glycols are obtained by reduction of esters of dibasic acids with Na and absolute alcohol.

The glycols are high boiling liquids ranging from 197°. The lower members are completely soluble in water and in organic solvents. They are heavier than water.

Ethylene glycol, "Glycol," ethandiol-1,2, $HOCH_2CH_2OH$, b. 197°. (EP 506–23.)

*Preparation.* 1. Aqueous ethylene chlorohydrin solution from

chlorine water and ethylene may be heated with sodium bicarbonate under slight pressure to produce the glycol.

$$ClCH_2CH_2OH + NaHCO_3 \rightarrow NaCl + HOCH_2CH_2OH + CO_2$$

The carbon dioxide is passed into NaOH to make bicarbonate for another batch. The aqueous glycol solution is concentrated by distillation.

2. The use of stronger bases and slightly different conditions will give ethylene oxide which distills out of the mixture (b. 12°). If it is kept in under pressure it reacts with water to give ethylene glycol which reacts with more ethylene oxide to give diethylene glycol and higher polyethylene glycols,

$$HOCH_2CH_2(OCH_2CH_2)_nOCH_2CH_2OH.$$

If the ethylene oxide is distilled from the mixture and heated with water and a trace of acid under pressure, ethylene glycol is formed smoothly.

*Reactions.* The reactions of ethylene glycol are essentially those of the primary alcohols except that they are complicated by the presence of two such groups and by the higher boiling points of glycol and its derivatives.

1. Oxidation probably yields all the theoretically possible products but these cannot be isolated in quantity because they are more readily oxidized than the glycol itself and are too high boiling to be removed readily from the sphere of oxidation.

The theoretical oxidation series from glycol would be:

| $CH_2OH$ | $CH_2OH$ | $CH_2OH$ | $CHO$ | $CO_2H$ | |
|---|---|---|---|---|---|
| $\rightarrow$ \| | $\rightarrow$ \| | $\rightarrow$ \| | $\rightarrow$ \| | $\rightarrow$ \| | $\rightarrow 2\,CO_2$ |
| $CH_2OH$ | $CHO$ | $CO_2H$ | $CO_2H$ | $CO_2H$ | |
| Ethylene glycol | Glycollic aldehyde | Glycollic acid | Glyoxylic acid | Oxalic acid | |

$$\begin{array}{l} \downarrow \\ CHO \\ | \\ CHO \end{array}$$

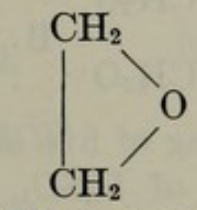
Glyoxal

Cold nitric acid oxidizes one of the alcohol groups giving glycollic acid. Heating the mixture gives oxalic acid.

2. With dehydrating agents to give acetaldehyde. This may be regarded as an ordinary dehydration to give the enol of acetaldehyde or as a rearrangement which is typical of the higher glycols.

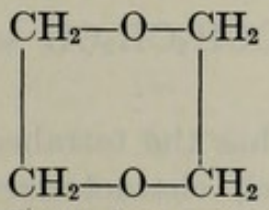
$$HOCH_2CH_2OH \rightarrow H_2O + CH_2{=}CHOH \rightarrow CH_3CHO$$

Heating alone at 500° gives the same change. The ethers which would be expected,



Ethylene oxide

and



Diethylene oxide (Dioxan) (EP554)

are both known but are not obtainable by direct dehydration of glycol. They are made from ethylene chlorohydrin.

3. Halide acids react readily with one hydroxyl giving a halohydrin.

$$HOCH_2CH_2OH + HX \rightarrow XCH_2CH_2OH$$

The resulting substance does not react readily with more HX.

4. Halides of phosphorus replace both hydroxyls. In the case of iodine, the resulting product tends to lose $I_2$ and give ethylene.

5. The alkali metals replace the alcohol H atoms. The mono sodium compound is formed readily but much less vigorously than with a monohydric alcohol. The disodium compound is only obtained by vigorous heating.

6. With organic acids to form mono- and di-esters. The former combine in the same molecule the solvent properties of a primary alcohol and an ester, $HOCH_2CH_2OCOR$. Acid anhydrides are used to advantage in making these esters. The reaction of ethylene glycol with acetic anhydride may be dangerously explosive.

With dibasic acids highly polymeric esters (M.W. about 3000) are obtained (Carothers 1929). Similar polymeric esters from dibasic acids and higher $\alpha\omega$-glycols (to $C_{10}$) have been made.

7. Nitric acid (with sulfuric acid) gives *glycol dinitrate*, $O_2NOCH_2CH_2ONO_2$, ("nitroglycol," which is valuable in dynamite to lower the otherwise relatively high freezing point of the nitroglycerine.)

8. Fused alkalies give hydrogen and oxalates.

9. With boric acid it forms a complex acid which is a good electrolyte and can be titrated with indicators (Boeseken, Rep. 1917, 64; 1930, 97)

$$H_3BO_3 + 2\,HOCH_2CH_2OH \rightarrow 3\,H_2O + \left[\begin{matrix} CH_2O\cdot & \cdot OCH_2 \\ | \quad B \quad | \\ CH_2O\cdot & \cdot OCH_2 \end{matrix}\right]^- H^+$$

The complex has the tetrahedral grouping of five atoms and 32 electrons which characterizes the ions of $H_2SO_4$, $H_3PO_4$ and $HClO_4$. Similar products are formed with arsenious acid. Whenever two hydroxyls on adjacent carbons can form this tetrahedral arrangement with a boron or an arsenic atom the conductivity is increased. The only thing which can prevent this union is the location of the two adjacent hydroxyls on opposite sides of the plane of a ring compound such as the furanose and pyranose forms of sugars.

10. With ketones and aldehydes and a trace of acid it forms cyclic acetals, dioxolones. This is the reaction involved in the formation of acetone derivatives of sugars.

Enormous amounts of ethylene glycol are used as anti-freeze in automotive radiators (Prestone). It has a lower molecular weight and lower viscosity than glycerol and is much less volatile than ethanol or methanol. When taken internally it is as dangerous as methanol (Hunt 1932).

**Propylene glycol,** propandiol-1,2, $CH_3CHOHCH_2OH$ (EP 529).

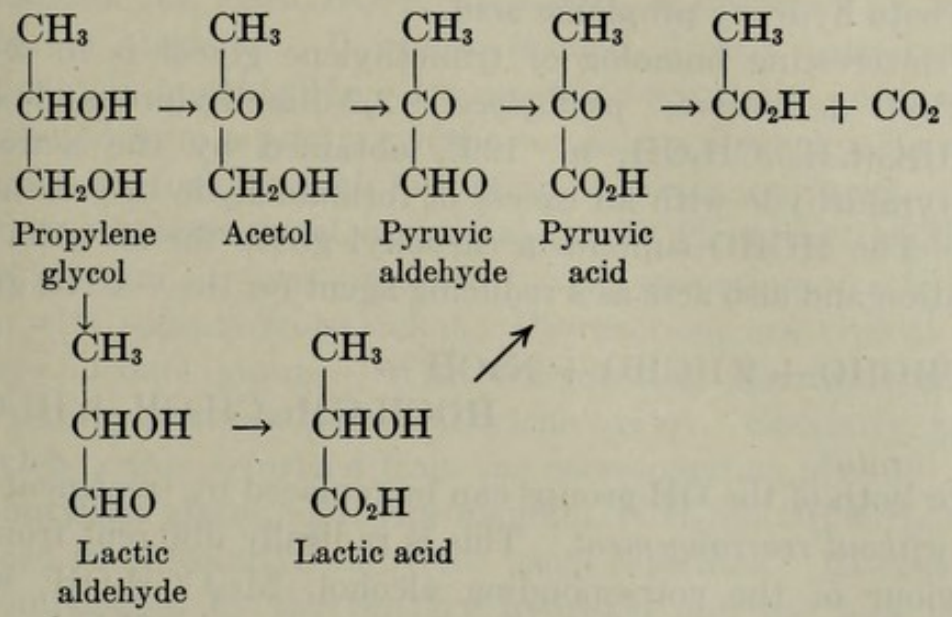
*Preparation.* Propylene obtained as a minor product in the cracking of propane is converted to the chlorohydrin by chlorine water and that is changed to the glycol by sodium carbonate solution.

$$CH_3CH=CH_2 \rightarrow CH_3CHOHCH_2Cl \rightarrow CH_3CHOHCH_2OH$$

It can also be obtained by heating glycerol with NaOH.

*Reactions.* These are like those of its lower homolog except that a secondary alcohol group is involved.

1. Again oxidation is not a practical means for obtaining the substances theoretically related to it as oxidation products.




2. Rearrangement, in the presence of acids or on heating, gives propionaldehyde.

3. Its molecule is asymmetric but its preparation gives an optically inactive mixture (racemic). When fermented it becomes levorotatory because the organism attacks the dextro form preferentially. Levo propylene glycol can be obtained from hydroxyacetone (acetol) by reduction by yeast (OS). This method has been applied to the synthesis of other optically active 1,2-glycols. The series of reactions is worth giving in detail. Chloroacetaldehyde (from the chlorination of paraldehyde) is treated with RMgX to give the 1-Cl-2-OH-compound. This is oxidized to the 1-Cl-ketone by dichromate and 5% sulfuric acid. Treatment with potassium formate in absolute methanol gives the 1-OH-ketone which on reduction by fermentation gives the optically active 1,2-glycol (Levene 1931).

Taken internally, propylene glycol is harmless (Hunt 1932). This probably is because its oxidation gives pyruvic and acetic acids.

**Trimethylene glycol,** propandiol-1,3, $HOCH_2CH_2CH_2OH$.

*Preparation.* By the fermentation of glycerol by *Schizomycetes.* It is also a by-product of the fermentation of glucose to glycerol (Rojahn 1921).

*Reactions.* Those of a di-primary alcohol with the hydroxyls far enough apart not to influence each other. Careful oxidation gives beta hydroxy propionic acid.

An interesting homolog of trimethylene glycol is its 2-*gem*-dimethyl derivative, *pentaglycol,* 2,2-dimethylpropandiol-1,3, $HOCH_2C(CH_3)_2CH_2OH$, m. 129°, obtained by the action of isobutyraldehyde with an excess of formaldehyde in presence of lime. The HCHO supplies a carbonyl group for an aldol condensation and also acts as a reducing agent for the $-CHO$ group.

$$Me_2CHCHO + 2\,HCHO + NaOH \rightarrow HOCH_2CMe_2CH_2OH + HCO_2Na$$

One or both of the OH groups can be replaced by treatment with HBr *without rearrangement.* This is radically different from the behaviour of the corresponding alcohol, $Me_3CCH_2OH$, which gives mainly rearranged products whenever the OH is removed (p. 128).

**Alpha butylene glycol,** butandiol-1,2, $CH_3CH_2CHOHCH_2OH$, b. 192°.

*Preparation.* 1. Pure butene-1 may be oxidized to the glycol by dilute $KMnO_4$.

2. Pure 1,2-dibromobutane may be converted to the diacetate of the glycol by heating with anhydrous sodium acetate. The acetate may then be saponified by alcoholic KOH. If the dibromide is to be converted directly to the glycol only very mild alkaline reagents can be used. Concentrated alkalies, either aqueous or alcoholic, tend to remove HBr to give $CH_3CH_2CBr=CH_2$, 2-bromobutene-1, and then ethyl acetylene.

*Reactions.* Like those of propylene glycol.

**Beta butylene glycol,** butandiol-2,3, $CH_3CHOHCHOHCH_3$, b. 180°, m. 27°, is prepared (1) from the pure olefin, (2) from the pure dibromide, or (3) by a special fermentation which also produces acetoin, MeCOCHOHMe, and diacetyl, MeCOCOMe (Lucidol Corp.). Its reactions are those of a di-secondary alcohol. Oxidation gives two molecules of acetic acid, probably through the formation of diacetyl. It can be determined by means of mild oxidation with bromine water to diacetyl, treatment with

hydroxylamine and conversion of the resulting dimethylglyoxime to the insoluble nickel compound (Matignon 1934).

**Butandiol-1,3,** $CH_3CHOHCH_2CH_2OH$, is prepared by the reduction of acetaldol. It is also formed directly from aqueous acetaldehyde and $Mg_xHg$. Its reactions are those which would be expected from a primary and a secondary alcohol. Its oxidation gives acetone through formation of acetoacetic acid.

**Tetramethylene glycol,** butandiol-1,4, $HOCH_2CH_2CH_2CH_2OH$, b. 108° (4 mm.) is best obtained by the reduction of ethyl succinate with sodium and alcohol. Its reactions are typical of its primary alcohol groups. With dehydrating agents, it readily gives tetrahydrofuran (tetramethylene oxide). Similarly, pentamethylene oxide is formed from the corresponding glycol.

**Isobutylene glycol,** methylpropandiol, $(CH_3)_2C(OH)CH_2OH$, is obtained from isobutylene by the usual reactions. Its reactions are complicated by the tertiary hydroxyl and the fork in the chain. In the presence of even dilute acids it rearranges readily to give isobutyraldehyde.

**Pinacol,** tetramethylglycol, 2,3-$Me_2$-butandiol-2,3, "pinacone," $(CH_3)_2C(OH)C(OH)(CH_3)_2$, m. 42°, b. 172°, is obtained from the bimolecular reduction of acetone by amalgamated magnesium (OS). It forms a hydrate with 6 $H_2O$, m. 46°. Its most important reaction is its rearrangement to pinacolone, $Me_3CCOMe$, on dehydration with acid reagents. Treatment with HBr gives the dibromide of tetramethylethylene and some pinacolone. By catalytic dehydration it is possible to obtain 2,3-$Me_2$-butadiene-1,3 ("methyl isoprene") from which "methyl rubber" can be made.

**Many higher glycols** have been prepared by the methods given above. The most readily available are the substituted ethylene glycols having the hydroxyls on adjacent carbons and the glycols having the hydroxyls at the two ends of a carbon chain ($\alpha\omega$). The former are made from the corresponding olefins either through the dibromides or by direct oxidation with permanganate or barium chlorate (Braun 1932) and also by the bimolecular reduction of ketones, certain aldehydes and esters.

1. The best known process is that of the reduction of ketones to pinacols. Hundreds of ketones have been thus reduced to pinacols. All pinacols on treatment with acids undergo the *pinacolone*

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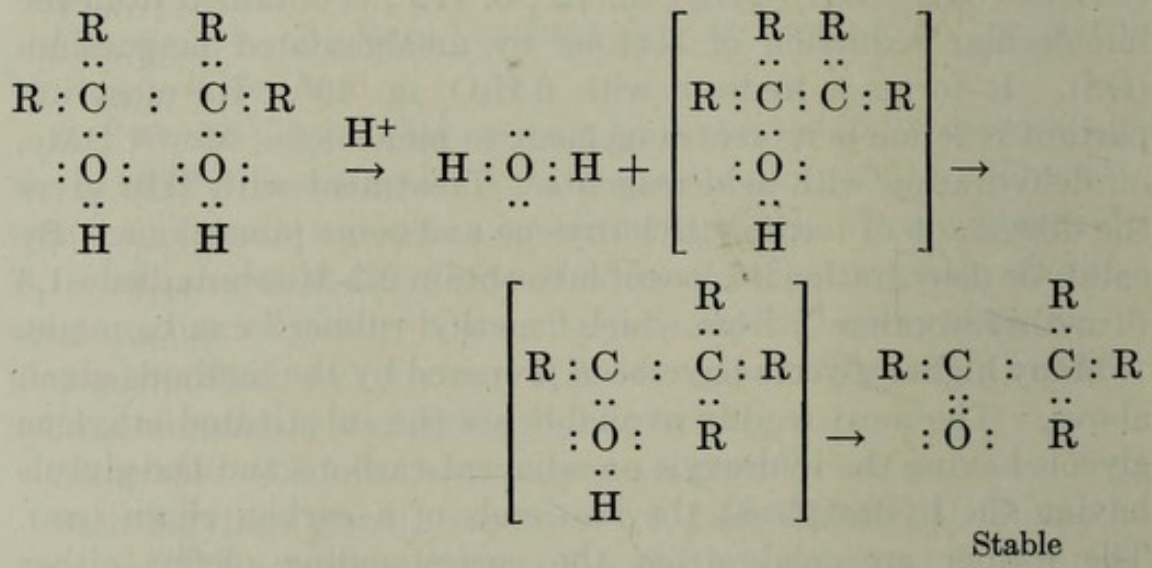
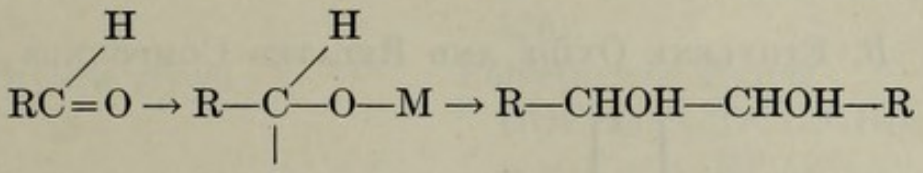
(*"pinacoline"*) *rearrangement*, $R_2C(OH)C(OH)R_2 \rightarrow R_3CCOR$. If the pinacol contains two different groups the general tendency is for the larger group to migrate. Many theories have been evolved to explain this and similar rearrangements (Whitmore 1932). One which was widely accepted involves an ethylene oxide as an intermediate. This is incorrect because many of these oxides have been found to be more stable than the related pinacols. An electronic picture of the reaction follows: The acid first forms an oxonium ion by union of hydrion with one of the alcohol groupings. This complex oxonium ion loses a molecule of water including the electron pair shared by the C and O, thus leaving the C with only six electrons, an unstable arrangement. From an adjacent atom the electronically deficient C can attract an electron pair with the group which it is holding. Apparently the atom which can most readily supply an electron pair is the C bearing the other hydroxyl in the glycol. This leaves that C with only six electrons, a condition which is overcome by the expulsion of the H attached to O as $H^+$ leaving four electrons shared by the C and O (a double bond).



Stable

The actual process is certainly not as complicated as the description. The breaking of the oxonium ion is like the opening of a valve which allows the electrons to flow to a more stable level. The shift of the groups is entirely incidental to this process.

2. Aldehydes can be reduced to glycols but less readily than ketones.



3. Esters in dry ether react with metallic sodium to give acyloins, R—CHOHCO—R, which can be reduced to glycols. Reduction by yeast gives optically active materials.

Glycols RCHOHCHOHR can exist in stereoisomeric forms (enantiomers). Usually the mesoform can be separated from the *dl*-form by patient application of fractionation by distillation and crystallization. Thus *sym*-dipropylglycol has been obtained in *meso*- and *dl*-forms, m. 124° and 24°, di-3,5-dinitrobenzoates, m. 200° and 125°.

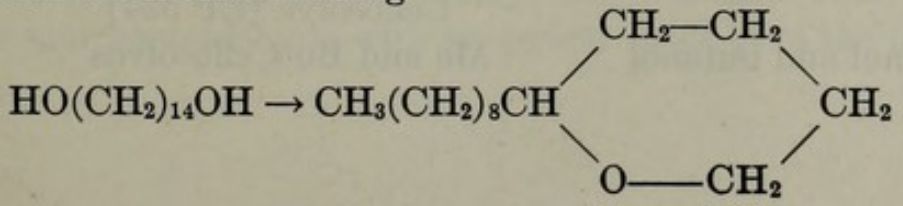
Glycols, RCHOHCHOHR, on acid treatment, undergo rearrangements to give $RCOCH_2R$ and $R_2CHCHO$ depending on the conditions and the groups involved. These products are due to the rearrangement of an H and an alkyl group respectively.

*Oxidation* of ethylene glycols splits the molecule between carbinol groups. This is probably the mechanism by which oxidation of an olefin splits it at the double bond. Lead tetraacetate produces this splitting.

$$R_2C(OH)C(OH)R_2 + Pb(OAc)_4 \rightarrow 2\,R_2CO + 2\,HOAc + Pb(OAc)_2$$

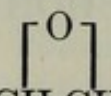
R may be any group or H.

$\alpha\omega$-Glycols are obtained from the reduction of dibasic esters with Na and absolute EtOH. They are polymethylene glycols. The bps. for the members $C_6$ to $C_{10}$ are (°C) 239, 250, 259, 172 (20 mm.), 179 (10 mm.). In most reactions the primary carbinol groups act independently. An exception is the action of dehydrating agents. Thus tetradecamethylene glycol with 50% sulfuric acid gives an inner ether which on oxidation with permanganate in acetic acid gives *n*-decanoic acid. Thus one of the hydroxyls has rearranged to the position to give an inner ether with a 6-membered ring

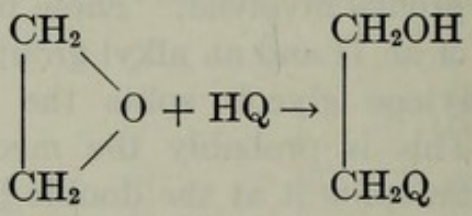


Glycols, $R_2C(OH)(CH_2)_nC(OH)R_2$ are made from dibasic esters with an excess of RMgX. (Rep. 1904, 73.)

### *B.* Ethylene Oxide and Related Compounds



**Ethylene oxide,** $CH_2CH_2$, b. 12°, is obtained by heating a solution of ethylene chlorohydrin with a base and distilling the oxide as formed (EP 533–51). A by-product is diethylene oxide, dioxan, $O(CH_2CH_2)_2O$ (C. and C.). Heat converts ethylene oxide to acetaldehyde much as cyclopropane is changed to propylene. Ethylene oxide is more stable than cyclopropane because the valence angle of oxygen involves less strain in a three membered ring than does that of carbon (Hibbert 1932). It is soluble in water without change in the absence of catalysts. The three-membered ring in ethylene oxide opens on proper treatment with active H compounds.



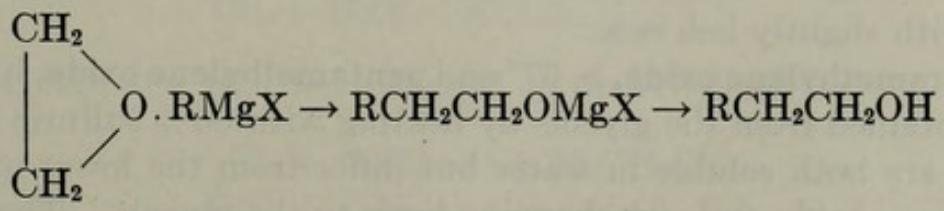
Such compounds include water (heat, pressure, and acid catalyst) acids, alcohols, ammonia, and amines. Many of the products obtained are important commercially (C. and C.).

| Reagent | Product |
|---|---|
| Water | Ethylene glycol |
| HBr | Ethylene bromohydrin |
| Acetic acid | Ethylene glycol monoacetate |
| HCN | $HOCH_2CH_2CN$ Ethylene cyanohydrin |
| $NaHSO_3$ | $HOCH_2CH_2SO_3Na$, Na isethionate |
| Acyl halides | β-halogen-ethyl esters, $RCO_2CH_2CH_2X$ |
| Ethanol | Ethylene glycol monoethyl ether, Cellosolve (EP 524) |
| Methanol and butanol | Me and Bu Cellosolves |

| Reagent | Product |
|---|---|
| Glycol | Diethylene glycol $HOCH_2CH_2OCH_2CH_2OH$ (EP 526) |
| Diethylene glycol | Polyethylene glycols $HOCH_2CH_2(OCH_2CH_2)_nOH$, $n = 1 - 9$ (EP 528) |
| Cellosolve | Monoethyl ether of diethylene glycol, Carbitol b. 198° (EP 528) |
| Me and Bu cellosolves | Me and Bu Carbitol (b. 222°) |
| Ammonia | Mono-, di- and tri-ethanol amines (EP 551) |
| $RNH_2$, $R_2NH$ | Substituted ethanol amines |

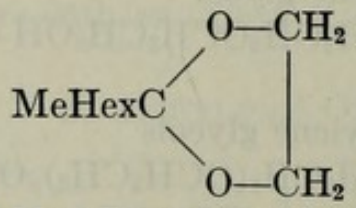
Diethyl amine and ethylene oxide do not unite dry but react readily in methanol at 40–60° (Horne 1932). β-Diethylaminoethanol, an intermediate for novocaine is obtained in good yield. Some of it reacts with more ethylene oxide to give $Et_2NCH_2CH_2(OCH_2CH_2)_nOH$ in which $n$ is 1 to 4. These are all soluble in water.

Ethylene oxide reacts with Grignard reagents of primary and secondary alkyls. The first product is an oxonium compound which reacts with water or acids like the original components. If this is heated by adding dry toluene and distilling off the ether, it rearranges (sometimes explosively!!) to give a true OMgX compound of an alcohol containing two more carbons than the alkyl used. The rearrangement of the intermediate product may also be achieved by allowing the ether solution to stand about a week (Marker).

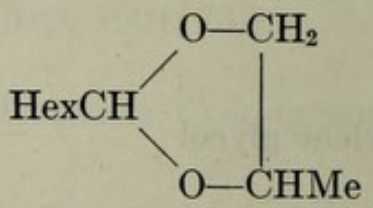


Ethylene oxide reacts with aldehydes and ketones in presence of stannic chloride to give cyclic acetals, dioxolones, containing a 5-membered ring. Thus methyl hexyl ketone with ethylene oxide and heptaldehyde with propylene oxide give the following

(Bogert 1933):




2-Me-2-Hex-1,3-dioxolone
b. 97° (23 mm).




4-Me-2-Hex-1,3-dioxolone
b. 103° (23 mm).

With bromine, ethylene oxide forms a red crystalline compound, m. 65°, b. 95°. This gives dioxan with HgO.

With solutions of hydrolyzable salts, it acts as a base, uniting with the acid formed.

$$2\ C_2H_4O + 2\ H_2O + MgCl_2 \rightarrow 2\ Mg(OH)_2 + C_2H_4(OH)Cl$$

Ethylene oxide with 90% liquid $CO_2$ is an important fumigant, especially for food stuffs because of the ease with which it can be removed (Carboxide, C. and C.).

Polyethylene oxides obtained by heating with a base have been studied extensively (Staudinger 1932, Sauter 1933, Hibbert 1933).

**Propylene oxide,** $CH_3\overset{\overset{O}{\frown}}{C}HCH_2$, is made from propylene chlorohydrin. Its reactions are like those of ethylene oxide. Addition usually gives a 2-hydroxyl, the other group adding to the 1-carbon. Ethylene Oxides, Ahr. 1920, 84 pp.

**Trimethylene oxide,** $\overset{\overset{\quad O \quad}{\frown}}{CH_2CH_2CH_2}$, b. 50°, is not obtainable from the glycol but is made from trimethylene chlorohydrin with bases. It gives addition reactions like those of ethylene oxide but with slightly less ease.

**Tetramethylene oxide,** b. 67° and **pentamethylene oxide,** b. 81°, are obtained from the glycols by heating with 60% sulfuric acid. They are both soluble in water but differ from the lower oxides by being stable and not changing back to the glycols. They do not give the addition reactions of the 1,2- and 1,3-oxides. The tendency to form a 6-membered ring is evidenced by the action of 50% sulfuric acid with tetradecamethylene glycol to form α-nonylpentamethylene oxide (p. 371).

**1,4-Dioxan,** diethylene oxide, $O(CH_2CH_2)_2O$, b. 101° is obtained by heating ethylene glycol with a little sulfuric acid and as a by-product of glycol manufacture. It gives oxonium compounds with acids, halogens, mercuric salts, iodoform, etc. Its sulfate, m. 101°, is insoluble. Dioxan is completely miscible with water. It forms an azeotrope with 20% water, b. 87°. Dioxan is toxic. It has valuable solvent properties (C. and C.).

Chlorination of dioxan gives di- and tetra-chloro derivatives (Boeseken 1931, Butler 1932, Summerbell 1932). The dichloro derivative is the vicinal isomer. Hydrolysis gives glycol and glyoxal. This is a practical source of derivatives of the latter substance. 2,3-$Cl_2$-dioxan with glycol forms *cis* and *trans* 1,4,5,8-naphthodioxan.

### *C.* Halohydrins

Halohydrins contain both hydroxyl and halogen atoms. The commonest type is the *alkylene halohydrins* with the OH and X on adjacent carbon atoms due to their formation from the olefin and a hypohalous acid. The other types are made from di- or poly-hydroxyl compounds by replacement of one hydroxyl by halogen. The result is a mixture of the desired product with polyhalogen compounds and unchanged material.

**Ethylene chlorohydrin,** glycol chlorohydrin, β-chloroethyl alcohol, 2-chloroethanol, $ClCH_2CH_2OH$, b. 132°, is readily obtainable in aqueous solution (EP 487). Chlorine and ethylene are passed into water under carefully controlled conditions. The water and chlorine react as usual.

$$Cl_2 + H_2O \rightleftharpoons HCl + HOCl$$

The Cl, HCl and HOCl can all add to the ethylene.

$$Cl_2 + C_2H_4 \rightarrow ClCH_2CH_2Cl$$
$$HCl + C_2H_4 \rightarrow CH_3CH_2Cl$$
$$HOCl + C_2H_4 \rightarrow ClCH_2CH_2OH$$

The speed with which HCl adds is so small as to be negligible in this process. At low concentrations the hypochlorous acid adds much more rapidly than chlorine. Usually when the concentra-

tion of ethylene chlorohydrin is greater than 5–10 per cent, the formation of ethylene dichloride proceeds more rapidly. At this point the process is interrupted and the product is distilled to obtain the constant boiling mixture of ethylene chlorohydrin and water containing 42 per cent of the former. Further concentration of the chlorohydrin is usually unnecessary since the solutions can be used to make ethylene oxide, ethylene glycol and related products (C. and C.).

*Reactions.* The halogen atom is unusually reactive.

1. Hydrolysis proceeds readily in the presence of weak bases.
2. Stronger bases remove HCl to give ethylene oxide.
3. Metathetical reactions go smoothly. Thus cyanides give *ethylene cyanohydrin*, $HOCH_2CH_2CN$, an intermediate for the preparation of hydracrylic acid, acrylic acid and its esters. Sodium sulfide gives *thiodiglycol* $(HOCH_2CH_2)_2S$, the intermediate for the original preparation of mustard gas (V. Meyer). Ethylene chlorohydrin is also an intermediate for the manufacture of malonic acid, phenylethyl alcohol, novocaine and indigo. For these purposes it is available in anhydrous form (C. and C.).

Ethylene chlorohydrin is a valuable plant stimulant (Denny).

Ethylene bromohydrin and iodohydrin are prepared similarly to the chlorine compound.

**Alpha propylene chlorohydrin,** 1-chloropropanol-2,

$$ClCH_2CHOHCH_3,$$

b. 127°, is the chief product of the addition of hypochlorous acid to propylene and of the action of HCl with propylene oxide. It is readily formed by the hydration of allyl chloride with sulfuric acid. Heating with water at 150° gives acetone and propionaldehyde, products of rearrangements. Heat alone converts it to acetone and propylene chloride.

**Beta propylene chlorohydrin,** 2-Cl-propanol-1,

$$CH_3CHClCH_2OH,$$

b. 134°, is formed in small amounts from propylene and HOCl but cannot be separated pure from the alpha compound. It is

best prepared from the latter by the following reactions (Henry 1903).

$$CH_3CHOHCH_2Cl \rightarrow CH_3CHOHCH_2OAc \rightarrow CH_3CHClCH_2OAc \rightarrow CH_3CHClCH_2OH$$

The reagents used are potassium acetate, thionyl chloride and *absolute methanol.* The last step is noteworthy as an *alcoholysis* of the ester which is successful whereas any hydrolytic process attacks the chlorine atom as well as the ester grouping.

**Trimethylene chlorohydrin,** 3-Cl-propanol-1,

$$ClCH_2CH_2CH_2OH,$$

b. 161°, is obtained from an excess of the glycol and a suitable reagent for replacing hydroxyl by Cl. The desired product is easily separated from the dichloride and the unchanged glycol which boil at 119° and 216°.

**Higher chlorohydrins** are made from the olefins and hypochlorous acid. As the olefins decrease in solubility in water an alternative method becomes valuable. This is the action of N-chlorourea in acetic acid (Detoeuf 1922).

Halohydrins, especially iodohydrins, react with silver nitrate to give a rearrangement much like the pinacoline rearrangement (Tiffeneau 1931).

### *D.* Trihydric Alcohols

Organic ortho acids, $HC(OH)_3$ and $RC(OH)_3$, are known only as alkyl derivatives, the orthoformates, orthoacetates, etc., obtained by the action of sodium and alcohols with the grouping $-CCl_3$. The orthoformates of the normal alcohols $C_1$ to $C_4$ boil 104° to 246° (Sah 1932).

**Glycerol,** glycerine, propantriol-1,2,3, $HOCH_2CHOHCH_2OH$, m. 17°, b. 290°, 170° (12 mm.), is obtained as a by-product of soap manufacture and by fermention of glucose by carefully controlling the pH of the solution by adding $Na_2CO_3$ or $NaHSO_3$ to cut down the formation of ethanol and $CO_2$ and increase that of glycerol and acetaldehyde (p. 107) (Rep. 1925, 68).

Glycerol is completely miscible with water and alcohol but practically insoluble in ether. It is a sweet viscous liquid, $d = 1.265$ at 15°. Glycerol can be synthesized in many ways but

these preparations are of no practical importance. Its formation from allyl alcohol and $KMnO_4$ may be regarded as a proof of its structure but, as usual with organic compounds, the latter depends on all of its reactions.

It is non-toxic and is used in medicinal, cosmetic, and food preparations, as an anti-freeze, in making nitroglycerine and for many uses depending on its strong hygroscopic properties such as in non-drying inks and the like.

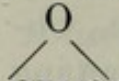
*Reactions:* These include the normal reactions corresponding to its primary and secondary alcohol groups.

1. Replacement of hydroxyl H by alkali metals is accomplished by heating with the metal or its hydroxide. The first H is fairly readily replaced, the second one with some difficulty and the third not at all. Even heavy metal hydroxides such as $Cu(OH)_2$ dissolve when heated with glycerol. Thus a copper solution containing glycerol gives no precipitate with bases.

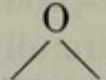
2. Esterification of the hydroxyl groups by acids.

(*a*) Inorganic acids. Hydrogen chloride gives two glycerol monochlorohydrins and two dichlorohydrins. Treatment of any of these with $PCl_5$ gives *glycerol trichlorohydrin*, 1,2,3-trichloropropane, b. 158°. While isomeric glycerol chlorohydrins cannot be separated, the mixture of mono- (b. above 200°) can be separated from the mixture of di-chlorohydrins (b. about 180°). The dinitrates of the monochlorohydrins have a very low freezing point and have been used as antifreeze in dynamite.

Treatment of the monochlorohydrin mixture with bases removes HCl to give *glycidol*, glycide alcohol, 2,3-epoxypropanol-1,



$CH_2CHCH_2OH$, b. 162°, which resembles glycerol in being soluble in alcohol and water but differs from it in being soluble in ether. Similarly, removal of HCl from the dichlorohydrin mixture gives *epichlorhydrin*, 1-chloro-2,3-epoxypropane,



$ClCH_2CH–CH_2$, b. 117°. The reactions of this substance are mainly those of the ethylene oxide ring rather than of the chlorine, thus illustrating the greater ease of *addition* reactions as compared with metathesis in organic compounds. Thus epichlor-

hydrin with RMgX gives $RCH_2CH(OMgX)CH_2Cl$ (McElvain 1930).

**Epiethylin,** glycidyl ethyl ether, $CH_2\overset{O}{\diagdown\diagup}CHCH_2OEt$, b. 126°, is made from the dichlorohydrin mixture and alcoholic NaOH. It has solvent properties for shellac, resins and gums.

The pure *alpha monochlorohydrin* of glycerol, 1-chloropropandiol-2,3, $ClCH_2CHOHCH_2OH$, b. 213°, 139° (18 mm.) is obtained by adding water to epichlorhydrin; the *beta monochlorohydrin*, $HOCH_2CHClCH_2OH$, b. 146° (18 mm.), by addition of HOCl to allyl alcohol; the *alpha dichlorohydrin*, $ClCH_2CHOHCH_2Cl$, 1,2-dichlorohydrin, from epichlorohydrin and HCl; and the *beta dichlorohydrin*, $ClCH_2CH_2ClCH_2OH$, b. 182°, from allyl chloride and HOCl. It is to be noted that the additions to the allyl compounds proceed contrary to Markownikoff's Rule in that the negative hydroxyl adds to the $CH_2$ instead of mainly to the CH as in propylene (cf. Kharasch 1933).

Nitric acid gives *nitroglycerine*, glycerol trinitrate, $C_3H_5(ONO_2)_3$, m. 12°, a valuable explosive both alone and absorbed in a porous material (dynamite, Nobel 1867) and with nitrocellulose in smokeless powders of the cordite and ballistite type. Formerly the absorbent used in dynamite was inert infusorial earth (Kieselguhr). Now wood powder or pulp and inorganic nitrates are used.

The esters of glycerol and phosphoric acid (Rep. 1916, 74) are found widely in animal and vegetable tissues combined with fatty acids and alkamines in phosphatides (lipoids, lipins) such as lecithins and cephalins (Pr. 225–40). The formula of a lecithin follows:

$$C_{17}H_{35}CO_2CH_2CH(OCOC_{17}H_{33})CH_2O\overset{\overset{O}{\|}}{\underset{\underset{OH}{|}}{P}}OCH_2CH_2NMe_3(OH)$$

Hydrolysis gives stearic, oleic and phosphoric acids, glycerol and choline. Many other fatty acids are found in lecithins. Other possible modifications depend on the attachment of the phosphoric

acid to glycerol in the beta position and on optical isomerism. The cephalins contain aminoethyl alcohol in place of choline. Sphingomyelin contains choline and sphingosine, probably $CH_3(CH_2)_{12}CH=CHCHOHCHOHCH_2NH_2$.

Glycerol forms ester acids with weak acids like boric acid. Peculiarly these ester acids are much stronger than the original ones. Thus borax, $Na_2B_4O_7$, which is strongly alkaline combines with glycerol to give a strong acid. This is another example of the formation of the complex ion of a strong acid by hydroxy groups on adjacent carbons (p. 366).

(*b*) Organic acids react with one, two or three of the hydroxyls to give esters. The preparation and identification of pure partially esterified glycerols are very difficult (Rep. 1929, 75–8). The tri-esters with the higher aliphatic acids occur as *fats* such as glyceryl tristearate (tristearin) etc. Many artifical glyceryl esters are known. *Monoformin* and *diformin* are the esters of glycerol with one and two molecules of formic acid. The three *acetins* are obtained by heating glycerol with acetic acid at suitable temperatures. They have value as high boiling solvents.

**Intarvin** is a synthetic edible fat made for the use of diabetics because it cannot yield acetoacetic acid in the body. Acetoacetic acid and the resulting acetone cannot be oxidized by the organism unless it is oxidizing carbohydrates at the same time. Intarvin is made from margaric acid $C_{16}H_{33}CO_2H$, an odd-numbered acid which, therefore, cannot give acetoacetic acid by successive losses of two carbon atoms (beta oxidation). The following are the steps in the preparation of Intarvin (McKee):

*a*. Stearic acid is heated with lime and calcium acetate and the resulting ketone is distilled out of the mixture.

$$(C_{17}H_{35}CO_2)_2Ca + (CH_3CO_2)_2Ca \rightarrow 2\,CaCO_3 + 2\,C_{17}H_{35}COCH_3$$

The stearone and acetone formed at the same time do no harm, the former staying in the reaction mixture and the latter distilling out before the desired product.

*b*. The ketone is oxidized by chromic acid mixture.

$$C_{17}H_{35}COCH_3 + 3[O] \rightarrow C_{16}H_{33}CO_2H + CH_3CO_2H$$

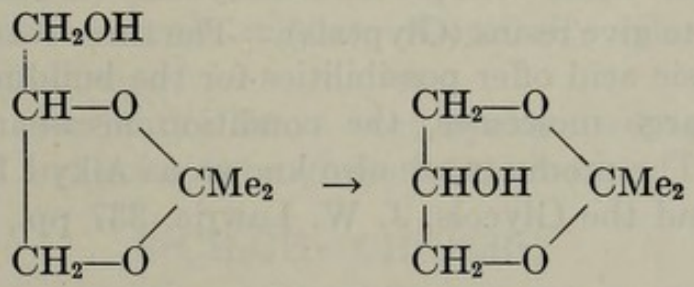
*c.* The resulting margaric acid is redistilled and then heated with glycerol.

$$C_3H_5(OH)_3 + 3\ C_{16}H_{33}CO_2H \rightarrow 3\ H_2O + (C_{16}H_{33}CO_2)_3C_3H_5$$

3. Ethers of glycerol can be obtained in the usual ways.

**Triethylin,** glyceryl triethyl ether, $C_3H_5(OEt)_3$, b. 185°, illustrates the effect of ether linkages on volatility. Heating glycerol with aqueous HCl gives diglycerol, $(HOCH_2CHOHCH_2)_2O$. The tetranitrate of this substance was formerly used to lower the melting point of nitroglycerine but is now largely replaced by glycol dinitrate.

4. Aldehydes and ketones, with acid condensing agents, give 5- and 6-ring acetals with glycerol (Rep. 1915, 68; 1929, 77). The latter is the more stable form. Thus glycerol and acetone with anhydrous $CuSO_4$ give a product which on methylation and hydrolysis gives glycerol alpha methyl ether showing that the acetal has formed in the 1,2-position. Treatment of the 1,2-acetal with a trace of HCl converts it to the 1,3-compound (Hibbert, 1930).




5. Heating with formic or oxalic acid gives allyl alcohol, the net result being a dehydration and reduction

$$C_3H_5(OH)_3 + HCO_2H \rightarrow 2\ H_2O + CH_2{=}CHCH_2OH + CO_2$$

6. Distillation with dehydrating agents like anhydrous $KHSO_4$ or $MgSO_4$ gives acrolein (OS).

$$C_3H_5(OH)_3 \rightarrow 2\ H_2O + CH_2{=}CHCHO$$

7. Oxidation. Of the ten theoretically possible oxidation products containing three carbon atoms five can be made by suitable choice of reagents and conditions.

(*a*) Mild oxidation by nitric acid, bromine, or $FeSO_4$ and $H_2O_2$ gives glycerose (E. Fischer), a mixture of glyceraldehyde, $CH_2OHCHOHCHO$, and dihydroxyacetone, $CH_2OHCOCH_2OH$. These are the simplest possible isomeric aldose and ketose. The sorbose bacterium gives dihydroxyacetone alone.

(*b*) More vigorous oxidation gives glyceric acid,

$$CH_2OHCHOHCO_2H$$

and tartronic acid, $HO_2CCHOHCO_2H$.

(*c*) Oxidation with bismuth nitrate yields mesoxalic acid, $HO_2CCOCO_2H$.

8. Fusion with KOH gives formates and acetates.

9. Iodine and phosphorus give allyl iodide if all reagents are anhydrous and isopropyl iodide if water is present. Some propylene is formed in both cases. $PBr_3$ and $PCl_3$ replace all three hydroxyls by halogen.

10. Various fermentations of glycerol give trimethylene glycol, dihydroxyacetone, lactic acid, propionic acid, butanol-1, *n*-butyric acid, succinic acid and *n*-caproic acid.

11. Glycerol reacts with phthalic anhydride and various other dibasic acids to give resins (Glyptals). The three reactive groups and the dibasic acid offer possibilities for the building up of tremendously large molecules, the condition necessary for resin formation. The products are also known as Alkyd Resins.

Glycerol and the Glycols, J. W. Lawrie, 337 pp., New York, 1928.

*Butantriol-1,2,3*, $CH_3CHOHCHOHCH_2OH$, is obtained from crotonaldehyde, $CH_3CH=CHCHO$, through the corresponding alcohol and its dibromide. *Pentaglycerol*, 1,1,1-trihydroxymethylethane, $CH_3C(CH_2OH)_3$, m. 199°, is made by condensing propionaldehyde and an excess of formaldehyde with lime. Two hydroxymethyl groups are introduced by aldol condensations and the third is formed by the reduction of the aldehyde group by formaldehyde in the alkaline medium. This is really a Cannizzaro reaction and resembles the biological processes by which aldehydes are converted to acids and alcohols. The reactions of pentaglycerol are the normal reactions of primary alcohols. It does not undergo the rearrangements which might

be expected from the neopentyl grouping which it contains (p. 128).

### *E.* Higher Polyhydric Alcohols

Orthocarbonic acid, $C(OH)_4$, is known only in its esters, $C(OR)_4$. The hydrated form of glyoxal, $(HO)_2CHCH(OH)_2$, probably exists in the solution of the monomeric substance and explains the failure of polymerization in solution.

Since the existence of more than one hydroxyl on a carbon atom is unusual, the first true member of this series contains four carbon atoms with a hydroxyl group on each.

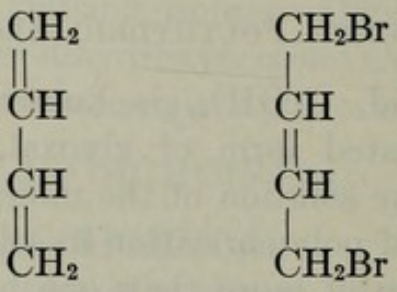
**i-Erythritol,** *i*-erythrite, *i*-tetritol, *i*-butantetrol-1,2,3,4, $CH_2OHCHOHCHOHCH_2OH$, m. 126°, is found free and as esters in certain lichens and algae. It gives reactions analogous to those of glycerol. In spite of the facts that its molecule is asymmetric and that it is a natural product, it is optically inactive. Moreover it cannot be resolved into dextrorotatory and levorotatory forms. It is thus the internally compensated or meso form, indicated as *meso-* or *i-* to distinguish it from the optically inactive racemic mixture of optically active molecules indicated as *dl-* or *r-*.

*Meso-* and dl-erythritol have been synthesized starting with butadiene-1,3 and going through its 1,4-dibromide,

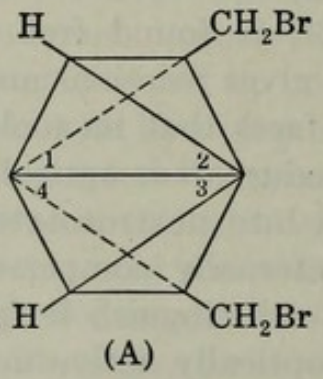
$$BrCH_2CH=CHCH_2Br,$$

which is obtained in two isomeric forms one solid and the other liquid at ordinary temperatures. Oxidation with $KMnO_4$ converts the solid to a glycol, $BrCH_2CHOHCHOHCH_2Br$, m. 87° and the liquid to an isomeric glycol, m. 135°. Treatment of the di-bromohydrins with KOH and ether gives di-epoxy compounds, $CH_2\overset{O}{\diagdown\diagup}CH\overset{O}{\diagdown\diagup}CH_2$, m. 14° and −15°. Treatment of these with dilute acid give erythritols, the first giving the racemic material, m. 72°, and the other the common or mesoerythritol, m. 126°. The space relations of these compounds can best be shown by tetrahedral models for the carbon atoms. The changes will be discussed at length because the principles involved are

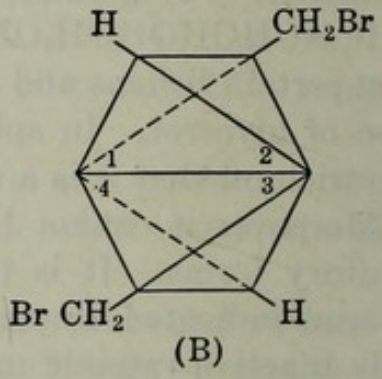
of the utmost importance in the study of the carbohydrates and other optically active substances.



The olefinic linkage formed by the 1,4-addition can exist in *cis* and *trans* forms (*A*) and (*B*)




(A)

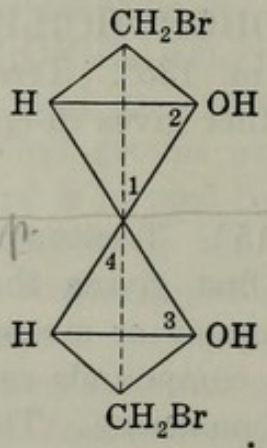



(B)

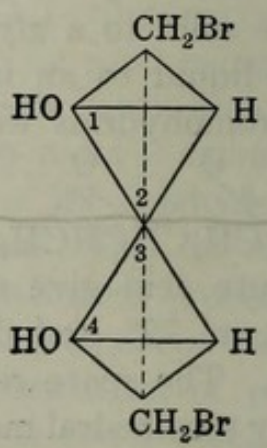
In one, the like groups can approach each other by a folding of the molecule along the double bond while in the other the like groups cannot approach each other. Oxidation by $KMnO_4$ adds 2−OH groups to the double bond.

1. Addition of 2−OH groups to (*A*), the *cis* form.

(*a*) Opening the double bond at the 2,3-end would give (C).




(C)



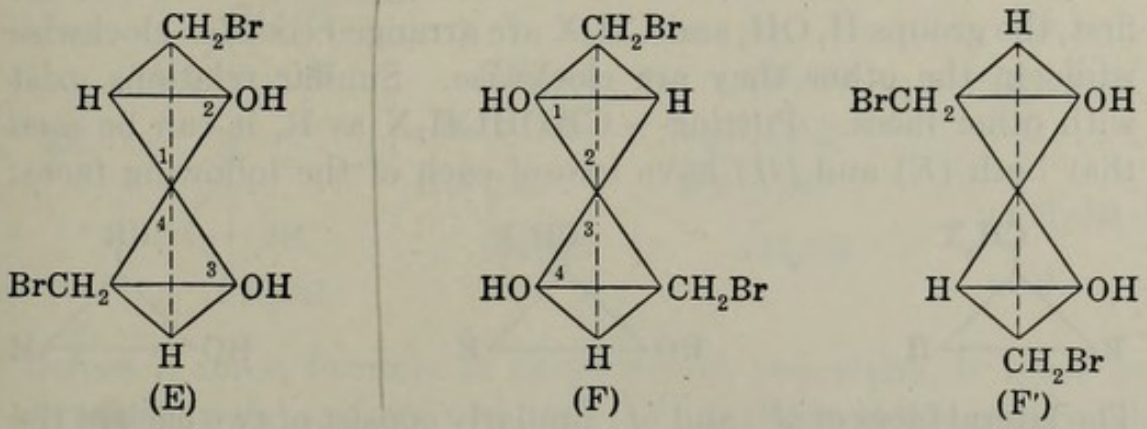

(D)

(*b*) Opening the double bond at the 1,4-end would give (*D*). Inspection of those models shows them to be identical rather than enantiomorphic since the rotation of (*D*) 180° in the plane of the paper will give (*C*). Looking at the top of (*C*) it will be seen that the groups H,OH,$CH_2Br$ are arranged counter-clockwise while an inspection of the bottom of the model shows the same groups in clockwise arrangement. Thus one carbon is the mirror image of the other and (*C*) is the internally compensated *meso-* form. Since removal of HBr from the adjacent OH and $CH_2Br$ groups and the addition of $H_2O$ to the epoxy grouping does not change the spatial arrangement around the two asymmetric carbon atoms, (C) would give *meso*-erythritol. Since the liquid 1,4-dibromide gives *meso*-erythritol it must be the *cis* form of configuration (A).

2. Addition of 2−OH groups to (B), the *trans* form

(*a*) At 2,3 to give (*E*)

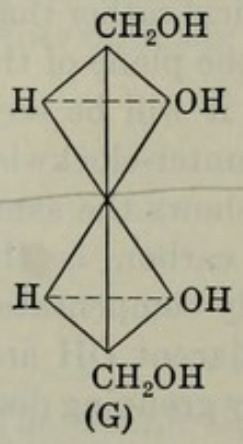
(*b*) At 1,4 to give (*F*).




Models (*E*) and (*F*) are enantiomers. Rotation of (*F*) in the plane of the paper through 180° gives (*F'*) which is not identical with (*E*). Conversion of the equimolar mixture of (*E*) and (*F*) to erythritol would give the racemic or *dl*-product which could be separated into the optically active isomers. Thus the solid dibromide of butadiene which gives *dl*-erythritol must be the *trans* form (*B*).

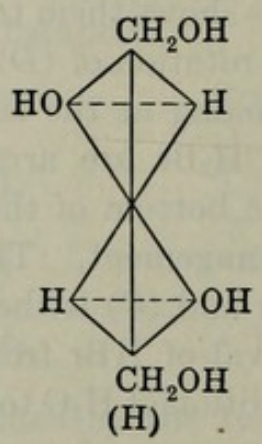
The models of the possible stereoisomeric erythritols are as

follows:

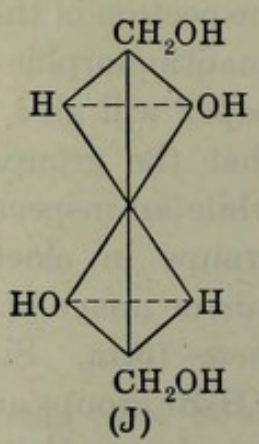



(G)

meso- or i-



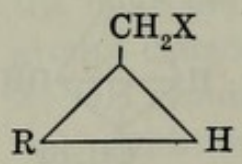

(H)

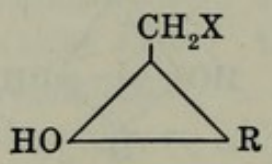


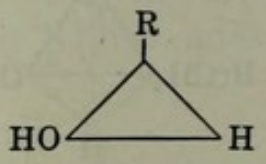

(J)

dl- or racemic-

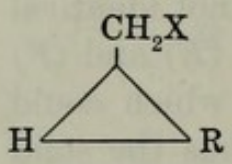
(*H*) corresponds to (*E*) and (*J*) to (*F*) as can be seen by comparing corresponding faces of the tetrahedra. Thus the top and bottom faces of (*E*) and (*H*) are all $HO\overset{H}{\triangle}CH_2X$ while the top and bottom faces of (*F*) and (*J*) are all $XCH_2\overset{H}{\triangle}OH$. Thus in the first, the groups H, OH, and $CH_2X$ are arranged counter-clockwise while in the other they are clockwise. Similar relations exist with other faces. Putting $-CHOHCH_2X$ as R, it can be seen that both (*E*) and (*H*) have two of each of the following faces:

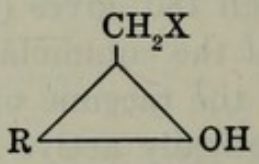


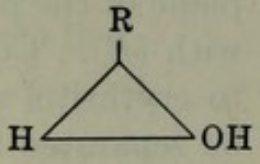




The lateral faces of (*F*) and (*J*) similarly consist of two each of the following:



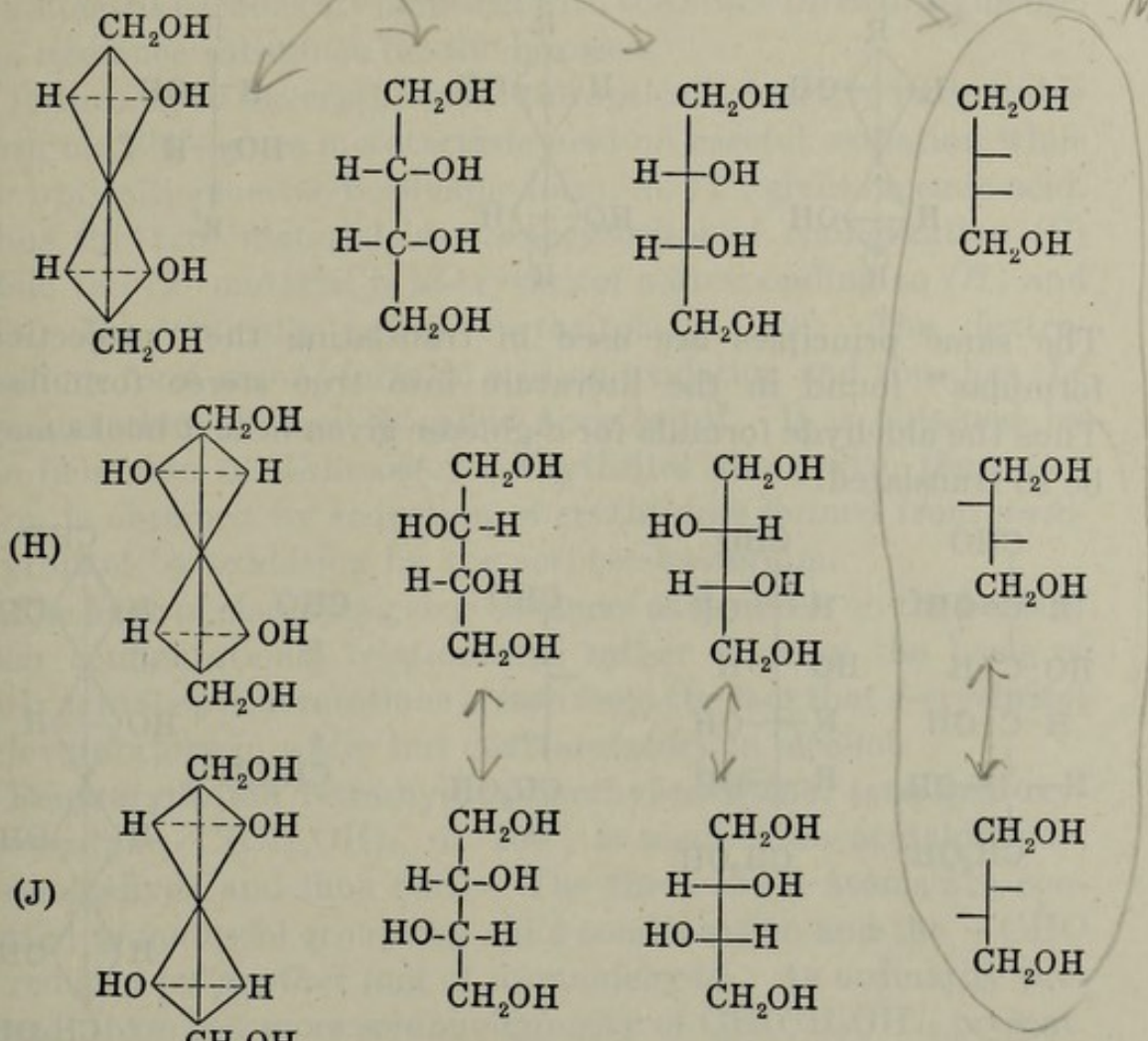



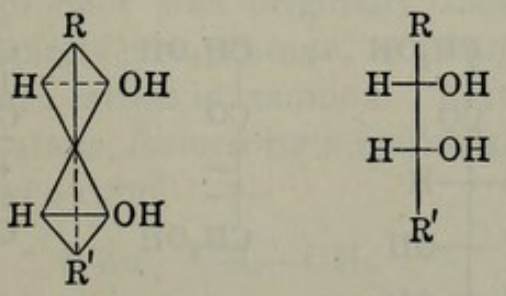

Each of these three is a mirror image of a face in the preceding three kinds of faces.

Space formulas are seldom used in printed discussion of stereoisomers because of the expense and trouble involved. Instead, "projections" of the space formulas are used. Thus the steric relations of the erythritols are given equally well by

each set of the following formulas:

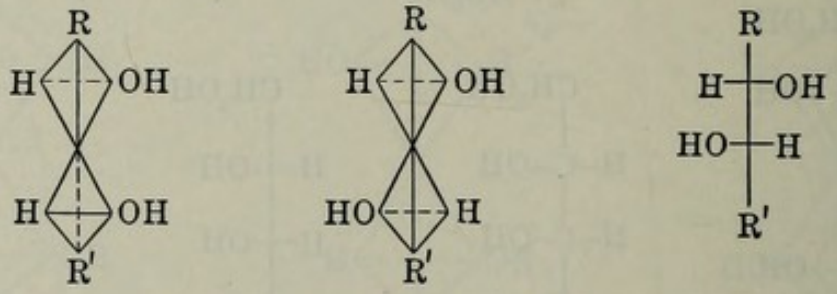



Before a space formula is projected on one plane, it must be *arranged in the accepted way with the optically inactive groups top and bottom and all the other groups back of the plane of the paper.* Thus the following projection would be incorrect:

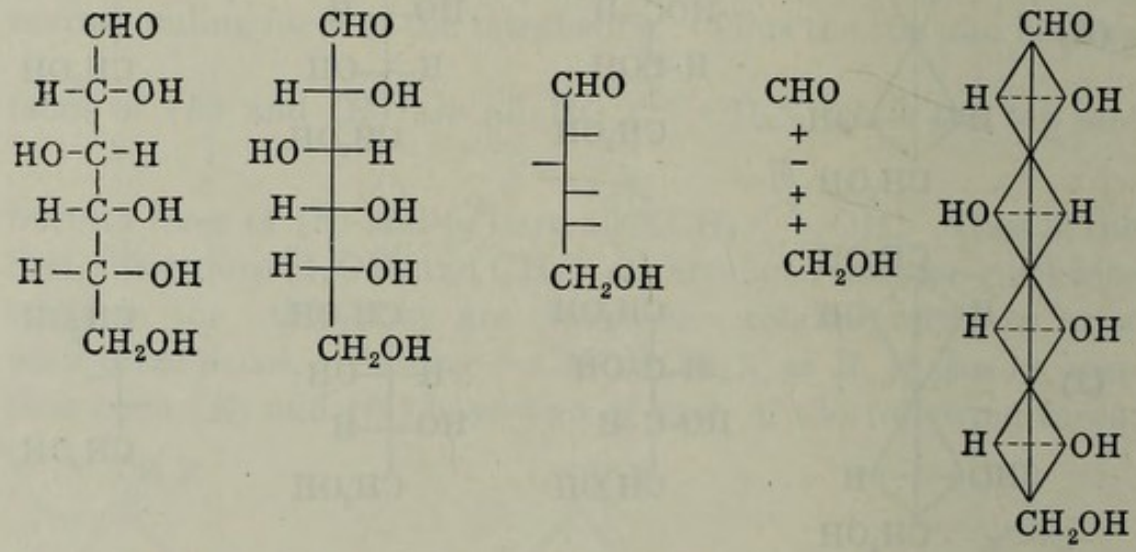



In this case the H and OH on the upper asymmetric C are *back* of the plane of the paper while the H and OH on the other carbon

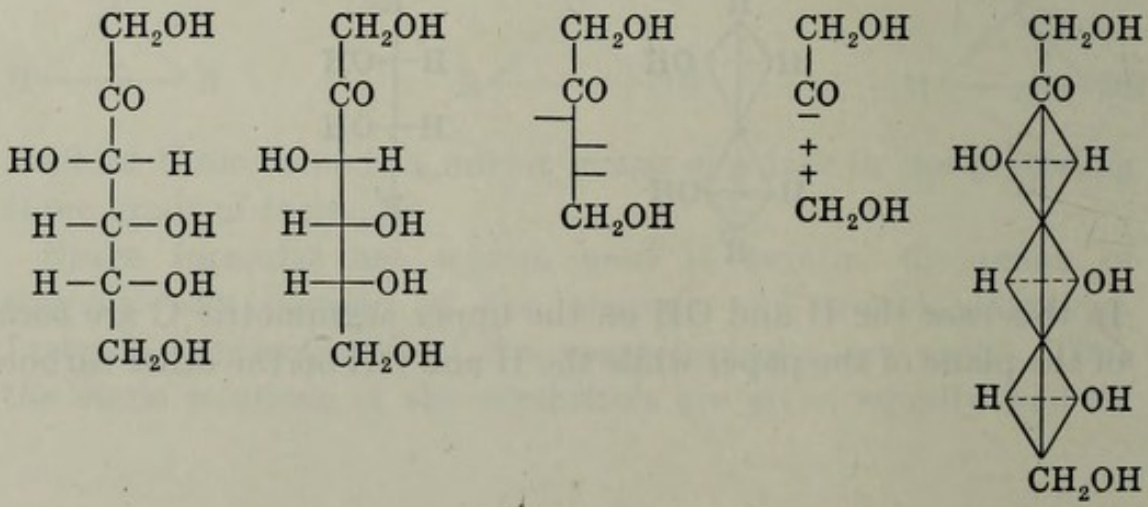
are in *front* of the paper. A proper procedure follows:




The same principles are used in translating the "projection formulas" found in the literature into true stereo formulas. Thus the aldehyde formula for *d*-glucose given in text books may be so translated.




Once again, caution must be urged against a literal acceptance of the terms *d*- and *l*- as indicating anything about the actual sign of the optical rotation of a substance. Thus the following formulas are used for ordinary fructose obtained by the inversion of cane sugar:



It is levorotatory but is called *d*-fructose because its three asymmetric carbons are identical with the lower three in *d*-glucose, the reference substance for the hexoses.

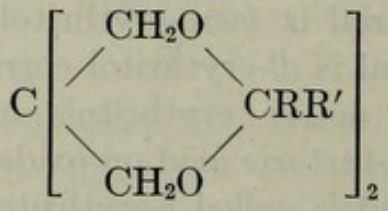
Returning to the erythritols—the optically inactive inseparable form m. 126°, gives mesotartaric acid on careful oxidation while the optically inactive resolvable form, m. 72°, gives racemic acid. Thus the 126° material is *meso*-erythritol of configuration (*G*) while the 72° material is *dl*-erythritol corresponding to (*H*) and (*J*). The optically active erythritols m. 89°. The dextrorotatory form gives *l*-tartaric acid on oxidation and thus has the configuration (*H*) and is called *l*-erythritol. It is obtained by the reduction of *d*-threose. *d*-Erythritol along with the *meso*-form is obtained by reduction of erythrulose formed from *meso*-erythritol by oxidation by the sorbose-bacterium.

The logic of classifying stereoisomers as *d*- and *l*- on the basis of their configurational relationships rather than on the basis of their actual optical rotations is seen from the fact that *d*-erythritol is levorotatory in water but dextrorotatory in alcohol.

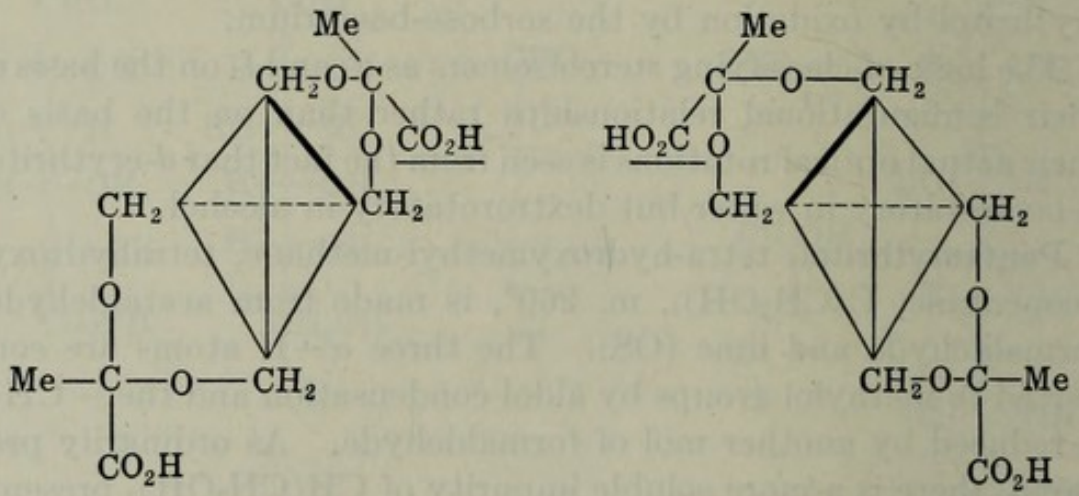
**Pentaerythritol,** tetra-hydroxymethyl-methane, tetrahydroxy-neopentane, $C(CH_2OH)_4$, m. 260°, is made from acetaldehyde, formaldehyde and lime (OS). The three $\alpha-H$ atoms are converted to methylol groups by aldol condensation and the $-CHO$ is reduced by another mol of formaldehyde. As ordinarily prepared, there is a more soluble impurity of $CH(CH_2OH)_3$ present. All four OH groups in pentaerythritol can be replaced by bromine by means of HBr. These can be replaced by acetate groups which can be hydrolyzed to give pentaerythritol, showing that rearrangement does not take place as in the case of neopentyl alcohol (p. 128). The tetrabromide reacts with zinc with rearrangement. The product was originally thought to be the normal product, spirobicyclopentane, containing two cyclopropane rings with one carbon in common. Actually the product is methylene-cyclobutane, formed by a rearrangement analogous to those of neopentyl alcohol.

$$C(CH_2Br)_4 \xrightarrow{2\ Zn} \begin{matrix} CH_2{-}CH_2 \\ | \quad\quad | \\ CH_2{-}C{=}CH_2 \end{matrix} + 2\ ZnBr_2$$

At one time it was thought that pentaerythritol did not have the typical tetrahedral structure but consisted of a pyramidal structure with the central C at the apex and the four methylol groups in *one plane.* This has been shown to be incorrect (Rep. 1929, 75–6) (Orthner 1930). One of many pieces of evidence is the existence of optical isomers of the acetal compounds

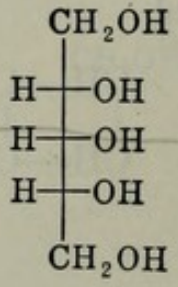


Pentaerythritol is condensed with ethyl pyruvate and the corresponding acids are resolved into *d*- and *l*- forms.



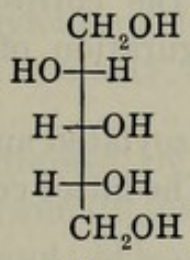
The two models are mirror images and are not identical. No plane of symmetry exists. A plane drawn through the heavily lined edge of the tetrahedron and bisecting the opposite edge would be a plane of symmetry except for the upper Me and $CO_2H$ which are in back and in front of the plane. The other Me and $CO_2H$ would lie in the plane.

**Pentahydric alcohols,** $CH_2OH(CHOH)_3CH_2OH$. The number of possible isomers may be predicted by stereochemical studies. One possibility, as shown by a "projection formula" is

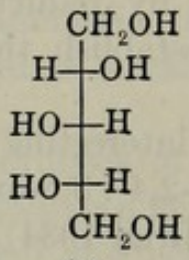


(a)

This formula is symmetrical and is identical with its mirror image. It is optically inactive by internal compensation. It represents *adonitol* which can be obtained by the reduction of either *d*- or *l*-ribose. Another possibility is obtained by interchanging the H and OH on the upper asymmetric C.



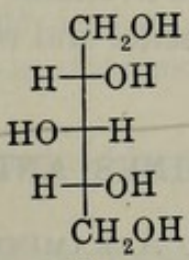
(b)



(c)

Formula (*b*) is not symmetrical and is enantiomorphic with formula (*c*). Thus (*b*) and (*c*) represent a pair of optical isomers. Formula (*b*) represents *d-arabitol* which can be obtained by the reduction of *d*-arabinose or *d*-lyxose. Formula (*c*) is *l-arabitol.*

If, in formula (*a*) the H and OH on the lower asymmetric carbon are interchanged formula (*c*) is obtained. If, however, the interchange is on the middle carbon, formula (*d*) is obtained.



(d)

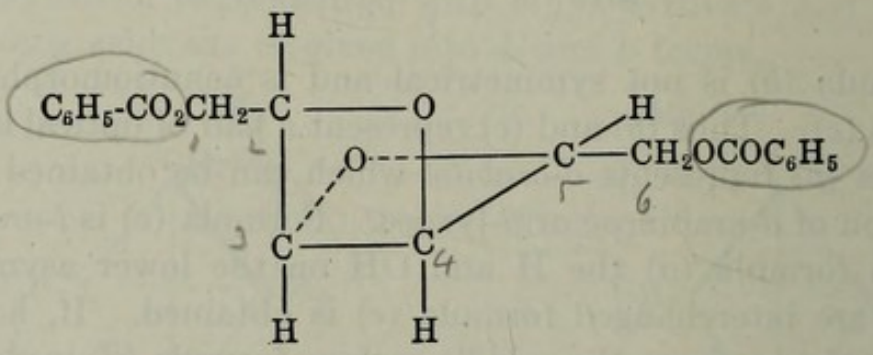
This formula is symmetrical and is identical with its mirror image. It represents another optically inactive form, *xylitol,* which is obtained by the reduction of either *d*- or *l*-xylose.

Thus the pentan-pentols exist in four stereoisomeric forms or one pair of optical isomers and two meso forms.

**Hexahydric Alcohols,** $CH_2OH(CHOH)_4CH_2OH$. A study of the stereochemical possibilities shows that four pairs of optical isomers and two meso forms correspond to this structural formula. *d*-mannitol, *d*-sorbitol, *d*-iditol and dulcitol are formed in various plant products. The first three are feebly levorotatory and the

last is optically inactive and cannot be resolved. It is thus a *meso* form. Sorbitol is converted to sorbose by the sorbose-bacterium whereas iditol is not, thus indicating that the former has the 2- and 3-OH groups on the same side of the chain whereas the latter does not. Most of the possible hexan-hexols have been made by reduction of the corresponding hexoses. These relations establish the configuration of the asymmetric carbons.

Mannitol gives interesting 1,6-benzoylated anhydrides, a mono 2,5-oxide and a di-2,4 : 3,5-oxide. The latter contains two stable 4-member rings (Brigl 1934).




Mannitol and sorbitol are available commercially (Atlas). *Heptahydric alcohols, perseitol* and *volemitol* are known.

## XVI. ALKAMINES AND DIAMINES

### *A.* Alkamines

These contain hydroxyl and amino groups. The primary product of the action of ammonia with a carbonyl compound having these groups on the same carbon is unstable.

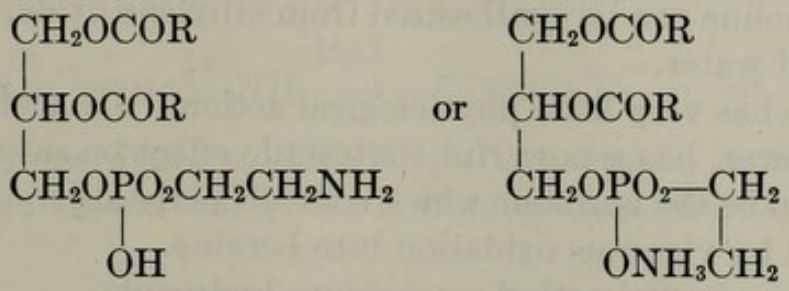
$$=C=O \rightleftharpoons =C(OH)NH_2 \rightarrow \text{complex products}$$

Sometimes the latter reaction is also reversible. If the functional groups are on different carbons the amino alcohols are stable compounds and show the reactions of both groups. The stronger basic properties of the nitrogen atom cause the reactions of the hydroxyl group with acid reagents to be largely masked. Thus an amino alcohol is less readily dehydrated or esterfied than is an

ordinary alcohol. The methods of introducing the OH and $NH_2$ groups follow the ordinary reactions.

**Mono-ethanolamine,** $\beta$-aminoethyl alcohol, colamine, $\beta$-hydroxyethylamine, $HOCH_2CH_2NH_2$, is available mixed with di- and tri-ethanolamines $(HOCH_2CH_2)_2NH$, $(HOCH_2CH_2)_3N$, formed from ethylene oxide and ammonia (C. and C.). The last substance is strongly basic and is a valuable emulsifying agent.

Colamine is obtained by the hydrolysis of cephalin, a *phosphatide* obtained from brains. *Cephalin* is a mixed ester of higher fatty acids, glycerol, phosphoric acid and colamine. It corresponds to the general formula.



The R groups may be alike or different and are usually the radicals of palmitic, stearic or oleic acids. Isomers are also known in which the phosphoric acid is attached to the beta position of the glycerol.

N-Methyl colamine is obtained by the degradation of morphine and other alkaloids.

**N-Disubstituted alkamines,** $R_2NCH_2CH_2OH$, are intermediates in the preparation of novocaine and related drugs. They are readily obtained from secondary amines and ethylene chlorohydrin or more economically, ethylene oxide.

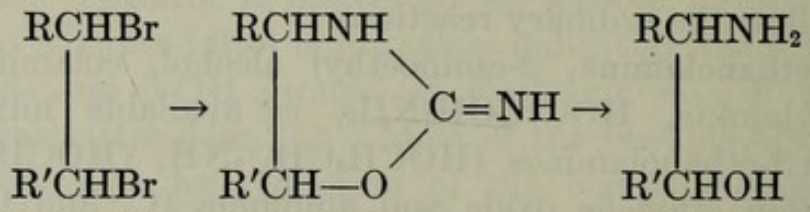
A special preparation of substituted aminoethanols is as follows (Rep. 1928, 89);

$$HOCH_2CH_2Cl + COCl_2 \rightarrow ClCO_2CH_2CH_2Cl \rightarrow RNHCO_2CH_2CH_2Cl \rightarrow RNHCH_2CH_2OH$$

The last step takes place with excess of KOH (Pierce 1928).

The conversion of alkylene dibromides to alkamines can be done by condensation with urea followed by the hydrolysis of

the resulting imino-oxazolidines.




**Choline,** ethanoltrimethylammonium hydroxide, bilineurine, sincaline, $HOCH_2CH_2NMe_3(OH)$, is found combined with fatty acids and glycerophosphoric acid in *lecithins*, distributed almost universally through the animal and vegetable kingdoms. The lecithins have formulas similar to cephalin but with a choline instead of an ethanolamine attached to the glycerophosphoric acid. Choline can be synthesized from ethylene oxide, trimethyl amine and water.

Choline has very little physiological action. Its acetyl derivative, however, has a powerful contractile effect on muscle and is believed to be the hormone which controls peristalsis. Choline is converted by vigorous oxidation into betaine.

**Neurine,** vinyltrimethyl ammonium hydroxide,

$$CH_2=CHNMe_3(OH),$$

is poisonous whereas choline is not. It is presumably one of the ptomaines formed by putrefaction.

**Muscarine,** was formerly believed to be choline aldehyde hydrate, $(HO)_2CHCH_2NMe_3(OH)$, but has more recently been assigned the formula $EtCHOHCH(CHO)NMe_3(OH)$. It is the active principle of the very poisonous mushroom (toad stool), *Amanita.*

**Morpholine,** $HN(CH_2CH_2)_2O$, combines the properties of a cylic ether and a secondary amine. The six-membered ring is easily closed starting either with diethanol amine or $\beta\beta'$ dichlorodiethyl ether and ammonia.

More complex *amino ethyl alcohols* can be obtained by

(*a*) The reduction of alpha amino esters by sodium and alcohol to give substances, $HOCH_2CH(R)NH_2$.

(*b*) The action of Grignard reagents on alpha amino aldehydes, ketones and esters to give substances, $R-CHOHCHNH_2-R'$, $RR'C(OH)CHNH_2-R''$, and $R_2C(OH)CHNH_2-R$. *Stovaine,* a cocaine substitute, is a benzoyl ester of such a compound. Its

preparation is as follows:

$$MeCOCH_2Cl \rightarrow MeCOCH_2NMe_2 \rightarrow$$
$$MeEtC(OH)CH_2NMe_2 \rightarrow MeEt(Me_2NCH_2)CCOC_6H_5$$

**Taurine,** 2-aminoethyl sulfonic acid, $H_2NCH_2CH_2SO_3H$ or, more properly $[\oplus H_3NCH_2CH_2SO_3\ominus]$ is found combined as taurocholic acid in bile. Its structure follows from its preparation starting with ethylene chlorohydrin

$$HOCH_2CH_2Cl \rightarrow HOCH_2CH_2SH \rightarrow HOCH_2CH_2SO_3H \rightarrow$$
$$ClCH_2CH_2SO_2Cl \rightarrow ClCH_2CH_2SO_3H \rightarrow H_2NCH_2CH_2SO_3H$$

### *B.* Diamines

Those having the amino groups on the same carbon are unstable.

$$=C(NH_2)_2 \rightarrow =C=NH \xrightarrow{H_2O} =C(OH)NH_2 \rightarrow =C=O$$

While methylene diamine, $CH_2(NH_2)_2$, is unstable, its dihydrochloride is stable and can be made from formamide (Rep. 1915, 82):

$$2\,HCONH_2 + CH_2O \rightarrow CH_2(NHCHO)_2 \rightarrow CH_2(NH_3Cl)_2$$

Those with the amino groups on different carbons are stable and show ordinary amine reactions.

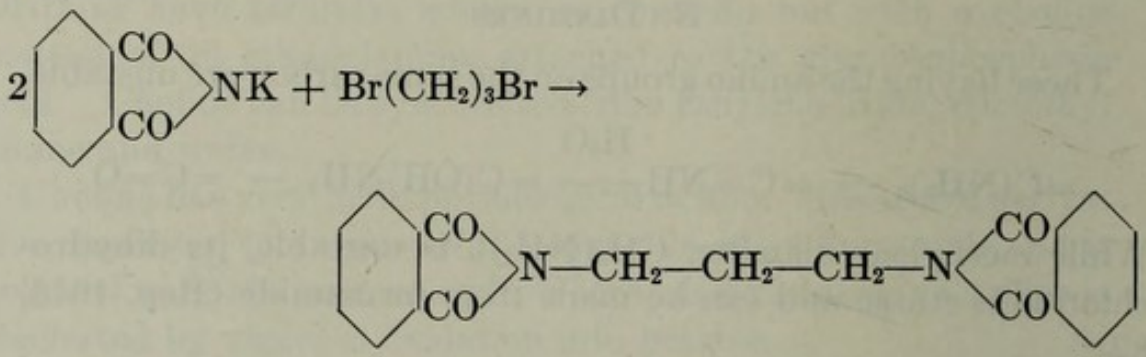
**Ethylene diamine,** 1,2-diaminoethane, $H_2NCH_2CH_2NH_2$, b. 116°, is readily available because of cheap ethylene dichloride obtained as a by-product in making ethylene chlorohydrin. Diethylene diamine (piperazine) $HN(CH_2CH_2)_2NH$ and triethylene diamine, $N(CH_2CH_2)_3N$ are also known. Ethylene diamine forms a monohydrate which can be distilled unchanged. When its hydrochloride is heated, two molecules form the 6-ring, piperazine

$$2\,HCl.NH_2CH_2CH_2NH_2.HCl \rightarrow$$
$$HCl.NH(CH_2CH_2)_2NH.HCl + 2\,NH_4Cl$$

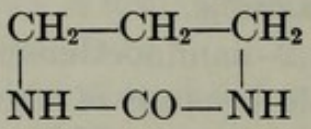
The first step is the formation of a molecule $NH(CH_2CH_2NH_2)_2$, in which the terminal $NH_2$ groups can approach closely in space and so can react more readily with each other than with $NH_2$ groups in other molecules.

In general, diamines can be made by catalytic reduction of amino nitriles. Thus aldehydes readily give $RCH(NH_2)CH_2NH_2$ while ketones less readily give $RR'C(NH_2)CH_2NH_2$. In the latter case the yield of amino nitrile is poorer and the final product also tends to form the 6-ring tetra-alkyl piperazine with elimination of the tertiary $NH_2$ groups from two molecules of the first product.

**Trimethylene diamine,** 1,3-diaminopropane, $H_2N(CH_2)_3NH_2$, b. 137°, prepared from the dibromide and ammonia gives the usual amine reactions. Its best preparation is by Gabriel's phthalimide synthesis.



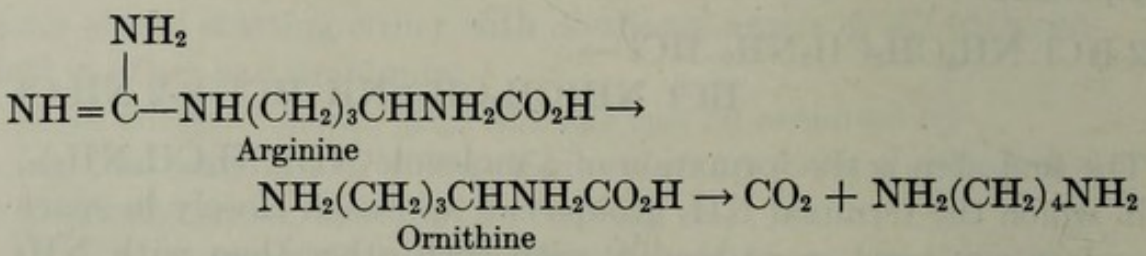
The trimethylene phthalimide is hydrolyzed by concentrated HCl. Heat has little effect on trimethylene diamine. It acts with diethylcarbonate to give the 6-ring trimethylene urea,



**Tetramethylene diamine,** 1,4-diaminobutane, putrescine,

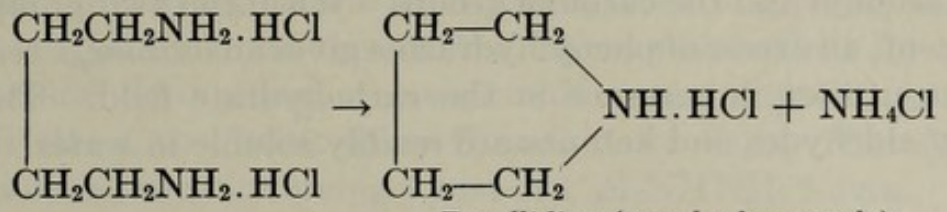
$$H_2N(CH_2)_4NH_2,$$

b. 158° is a product of decaying flesh produced by the bacterial decomposition following protein hydrolysis.



It can be prepared from the corresponding dibromide or, better,

by reduction of *ethylene dicyanide* with Na and absolute ethanol. Besides giving the ordinary primary amine reactions, putrescine forms a five-membered ring on heating.




Pyrollidine (tetrahydropyrrole)

**Pentamethylene diamine,** cadaverine, $H_2N(CH_2)_5NH_2$, b. 179°, is formed in the decay of lysine,

$$NH_2(CH_2)_4CHNH_2CO_2H \rightarrow CO_2 + NH_2(CH_2)_5NH_2$$

Heat converts it, by loss of $NH_3$, to pentamethylene imine, $(CH_2)_5NH$, piperidine (hexahydropyridine), another example of the ease of closure of a 6-ring.

Two *higher amines* have been isolated from sperm, spermidin, $NH_2(CH_2)_3NH(CH_2)_4NH_2$, and spermin,

$$NH_2(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2.$$

The latter has been synthesized by a simple series of reactions.

$$\underset{\text{Phenol}}{C_6H_5OH} + \underset{\text{In excess}}{Br(CH_2)_3Br} \rightarrow C_6H_5O(CH_2)_3Br$$

$$BrCH_2CH_2Br \rightarrow CNCH_2CH_2CN \rightarrow NH_2(CH_2)_4NH_2$$

$$2\,C_6H_5O(CH_2)_3Br + NH_2(CH_2)_4NH_2 \rightarrow$$

$$C_6H_5O(CH_2)_3NH(CH_2)_4NH(CH_2)_3OC_6H_5 \xrightarrow{HBr}$$

$$Br(CH_2)_3NH(CH_2)_4NH(CH_2)_3Br \xrightarrow{NH_3} \text{spermin.}$$

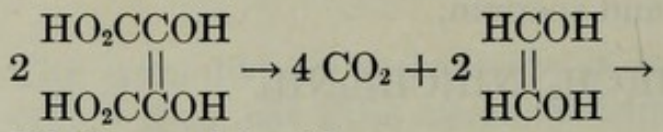
## XVII. HYDROXY ALDEHYDES AND KETONES

In addition to giving the typical reactions of alcohols and aldehydes these compounds show in a remarkable way the tendency for reaction between alcohols and aldehydes. It is apparently very difficult to have these two groups in the free condition in the

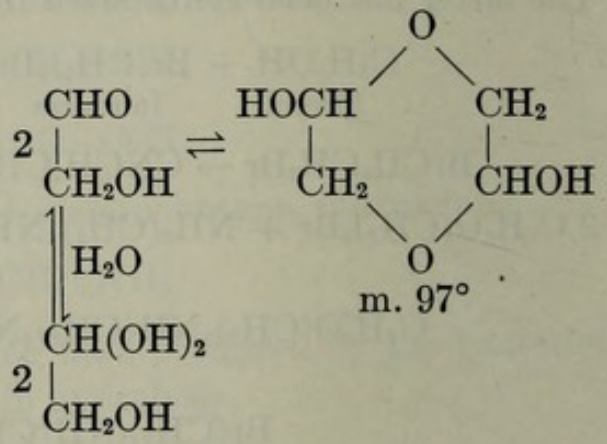
same molecule. There is a constant tendency for ring formation, between two molecules if the groups are close together or within the same molecule if there are at least two carbon atoms between the carbonyl and the carbinol groups When the two groups are adjacent, an excess of phenylhydrazine gives an *osazone*, a reaction of the utmost importance in the carbohydrate field. The hydroxy aldehydes and ketones are readily soluble in water.

### *A.* Hydroxy Aldehydes

**Glycollic aldehyde,** hydroxyacetaldehyde, ethanolal, glycolose, $HOCH_2CHO$, is obtained by the careful hydrolysis of bromoacetaldehyde. It exists only in aqueous solution. A crystalline dimer can be made by heating dihydroxymaleic acid (Fenton 1899). Its freshly prepared solution shows the molecular weight of the dimer but on standing three days the solute has the single molecular weight. A very interesting series of changes is involved in these processes.




Dihydroxymaleic acid




The decarboxylation leaves an *enediol* which changes to the carbonyl form. Two molecules unite as a double *hemiacetal* having a six-membered ring and a high degree of symmetry, thus giving the high melting point. The crystalline dimer can be vaporized under diminished pressure giving the monomeric vapor which condenses to the crystalline product again. On standing in aqueous solution, the stable hydrated monomer is formed.

Careful oxidation converts it to glycollic acid $HOCH_2CO_2H$. Dilute alkalies cause an aldol condensation producing trihydroxybutyraldehyde, an aldotetrose. Further condensation gives a hexose. Phenylhydrazine forms the osazone of glyoxal, m. 169°. This is a general reaction in the carbohydrate field for giving crystalline derivatives of compounds containing the grouping $-CHOH-CO-$, with either H or C at the ends. The steps in the process, each involving 1 mol of $C_6H_5NHNH_2$ follow:

$$HOCH_2CHO \rightarrow \underset{\text{Phenylhydrazone of glycollic aldehyde}}{HOCH_2CH=NNHC_6H_5} \rightarrow$$

$$\underset{\text{Mono-phenylhydrazone of glyoxal}}{OCHCH=NNHC_6H_5} \rightarrow \underset{\text{Di-phenylhydrazone or phenyl } \textit{osazone} \text{ of glyoxal}}{C_6H_5NHN=CHCH=NNHC_6H_5}$$

The second step involves the oxidation of the CHOH group to a carbonyl group by the phenylhydrazine, the latter being reduced to aniline and ammonia. Since phenylhydrazine does not ordinarily oxidize alcohols the process calls for a special explanation. This oxidation takes place only when the carbinol group is *alpha* to a carbonyl group. Thus $MeCOCH_2CH_2OH$ does not give an osazone. As is so often the case, when peculiar reactions are given by a carbon alpha to a carbonyl group, enolization or a similar process is involved. Once again a system of the type $HM-Q=Z \rightleftharpoons M=Q-ZH$ appears. Thus

$$HOCH_2CH=NNHAr \rightleftharpoons HOCH=CH-NHNHAr$$

The latter is an enol, a type of substance very easily oxidized.

Glycollic aldehyde reduces ammoniacal silver solution and alkaline copper solutions (Fehling's solution). With alpha naphthol and sulfuric acid it gives the violet color characteristic of sugars (Molisch Test, 1886). It gives a yellow color when heated with alkalies.

**Lactic aldehyde,** propanol-2-al, $\alpha$-hydroxypropionaldehyde, $CH_3CHOHCHO$, exists in a crystalline dimeric form, m. 105°. To prepare it, methylglyoxal, MeCOCHO, is treated with 2% alcoholic HCl to give the diethyl acetal, $MeCOCH(OEt)_2$, b. 162°. This is reduced by sodium and alcohol to lactic aldehyde diethyl

acetal, $MeCHOHCH(OEt)_2$, which is converted to the dimer of the aldehyde on standing with excess 0.1 N sulfuric acid. In common with other alpha hydroxyaldehydes, lactic aldehyde can be prepared from the proper polymeric aldehyde. Thus para-propionaldehyde, $(MeCH_2CHO)_3$ treated with bromine at $-10°$ and then with EtOH gives the acetal, $MeCHBrCH(OEt)_2$. Careful hydrolysis with water gives a solution of lactic aldehyde.

Distillation of the dimeric form under diminished pressure gives the monomer which quickly reverts to the dimer. Distillation at higher temperatures gives an isomerization to acetol, $MeCOCH_2OH$. The hydrolysis of the acetyl derivative of lactic aldehyde prepared from Ag acetate and alpha iodopropionaldehyde gives acetol.

Lactic aldehyde under the influence of very dilute alkali gives acetylcarbinol (acetol) (Nef 1904). This is the same change as the conversion of glucose to mannose and probably goes through the enediol (Lewis).

$$MeCHOHCHO \rightleftharpoons MeC(OH)=CHOH \rightleftharpoons MeCOCH_2OH$$

This type of change is very important in the interconversion of aldoses and ketoses.

In solution, the dimer of lactic aldehyde slowly changes to the monomer, probably in hydrated form.

$$\begin{matrix} MeCH—O—CHOH \\ \quad | \qquad\quad | \\ HOCH—O—CHMe \end{matrix} \rightleftharpoons 2\,MeCHOHCHO \overset{H_2O}{\rightleftharpoons} MeCHOHCH(OH)_2$$

With phenylhydrazine it first gives the phenylhydrazone of the aldehyde and then the osazone of methylglyoxal,

$$MeC(=NNHPh)CH(=NNHPh),$$

m. 145°.

**β-Hydroxypropionaldehyde,** hydracrylic aldehyde, propanol-3-al, $HOCH_2CH_2CHO$, $b_{18}$. 90°, can be made from acrolein, $CH_2=CHCHO$, and water at 100° (Nef 1904). It differs from the alpha hydroxyaldehydes in not forming a dimer. Such a process would involve the formation of an 8-membered ring. It reduces ammoniacal silver solution but not Fehling's solution. Dehydration gives acrolein. It forms no osazone.

**α-Hydroxyisobutyraldehyde,** 2-methylpropanol-2-al,

$$(CH_3)_2C(OH)CHO,$$

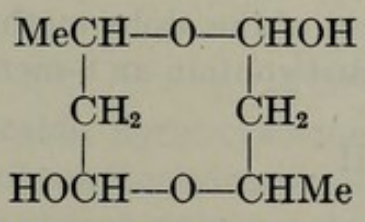
b. 137°, can be made by hydrolysis of the corresponding alpha bromo aldehyde with water. It forms a *hydrate*, m. 70°. The probability is that all aldehydes form such hydrates. In this case the molecule is sufficiently symmetrical to form crystals readily. Bases cause the Cannizzaro reaction, disproportionation to the corresponding alcohol and acid (as its salt). As usual this reaction is characteristic of aldehydes with no alpha hydrogen. On standing, it gives a crystalline polymer, m. 65°. It gives no osazone. Thus osazone formation is dependent on the groupings $-COCH_2OH$ and $-COCHOH-$. Phenyl hydrazine is not a strong enough oxidizer to break the carbon chain.

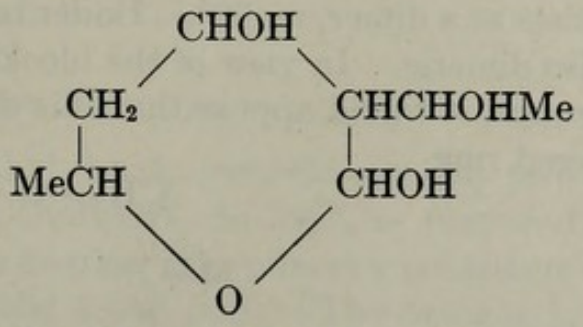
**Acetaldol,** aldol, butanol-3-al, β-hydroxybutyraldehyde,

$$CH_3CHOHCH_2CHO,$$

$b_{20}$. 83°, is formed by the action of a trace of very weak acid or alkaline reagents such as dilute HCl or sodium carbonate on acetaldehyde (Wurtz 1872). It can be distilled under reduced pressure but at temperatures above 85° it loses water because of the active alpha hydrogen atoms and forms crotonic aldehyde, $MeCH=CHCHO$. It reduces ammoniacal silver solution, being oxidized to β-hydroxybutyric acid. Aluminum amalgam and water reduce it to 1,3-butylene glycol. Yeast gives the *dextrorotatory* glycol.

On standing, aldol forms a dimer, m 90° (Paraldol) which reverts to the monomeric form on distillation. The high melting point of the dimer would indicate a symmetrical structure. Two of the possibilities are




The former has the disadvantage of an improbable 8-membered

ring. The latter would be the result of an aldol condensation followed by an inner hemiacetal formation. Depolymerization would involve a reversal of the aldol condensation which is entirely possible especially when the $\alpha-H$ is also alpha to a carbinol group.

Paraldol, on heating at 170°, gives the ester,

$$MeCHOHCH_2CO_2CH_2CH_2CHOHMe$$

(Ostromisslenski 1916). While such a disproportionation of aldehydes, 2 RCHO → $RCO_2CH_2R$, is well known, it is hard to understand why there is no dehydration under the conditions used.

Paraldol, heated with a trace of iodine, gives an 80% yield of crotonaldehyde (Hibbert 1915).

Aldol forms an oily phenylhydrazone but *not* an osazone. The alcohol group must be alpha to the hydrazone group to undergo the oxidation by phenylhydrazine necessary for osazone formation.

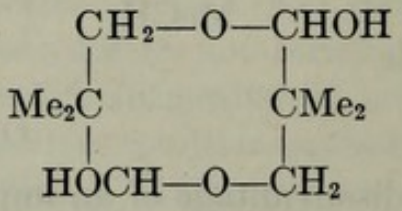
*p*-Bromophenylhydrazone of aldol, m. 128°.

Products related to aldol are dialdan, $C_8H_{14}O_3$, m. 140°, and isodialdan (tetraldan), $C_{16}H_{28}O_6$, m. 113°. The structures usually assigned are not reasonable considering their high melting points. Dialdan can be converted to an alcohol and an acid. It also forms a diacetate. Isodialdan shows no reactions of aldehydes, alcohols or double bonds.

**Formisobutyraldol,** 2,2-dimethylpropanolal, pentaldol,

$$HOCH_2C(CH_3)_2CHO,$$

b. 173° dec., can be made from isobutryaldehyde and 1 mol of formaldehyde at low temperature with weak alkalies. More vigorous treatment reduces the aldehyde group to $CH_2OH$. It exists as a dimer, m. 90°. Under reduced pressure the vapors are also dimeric. In view of the blocking effect of the alpha methyl groups, it would appear that this dimer must contain an 8-membered ring



The existence of such a structure would be remarkable evidence of the inability for hydroxyl and carbonyl groups to exist as such in the same molecule. This property is of the utmost importance in the sugars. Another explanation of dimers which apparently involve 8-membered rings is that they are really 1,3-propylene oxides polymerized through the unsaturated affinity of the bridge oxygen (Rep. 1924, 74).

The reactions of formisobutyraldol are those to be expected from a primary alcohol and an aldehyde with no $\alpha-H$. Oxidation gives first hydroxypivalic acid, $HOCH_2CMe_2CO_2H$, and then dimethylmalonic acid. Reduction gives the 1,3-glycol. Alkali gives the Cannizzaro reaction. With acetaldehyde and $K_2CO_3$ it gives 2,2-$Me_2$-pentandiol-1,3-al-5.

**Higher hydroxy aldehydes** which have the hydroxyl in the gamma or delta position exist as inner hemiacetals. (Rep. 1922, 78.) The properties of these substances are somewhat like those of the aldopentoses and aldohexoses. The aldehyde reactions are modified. Methyl alcoholic HCl, instead of giving an acetal $-CH(OMe)_2$, gives a methyl derivative of the cyclic hemiacetal exactly analogous to the methyl glucosides. Even when the hydroxyl group is farther away, ring formation is possible. Thus $\omega$-hydroxynonylic aldehyde with MeOH and HCl gives a cyclic acetal, $(CH_2)_7CHOMe$ (Rep. 1925, 71). Evidently such a

$$\begin{array}{l} | \quad | \\ CH_2—O \end{array}$$

compound cannot have a ring lying in a plane. The cyclic forms of the hydroxy aldehydes and ketones are *lactoles*. Typical examples are $\gamma$-butyrolactole, $\delta$-valerolactole, and $\gamma$-valerolactole related to butanol-4-al, pentanol-5-al and pentanol-4-al.

The compound $C_{15}H_{31}CHOHCH_2CH_2CHO$ exists in dynamic isomerism with the aldolactole (Rep. 1924, 74).

## *B.* Hydroxy Ketones

**Acetol,** hydroxyacetone, methyl ketol, pyruvic alcohol, propanolone, acetylcarbinol, $CH_3COCH_2OH$, b. 147°, is prepared from chloro- or bromoacetone by heating with pure dry potassium formate in absolute methanol (Nef 1904) (OS). The halogen is first replaced by the formate group and the latter is then removed

by alcoholysis. $ROCHO + MeOH \rightarrow ROH + HCO_2Me$. This procedure is useful for converting to alcohols, halides which give undesirable reactions with alkaline reagents. Acetol reduces Fehling's solution and ammoniacal silver solution. In common with other alpha hydroxy carbonyl compounds, it owes this property to its ability to form an enediol, very sensitive to oxidation, $MeC(OH)=CHOH$. The product of the oxidation of acetol with alkaline cupric solutions is lactic acid, $MeCHOHCO_2H$ (Kling 1903).

Acetol gives a phenylhydrazone and the osazone of methylglyoxal, m. 145°. Biochemical reduction by means of a fermenting sugar solution gives levorotatory propyleneglycol (Levene, OS). The reverse process takes place when the Sorbose-bacterium acts on propylene glycol. This organism has the ability to convert $-CHOHCH_2OH$ to $-COCH_2OH$. With HCl and EtOH, acetol gives the ether, $MeCOCH_2OEt$. With HCl and MeOH, however, it gives the dimethyl ether of the cyclic dimer, m. 127°. This does not reduce Fehling's solution. Heating with dilute acid converts it to acetol. The monomeric methyl ether can be obtained from methyl propargyl ether,

$$MeOCH_2C\equiv CH,$$

and mercuric salts. It reduces Fehling's solution in the cold. A substance of the structure, $MeOCH_2COMe$ would not be expected to be so strong a reducing agent since neither ketones nor ethers are readily oxidized. It is probable that its easy oxidation in common with that of substances containing the $-COCHOH-$ grouping is due to the formation of the very reactive enediol or related ether

$$MeCOCH_2OMe \rightleftharpoons MeC(OH)=CHOMe.$$

The C=C group is well known to be sensitive to oxidation. Moreover a carbon already attached to O is more readily oxidized than one not so attached. Thus an enediol of this type would be readily oxidized. The oxidation during osazone formation is probably due to a similar process (p. 399).

In water solution, acetol is believed to exist largely as an internal hemiacetal or, more probably, as a cyclic dimer.

**Propionylcarbinol,** butanol-1-one-2, ethyl ketol, ethyl hydroxymethyl ketone, $CH_3CH_2COCH_2OH$, b. 156°, can be made from chloromethyl ethyl ketone through its formate like acetol. The water solution is strongly acid and is believed to contain the hemi-acetal, 1,2-epoxybutanol-2. An ordinary cyclic dimer would not be expected to give acid properties.

The ethers of alpha hydroxy ketones can be prepared as follows

$$ROH + H_2CO + HCl \rightarrow ROCH_2Cl \rightarrow$$

$$ROCH_2CN \xrightarrow{R'MgX} ROCH_2COR'.$$

$$ROH + R'CHO + HCl \rightarrow ROCHClR' \rightarrow$$

$$ROCH(CN)R' \xrightarrow{R''Mg\ X} ROCH(R')COR''$$

Each step gives a good yield.

Another useful preparation for monoalkyl ketols, $RCOCH_2OH$, starts with chloroacetaldehyde and the Grignard reagent, followed by oxidation of the secondary alcohol group by chromic acid mixture and the replacement of the chlorine through the formate (Levene).

**Acetoin,** acetylmethylcarbinol, dimethyl ketol,

$$CH_3COCHOHCH_3,$$

m. 15°, b. 145°, can be made by the partial reduction of diacetyl with Zn and acid but it is available commercially (Lucidol Corp.), as a product of fermentation. It is presumably formed in this process from acetaldehyde by a dismutation (disproportionation) resembling the benzoin condensation of aromatic aldehydes $2\ MeCHO \rightarrow MeCOCHOHMe$. It is the intermediate product for the diacetyl, MeCOCOMe, and 2,3-butyleneglycol formed in the same fermentation.

At least three crystalline dimers of acetoin have been described. These all revert to the monomer on distillation. In water solution it exists in the hydroxy ethylene oxide form. The nature of the dimers is not settled (Rep. 1930, 95).

Acetoin gives a phenylhydrazone, m. 84°, and the osazone of diacetyl, m. 242°.

Acetoin is the simplest of the acyloins, RCOCHOHR obtain-

able from acid chlorides and from organic esters by the action of Na in moist ether (Corson 1930). The reaction probably takes place through the formation of the disodium derivative of the enediol. When the latter is liberated, it ketonizes (Bouveault 1906).

$$2\,RCOCl \xrightarrow{Na} NaCl + \underset{\underset{ONa}{|}}{RC} = \underset{\underset{ONa}{|}}{CR} \rightarrow \underset{\underset{OH}{|}}{RC} = \underset{\underset{OH}{|}}{CR} \rightarrow RCOCHOHR$$

Acyloins, on heating, undergo a strange dismutation giving a diketone RCOCOR and an aldehyde.

Mixed acyloins may be made from aldehyde cyanohydrins and the Grignard reagent. One mol of the latter is wasted by action with the OH group.

$$RCHO \rightarrow RCH(OH)CN \rightarrow RCHOHCOR'$$

Mixed acyloins in which R′ is larger than R undergo a rearrangement to RCOCHOHR′ when heated in alcohol solution with a trace of acid. The tendency is apparently to form the smallest possible acyl group (Rep. 1927, 65).

**β-Acetyl ethyl alcohol,** acetonylcarbinol, butanol-4-one-2, $CH_3COCH_2CH_2OH$, $b_{30}$. 110°, can be made from acetone and formaldehyde with potassium carbonate solution. As usual with this type of reaction the difficulty is to stop it after the first step. The other five alpha hydrogen atoms of the acetone tend to react. The water soluble product, on standing, changes to a viscous insoluble oil.

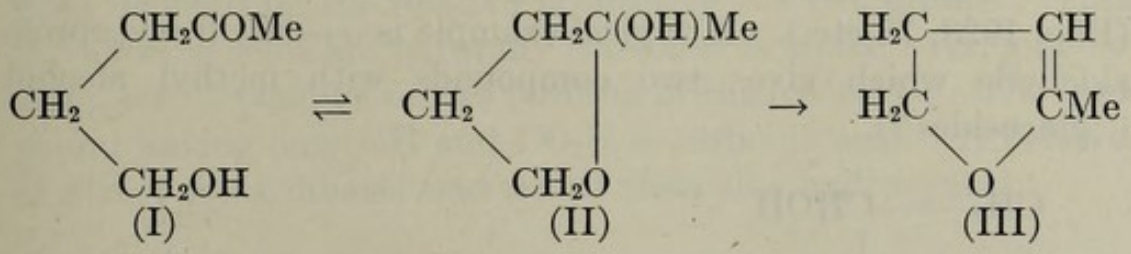
**Methylacetonylcarbinol,** pentanol-4-one-2,

$$CH_3CHOHCH_2COCH_3,$$

b. 177°, can be made from acetone and acetaldehyde with KCN solution. On heating at 250° it becomes ethylidene acetone, MeCH=CHCOMe. The difficulty with which it loses water is in sharp contrast to the behavior of the product from benzaldehyde and acetone which loses water spontaneously. Phenylhydrazone, m. 103°. No osazone.

**Methyl γ-hydroxypropyl ketone,** β-hydroxyethylacetone, pentanol-5-one-2, $CH_3COCH_2CH_2CH_2OH$, $b_{100}$ 145°, can be made

from sodium acetoacetic ester and excess ethylene dibromide followed by the usual ketone splitting. The second bromine atom is hydrolyzed in the process. On heating, it gives 2-Me-4, 5-dihydrofuran (III). It reduces ammoniacal silver solution *on heating*. Since neither ketones nor primary alcohols give this reaction the formula (I) does not agree with the facts. The hydroxyl and carbonyl group are far enough apart to react through ring formation to give an inner hemiacetal (II).

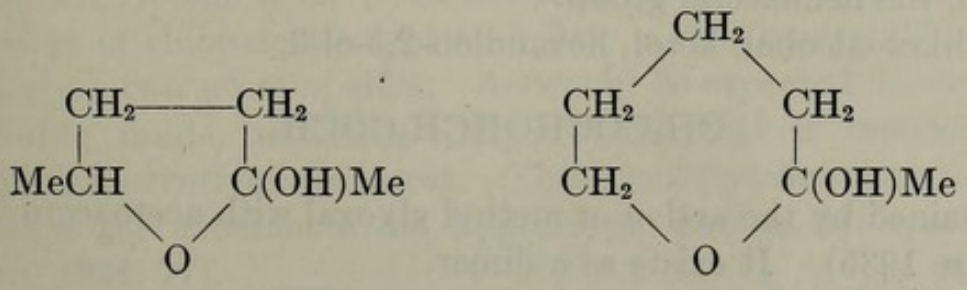



This type of substance is more readily oxidizable, as in the case of gamma sugars.

The primary alcohol group shows normal reactions, replacement on treatment with HBr and oxidation to carboxyl (levulinic acid). The carbonyl group can be reduced (pentandiol-1,4) and reacts normally with the Grignard reagent.

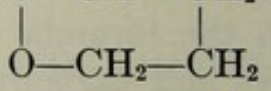
**Diacetone alcohol,** dimethylacetonylcarbinol, 2-Me-pentanol-2-one-4, $(CH_3)_2C(OH)CH_2COCH_3$, b. 166°, is obtained by the aldol condensation of acetone in the presence of a solid base (OS). On dehydration, it gives mesityl oxide, $Me_2C=CHCOMe$, a typical alpha beta unsaturated ketone.

**Hexanol-5-one-2,** $CH_3CHOHCH_2CH_2COCH_3$, $b_{100}$ 142°, and *Hexanol-6-one-2,* $HO(CH_2)_4COCH_3$, $b_{100}$ 157°, differ notably in that the first reduces Fehling's solution and ammoniacal silver solution on heating while the latter does not. This recalls the difference in activity of the furanose (gamma) and pyranose sugar derivatives. Both these ketones exist as cyclic compounds:

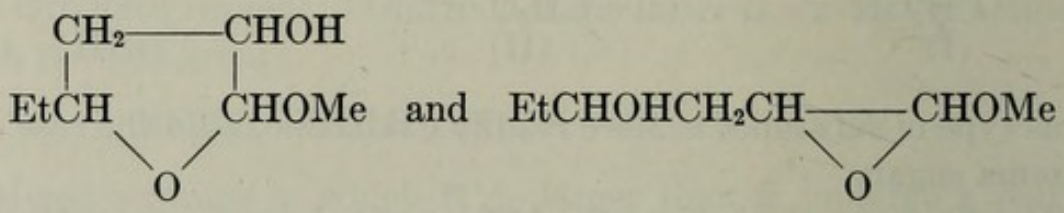


They could be regarded as tetradesoxy-fructofuranose and -fructopyranose respectively.

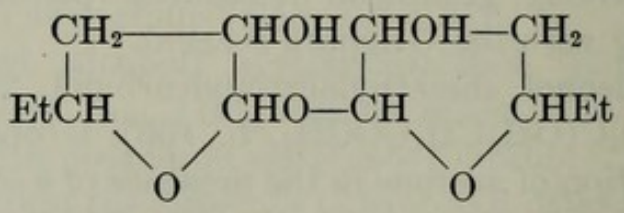
Both these hydroxy ketones, on long heating, give anhydrides, the first 2,5-$Me_2$-2,3-dihydrofuran b. 70° (red violet color with pine shaving and HCl) and the second



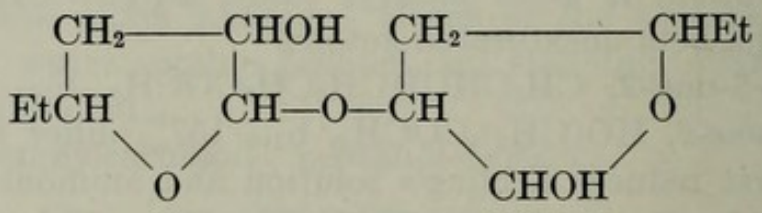
**Polyhydroxy aldehydes and ketones,** even more nearly related to the sugars, have been made by Helferich and his students (Rep. 1923, 78 etc.). A typical example is $\alpha\gamma$-dihydroxycaproic aldehyde which gives two compounds with methyl alcohol ("glucosides").



Two mols of the aldehyde form a "biose."



or



These would correspond to a non-reducing and a reducing biose respectively since the second contains a potential aldehyde group, the hemiacetal group.

A diketoalcohol, ketol, hexandion-2,5-ol-3,

$$CH_3COCHOHCH_2COCH_3,$$

is obtained by the action of methyl glyoxal with acetoacetic acid (Henze 1935). It exists as a dimer.

## XVIII. HYDROXY MONOBASIC ALIPHATIC ACIDS

### *A.* Mono-hydroxy Acids

These acids are found widely distributed in nature in fruit juices. They show the individual properties of alcohols and acids and also special properties due to the presence of both these reactive groups in the same molecule. The nature of these reactions depends on the relative position of the two groups. Thus the hydroxyacids are naturally classified as alpha, beta, gamma, delta, etc. depending on the position of the hydroxyl. The compound having only OH and $CO_2H$ is carbonic acid. It behaves as a very weak dibasic acid rather than as a hydroxyacid.

### Alpha Hydroxyacids

**Glycollic acid,** hydroxyacetic acid, $HOCH_2CO_2H$, occurs in dimorphic forms, m. 63° and 80°.

*Preparation.* 1. By boiling monochloroacetic acid with water in presence of a substance like $CaCO_3$.

2. By oxidizing glycol with dil $HNO_3$.

3. By electrolysis of oxalic acid solution with lead electrodes. Such a reduction of a carboxyl group is unusual.

4. An even more unusual preparation is that from "potassium carbonyl" (Joannis 1914). CO is passed through a solution of metallic potassium in liquid $NH_3$ at $-50°$ and the product is cautiously hydrolyzed.

$$2\,KNH_3 + 2\,CO \rightarrow KOC{\equiv}COK \rightarrow HOCH_2CO_2K$$

*Reactions.* 1. It gives the usual reactions of a primary alcohol and a carboxylic acid.

2. Several "anhydrides" of glycollic acid are known.

(*a*) Diglycollic acid, $O(CH_2CO_2H)_2$, is obtained by boiling a solution of chloroacetic acid with lime. It is a crystalline solid and gives two series of salts. As would be expected, it can form a 6-ring imide, $O(CH_2CO)_2NH$. While this is tasteless, its N-alkyl derivatives are sweet. This property cannot be utilized because the substances are hygroscopic and easily hydrolyzed (Rep. 1921, 77).

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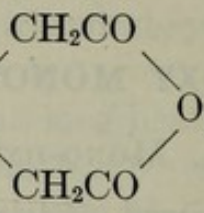
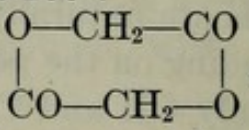
(*b*) Diglycollic anhydride,  , is obtained by heating the corresponding acid.

(*c*) "Glycollic anhydride" is really an ester

$$HOCH_2CO_2CH_2CO_2H,$$

formed by heating glycollic acid at 100°.

(*d*) Glycollide, a cyclic di-ester,  , m. 87°, formed by vacuum distillation of sodium bromoacetate.

(*e*) Polyglycollide, $(-OCH_2CO-)x$, a solid, large ring polymer.

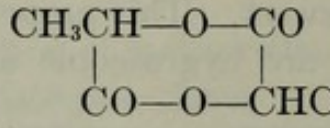
**Lactic acid,** $\alpha$-hydroxypropionic acid, $CH_3CHOHCO_2H$. Because of its asymmetric molecule due to a carbon attached to four different groups, lactic acid can exist in *d*- and *l*-forms. Most lactic acid is prepared in the *dl*-form by various fermentations of carbohydrates in the presence of calcium carbonate. Dextrorotatory lactic acid, *sarcolactic acid*, is formed in the muscles from glycogen. If certain types of *Penicillium* are allowed to grow in a solution of ammoniun *dl*-lactate, the dextrorotatory form remains unchanged. Levorotatory lactic acid is formed by the fermentation of sucrose by *Bacillus acidi levolactici*. In the systematic classification of optically active substances, levorotatory lactic acid is related to *d*-malic acid and is consequently properly named *d*-lactic acid while the lactic acid of muscle is *l*-lactic acid.

Ethyl lactate for use as a lacquer solvent is made directly from the cyanohydrin of acetaldehyde.

$$MeCHOHCN + H_2SO_4 + EtOH + H_2O \rightarrow MeCHOHCO_2Et + NH_4HSO_4$$

*Reactions.* 1. The usual acid and secondary alcohol reactions.

2. Heat alone or with dehydrating agents changes it to *lactide*.



3. With acids at about 130° it loses a molecule of formic acid.

$$CH_3CHOHCO_2H \rightarrow HCO_2H + CH_3CHO$$

These reactions are typical of alpha hydroxy acids.

The configurational relations of optically active forms of hydroxyacids, amino acids, halogen acids and simple carbohydrates have been studied in great detail (Levene, Rev. *2*, 179–216).

**α-Hydroxybutyric acid,** $CH_3CH_2CHOHCO_2H$, is made (a) from *n*-butyric acid through the α-halogen acid or (b) from propionaldehyde through its cyanohydrin. Its reactions are typically like those of lactic acid.

**α-Hydroxyisobutyric acid,** $(CH_3)_2C(OH)CO_2H$ is made (a) by hydrolyzing the cyanohydrin of acetone, (b) by mild oxidation of isobutyric acid (the tertiary H is easily oxidized by dilute $KMnO_4$), (c) by oxidation of trimethylethylene glycol by nitric acid (rearrangement), and (d) by hydrolysis of "acetone chloroform," $(CH_3)_2C(OH)CCl_3$, obtained by an aldol condensation between acetone and chloroform.

The reactions of α-hydroxyisobutyric acid are like those of other α-hydroxy acids except that the fork in the chain makes decomposition and oxidation easier. Iodine does not cause the dehydration of the tertiary alcohol group. The esters with $P_2O_5$ give methacrylic esters, $CH_2=CMeCO_2R$.

**α-Hydroxy-*n*- and *iso*-valeric acids** are made through the α-halogen acids or the cyanohydrins. Their reactions are normal, except that the iso acid on dehydration gives ββ-dimethylacrylic acid instead of a lactide, thus indicating the reactivity of a tertiary H.

$$Me_2CHCHOHCO_2H \rightarrow Me_2C=CHCO_2H$$

The salts of α-hydroxyisohexoic acid are sweet, the intensity of the taste varying in the optical isomers in the order

$$d- > dl- > l-$$

(Rep. 1920, 59).

The conductivity of α-hydroxyacids is increased by addition of boric acid (Boeseken 1921, Rep. 1922, 71). This is undoubtedly due to the formation of a more highly ionized complex acid be-

tween the boron atom and the hydroxyls in the 1,2 position. The effect on the conductivity is less in acids, $RR'C(OH)CO_2H$ than in $RCHOHCO_2H$.

*Cerebronic acid* is an $\alpha-(OH)-C_{25}$ acid with a branched chain (Rep. 1922, 72).

The amides of $\alpha$-hydroxyacids react with ketones and HCl to give oxazole derivatives, $\begin{matrix} RCH—O \\ | \quad\quad | \\ OCNHCR'R'' \end{matrix}$. Probably the first step involves an "aldol" condensation between an amido H and the CO group to give $RCHOHCONHC(OH)R'R''$. This has two hydroxyl groups in the 1,4 position so that dehydration gives a 5-ring.

$\alpha$-Hydroxyacid amides with bromine and KOH give aldehydes (Rep. 1922, 77). The Hofmann reaction would give $RCH(OH)NH_2$ which readily loses $NH_3$ to form the aldehyde.

## Beta Hydroxyacids

**Hydracrylic acid,** ethylene lactic acid, $\beta$-hydroxy propionic acid, $HOCH_2CH_2CO_2H$.

*Preparation.* 1. By partial oxidation of trimethylene glycol.

2. By hydrolysis of ethylene cyanohydrin.

3. By heating acrylic acid with alkalies. The addition of water takes place contrary to Markownikoff's Rule, probably by 1,4-addition.

*Reactions.* 1. Ordinary primary alcohol and carboxylic acid reactions.

2. Heat, dehydrating agents, and even heating with acids give acrylic acid.

$$HOCH_2CH_2CO_2H \rightarrow CH_2=CHCO_2H + H_2O$$

There is no tendency to form cyclic compounds because these would have either 4- or 8-membered rings. This ready conversion to alpha-beta unsaturated acids is characteristic of beta hydroxy acids and is dependent on the unusual reactivity of alpha H.

**β-Hydroxybutyric acid,** $CH_3CHOHCH_2CO_2H$ is obtained (a) from acetoacetic ester by reduction and hydrolysis, (b) by the partial oxidation of aldol, and (c) by the direct oxidation of

butyric acid by hydrogen peroxide. Its reactions are like those of hydracrylic acid except that the hydroxyl is on a secondary carbon and is, consequently, more easily removed to give an unsaturated compound. This removal of the OH takes place entirely with the alpha H and not at all with the gamma H. This acid occurs with acetoacetic acid in diabetic urine. Presumably it is more difficult to oxidize in the body than the $\alpha$-hydroxyacids (Witzemann 1926).

**β-Hydroxy*iso*butyric acid,** $HOCH_2CH(CH_3)CO_2H$, cannot be prepared by ordinary methods. These give $\alpha$-methyl acrylic acid instead, thus illustrating the reactivity of a hydrogen which is both tertiary and alpha. A 40% yield of the ester can be obtained by the action of trioxymethylene (polymer of formaldehyde) and ethyl $\alpha$-Br-propionate with zinc.

$$MeCHBrCO_2Et + HCHO + H_2O + Zn \rightarrow MeCH(CH_2OH)CO_2Et + BrZnOH$$

A lactone, $MeCH\underset{O=C-O}{CH_2}$, can be obtained by the action of silver nitrate on sodium $\beta$-iodoisobutyrate.

**β-Hydroxy-*n*-valeric acid,** $CH_3CH_2CHOHCH_2CO_2H$, is best made from the chlorohydrin of butene-1 through the cyanohydrin. Treatment of the $\beta$-halogen valeric acids with alkalies gives mainly the $\alpha\beta$-unsaturated acid.

**β-Hydroxy*iso*valeric acid,** $(CH_3)_2C(OH)CH_2CO_2H$, is obtained by the direct oxidation of isovaleric acid. In common with other *tertiary β-hydroxyacids* it can be obtained from a ketone and $\alpha$-bromoesters in the presence of amalgamated zinc (Reformatzky).

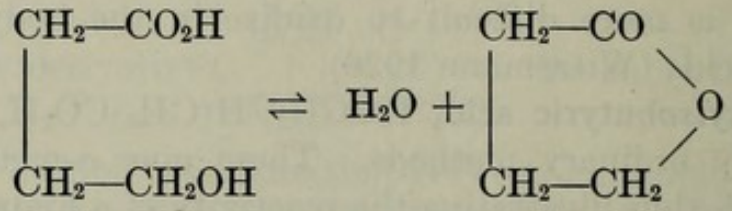
$$Me_2CO + Zn + BrCH_2CO_2Et \rightarrow Me_2C(OZnBr)CH_2CO_2Et \rightarrow Me_2C(OH)CH_2CO_2H$$

Similarly, methyl ethyl ketone and $\alpha$-bromopropionic ester would give $\alpha\beta$–$Me_2$–$\beta$–OH– valeric acid.

Beta lactones are possible when the alpha carbon has two alkyl groups. These prevent the ordinary dehydration to give an alpha beta unsaturated acid and also favor ring closure.

### Gamma Hydroxyacids

**γ-Hydroxybutyric acid,** $HOCH_2CH_2CH_2CO_2H$, exists only in solution and as its derivatives such as salts, esters, etc. The free acid readily forms an internal ester or lactone because the carboxyl and hydroxyl groups can approach each other closely in space.



The product is *butyrolactone,* (butanolide-1,4), a gamma lactone.

Butyrolactone is made from ethylene chlorohydrin through the acetoacetic ester or malonic ester synthesis. A later modification of this method uses vinyl beta-chloroethyl ether (Cretcher). The starting material is the very cheap dichlorodiethyl ether obtained in the ethylene solvent industry (C. and C.). This is treated with alkali to remove one HCl.

Na Malonic Ester + $ClCH_2CH_2OCH=CH_2 \rightarrow$

$$CH_2=CH—OCH_2CH_2CH(CO_2R)_2 \xrightarrow{NaOH}$$

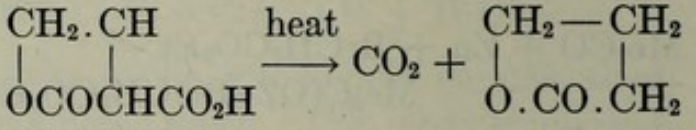
$$CH_2=CH—O—CH_2CH_2CH(CO_2Na)_2 \xrightarrow{Acid}$$

$$\left[CH_3—\underset{\displaystyle OH}{\underset{|}{CH}}—OCH_2CH_2CH(CO_2H)_2\right] \rightarrow$$

(*a*)

$$[CH_3CHO + HOCH_2CH_2CH(CO_2H)_2] \rightarrow$$

(*b*)

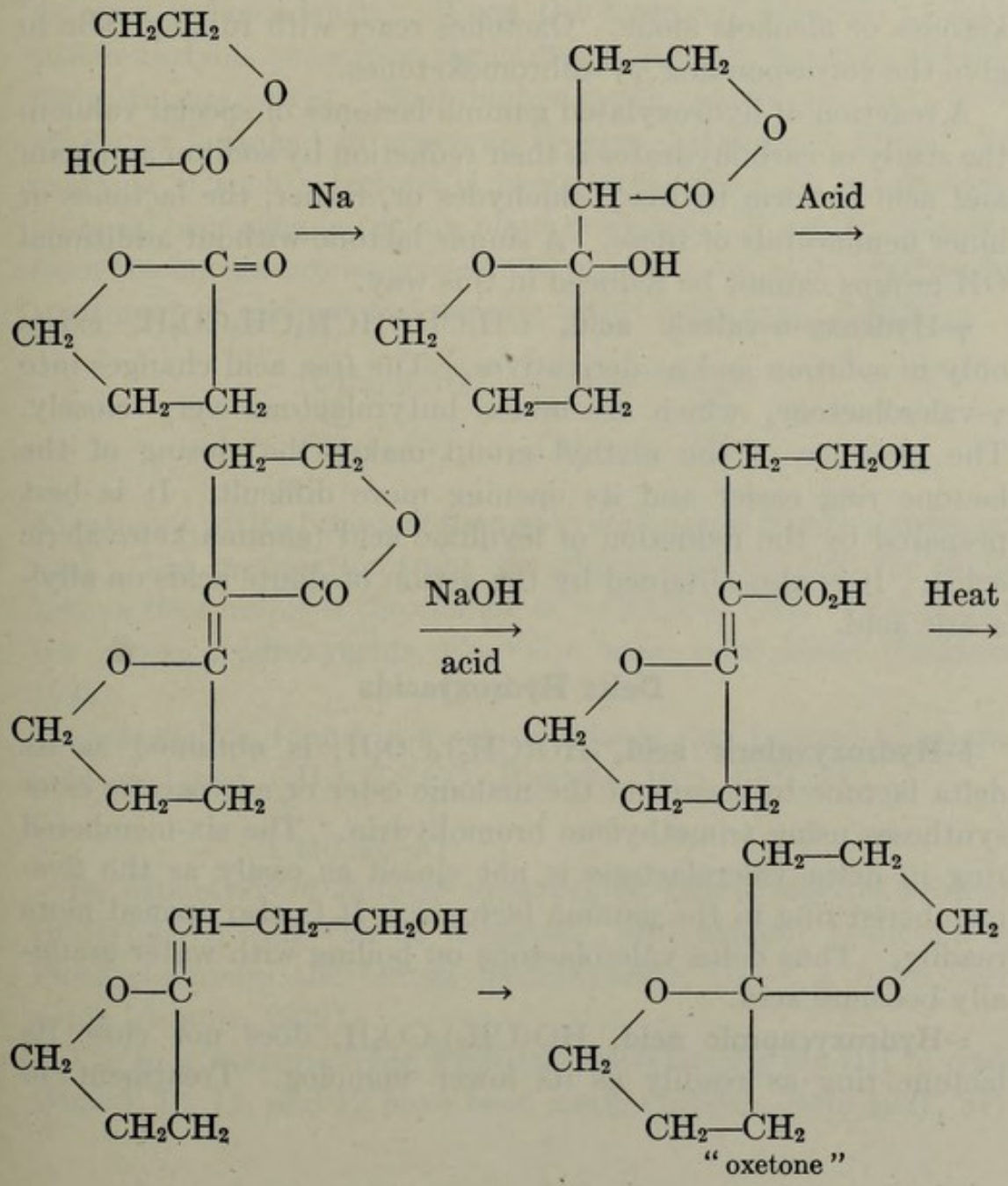


Compound (*a*) is formed by the hydration of the double bond in the presence of acid. It is a hemiacetal and consequently unstable. Thus the ether linkage $CH_2=CHOR$ differs from other ether linkages in being easily split by dilute acids. Compound (*b*) is a gamma hydroxy acid and immediately changes to the lactone.

*Reactions.* Butyrolactone reacts with (*a*) bases, (*b*) alcohols (acid catalysts), (*c*) halogen acids, (*d*) ammonia, (*e*) amines, etc., to give derivatives of γ-hydroxybutyric acid.

The presence of substituents changes the ease of opening of the lactone ring.

Metallic sodium and a trace of sodium ethylate cause a typical "aldol" condensation between the carbonyl group of one molecule of butyrolactone and the alpha H of another. Treatment with acid dehydrates the first product formed. Removal of $CO_2$ leaves "oxetone," a "lactone" or "inner acetal" of a γγ′-dihydroxy ketone.



All the steps involve well-known reactions except the last one in which the grouping C=C−C−C−O adds to itself to give a 5-membered ring. This same tendency causes $\beta\gamma$-unsaturated acids to change to lactones. The oxetone consists of two five-membered rings at right angles to each other in space with one carbon common to both rings. Such a combination of two rings with one atom in common is a *spiro* system. Homologous oxetones are obtained from higher gamma lactones.

The type of ring in oxetone resembles that found in many carbohydrates. Like many of the simpler sugars, oxetone reduces ammoniacal silver nitrate. This reaction is not given by ketones or alcohols alone. Oxetones react with fuming HBr to give the corresponding $\gamma\gamma'$-dibromoketones.

A reaction of hydroxylated gamma lactones of special value in the study of carbohydrates is their reduction by sodium amalgam and acid to form hydroxy aldehydes or, rather, the lactones or inner hemiacetals of these. A simple lactone without additional OH groups cannot be reduced in this way.

**$\gamma$-Hydroxy-*n*-valeric acid,** $CH_3CHOHCH_2CH_2CO_2H$, exists only in solution and as derivatives. The free acid changes into $\gamma$-valerolactone, which resembles butyrolactone very closely. The presence of the methyl group makes the closing of the lactone ring easier and its opening more difficult. It is best prepared by the reduction of levulinic acid (gamma ketovaleric acid). It is also obtained by the action of dilute acids on allylacetic acid.

## Delta Hydroxyacids

**$\delta$-Hydroxyvaleric acid,** $HO(CH_2)_4CO_2H$, is obtained as its delta lactone by means of the malonic ester or acetoacetic ester syntheses using trimethylene bromohydrin. The six-membered ring in delta valerolactone is not closed as easily as the five-membered ring in the gamma lactones. It is also opened more readily. Thus delta valerolactone on boiling with water gradually becomes acid.

**$\varepsilon$-Hydroxycaproic acid,** $HO(CH_2)_5CO_2H$, does not close its lactone ring as readily as its lower homolog. Treatment of

$\epsilon$-bromocaproic acid with NaOEt gives mainly a polymeric lactone $[O(CH_2)_5CO_2(CH_2)_5CO]x$ (Marvel 1929).

Gamma-, delta-, and epsilon-lactones behave as esters in acting with Na and EtOH to give the corresponding glycols (Rep. 1906, 120).

Lactones, Ahr. 1903, 64 pp.; 1920, 36 pp.

**Hydroxyl derivatives of many higher aliphatic acids** have been made. In general they follow the properties of the corresponding classes of simpler hydroxy acids. As the hydroxyl group is farther removed than the delta position, it and the carboxyl tend to react independently. When the hydroxyl group is at least twelve carbons away from the carboxyl, it again becomes possible for lactones to exist. Such higher cyclic compounds have their atoms so arranged in space as to give "strainless rings." An example of such a lactone is pentadecanolide-1,15, a musk-like material occurring in certain plant products. It can be obtained from the omega-bromo-acid and silver oxide, or, more readily, by treatment of cyclopentadecanone with Caro's acid, $H_2SO_5$,

$$\begin{array}{l} (CH_2)_{12}CH_2 \\ \quad\vert\quad\quad\vert \\ CH_2\text{—}CO \end{array} \rightarrow \begin{array}{l} (CH_2)_{12}\text{——}CH_2 \\ \quad\vert\quad\quad\quad\vert \\ CH_2\text{—}O\text{—}CO \end{array}$$

Treatment with a base and then with acid would give the hydroxy-acid. The preparation from the dibasic acid through the cyclic ketone thus involves the change of a $CO_2H$ to OH. In this way the omega hydroxyacids, $C_{13}-C_{17}$, have been made (Ruzicka 1928).

*Ambrettolide*, found in musk, is a large ring lactone of an unsaturated acid, $\begin{array}{l} CH(CH_2)_5CO \\ \Vert\quad\quad\vert \\ CH(CH_2)_8O \end{array}$ (Ruzicka, Rep. 1927, 89).

By ozonolysis of suitable unsaturated esters, aldehydo-esters, $OCH(CH_2)_nCO_2R$, can be obtained. By catalytic reduction of these aldehydes the omega hydroxyacids, $C_9-C_{13}$, have been made (Adams, 1929).

The four isomeric hydroxystearic acids having the OH in positions 9, 10, 11, and 12 have been made (Adams, Rep. 1927, 87).

The melting points of the 9-, and 10-(OH) acids and a 3 : 7 mixture of the two are 74–75°, 81–82° and 74–76° respectively.

Hydroxyacids in which neither small nor large rings can be formed give chain polymers on heating. Thus ω-hydroxydecanoic acid gives polymers of M.W. 1000–9000 and the general formula $HO(CH_2)_9CO_2[(CH_2)_9CO_2]_x(CH_2)_9CO_2H$. No cyclic compounds were found (Adams 1929).

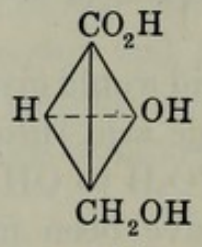
**Sabinic** and **juniperic acids** are ω-hydroxy derivatives of the normal $C_{12}$ and $C_{16}$ acids.

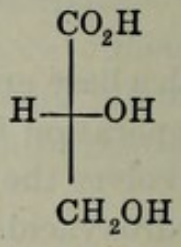
**Jalapinolic acid** is 11-(OH)-hexadecanoic acid. It has been synthesized from *n*-amyl-MgBr and methyl 10-aldehydo-decanoate (Davies, Adams 1928).

10-Hydroxystearic acid is obtained by hydrating oleic acid with sulfuric acid. No evidence for the simultaneous formation of the 9-OH compound exists.

### *B.* Polyhydroxy Acids

**Glyceric acid,** $HOCH_2CHOHCO_2H$, is obtained by careful oxidation of glycerol. *d*-Glyceric acid has the same configuration as *d*-lactic acid. Both are dextrorotatory.

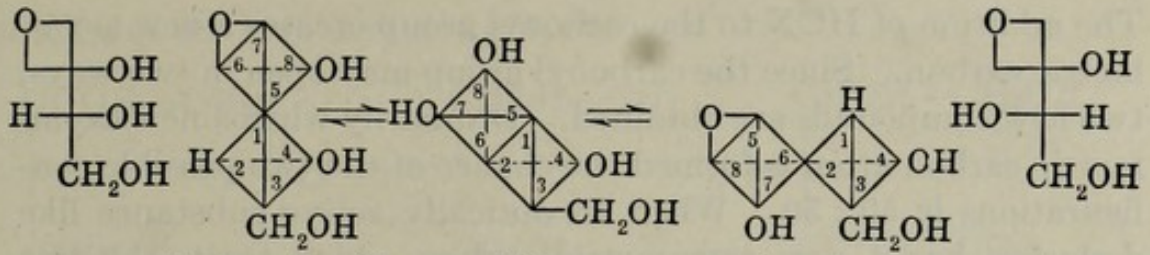



Besides the usual reactions expected from its primary and secondary alcohol groups and its carboxyl group, glyceric acid in either of its optically active forms undergoes a process of *racemization* on heating with water, alone or in the presence of an organic base such as quinoline. Since this process takes place readily only with an alpha asymmetric carbon, it probably goes through an enol form.

$$HOCH_2CHOHCO_2H \rightleftharpoons HOCH_2C(OH)C(OH)_2 \rightleftharpoons HOCH_2CHOHCO_2H$$

*d*- or *l*- *dl*-



d-glyceric acid enol form l-glyceric acid

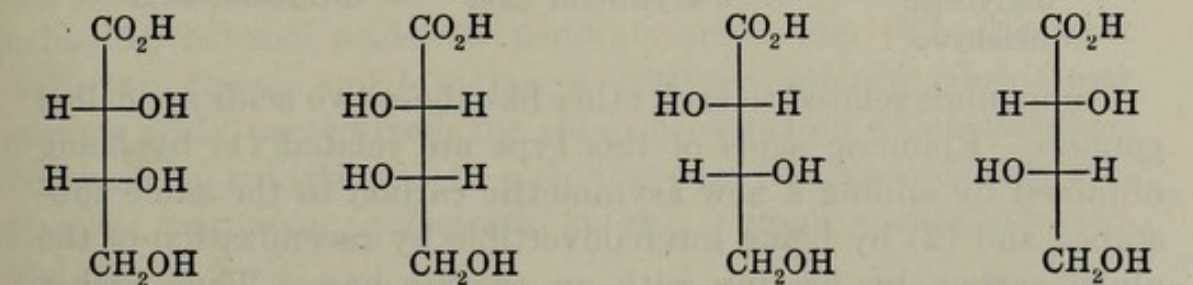
The result is a 50 : 50 or racemic mixture of the *d*- and *l*- forms. The enol is symmetrical as regards the two OH groups and the double bond. This double bond can break with the shift of an H atom from a hydroxyl. If the double bond opens at the bond 2,6, the *d*- form is regenerated, if it opens at 1,5, the *l*- form is obtained.

**Homologs of glyceric acid** have been made from unsaturated acids by mild oxidation or through the dibromides or chlorohydrins.

Enantiomeric 9,10-$(OH)_2$-stearic acids, m. 95° and 132°, are obtained by oxidizing oleic and elaidic acids with $H_2O_2$ in acetic acid or acetone. By alkaline oxidation, oleic acid gives the 132° acid (Rep. 1926, 99).

**3,12-Dihydroxypalmitic acid** is obtained with *d*-glucose and *l*-rhamnose from rhamnoconvolvulic acid.

**Trihydroxy n-butyric acids,** $HOCH_2CHOHCHOHCO_2H$, exist in four optically active forms.



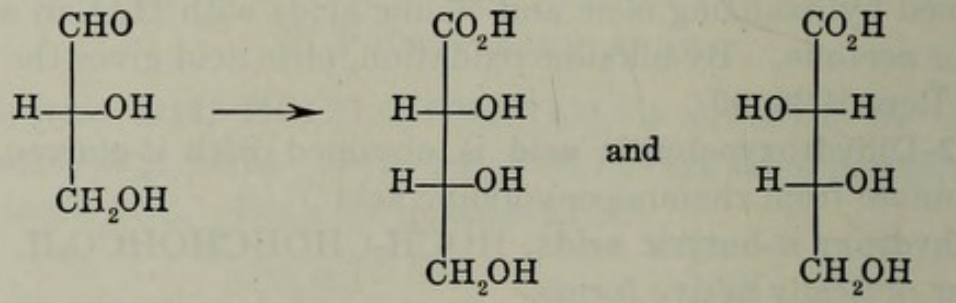
d-erythronic acid l-erythronic acid d-threonic acid l-threonic acid

The names show the relation to the aldo tetroses, erythrose and threose. These acids have been prepared from pentoses and hexoses. They may be built up from the glyceraldehydes by the cyanohydrin synthesis.

$$HOCH_2CHOHCHO \rightarrow HOCH_2CHOHCHOHCN \rightarrow HOCH_2CHOHCHOHCO_2H$$

The addition of HCN to the carbonyl group creates a new asymmetric carbon. Since the carbonyl group may open in two ways, two new compounds are obtained. Ordinarily when a new asymmetric carbon atom is formed the chance of the two possible configurations is 50 : 50. When an optically active substance like *d*-glucose has a new asymmetric carbon added to it, the two possibilities are *not* formed in equal amounts. In some cases one form appears almost to the complete exclusion of the other form. A process in which a new asymmetric carbon is created in other than 50 : 50 proportions because the initial material is already optically active is called an *asymmetric synthesis.* Many such processes have been carried out. They represent the normal course of events in natural processes in which it is decidedly unusual to have a *dl* mixture formed.

The results from the two glyceraldehydes by the cyanohydrin synthesis are as follows:

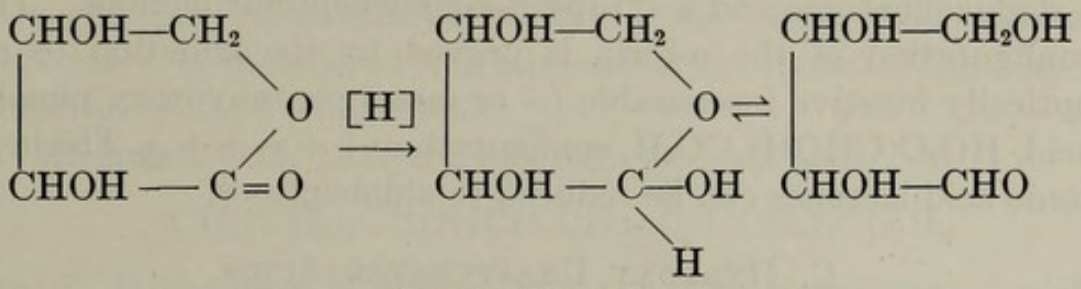



d-glyceric aldehyde | d-erythronic acid | d-threonic acid

Compounds related to each other like these two acids are called *epimers.* Epimeric acids of this type are related (1) by being obtained by adding a new asymmetric carbon to the same substance and (2) by being interconvertible by racemization of the alpha carbon by heating with an organic base. Thus, either *d*-erythronic acid or *d*-threonic acid when treated in this way gives an equilibrium mixture of the two.

The tetronic acids readily change to gamma lactones. As is usual with such lactones, these can be reduced by sodium amalgam. Enough acid is added to prevent the opening of the lactone ring by an accumulation of alkali. The resulting sodium salts are not reducible. This is probably another example of the

activity of the carbonyl group in an ester.



Lactone form of a γ-hydroxy aldehyde an internal hemiacetal

The situation may not be as simple as this, since unhydroxylated lactones are not thus reducible.

**Trihydroxyisobutyric acid,** $(HOCH_2)_2C(OH)CO_2H$, is obtained from dihydroxy acetone by the cyanohydrin synthesis.

**Aleuritic acid** is 9,10,16-$(OH)_3$-palmitic acid. Dilute alkali splits it to give azelaic acid and 7-OH-heptoic acid (Rep. 1927, 85).

**Sativic acid** is 9,10,12,13-$(OH)_4$-stearic acid (Rep. 1922, 72).

**The higher -onic acids,** $HOCH_2(CHOH)_nCO_2H$, can be built up from the lower aldoses by the cyanohydrin synthesis or can be obtained by careful oxidation of the aldoses. Their lactones are readily reduced to the corresponding aldoses. Since the addition of one new asymmetric carbon takes place in two ways, the building up of the series gives the following optical isomers, 8 pentonic acids, 16 hexonic acids, 32 heptonic acids, etc. The *pentonic acids*, are the *d-* and *l-* forms of *arabonic, xylonic, ribonic* and *lyxonic* acids, named from the aldopentoses from which they can be made by oxidation. In a similar way the *hexonic acids* are, *gluconic, mannonic, galactonic, gulonic, talonic, idonic, altronic,* and *allonic acids.*

Gluconic acid on prolonged heating at a relatively low temperature gives the delta-lactone. More vigorous heating of the acid gives the more stable gamma lactone.

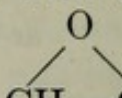
*d*-Galactonic and *d*-talonic acids have been obtained in crystalline form (Hedenburg 1927). The other hexonic acids exist as gums or as crystalline lactones.

Each of the aldohexoses gives an "alpha" and a "beta" heptonic acid which is named after it. The α- and β- refer to the configuration of the new asymmetric carbon and *not* to a position in the chain. The α-form has the configuration H + OH for the

new asymmetric carbon. Thus *d*-glucose gives a crystalline $\alpha$-*d*-glucoheptonic and a syrupy $\beta$-*d*-glucoheptonic lactone. The configuration of the $\alpha$-form is proved by its oxidation to an optically inactive inseparable (*i*- or *meso*) pentahydroxy pimelic acid, $HO_2C(CHOH)_5CO_2H$, configuration $++-++$. The heptonic acid lactones can be reduced to aldoheptoses.

### *C.* Hydroxy Unsaturated Acids

**Hydroxy olefinic acids** are isomeric with the aldehydic and



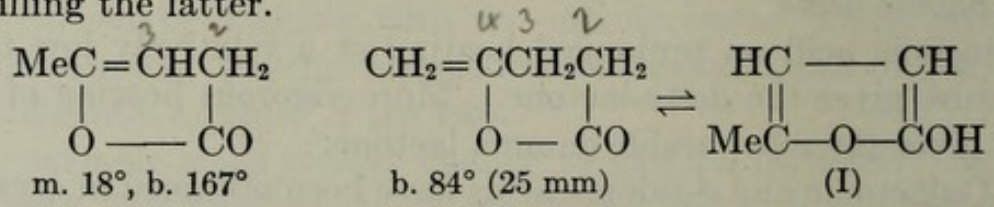
ketonic acids and with glycidic acid, $CH_2$—$CHCO_2H$, and its homologs. They are very rare except for ricinoleic acid in the glycerides of castor oil.

**β-Hydroxyacrylic acid,** $HOCH=CHCO_2H$, is stable only as the Na derivative of the ester obtained from formic and acetic esters and sodium in ether. The free ester changes to a benzene derivative, ethyl trimesate.

**α-Hydroxy-vinylacetic acid,** ethenylglycollic acid, buten-3-ol-2-oic acid, $CH_2=CHCHOHCO_2H$, m. 40°, can be made from acrolein through its cyanohydrin. It gives the reactions of an olefin and of an $\alpha$-hydroxy acid. At 190° it loses $CO_2$.

**β-Hydroxyisocrotonic acid,** $CH_3C(OH)=CHCO_2H$, exists as the ether acid or the ether acid esters $CH_3C(OR)=CHCO_2H$ and its esters, formed from $\beta$-chloroisocrotonic acid or its esters and Na alcoholates. Methyl ether acid, m. 128°, ethyl ether acid, m. 137°.

**γ-Hydroxy-penten-3 or 4-oic acids,** exist only as the lactones, the alpha and beta anhydrides of levulinic acid, obtained by distilling the latter.



m. 18°, b. 167° b. 84° (25 mm) (I)

The more volatile and stable alpha compound may exist as a furan derivative (I).

**Ambrettolic acid,** 16-hydroxyhexadecen-7-oic acid,

$$HOCH_2(CH_2)_7CH=CH(CH_2)_5CO_2H,$$

is contained in small amounts in musk-kernel oil (Rep. 1927, 88). Ozonolysis gives pimelic and azelaic acids. Its lactone, *ambrettolide* has a 17-membered ring and smells like musk. The dihydro derivative has a similar odor.

**Ricinoleic acid,** 12-hydroxyoctadecen-9-oic acid,

$$CH_3(CH_2)_5CHOHCH_2CH=CH(CH_2)_7CO_2H,$$

m. 5°, in the form of glycerides is the chief component of castor oil. It can be purified by crystallization of its lithium salt. The pure acid is dextrorotatory and shows neutralization and iodine numbers of 188.1 and 84.7 (Calc. 188.2 and 85.0). (Andre 1932.) The structure of ricinoleic acid has been proved in a variety of ways. One of the most interesting uses the steps: *a*. Treatment with bromine, *b*. Conversion to an acetylenic compound, *c*. Hydration to a ketone and conversion to the oxime, *d*. Beckmann rearrangement of the oxime and hydrolysis of the products (Goldsobel 1894). The substances identified were:

$Me(CH_2)_5CHOHCH_2CH_2CO_2H$ and its lactone; $NH_2(CH_2)_7CO_2H$;

$\alpha$-hexyltrimethyleneimine, $Me(CH_2)_5\overline{CHCH_2CH_2NH}$; and azelaic acid, $HO_2C(CH_2)_7CO_2H$

Ozonolysis of ricinoleic acid gives 3-OH-pelargonic acid and azelaic acid and its half aldehyde. Hydrogenation gives 12-OH-stearic acid. Ricinoleic acid polymerizes readily. Nitrous acid converts it to ricinelaidic acid (*trans*), m. 53°.

The double bond in ricinoleic acid may be in the 10- position (Barbot 1935).

The pyrolysis of castor oil under reduced pressure gives undecylenic acid, $CH_2=CH(CH_2)_8CO_2H$ and heptaldehyde in yields of 10–20% and 30–60%. The same splitting occurs when methyl ricinoleate is heated (Rep. 1928, 83). A yield of the unsaturated ester of 68% has been obtained (Grün 1922). The unmanageable polymer usually obtained in these processes can be avoided by adding rosin before heating (Bruson 1933).

Alkali salts of ricinoleic acid (soaps), when heated with excess alkali give capryl alcohol (methylhexylcarbinol) sodium sebacate and $H_2$. (OS).

The splitting of ricinoleic acid at $C_{11}$ by heat and at $C_{10}$ by alkali fusion is noteworthy.

Sodium ricinoleate has valuable properties in counteracting various bacterial toxins.

An isomer hydroxyoleic acid has been obtained from the liquid waxes of the castor oil fish (Cox 1932). A dihydroxyoleic acid has been found in whale oil (Moore 1919).

## XIX. DICARBONYL COMPOUNDS

### *A.* Dialdehydes

**Glyoxal,** oxalic aldehyde, ethandial, O=CHCH=O, is formed in various solid and liquid polymeric forms in poor yields by the oxidation of glycol, or acetaldehyde by nitric acid. Such an oxidation of a methyl group in preference to the easily oxidizable aldehyde group is remarkable. It is favored by certain catalysts such as silica gel. This same oxidation can be achieved by means of selenium dioxide which does not oxidize an aldehyde group but converts $\alpha-CH_2$ to CO. Ethanol with $SeO_2$ in an autoclave at 200° gives a 40% yield of glyoxal. When glyoxal is needed as an intermediate it can be obtained in the reaction mixture by the hydrolysis of $Cl_2$-dioxan (Butler 1932).

$$\begin{matrix} ClCH—O—CH_2 \\ | \qquad\quad | \\ ClCH—O—CH_2 \end{matrix} + 2\,H_2O \rightarrow \begin{matrix} CHO \\ | \\ CHO \end{matrix} + 2\,HCl + (CH_2OH)_2$$

*Monomeric glyoxal* can be obtained as a green vapor by heating the polymer with $P_2O_5$. This vapor condenses to yellow crystals, m. 15°, b. 50°. The yellow crystals become colorless on strong cooling. (Rep. 1907, 81.) Glyoxal is the simplest colored organic compound. Its chromophore is O=C−C=O (Will).

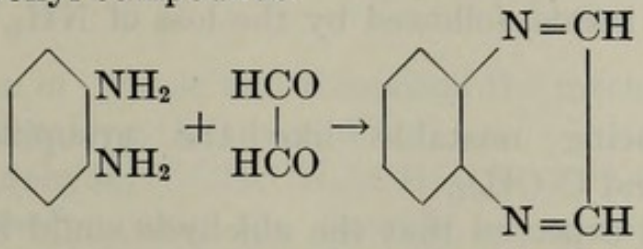
Glyoxal gives the usual aldehyde reactions except that it has no alpha hydrogen. Thus alkalies convert it to glycollic acid (Cannizzaro). It reacts with ammonia to give glyoxaline (imidazole), the parent substance of a great variety of substances obtainable from "1,2" dicarbonyl compounds, ammonia and aldehydes and from "1,2" diamines and aldehydes. The mechanism of the reaction of glyoxal with $NH_3$ has never been proved

but it is assumed that one molecule breaks into formic acid and formaldehyde and the latter reacts as follows:

$$\begin{matrix}\text{CHO}\\|\\\text{CHO}\end{matrix} + 2\,NH_3 + HCHO \rightarrow \begin{matrix}\text{CHNHCH}\\\|\quad\quad\|\\\text{CH—N}\end{matrix}$$

A minor product is *glycosine*, the result of the action of 4 $NH_3$ and 3 glyoxal, $\begin{matrix}\text{HCNHC—CNHCH}\\\|\quad\|\quad\|\quad\|\\\text{HC—N}\quad\text{N—CH}\end{matrix}$. With phenylhydrazine, glyoxal gives a di-phenylhydrazone or *osazone*, m. 168°. This type of compound is very important in the sugar series.

Glyoxal unites with *o*-phenylene diamine to give quinoxaline, parent substance of many compounds formed from 1,2-diamines and 1,2-dicarbonyl compounds.




A solution of monomeric glyoxal reduces ammoniacal silver solution but not Fehling's solution. On the other hand trimeric glyoxal reduces the latter, suggesting the structure

$$OCHCHOHCOCHOHCOCHO$$

or an enediol related to it which would be expected to act like a reducing sugar.

**Malonic aldehyde,** propandial, $OCHCH_2CHO$, is known only in water solution and there probably only in the enol form, $HOCH=CHCHO$. The steps by which its preparation has been attempted are as follows:

$$\text{Acrolein dibromide} \xrightarrow[\text{Acid}]{\text{EtOH}} BrCH_2CHBrCH(OEt)_2 \xrightarrow{\text{base}}$$

$$CH\equiv CCH(OEt)_2 \xrightarrow{\text{NaOEt}} EtOCH=CHCH(OEt)_2 \xrightarrow{H_2O}$$

$$EtOCHOHCH_2CH(OEt)_2 \rightarrow$$

$$O=CHCH_2CH=O \rightleftharpoons HOCH=CHCHO$$

The resulting water solution is strongly acid indicating the presence of the enol form. With benzene diazonium chloride it gives a derivative of malonic aldehyde.

$$C_6H_5N_2Cl \rightarrow C_6H_5NH-N=C(CHO)_2$$

**Succindialdehyde,** butandial, $OCHCH_2CH_2CHO$, is obtained (1) by the ozonization of diallyl, made from allyl iodide by the Wurtz reaction and (2) from pyrrole.

$$\begin{matrix} CHNHCH \\ \| \quad\quad \| \\ CH\text{—}\quad\quad CH \end{matrix} \xrightarrow{NH_2OH} HON=CHCH_2CH_2CH=NOH \xrightarrow{HNO_2} HCOCH_2CH_2CHO$$

The first step probably consists in the addition of hydroxylamine at the double bonds, followed by the loss of $NH_3$, the grouping $\begin{matrix} NH_2 \\ \diagup \\ C\text{—}NHOH \end{matrix}$ being unstable like the groupings $C(NH_2)_2$, $C(OH)NH_2$, and $C(OH)_2$.

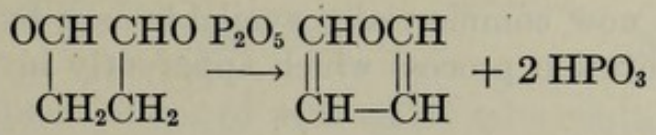
It might be expected that the aldehyde could be made from the chloride of succinic acid by the method of Rosenmund ($Pd + H_2$). This is impossible because the ordinary methods of making acid chlorides fail with succinic acid. Thus the steps which would give succinic aldehyde give butyrolactone.

$$\begin{matrix} CH_2\text{—}CO_2H \\ | \\ CH_2\text{—}CO_2H \end{matrix} \xrightarrow{PCl_5} \left[ \begin{matrix} \quad\quad O \\ \quad\quad // \\ CH_2\text{—}C\text{—}Cl \\ | \\ CH_2\text{—}C\text{—}OH \\ \quad\quad \backslash\backslash \\ \quad\quad O \end{matrix} \right] \rightarrow \begin{matrix} CH_2\text{—}C=O \\ | \quad\quad \diagdown \\ \quad\quad\quad O \xrightarrow{PCl_5} \\ | \quad\quad \diagup \\ CH_2\text{—}C=O \end{matrix}$$

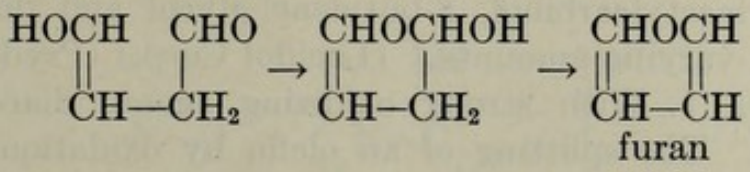
$$\begin{matrix} CH_2\text{—}CCl_2 \\ | \quad\quad \diagdown \\ \quad\quad\quad O \\ | \quad\quad \diagup \\ CH_2\text{—}C=O \end{matrix} \xrightarrow[Pd]{2\,H_2} \begin{matrix} CH_2\text{—}CH_2 \\ | \quad\quad \diagdown \\ \quad\quad\quad O \\ | \quad\quad \diagup \\ CH_2\text{—}C=O \end{matrix}$$

As soon as one OH is replaced by Cl, this Cl is very near the other OH in space. HCl is split out to form the anhydride (5-membered ring).

In addition to the usual aldehyde reactions, succindialdehyde readily forms the 5-membered ring compounds, *furan*, *pyrrole*, and *thiophene* when treated with dehydrating agents, ammonia and sulfides of phosphorus.



This probably involves an enolization of one of the aldehyde groups followed by the formation of a gamma lactonic ring with the other aldehyde group.



In the formation of pyrrole and thiophene the mechanism is the same, NH and S taking the place of O.

**Glutaric dialdehyde,** $OCH(CH_2)_3CHO$, b. 72° (10 mm), is obtained by decomposing the ozonide of cyclopentene. It readily changes to a glassy polymer which gives the monomer on vacuum distillation.

Higher dialdehydes can be made from the chlorides of the dibasic acids (Rosenmund, 1921).

$$ClCO(CH_2)_nCOCl \xrightarrow[Pd]{H_2} HCO(CH_2)_nCHO + 2\,HCl$$

### *B.* Diketones

**Diacetyl,** butandione, $CH_3COCOCH_3$, b. 88°, can be made from methyl ethyl ketone.

1. By conversion to the isonitroso compound, the monoxime of diacetyl

$$MeCOCH_2Me + HNO_2 \rightarrow MeCOC(NOH)Me$$

This can be converted to diacetyl by hydrolysis with HCl or by careful treatment with nitrous acid.

$$=C=NOH + H_2O + HCl \rightarrow =C=O + NH_2OH.HCl$$
$$=C=NOH + HNO_2 \rightarrow =C=O + N_2O + H_2O$$

2. By bromination in ethyl bromide, followed by hydrolysis to methylacetylcarbinol with bicarbonate solution and oxidation by ferric chloride to diacetyl (Ekeley).

3. By oxidation with selenium dioxide.

Diacetyl is now commercially available as a by-product of a special fermentation process which apparently involves the following steps:

$$\text{Glucose} \rightarrow \text{MeCOCO}_2\text{H} \rightarrow \text{MeCHO} \rightarrow \text{MeCHOHCOMe} \rightarrow \text{MeCOCOMe} + \text{MeCHOHCHOHMe}$$

The methylacetylcarbinol, $\beta$-butylene glycol and diacetyl are obtained in varying amounts. (Lucidol Corp.) (Pryde 143).

*Reactions.* 1. With strong oxidizing agents diacetyl gives acetic acid. The splitting of an olefin by oxidation probably goes through similar steps.

$$\begin{array}{cccccc} -\text{CH} & & -\text{CHOH} & & -\text{C=O} & -\text{CO}_2\text{H} \\ \| & \rightarrow & | & \rightarrow & | & \rightarrow \\ -\text{CH} & & -\text{CHOH} & & -\text{C=O} & -\text{CO}_2\text{H} \end{array}$$

2. Diacetyl gives glyoxalines and quinoxalines.

3. Diacetyl reacts with alkalies to give first an ordinary aldol condensation between two molecules and then a similar condensation *within* the large molecule forming a six membered ring. In this way substituted para *quinones* are obtained from many alpha diketones.

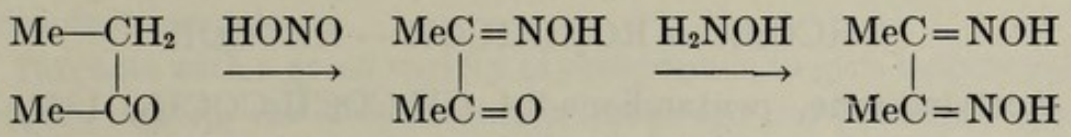
$$2\ \text{MeCOCOMe} \rightarrow \begin{array}{l} \text{OH} \\ | \\ \text{Me—CO—C—Me} \rightarrow \\ | \\ \text{Me—CO—CO—CH}_2 \end{array}$$

$$\begin{array}{l} \text{OH} \\ | \\ \text{CH}_2\text{—CO—C—Me} \\ | \qquad\qquad | \\ \text{Me—C——CO—CH}_2 \\ | \\ \text{OH} \end{array} \rightarrow \begin{array}{l} \text{HC—CO—CMe} \\ \| \qquad\quad \| \\ \text{MeC—CO—CH} \end{array}$$

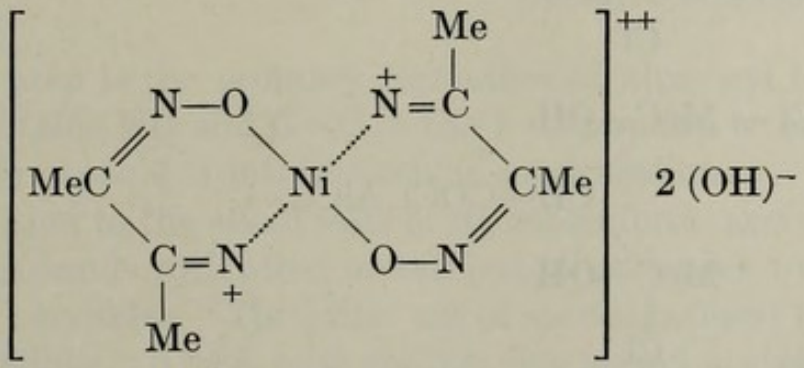
*p*-xyloquinone

The dioxime of diacetyl (*dimethyl glyoxime*) is prepared from

the isonitroso compound of methyl ethyl ketone and hydroxylamine. It is an important analytical reagent for nickel.



The red precipitate obtained with nickel salts contains two molecules of dimethyl glyoxime for each atom of nickel. It exists in stereoisomeric forms (Rep. 1923, 86). The compound is pictured as involving two ordinary and two subsidiary or coordination valences of nickel (Werner).



After the nickel has attached itself to one molecule of the dimethyl glyoxime by replacing the OH hydrogen, the nitrogen at the other end of the chain is in the 1 : 6 position to the Ni atom and, therefore near it in space. It might be thought that the Ni would replace the other H and give a compound with one atom of Ni for one molecule of the dioxime. Such does not happen because of the difficulty in forming a seven-membered ring. Thus the nickel forms a complex ion in which it acts as the common atom in a spiro system. Six-membered rings of this type in which the closure is through subsidiary valences of elements like oxygen, nitrogen and the metals are increasingly common in organic chemistry (chelate rings).

Diacetyl may be purified by means of the compound

$$(MeCO)_2 . 2\,H_3PO_4$$

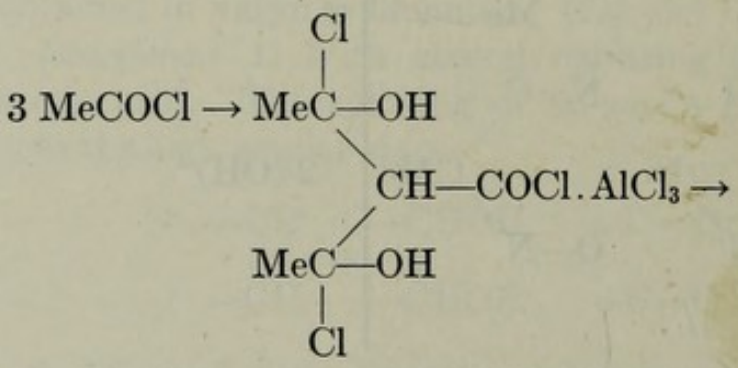
(Oliver).

A general preparation of alpha diketones (1,2-diketones) is by

catalytic dehydrogenation of acyloins obtained from esters and Na (Rep. 1906, 82).

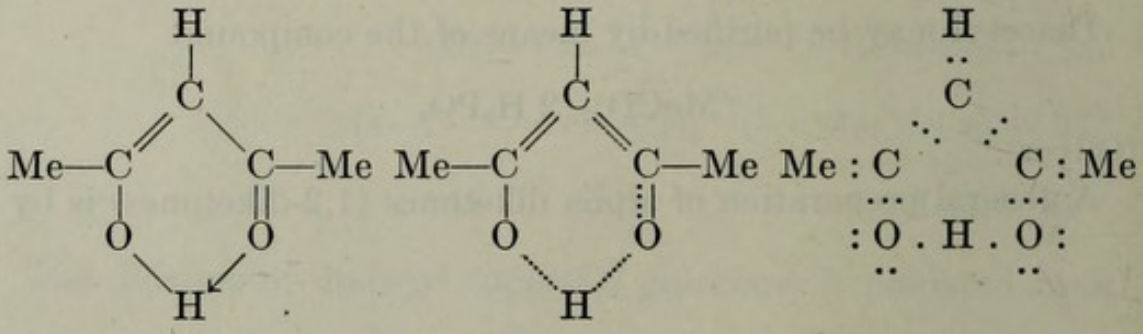
$$2\ RCO_2Et \rightarrow RCHOHCOR \rightarrow RCOCOR$$

**Acetylacetone,** pentandione-2,4 $CH_3COCH_2COCH_3$, 136°, is prepared (1) by condensing ethyl acetate with acetone and (2) from acetyl chloride and aluminum chloride. The latter reaction consists in the condensation of 2 alpha H atoms from one $CH_3COCl$ with the carbonyl groups of two others. When the aluminum chloride addition product is decomposed by water the resulting acid loses $CO_2$.



$$(MeCO)_2CHCO_2H \rightarrow CO_2 + MeCOCH_2COMe$$

Acetylacetone is a typical *beta diketone* or *1,3-diketone.* It is a typical tautomeric or desmotropic substance. Under ordinary conditions it consists of the enol-keto forms in the ratio 3 : 1. When freshly distilled from a glass apparatus, it consists almost entirely of the enol form, the alkali in the glass having catalyzed the enolization. Moreover, the enol form is unusually volatile. This property is explained on the basis of a chelate ring involving a coordinate link between the carbonyl oxygen and the hydroxyl hydrogen (Sidgwick; Rep. 1926, 127). Various means of representing the resulting ring compound may be used.

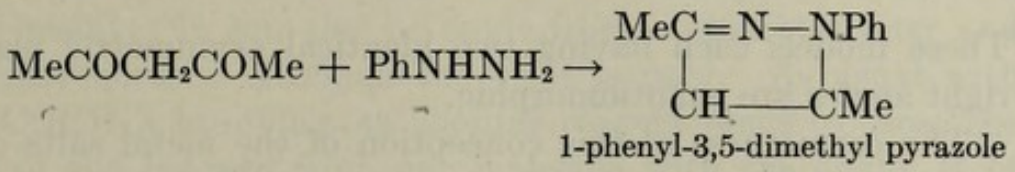


In the first formula a dotted line is often used in place of the arrow.

Its sodium derivative acts with organic halides to give com-

pounds of the types $(CH_3CO)_2CHR$ and $(CH_3CO)_2CRR'$. Its reactions are typical of the large number of beta diketones, beta ketonic esters, etc.

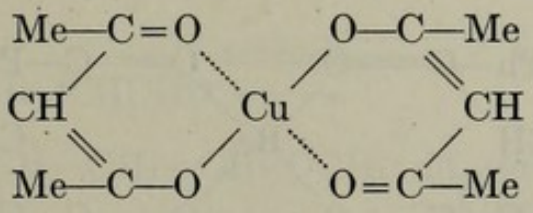
It reacts with a great variety of compounds to give heterocyclic rings. Among the best known of these are the pyrazoles (pyrroles with the $\alpha-CH$ replaced by N) obtained from phenyl hydrazine and similar compounds.




1-phenyl-3,5-dimethyl pyrazole

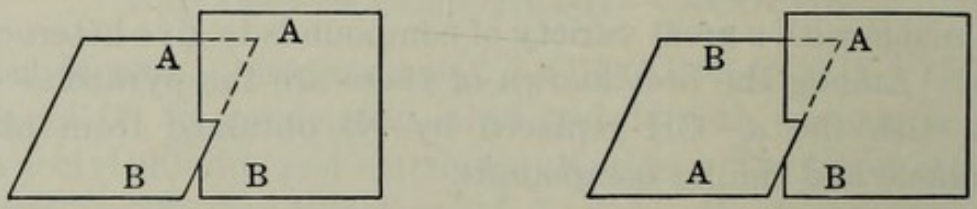
The first step is the ordinary formation of a phenyl hydrazone which contains NH and C=O in the 1 : 5 position to each other, thus being capable of intramolecular condensation.

In addition to the alkali salts of its enolic form, acetyl acetone gives compounds with other metals including copper, iron, aluminum and beryllium. The latter are of special interest because of their volatility. These salts contain one acetyl acetone residue for each valence of the metal and are pictured as involving both normal and auxiliary valences of the metals. Thus the copper salt is formulated as containing two six-membered chelate rings both including the Cu atom (Sidgwick).



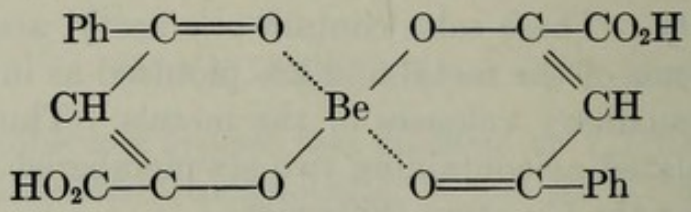

Without a knowledge of the facts expressed in Baeyer's Strain Theory, it might have been expected that *one* molecule of acetyl acetone would form a di-enol and combine with *one* copper atom. Such a combination would contain a seven-membered ring. Such a ring does not form when there is the possibility of a six-membered ring. The formulation with the Cu atom as the center of a spiro system of two unsymmetrical six-membered rings would indicate the possibility of enantiomorphism. This is evident when it is recognized that the planes of the two rings must be

about at right angles to each other. A simple diagram will show the possibilities

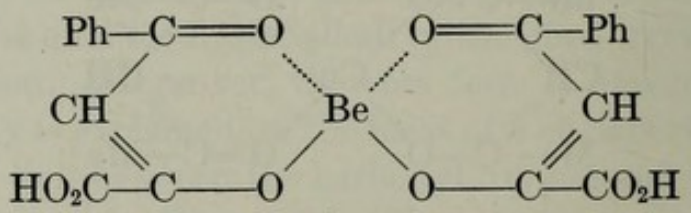



These models each having two identical asymmetric planes at right angles are enantiomorphic.

The correctness of this conception of the metal salts of beta diketones is shown by the resolution of a similar compound of beryllium into its optical isomers (Mills and Gotts). Beryllium forms a compound with two molecules of benzoyl pyruvic acid, $PhCOCH_2COCO_2H$ which still has free carboxyl groups. By means of optically active bases like brucine, *d*- and *l*- forms of the beryllium complex can be separated.




"*d*"




"*l*"

The formulation of the metal atom as being held by two ordinary "bonds" and two "coordinate links" is made because of our respect for ordinary valence conceptions. The properties of the substances themselves would not indicate such a difference in the four attachments of the metal atom.

Beta diketones having one or both of the methylene H atoms substituted are split by Grignard reagents (Kohler 1931).

*Acetonylacetone*, hexandione-2,5, $CH_3COCH_2CH_2COCH_3$, b. 188°, is made from acetoacetic ester by treating its sodio compound with $I_2$ and decarboxylating the resulting product.

$$\begin{matrix} MeCOCH—CO_2R \\ | \\ MeCOCH—CO_2R \end{matrix} \xrightarrow[\text{base}]{\text{dil}} \xrightarrow{\text{acid}} \xrightarrow{\text{heat}} 2\,CO_2 + \begin{matrix} MeCOCH_2 \\ | \\ MeCOCH_2 \end{matrix}$$

Bimolecular electrolytic oxidation of acetoacetic ester gives a similar result. It can also be made from acetoacetic ester and monochloroacetone although the yield is poor. As usual with the $-COCH_2X$ grouping, an alkaline reagent tends to cause the action of the halogen from one molecule with the enolic H of another.

Acetonyl acetone is available commercially (C. and C.).

Like all *gamma* dicarbonyl compounds, acetonyl acetone readily forms five-membered rings giving substituted furans, pyrroles and thiophenes.

**Higher symmetrical diketones,** $RCO(CH_2)_nCOR$, in which $N > 2$, can be made from RZnX and dibasic acyl chlorides. The zinc compounds do not react with the ketones as would RMgX.

**δ-Diketones** (1:5) do not exist. Reactions which would be expected to give them produce cyclic products as the result of condensation within the molecule.

$$2\,CH_3COCH_2CO_2R + HCHO \xrightarrow{\text{amines}}$$

$$\begin{matrix} CH_3COCH—CH_2—CHCOCH_3 \\ | \qquad\qquad | \\ CO_2R \qquad CO_2R \end{matrix} \xrightarrow[\text{base}]{\text{dil}} \xrightarrow{\text{acid}} \xrightarrow{\text{heat}}$$

$$[CH_3COCH_2CH_2CH_2COCH_3] \rightarrow$$

$$\begin{matrix} \qquad OH \\ \qquad | \\ CH_3—C—CH_2—CH_2 \\ \qquad | \qquad\quad | \\ \qquad CH_2—CO—CH_2 \end{matrix} \rightarrow \begin{matrix} CH_3—C—CH_2—CH_2 \\ \quad \| \qquad\quad | \\ \quad CH—CO—CH_2 \end{matrix}$$

3-Methyl-cyclo-hexen-2-one
1-Methyl-3-keto-cyclohexene

**ε-Diketones** (1:6) can exist as such without ring closure. Thus $MeCO(CH_2)_4COMe$, obtained from Na acetoacetic ester and ethylene bromide is stable. The corresponding 4,4,5,5-$Me_4$-compound exists only in the cyclic form (Rep. 1927, 114). $Me_2CCH_2C(OH)Me$. This shows the influence of methyl groups
$Me_2C$——$CHCOMe$
in favoring ring closure. Many reactions of the 1:6-diketones give ring compounds. Thus reduction gives a considerable amount of pinacol formation within the molecule and alkaline condensing agents give the aldol condensation intramolecularly.

$$\begin{matrix} CH_2CH_2C(OH)Me \\ | \quad\quad | \\ CH_2CH_2C(OH)Me \end{matrix} \leftarrow \begin{matrix} CH_2CH_2COMe \\ | \quad\quad\quad | \\ CH_2CH_2COMe \end{matrix} \rightarrow \begin{matrix} CH_2CH_2C(OH)Me \\ | \quad\quad\quad | \\ CH_2 - CHCOMe \end{matrix}$$

A *1:7 diketone* undergoes the internal aldol condensation to give a 6-ring while a 1:8 diketone gives no intramolecular reaction.

Aliphatic *triketones* are rare. Only two examples will be given, one with the CO groups together and the other with them separated.

**Triketopentane,** pentantrione, $CH_3(CO)_3CH_3$, b. 55° (12 mm), is obtained by condensing acetylacetone with *p*-nitrosodimethylaniline and hydrolyzing the product with acid

$$(MeCO)_2CH_2 + ONC_6H_4NMe_2 \rightarrow (MeCO)_2C{=}NAr \rightarrow (MeCO)_2CO + ArNH_2$$

The free ketone is orange red. It forms a colorless hydrate. Bases give acetates and formaldehyde readily. It combines readily with acetyl acetone to give $(MeCO)_2C(OH)CH(COMe)_2$.

**Diacetylacetone,** heptantrion-2,4,6,$(CH_3COCH_2)_2CO$, does not exist as the triketone but in a cyclic form related to dimethyl pyrone (Collie 1922).

### *C.* Ketoaldehydes

**Pyruvic aldehyde,** methyl glyoxal, pyroracemic aldehyde, propanalone $(CH_3COCHO)_4$, is obtained in polymeric form.

1. From acetone through the isonitroso compound.

$$MeCOCH_3 + HON{=}O \rightarrow MeCOCH_2N(OH)_2 \rightarrow$$

$$MeCOCH{=}NOH \xrightarrow{NaHSO_3} MeCOCHOHSO_3Na \xrightarrow{acid} MeCOCHO \text{ solution}$$

2. From ozonolysis of mesityl oxide, $Me_2C{=}CHCOMe$ (Harries, Rep. 1905, 74).

3. By oxidation of acetone with $SeO_2$

$$CH_3COCH_3 + SeO_2 \rightarrow CH_3COCHO + H_2O + Se$$

The monomeric form of pyruvic aldehyde is difficultly obtainable (Rep. 1907, 83).

With formaldehyde and ammonia, Me-glyoxaline is obtained.

$$MeCOCHO + 2\,NH_3 + HCHO \rightarrow MeC\underset{\|}{\overset{N}{C}}CH_2\underset{\|}{\overset{N}{C}}H$$

It is significant that sugars heated with $NH_4OH$ give the same product (Rep. 1917, 68).

Various organisms and alkalies convert pyruvic aldehyde to lactic acid by dismutation.

In general $\alpha$-keto aldehydes, RCOCHO, can be made as follows:

1. From methyl ketones.

$$RCOCH_3 \rightarrow RCOCH_2Br \rightarrow RCOCH_2OCOCH_3 \rightarrow$$

$$RCOCH(Br)OCOCH_3 \xrightarrow{heat} CH_3COBr + RCOCHO$$

In the first step, an isomeric bromoketone is formed and has to be separated from the desired bromomethyl ketone.

2. From dichloroacetic ester (Rep. 1914, 78).

$$Cl_2CHCO_2Et \rightarrow (EtO)_2CHCO_2Et \xrightarrow[CH_3CO_2Et]{NaOEt + Na}$$

$$(EtO)_2CHCOCH_2CO_2Et \xrightarrow{Na} \xrightarrow{RX}$$

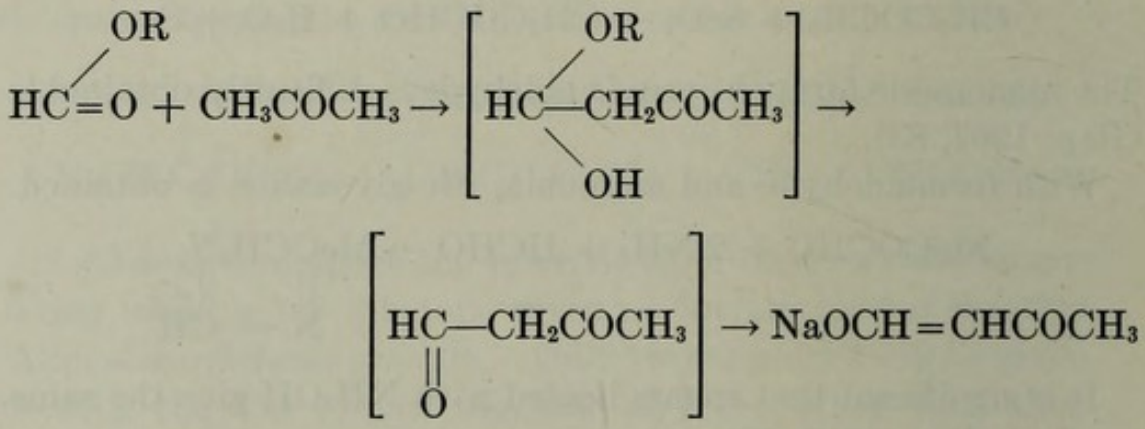
$$(EtO)_2CHCOCHRCO_2Et \xrightarrow{Acid} O{=}CHCOCH_2R$$

3. By oxidation of the $\alpha$-$CH_2$ group in aldehydes by $SeO_2$

$$RCH_2CHO + SeO_2 \rightarrow RCOCHO + Se + H_2O$$

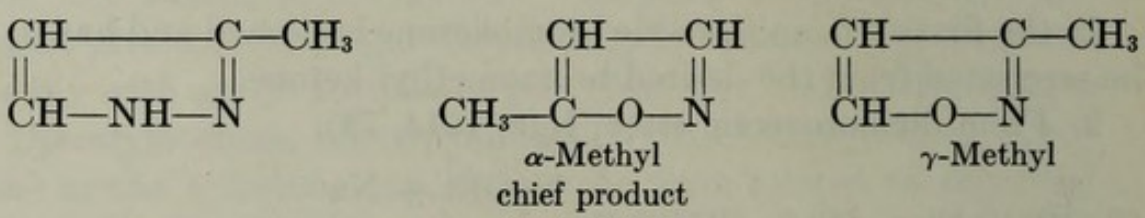
The $\alpha$-ketoaldehydes show the yellow-green color characteristic of glyoxal. They show a corresponding tendency to polymerize.

**Butanon-3-al,** ($CH_3COCH_2CHO$), a *beta* keto aldehyde which would be expected from the condensation of a formic ester with acetone in the presence of sodium ethylate (Claisen) exists only as the sodium salt of the enol form, buten-1-on-3-ol-1.



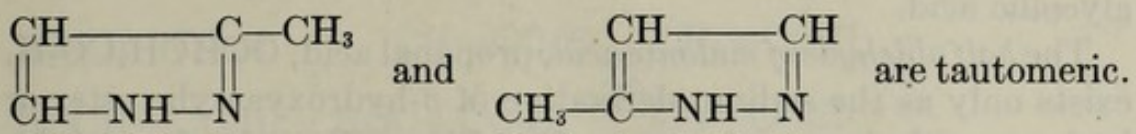
The sodium salt is very soluble in water. When it is treated with acid to liberate the free aldehyde or enol, triacetyl benzene is obtained. Three molecules condense by the usual aldol condensation mechanism and then an alpha H and a carbonyl group in the large molecule are near enough to each other to condense to a ring.

The Na salt of the enol also reacts with hydrazine to form methyl pyrazole and with hydroxylamine to give methyl isoxazoles.




The first step in each case is the ordinary reaction with one of the carbonyl groups. This is followed by an internal condensation to give a five-membered ring. Of the two carbonyl groups or their equivalent the terminal one would be expected to be most reactive. This is confirmed by the predominance of the $\alpha$-methyl

isoxazole. In the case of the pyrazole there is no chance for isomerism since



are tautomeric.

In general *beta ketoaldehydes* are known only as the metal derivatives of hydroxymethylene methyl ketones, $NaOCH=CHCOR$.

**Levulinic aldehyde,** levulic aldehyde, gamma ketovaleraldehyde, $CH_3COCH_2CH_2CHO$, is obtained by the ozonolysis of caoutchouc or, better, of methylheptenone,

$$Me_2C=CH(CH_2)_2COMe$$

(Harries). It does not polymerize. It gives the reactions expected of a dicarbonyl compound except that it does not give the Angeli-Rimini reaction for aldehydes. It reduces Fehling's solution even in the cold.

**Mesoxalic dialdehyde,** OCHCOCHO, has been obtained in aqueous solution, as the stable hydrate and as a solid polymer (Rep. 1905, 79).

1. By ozonolysis of phorone, $Me_2C=CHCOCH=CMe_2$, in chloroform followed by careful hydrolysis of the explosive diozonide.

2. By the action of nitrous acid on di-isonitrosoacetone, $HON=CHCOCH=NOH$.

## XX. ALDEHYDE ACIDS AND KETONE ACIDS

### *A.* Aldehyde Acids

**Glyoxylic acid,** ethanal acid, $OCHCO_2H$, $(HO)_2CHCO_2H$, is made (1) by the hydrolysis of dichloroacetic acid and (2) as a by-product in the electrolysis of oxalic acid with lead electrodes (Rep. 1926, 98). In the solid state and in its salts it always contains a molecule of water which probably indicates the hydration of the carbonyl group as in chloral hydrate and in mesoxalic acid. Thus it is sometimes called dihydroxy acetic acid.

In solution, it gives typical aldehyde and acid reactions. With

bases, it disproportionates to form salts of oxalic and glycollic acids. Reduction gives tartaric acid in addition to the expected glycollic acid.

The *half aldehyde of malonic acid*, propanal acid, $OCHCH_2CO_2H$, exists only as the sodium derivative of $\beta$-hydroxyacrylic ester or hydroxymethyleneacetic ester, $NaOCH=CHCO_2R$, formed by condensing esters of formic and acetic acids. The Na compound reacts readily with acetyl chloride to give the acetate,

$$CH_3CO_2CH=CHCO_2R.$$

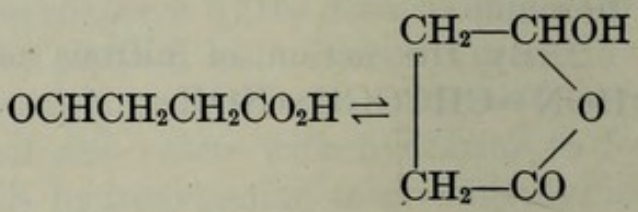
The sodium compound, on acidification, condenses to a benzene-1,3,5-tricarboxylic ester. As usual three molecules condense giving a compound in which an internal condensation can give a six-membered ring.

The *half aldehyde of succinic acid*, butanal acid,

$$OCHCH_2CH_2CO_2H,$$

exists in the lactone form (inner hemi-acetal). It can be made by the malonic ester or acetoacetic ester synthesis using the acetal of monochloroacetaldehyde.

$$(EtO)_2CHCH_2Cl \rightarrow (EtO)_2CHCH_2{-}CH_2CO_2H \rightarrow$$



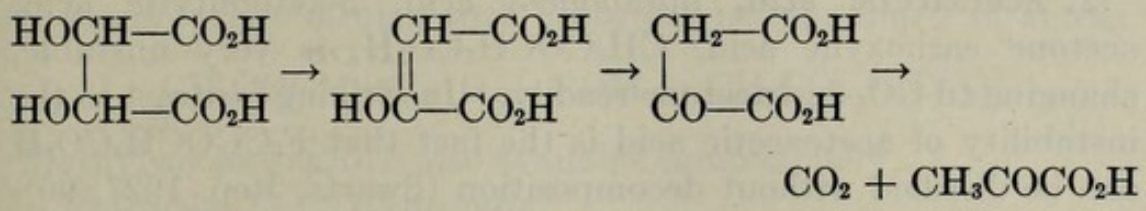

The lactone form of the aldehyde is in equilibrium with the free aldehyde form since it gives typical aldehyde reactions.

**Higher aldehyde acids** have been prepared by ozonizing unsaturated acids (Adams). Thus oleic and erucic acids give $OCH(CH_2)_7CO_2H$, nonanal acid, and $OCH(CH_2)_{11}CO_2H$, tridecanal acid.

### *B.* Keto Acids

1. **Pyruvic acid,** pyroracemic acid, propanone acid, keto propionic acid, $CH_3COCO_2H$, m. 13°, b. 165°. The enol form $CH_2=COHCO_2H$ is called *glucic acid.*

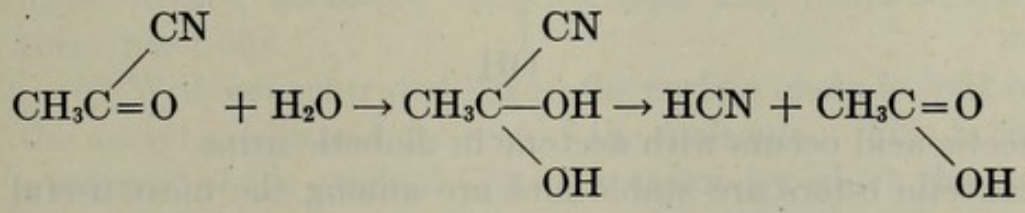
*Preparation:* 1. By heating tartaric acid either alone or with $NaHSO_4$.

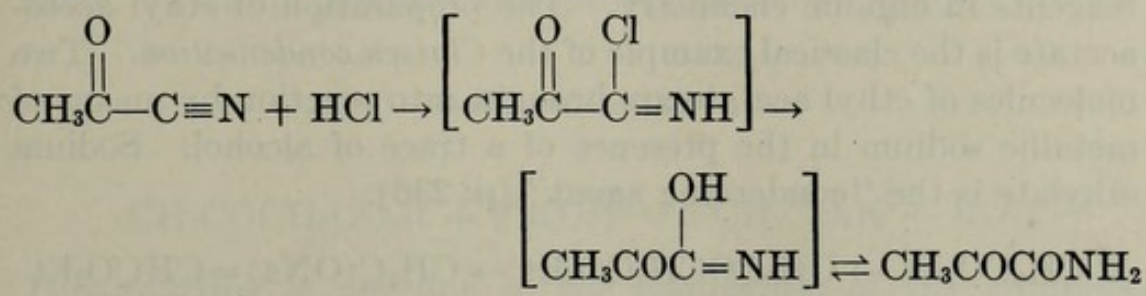


$$CO_2 + CH_3COCO_2H$$

The last step involves the usual loss of $CO_2$ by a beta carbonyl acid on heating.

2. From acetyl chloride through the cyanide. The intermediate acetyl cyanide behaves peculiarly on hydrolysis. With water or bases it gives acetic acid and HCN but with concentrated HCl it gives the amide of pyruvic acid which can then be hydrolyzed to the acid itself.





*Reactions.* 1. Usual acid and ketone reactions.

2. It reduces ammoniacal silver solutions. Its reducing properties are important in its role as an intermediate in alcoholic fermentation.

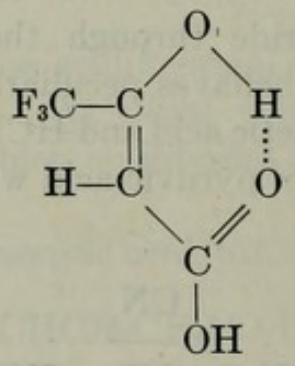
3. Heated with dilute sulfuric acid, it gives $CO_2$ and acetaldehyde. Concentrated $H_2SO_4$ gives CO and acetic acid.

4. Heated alone or with HCl, it gives methyl succinic acid (pyrotartaric acid). This peculiar change probably involves an "aldol" condensation followed by loss of $CO_2$ and an intramolecular oxidation and reduction.

5. It polymerizes to a non-volatile syrup.

6. With reducing agents it gives *dl*-lactic acid and *dl*-dimethyltartaric acid.

2. **Acetoacetic acid,** butanone-3 acid, β-ketobutyric acid, acetone carboxylic acid, $CH_3COCH_2CO_2H$, is very unstable, changing to $CO_2$ and acetone readily. In striking contrast to the instability of acetoacetic acid is the fact that $F_3CCOCH_2CO_2H$ can be distilled without decomposition (Swarts, Rep. 1927, 90). This may be due to a stabilizing of a chelate ring by the trifluoromethyl group.




Acetoacetic acid occurs with acetone in diabetic urine.

Acetoacetic esters are stable and are among the most useful reagents in organic chemistry. The preparation of ethyl acetoacetate is the classical example of the *Claisen condensation.* Two molecules of ethyl acetate are brought into reaction by means of metallic sodium in the presence of a trace of alcohol. Sodium ethylate is the "condensing agent" (p. 236).

$$2\ CH_3CO_2Et \rightarrow CH_3COCH_2CO_2Et \rightarrow CH_3C(ONa)=CHCO_2Et$$

The percentages of the enol and keto forms under different conditions have been determined by chemical means (K. H. Meyer), and by physical means (Gladstone, Bruhl, Perkin, Sr., Drude). The ordinary ester is more than 90 per cent keto. It has been possible to prepare the practically pure forms (Knorr). The enol reacts instantly with ferric chloride giving an intense violet-red color. The pure keto form gives this color only on standing. The keto form is solid at −78° while the enol is still liquid at that temperature.

**Acetoacetic Ester,** ethyl acetoacetate $CH_3COCH_2CO_2Et$, b. 181° is available commercially as an intermediate for dyes, drugs

and perfumes. It is usually prepared from ethyl acetate and sodium. Acetoacetic esters are also prepared by the action of the appropriate alcohol with acetylketene (the dimer of ketene)

$$CH_3COCH{=}C{=}O + ROH \rightarrow CH_3COCH_2CO_2R$$

Methyl acetoacetate is also available commercially.

*Reactions.* 1. "Hydrolysis."

(*a*) With dilute bases, the ester is saponified in the usual way.

$$CH_3COCH_2CO_2R + NaOH \rightarrow ROH + CH_3COCH_2CO_2Na$$

On acidification, the liberated acetoacetic acid decomposes.

$$CH_3COCH_2CO_2H \rightarrow CO_2 + CH_3COCH_3$$

Alpha mono and disubstituted acetoacetic esters give mono and disubstituted acetones, $CH_3COCH_2R$ and $CH_3COCHRR'$, by these reactions.

(*b*) With concentrated bases, the carbon chain is split between the acetyl group and the rest of the molecule. This is therefore a reversal of the original Claisen reaction by which the ester was made. This splitting is characteristic of the grouping

$$-CO-\underset{|}{\overset{|}{C}}-CO-.$$

$$CH_3COCH_2CO_2R + 2\,KOH \rightarrow 2\,CH_3CO_2K + ROH$$

This splitting is not due to the enolization of the grouping, $-COCH_2CO-$, because alpha mono and disubstituted acetoacetic esters are split in the same way by concentrated alkalies. In fact the disubstituted esters are most easily split. From the substituted esters mono and disubstituted acetic acids, $RCH_2CO_2H$ and $RR'CHCO_2H$ are obtained.

$$CH_3COCRR'CO_2Et + 2\,KOH \rightarrow CH_3CO_2K + RR'CHCO_2K + EtOH$$

The grouping $-CO-\underset{|}{\overset{|}{C}}-CO-$ is thus *formed* under the influence of traces of alkaline reagents such as NaOEt and $NaNH_2$ and is

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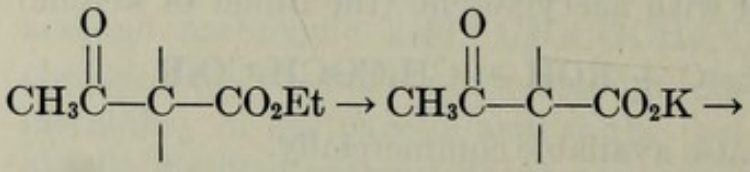
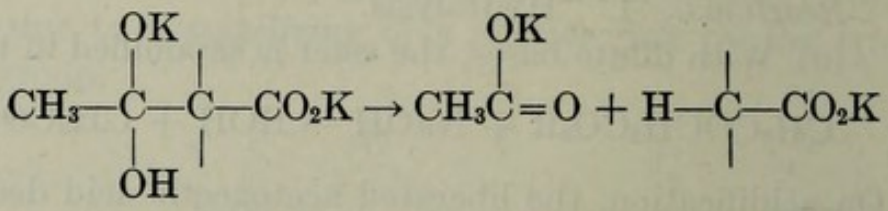
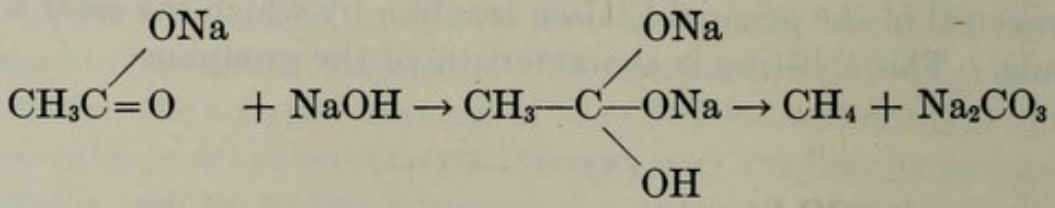
*split* by concentrated alkaline reagents such as alcoholic KOH. The steps in the splitting are probably:



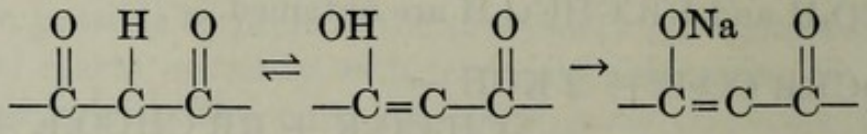


This splitting is much like that of the grouping, $Cl_3C-\overset{\overset{O}{\|}}{C}-$, by KOH to give $CHCl_3$ and $-CO_2K$. A similar splitting also results from the action of ketones with an excess of sodamide. The decarboxylation of acids by heating their sodium salts with soda-lime probably follows a similar course.



Thus the grouping $C-C(OH)OM$ must be added to the unstable groupings. It tends to become CH and $-CO_2M$ under suitable conditions depending on the other groups present.

2. The most striking reaction of acetoacetic ester and of all other beta dicarbonyl compounds having at least one alpha H is their ready reaction with alkali metals to give metallic derivatives of the enols.



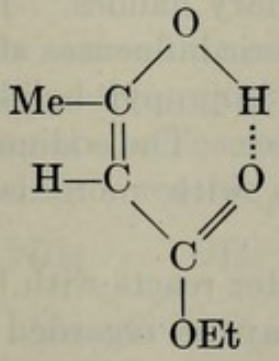
The shift of the H (proton) is *prototropy* (Rep. 1927, 106). Acetoacetic ester reacts with sodium, sodium alcoholates and sodamide to give sodium acetoacetic ester. Acidification of the sodium derivatives gives the enol form which rapidly changes to

the equilibrium keto-enol mixture (Rep., 1911, 100; 1912, 108; 1922, 66).

The enol form of acetoacetic acid differs from the keto form in being more volatile, less soluble in water and more soluble in organic solvents (Rep. 1925, 70). Such properties do not correspond with the ordinary formulas

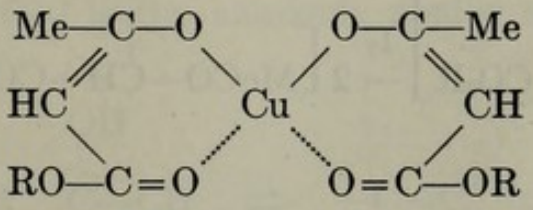
$$CH_3COCH_2CO_2Et \quad \text{and} \quad CH_3C(OH)=CHCO_2Et.$$

Usually a hydroxyl derivative is less volatile than a corresponding carbonyl compound. Thus the boiling points of *n*-propyl, isopropyl, allyl, and propargyl alcohols are 97°, 82°, 96° and 115° while those of propionaldehyde, acetone and acrolein are 48°, 56° and 52°. The lower boiling point of the enol form of acetoacetic ester is explained by a *chelate ring* structure in which the H of the hydroxyl is *coordinated* with the carbonyl oxygen. The coordination of the H intramolecularly prevents its coordination with the oxygen of another molecule which would cause *association* and increase in boiling point.




Calcium acetoacetic ester is obtained by heating the ester with $CaC_2$.

Acetoacetic ester gives a copper compound soluble in organic liquids. This is a chelate compound (Sidgwick).




A similar compound is formed with beryllium.

Sodium acetoacetic ester acts with reactive halides such as the

alkyl and acyl halides, halogen derivatives of esters, ketones, acetals, etc., to give sodium halide and a new organic molecule. The fact that the new molecule has its parts linked through C rather than through oxygen caused much confusion and discussion as to the position of the Na in sodium acetoacetic ester. Two facts seem to emerge, (1) the Na is attached to O, (2) the entering carbon group which "replaces" the Na is attached to C. In other words the conception of simple replacement must be revised. As we have seen, the apparently conflicting facts may be reconciled by assuming that the sodium derivative gives an organic ion which is capable of rearrangement (Rep. 1908, 81; 1927, 108) (p. 166).

After one radical has been introduced a sodium derivative may again be made and another radical introduced. In using these reactions it must constantly be kept in mind that the sodium derivative is a strongly alkaline reagent and that organic halides can react with alkaline reagents to give olefins. Thus better yields of substituted acetoacetic esters are obtained with primary halides than with secondary halides. Tertiary halides give olefins almost entirely. Steric influences also limit the usefulness of these reactions. Thus isopropyl halides give a fair yield of isopropyl acetoacetic ester. The sodium derivative of isopropyl acetoacetic ester reacts with more isopropyl halide to give propylene entirely.

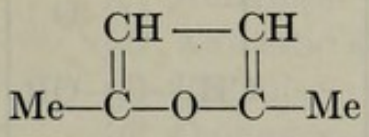
Sodium acetoacetic ester reacts with halogens to give diacetosuccinic ester. This may be regarded as an oxidation of the organic ions by the halogen.

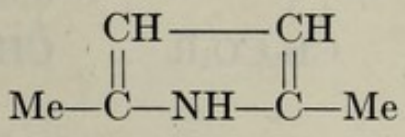
$$2\ \mathrm{MeC(ONa)=CHCO_2R} \rightarrow 2\left[\mathrm{MeC(O^{\ominus})=CH-CO_2R}\right] \rightleftharpoons$$

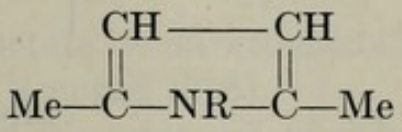
$$\left[\mathrm{MeC(=O)-\overset{\ominus}{C}H-CO_2R}\right] \xrightarrow{I_2} 2\left[\mathrm{MeCO-\underset{|}{C}H-CO_2R}\right] + 2\,I^- \rightarrow \mathrm{MeCOCH(CO_2R)_2}$$

Diacetosuccinic ester, as a *beta keto ester* gives reactions like

those of acetoacetic ester itself and as a *gamma diketone* it gives 5-ring heterocyclic compounds. Thus with acid, with ammonia, and with primary amines it gives 2,5-$Me_2$-derivatives of 3,4-dicarboxylic derivatives of furan, of pyrrole and of N-substituted pyrroles.



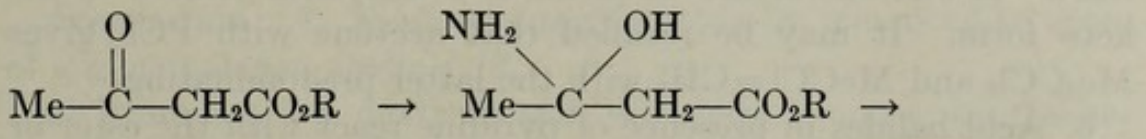


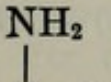


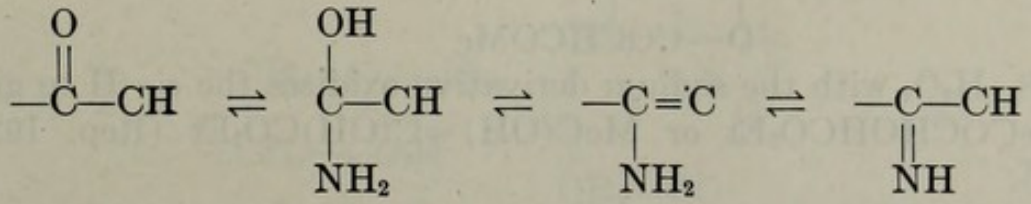
3. Acetoacetic ester reacts with aldehydes in the presence of secondary amines (Knoevenagel) to form compounds of the type, $MeCOCH(CO_2Et)—CHR—CH(CO_2Et)COMe$ which undergo the ketone and acid splittings characteristic of beta ketonic compounds and also give the reactions of delta keto esters and of delta (1 : 5) diketones.

4. The ketone group in acetoacetic ester gives the usual reactions. In many cases the resulting product has an active H near the ester group. An internal condensation results in ring closure.

(*a*) Ammonia gives β-amino-crotonic ester.

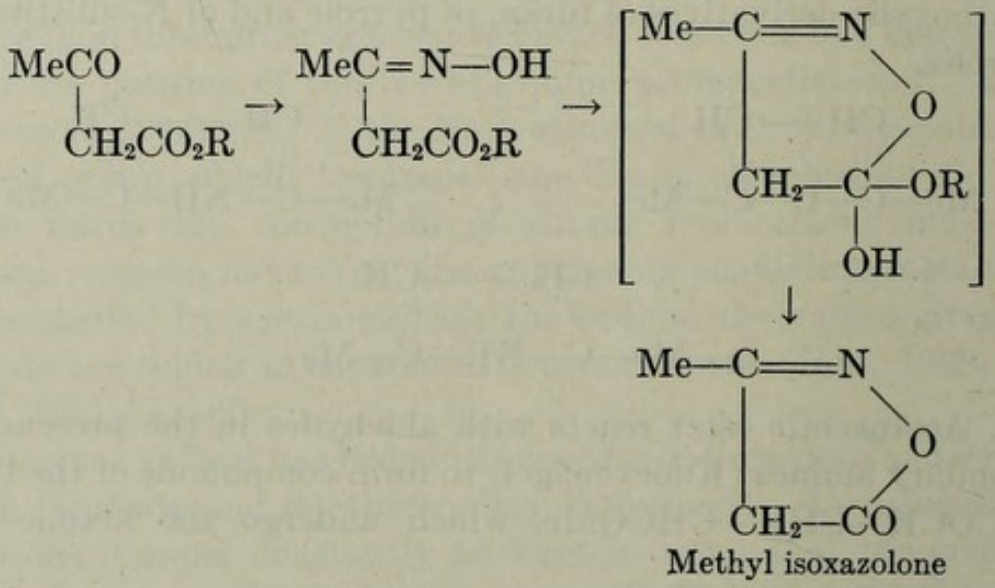


The form  is the ammonia analog of an enol. The equilibria



are of great importance in the biological interconversion of ketonic and amino acids.

(*b*) Hydroxylamine.




Methyl isoxazolone

(*c*) Similarly phenylhydrazine gives phenyl methyl pyrazolone, Ph—N——N , and sym-phenylmethylhydrazine gives
COCH$_2$CMe

phenyl dimethyl pyrazolone.

5. $PCl_5$ gives $\beta$-chlorocrotonic ester, $MeCCl=CHCO_2R$. This may indicate action with the enol form or the loss of HCl from the $\alpha-H$ and one of the Cl atoms of a dichloride related to the keto form. It may be recalled that acetone with $PCl_5$ gives $Me_2CCl_2$ and $MeCCl=CH_2$ with the latter predominating.

6. Acid halides in presence of pyridine react with the ester or its sodium derivative to give an ester of the enol form instead of a C— compound.

$$MeC(ONa)=CHCO_2Et \rightarrow MeC(OCOR)=CHCO_2Et$$

7. Strong heating of acetoacetic ester gives *dehydracetic* acid, (Adams 1924), MeC=CHCO .
O—COCHCOMe

8. $H_2O_2$ with the sodium derivative oxidizes the $\alpha-H$ to give $MeCOCHOHCO_2Et$ or $MeC(OH)=C(OH)CO_2Et$ (Rep. 1926, 98).

9. Among miscellaneous reactions of acetoacetic ester may be included the following:

(*a*) Aldehyde ammonias → dihydropyridines
(*b*) Ureas → uracils.
(*c*) Amidines → pyrimidines.
(*d*) Aromatic amines → dyes.
(*e*) Phenols → coumarines.
(*f*) Quinones → coumarones.

Ethyl $\alpha$-Br-acetoacetate is converted to the $\gamma$-Br-compound in presence of dry HBr (Conrad 1896).

Many other *beta ketonic acids and esters* have been obtained in the same way as acetoacetic ester by the Claisen condensation. It must be remembered that the condensation involves the $\alpha-H$ of one molecule and the carbonyl group of another.

Another preparation of *beta ketonic acids* involves the hydration of an $\alpha\beta$-triple bond by means of sulfuric acid. The preparation from an aliphatic acid follows:

$$RCH_2CH_2CO_2H \rightarrow RCH_2CHBrCO_2H \rightarrow RCH{=}CHCO_2H \rightarrow$$
$$RCHBrCHBrCO_2H \rightarrow RC{\equiv}CCO_2H \rightarrow$$
$$RC(OH){=}CHCO_2H \rightarrow RCOCH_2CO_2H$$

**Levulinic acid,** $\gamma$-ketovaleric acid, $\beta$-acetylpropionic acid, $CH_3COCH_2CH_2CO_2H$, m. 33°, b. 246°.

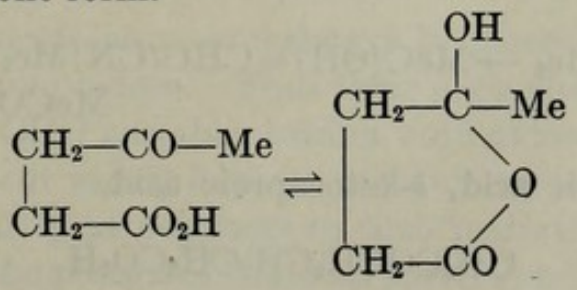
*Preparation.* 1. From acetoacetic ester by means of an ester of a monohalogen acetic acid.

2. From sucrose, dextrose and, especially levulose, by the action of dilute HCl or $H_2SO_4$ (Schuette 1931).

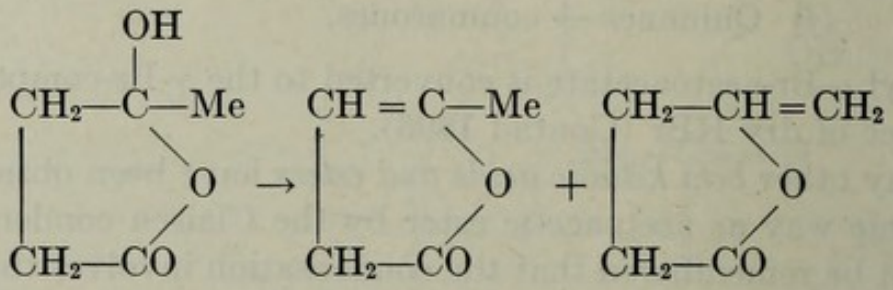
$$C_6H_{12}O_6 \rightarrow CH_3COCH_2CH_2CO_2H + CO + H_2O$$

The mechanism of this change is not known.

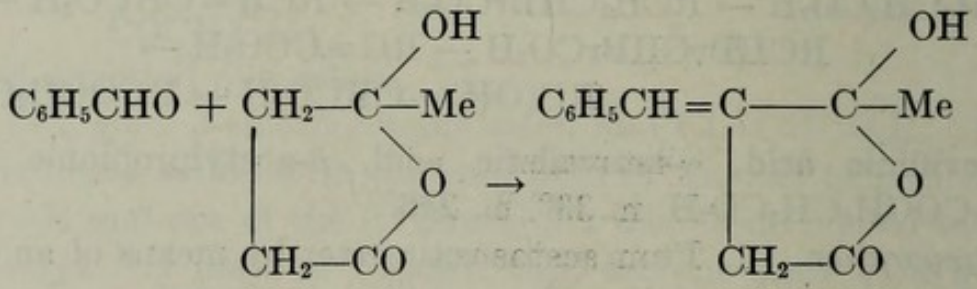
*Reactions.* Its reactions indicate that levulinic acid exists chiefly in a lactone form.



1. It forms salts and esters normally.
2. With acid chlorides, it gives γ-chloro-γ-valerolactone instead of a true acid chloride.
3. Its esters react with ammonia to give γ-amino-γ-valerolactone instead of an acid amide.
4. Acetic anhydride gives a definite crystalline acetate.
5. Long heating gives "alpha" and "beta" angelica lactones.



6. Sodium amalgam gives sodium γ-hydroxyvalerate.
7. Benzaldehyde condenses with a beta H in acid solution and with a delta H in basic solution (both are "alpha" to the CO group).



$$C_6H_5CHO + CH_3COCH_2CH_2CO_2Na \rightarrow C_6H_5CH{=}CH{-}COCH_2CH_2CO_2Na$$

**Mesitonic acid,** a homolog of levulinic acid is obtained by boiling mesityl oxide with KCN. Undoubtedly HCN first adds to the conjugated system and the resulting cyanide is then hydrolyzed.

$$MeCOCH{=}CMe_2 \rightarrow MeC(OH){=}CHC(CN)Me_2 \rightarrow MeCOCH_2CMe_2CO_2H$$

**γ-Acetobutyric acid,** δ-ketocaproic acid,

$$CH_3COCH_2CH_2CH_2CO_2H,$$

is made by oxidizing the corresponding primary alcohol obtained by the acetoacetic ester synthesis from trimethylene dibromide.

$$Br(CH_2)_3Br \rightarrow MeCO(CH_2)_4Br \rightarrow MeCO(CH_2)_4OH \rightarrow MeCO(CH_2)_3CO_2H$$

Reduction of the acid gives δ-hydroxy acid which then forms δ-caprolactone.

**Higher ketoacids** can be obtained by a variety of reactions. Two of these involve the acid chlorides of ester acids,

$$ClCO(CH_2)_nCO_2Et.$$

1. Alkyl zinc halides give $RCO(CH_2)_nCO_2Et$. Unlike the Grignard reagent, the alkyl zinc compounds do not react readily with ester or ketone groups.

2. Sodiomalonic ester and sodioalkylmalonic esters, followed by hydrolysis and decarboxylation give $CH_3CO(CH_2)_nCO_2Et$ and $RCH_2CO(CH_2)_nCO_2Et$. Thus the ester chloride of adipic acid and malonic ester give a 48% yield of ε-ketoheptoic acid.

3. A third method is the action of solutions of mercuric salts or of sulfuric acid with acetylenic acids (Rep. 1927, 88). Thus 10-ketostearic acid can be obtained in the following steps starting with oleic acid.

$$Me(CH_2)_7CH=CH(CH_2)_7CO_2H \rightarrow -CHBrCHBr- \rightarrow -C\equiv C- \rightarrow Me(CH_2)_7CO(CH_2)_8CO_2H$$

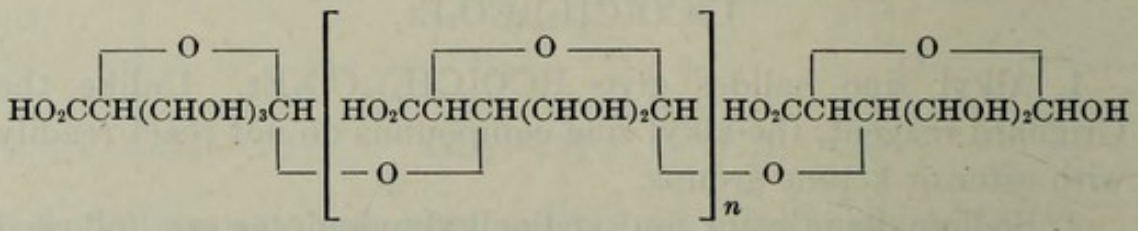
**Lactarinic acid,** $CH_3(CH_2)_{11}CO(CH_2)_4CO_2H$ is related to petroselic acid and tariric acid, the corresponding 5,6-olefinic and acetylenic acids (Rep. 1925, 80).

**Geronic** and **isogeronic acids** are $MeCO(CH_2)_3CMe_2CO_2H$ and $MeCOCH_2CMe_2(CH_2)_2CO_2H$ (Simonsen I 92).

### *C.* Hydroxy Aldehyde Acids

The *-uronic acids* have a carboxyl in place of the primary alcohol group in an aldose. Thus their open chain formulas are $HO_2C(CHOH)_nCHO$ and they exhibit both aldose and acid reactions. They occur widely in plant and animal tissues as complex polyuronides partly as polymers in such materials as the algins of seaweed and the pectins of fruit and partly combined with other

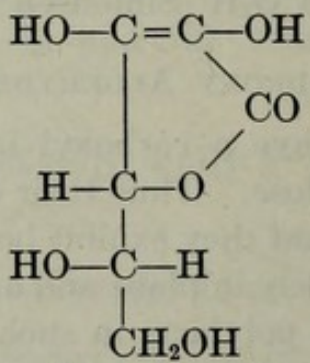
materials as in the hemicelluloses and glycoproteins. Because of their wide occurrence in plants and animals they are found in soils (Shorey 1930). The commonest of these acids are *d-glucuronic acid* (glycuronic acid) and *d-galacturonic* acid. Glucuronic acid is formed by oxidation in the animal organism. The aldehyde end of the molecule is apparently protected by glucoside formation. Thus when borneol is fed to a dog, borneol glucuronic acid is excreted (Quick 1933). Pectin consists largely of polygalacturonic acids (Morell, Link 1934),



The hexuronic acids are easily decarboxylated by boiling with 12% HCl, *d*-glucuronic acid giving *d*-xylose and *d*-galacturonic acid giving *l*-arabinose. More vigorous treatment gives furfural.

*d*-Mannuronic acid has been made from the alginic acid of certain sea weeds (Cretcher 1932). (Link 1932.)

Ascorbic acid obtained from the adrenal cortex, oranges, cabbages and other materials of high antiscorbutic action (Vitamin C) was formerly regarded as a hexuronic acid (Szent-Gyorgi 1928) (King 1929–32). It is actually isomeric with such a substance, being the enediol form of a keto sugar acid instead of an aldehyde sugar acid. Ascorbic acid and its analogs have been the subject of intense study. It has beeen synthesized and found to have the same Vitamin C action as the natural product (Rep. 1933, 167–175; 1934, 177–187).



*l*-ascorbic acid

The most striking property of ascorbic acid is its easily reversible oxidation. This may well involve the system

$$\begin{array}{l} \mathrm{H{-}O{-}C{=}C{-}O{-}H} \\ \qquad\quad | \quad | \end{array} \underset{\text{red.}}{\overset{\text{oxid.}}{\rightleftharpoons}} \begin{array}{l} \mathrm{O{=}C{-}C{=}O} \\ \qquad | \quad | \end{array}$$

## XXI. DIBASIC ACIDS

### *A.* Saturated Dibasic Acids

**Oxalic acid,** ethane diacid, $HO_2CCO_2H$, crystallizes as the ortho acid, $(HO)_3CC(OH)_3$. This is another example of the stability of more than one hydroxyl on a single carbon in a molecule containing strongly acid groups. It is a much stronger acid than its homologs. It naturally differs from them in many ways because it does not have its carboxyl groups attached to a hydrocarbon residue.

*Preparation.* 1. Heating formates under reduced pressure.

$$2\,HCO_2Na \rightarrow H_2 + (CO_2Na)_2$$

2. Fusion of carbohydrates (cellulose, saw dust) with mixed NaOH and KOH. Units in the cellulose react as follows:

$$\begin{array}{l} | \\ (\mathrm{CHOH})_2 \\ | \end{array} + 2\,KOH \rightarrow (CO_2K)_2 + 3\,H_2$$

The reaction mixture is extracted with water, the extract is treated with lime to regenerate the alkalies and form insoluble calcium oxalate which is converted to oxalic acid by $H_2SO_4$.

3. Oxidation of carbohydrates by nitric acid.

4. Hydrolysis of cyanogen, $(CN)_2$. This is carried out with water, or preferably, with concentrated HCl which gives oxamide first. Bases react as with halogens giving NaCN and NaOCN.

5. From $CO_2$ and hot sodium. This is like a pinacol reduction of a ketone

$$2\,\mathrm{O{=}C{=}O} + 2\,Na \rightarrow 2\begin{array}{l} \mathrm{O{=}C{-}ONa} \\ \quad | \end{array} \rightarrow \begin{array}{l} \mathrm{OCONa} \\ | \\ \mathrm{OCONa} \end{array}$$

*Reactions.* 1. Heat gives $CO_2$ and formic acid and the latter decomposes partly into $CO + H_2O$. It is not possible to make oxalic anhydride.

2. Heating with glycerol gives formic acid or allyl alcohol depending on conditions.

3. Oxidizing agents like $KMnO_4$ convert oxalic acid to $CO_2$ and water. This is another example of the splitting of a carbon chain by adding two OH groups at a point where adjacent carbons are already partly oxidized.

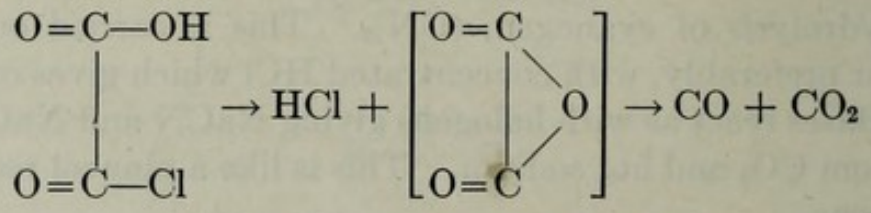
$$(CO_2H)_2 + [O] + H_2O \rightarrow 2\,HOCO_2H \rightarrow 2\,H_2O + 2\,CO_2$$

It reduces ferric compounds. It is thus valuable in removing iron rust and ink stains by changing them to the more soluble ferrous compounds. This same property is utilized in photography in making platinum prints. While potassium ferric oxalate, $K_3Fe(C_2O_4)_3$, is stable in the dark, it is readily reduced to the ferrous compound by light. Thus it is used on photographic paper which, after exposure, is treated with platinous chloride solution thus precipitating platinum wherever the ferric compound has been reduced by exposure to light. An abnormal reducing power is reported for a sample of oxalic acid treated with insufficient $KMnO_4$ to oxidize it completely (Rep. 1928, 78).

4. Electrolytic reduction with lead cathodes gives glycollic acid and some glyoxyllic acid.

5. Dehydrating agents like concentrated $H_2SO_4$ give $CO_2$, CO and $H_2O$.

6. Acid chlorides ordinarily act as dehydrating agents with oxalic acid. This is presumably because as soon as one OH is replaced the half acid chloride HOCOCOCl reacts internally instead of reacting with more of the reagent used.



By using a very large excess of $PCl_5$ both OH groups can be replaced practically simultaneously and a fair yield of oxalyl chloride, $(COCl)_2$, m. 12°, b. 64°, obtained (Diels).

7. (*a*) Alcohols readily give esters. $MeO_2CCO_2Me$, m. 54°.

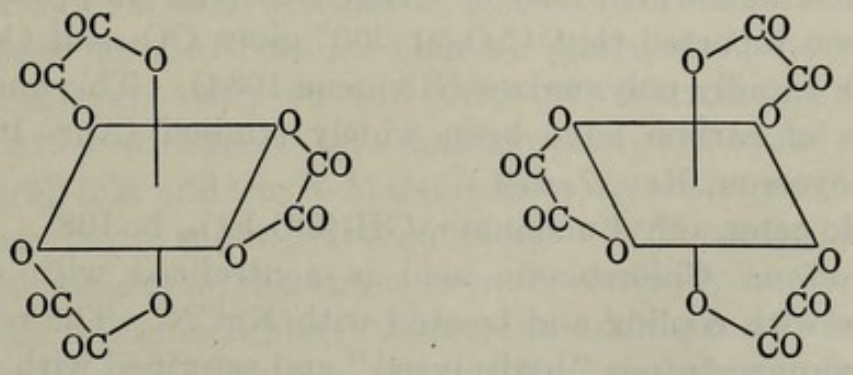
(*b*) The esters can be partially saponified to the ester salts, $RO_2CCO_2M$.

(*c*) From the ester salts, free ester acids, ester acid chlorides, etc., can be made.

(*d*) Oxalic esters react with $PCl_5$ to give dichloro oxalic esters, $RO_2CCCl_2-OR$, which react with sodium alcoholates to give tetra alkyl oxalates, $RO_2CC(OR)_3$, esters of the unknown half ortho acid, $HO_2CC(OH)_3$. Tetramethyl and tetraethyl oxalates boil at 76° and 98° at 12 mm. respectively.

8. Oxalic acid yields an amide, a nitrile, etc., by the usual methods. It also forms mixed compounds such as *oxamic acid*, $NH_2COCO_2H$ and its esters, cyanocarbonic esters, $NCCO_2R$, etc.

9. With heavy metal compounds, insoluble oxalates are formed. These are soluble in excess of soluble oxalates to give soluble complexes. Thus chromium gives a soluble potassium oxalochromate, $K_3Cr(C_2O_4)_3$. The physical reality of the complex ion is proved by the existence of this compound in optically active forms (Werner). The six valences of the three oxalate groups can occupy the six coordination points of the central metal in two ways. The products are enantiomorphic. The six coordination points may be regarded as at the points of a regular octahedron with the metal at the center.




10. Oxalic acid gives the expected normal and acid salts, $M_2C_2O_4$ and $MHC_2O_4$. It also gives a peculiar acid salt of which potassium tetroxalate, $KHC_2O_4.H_2C_2O_4.2\,H_2O$, is an example.

This salt is a valuable standard for bases and oxidizing agents because it can be prepared and kept in a high state of purity.

Oxalic acid is poisonous presumably because of the insolubility of calcium oxalate. The toxic nature of ethylene glycol when taken internally is probably due to its oxidation to oxalic acid.

**Malonic acid,** propane diacid, $CH_2(CO_2H)_2$, m. 134°, is obtained from its ester which has important synthetic uses. The free acid decomposes when heated to about 160° to give $CO_2$ and acetic acid. In general, two carboxyls attached to the same carbon form an unstable arrangement.

$$=C(CO_2H)_2 + \text{heat} \rightarrow CO_2 + =CHCO_2H.$$

Substituted malonic acids decompose even more readily to give the corresponding substituted acetic acids, $RCH_2CO_2H$ and $RR'CHCO_2H$. Malonic acid gives all the reactions of carboxylic acids in which either one or both carboxyls may be involved except the formation of an ordinary anhydride. Such an anhydride would have a 4- or 8-membered ring depending on whether one or two molecules took part in its formation. Malonic acid with $P_2O_5$ gives small yields of *carbon suboxide*, $C_3O_2$, $O=C=C=C=O$, m. −107°, b. 6°, a diketene (Rep. 1906, 101). It can also be made by the action of zinc with dibromomalonyl chloride. Like other ketenes it acts with active H compounds. Thus water, alcohol, and ammonia give malonic acid, its ester and amide. A less expected reaction is that with formic acid to give a substance which may be $CH_2(COCO_2H)_2$ (Rep. 1908, 85). It has been reported that $C_3O_2$ at 200° gives $CO_2$ and $C_2$, a red gas which rapidly polymerizes (Klemenc 1934). This and other suboxides of carbon have been widely studied (Ahr. 1924, 17 pp). (Reyerson, Rev. 7, 479.)

**Malonic ester,** ethyl malonate, $CH_2(CO_2Et)_2$, b. 198°.

*Preparation.* Chloroacetic acid is neutralized with sodium carbonate with cooling and treated with NaCN. The resulting sodium cyanoacetate is "hydrolyzed" and esterified with alcohol and HCl.

$$CN-CH_2CO_2Na + 2\,EtOH + 2\,HCl \rightarrow CH_2(CO_2Et)_2 + NaCl + NH_4Cl$$

*Reactions.* 1. Usual ester reactions involving one or both of the ester groups.

2. Replacement of the methylene hydrogens is possible as in acetoacetic ester. Although malonic ester exists practically entirely in the "keto" form, its sodium derivative has the enol structure, $EtOCO-CH=C(ONa)OEt$. Sodium malonic ester reacts with certain halides to give substitution on the methylene carbon. Such substituted malonic esters form sodium derivatives which can react again with halides. It must not be assumed that treatment of malonic ester with one equivalent each of Na and RX will give exclusively a monosubstitution product, $RCH(CO_2Et)_2$. Thus equimolar amounts of Na, malonic ester and benzyl chloride give the following ratios of mono- and dibenzyl malonic esters: in MeOH or EtOH about 2 : 1; in toluene from 2 : 1 to 12 : 1 and with no solvent about 1 : 1 (Dunn 1932). The formation of the disubstituted product is due to the equilibrium.

$$\text{Na-Malonic ester} + \text{R-Malonic ester} \rightleftharpoons \text{Malonic ester} + \text{Na-R-Malonic ester}$$

There is a competition between the two sodium derivatives for the unreacted halide. Fortunately the competition for the sodium is usually in favor of the malonic ester. With halides containing two or more carbons the mono- and di- substituted malonic esters can be separated by fractional distillation. Thus Et- and $Et_2$-malonic esters b. 201° and 223°. The methyl malonic esters offer a hopeless mixture because malonic esters, the Me- and $Me_2$-malonic esters b. 198°, 199° and 196°. If a Me and another group, R, are to be introduced into malonic ester, the latter should be introduced first and the R-Malonic ester should be purified before treatment with more Na and MeX. In general, in making RR′-malonic esters, the larger or more sterically hindered group should be introduced first. Instead of adding more Na and the other halide to the reaction mixture it is advisable to isolate and purify the mono-substituted malonic ester. Otherwise the final reaction product will contain $R_2$-malonic and $R'_2$-malonic esters in addition to the desired product. Such a mixture may be very difficult to separate. In making $R_2$-malonic esters the two

equivalents of Na and RX may be added at once. It is not correct to assume that this procedure gives a disodiomalonic ester. Such a substance would have the *improbable* formula,

$$ROC(ONa)=C=C(ONa)OR.$$

The limitations as to halides which can be used with Na-malonic ester are the same as with Na-acetoacetic ester.

The mono- and di- substituted malonic esters can be converted to the acids and then heated to give $RCH_2CO_2H$, $R_2CHCO_2H$ and $RR'CHCO_2H$. An example of going up the series by means of the sodiomalonic ester synthesis is the preparation of the even normal acids and related substances from $C_{20}$ to $C_{30}$ starting with stearic acid. The main changes involved in each addition of $C_2$ follow:

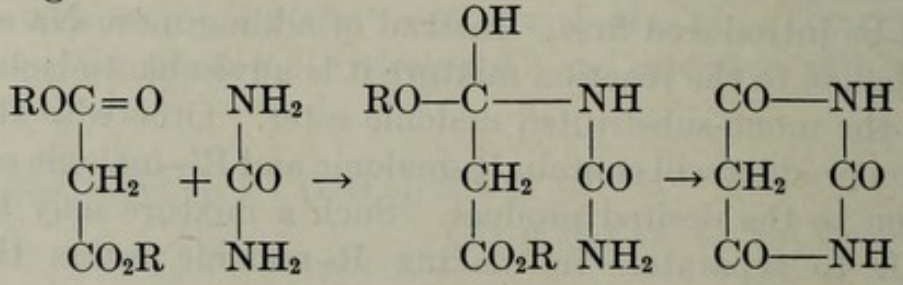
$$RCO_2H \rightarrow RCH_2OH \rightarrow RCH_2X \rightarrow RCH_2CH(CO_2Et)_2 \rightarrow RCH_2CH_2CO_2H$$

4. Another replacement of the methylene hydrogens of malonic acid or its esters involves an aldol condensation with an aldehyde and a condensing agent such as piperidine or other secondary amine (Knoevenagel).

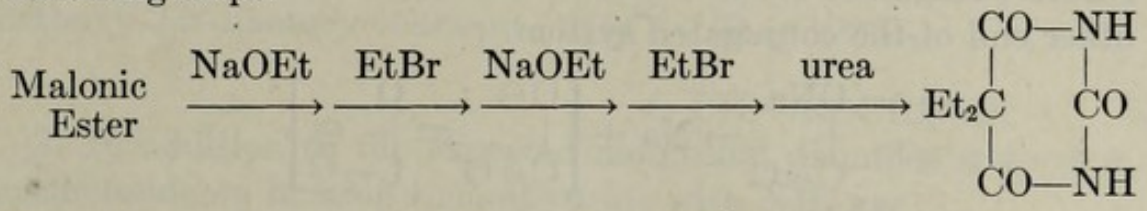
$$RCHO + H_2C(CO_2H)_2 \rightarrow [RCHOHCH(CO_2H)_2] \rightarrow RCH=C(CO_2H)_2$$

The intermediate "aldol" is unstable because of the reactive $\alpha-H$. The resulting dibasic acid loses $CO_2$ readily. These reactions thus become a source for *$\alpha\beta$-unsaturated acids.*

5. With urea and NaOEt as a condensing agent the carbethoxyl groups react to give barbituric acid. The primary condensation gives a molecule which can condense internally to give a 6-membered ring.

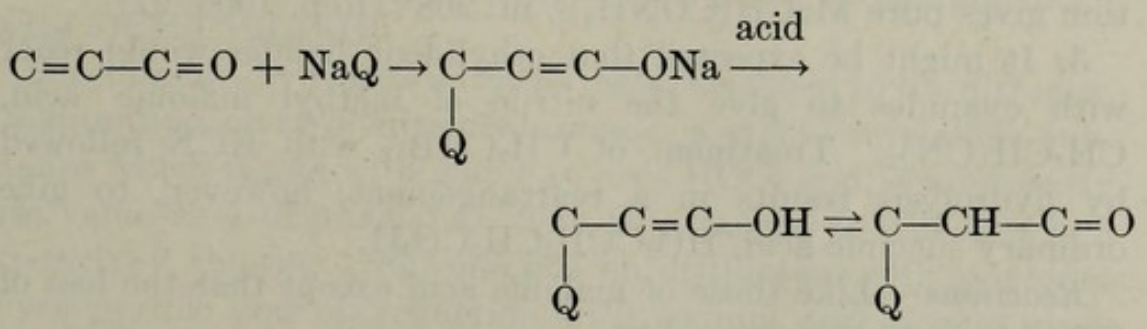


The substituted barbituric acids are important soporifics. They are obtained from the disubstituted malonic esters. Thus Veronal (Barbital), C-diethyl barbituric acid is obtained in the following steps.




Variation in the two groups on the methylene carbon introduces slight changes in the soporific effect.

6. Sodium malonic ester, in common with all similar compounds such as sodium acetoacetic ester, sodium cyanoacetic ester, sodium nitromethane, sodium phenyl nitromethane, etc., adds to alpha beta unsaturated carbonyl compounds (Michael, Kohler). The addition takes place to the conjugated system.

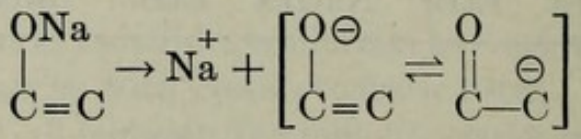



Since some of the enol present can act as the "acid" the addition of the keto esters can be induced by small amounts of NaOEt. One of the earliest examples of this reaction, although it was not so recognized at the time was the action of sodium malonic ester with ethyl alpha bromoisobutyrate. The expected result was *not* obtained. Instead of dimethyl succinic acid, the final product *obtained* was alpha methyl glutaric acid. The alkaline sodium malonic ester first removed HBr from the very reactive tertiary halide to give $\alpha$-methylacrylic ester, to which more sodium malonic ester then added.

$$Me_2CBrCO_2R \rightarrow CH_2=C(Me)CO_2R \rightarrow$$
$$(RO_2C)_2CH-CH_2CH(Me)CO_2R \rightarrow HO_2CCH_2CH_2CHMeCO_2H$$

Hundreds of cases of this type of addition to $\alpha\beta$-unsaturated compounds have been studied. The formation of a C—C

linkage from an O—Na "linkage" is explained as in the action of the sodium derivatives with halides. In order for addition to take place, the Na must leave the rest of the molecule. This reactive fragment or ion can then rearrange before adding to the other end of the conjugated system.



**Methylmalonic acid,** isosuccinic acid, $CH_3CH(CO_2H)_2$.

*Preparation.* 1. From $\alpha$-halogen propionic acid through the $\alpha$-cyano compound.

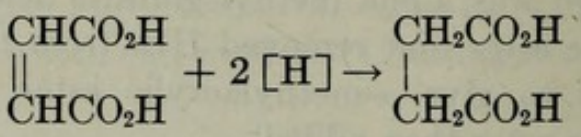
2. From sodium malonic ester and methyl iodide or bromide. Dimethyl malonic ester is formed at the same time. These esters cannot be separated because they boil at practically the same temperature. Conversion to the amides and careful crystallization gives pure $MeCH(CONH_2)_2$, m. 208° (Rep. 1906, 97).

3. It might be expected that ethylidene halides would react with cyanides to give the nitrile of methyl malonic acid, $CH_3CH(CN)_2$. Treatment of $CH_3CHBr_2$ with KCN followed by hydrolysis results in a rearrangement, however, to give ordinary succinic acid, $HO_2CCH_2CH_2CO_2H$.

*Reactions.* Like those of malonic acid except that the loss of $CO_2$ takes place more readily.

**Succinic acid,** ethylene dicarboxylic acid, butane diacid, $HO_2CCH_2CH_2CO_2H$, m. 183°, has been obtained by the distillation of scrap amber (hence its name) and by fermentation of tartaric acid.

*Preparation.* 1. By the electrolytic reduction of maleic and fumaric acids obtained by the catalytic oxidation of benzene.



2. By hydrolysis of the dinitrile from ethylene chloride and NaCN.

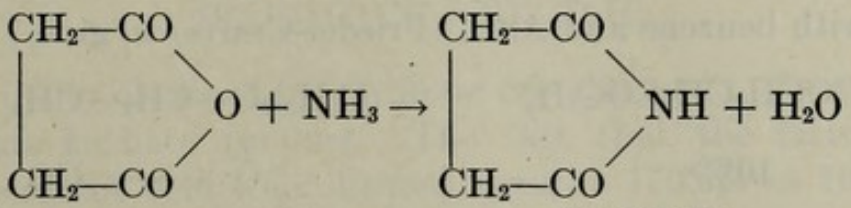
*Reactions.* 1. Heat gives succinic anhydride, m. 120°, b. 261°, containing a 5-membered ring. A better preparation is by the action of thionyl chloride.

2. It gives many of the ordinary reactions of carboxylic acids either with one or both of its acid groups.

Ethyl succinate with Na undergoes a double Claisen reaction to give succinylosuccinic ester, succinosuccinic ester, 1,4-dicarbethoxy-2,5-diketocyclohexane, $RO_2C—CH—COCH_2$.

$CH_2—COCHCO_2R$

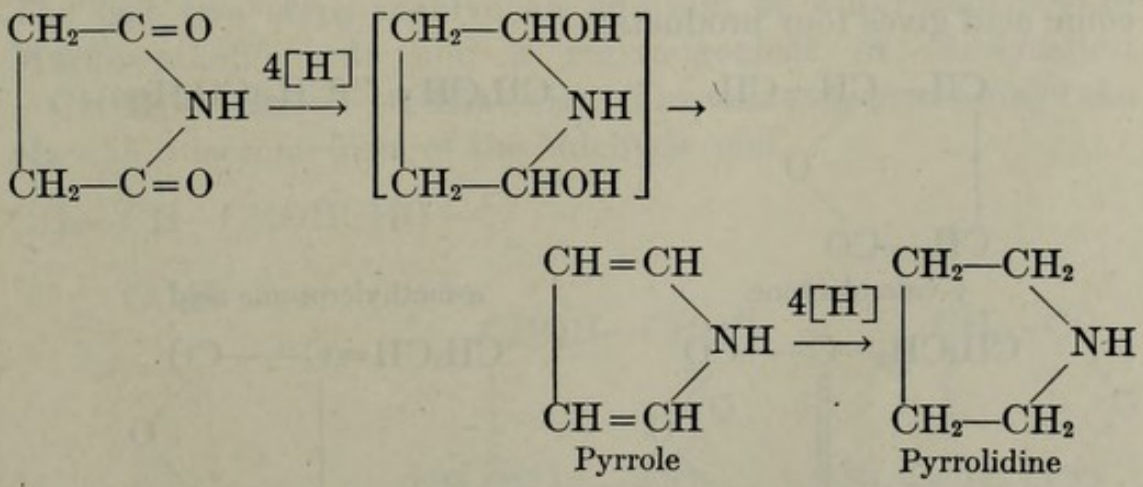
3. In addition to the expected mono and diamides it gives a cyclic imide on heating the anhydride with $NH_3$ gas.



*Succinimide*

On hydrolysis the ring first opens to form succinamic acid, $NH_2COCH_2CH_2CO_2H$.

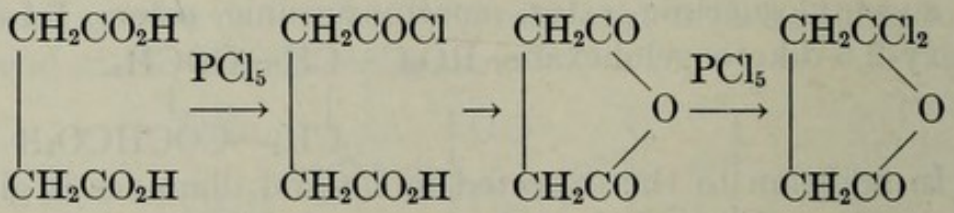
Succinimide gives salts with the metal attached to the nitrogen. Chlorination gives N-succinchlorimide, a stable crystalline substance which reacts with water to give HOCl and, consequently has value as a disinfectant. The Cl attached to nitrogen is a "positive" chlorine. Succinimide on distillation with zinc dust gives pyrrole and on reduction with sodium and alcohol gives pyrrolidine (tetrahydropyrrole).



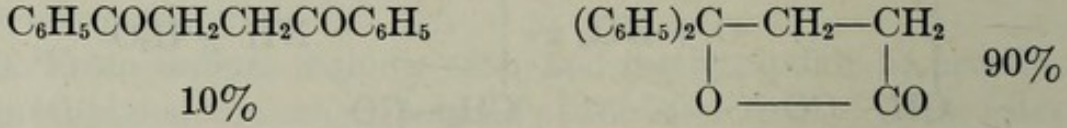
Pyrrole Pyrrolidine

Pyrrole is of great interest because its ring forms the chief building unit of chlorophyll and of hemoglobin.

4. Treatment with $PCl_5$ gives a small amount of the expected dichloride, $ClCOCH_2CH_2COCl$, but mainly an unsymmetrical dichloride related to butyrolactone.

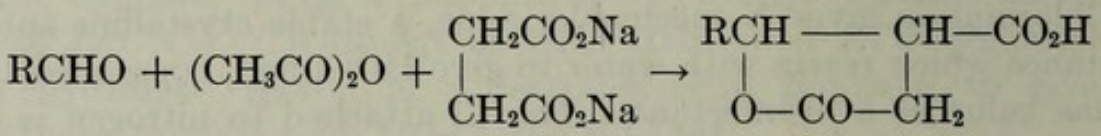


Evidence for this is that the product of $PCl_5$ with succinic acid reacts with benzene and $AlCl_3$ (Friedel-Crafts) to give

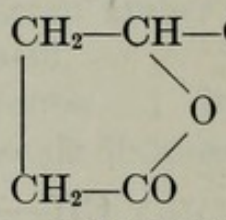


A better yield of the true symmetrical dichloride can be obtained by using a large excess of $PCl_5$ as in the preparation of oxalyl chloride.

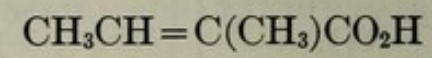
5. The Perkin reaction gives *paraconic acids*,



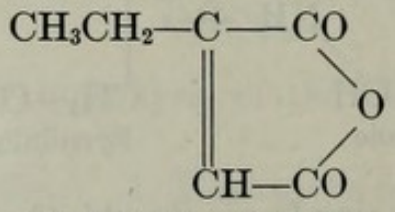
The initial condensation product has a hydroxyl and a carboxyl in the 1,4-position and immediately forms a $\gamma$-lactone. The paraconic acids decompose on distillation. Thus methyl paraconic acid gives four products:



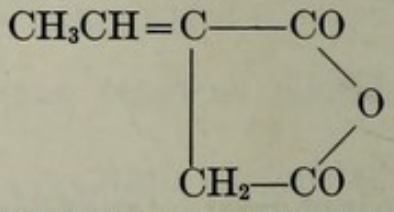
$\gamma$-valerolactone



$\alpha$-methylcrotonic acid

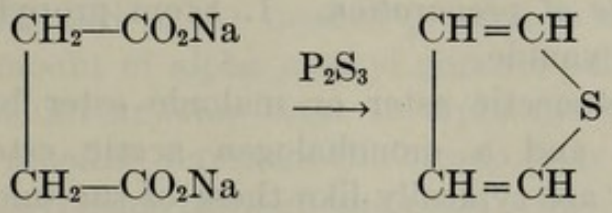


ethyl maleic anhydride
" Methyl citraconic anhydride "



ethylidene succinic anhydride
" Methyl itaconic anhydride "

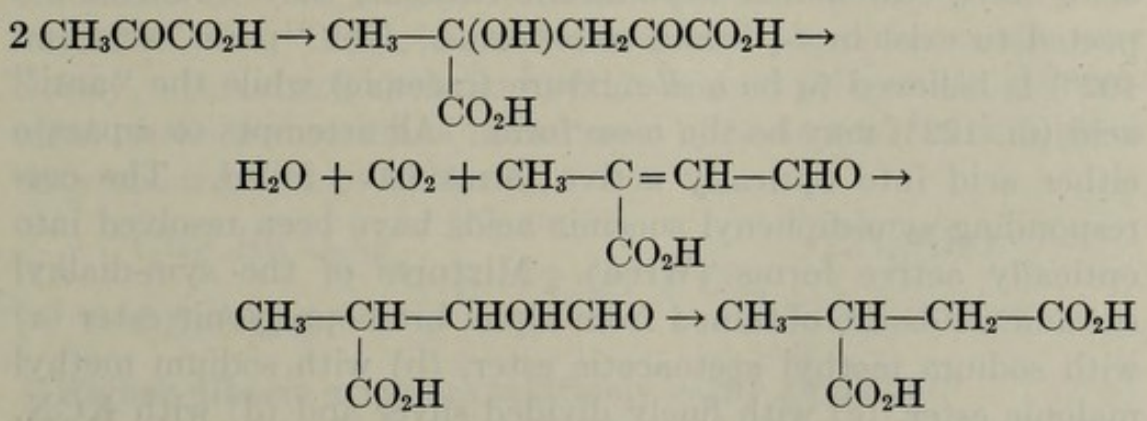
6. Sodium succinate and succinic anhydride react with $P_2S_3$ to give thiophene.



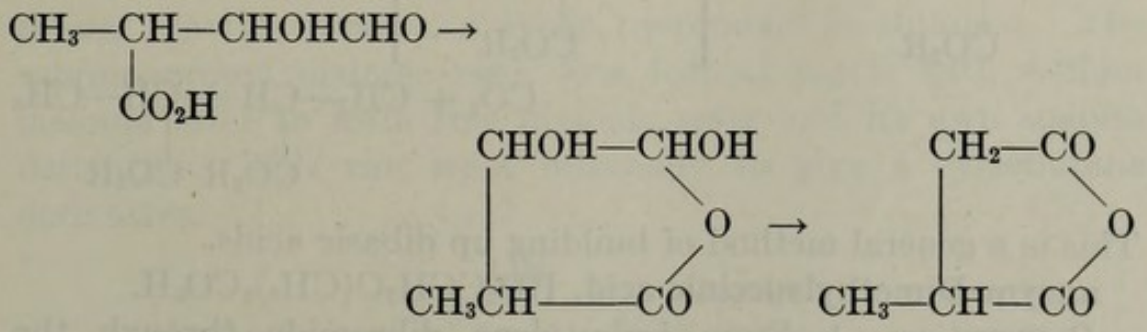
**Methylsuccinic acid,** pyrotartaric acid,

$$HO_2CCH(CH_3)CH_2CO_2H,$$

was originally obtained by distilling tartaric acid. Pyruvic acid is an intermediate product. The fact that the latter gives methyl succinic acid when heated alone to 170° or at 100° with HCl, indicates a rearrangement.



The last two steps involve an addition of water contrary to Markownikoff's rule and a rearrangement or dismutation $-CHOH-CHO \rightarrow -CH_2CO_2H$. This rearrangement may take place in a lactone form of the aldehyde acid.



An even stranger formation of methylsuccinic acid is by the catalytic hydrogenation of sodium lactate solution under pressure

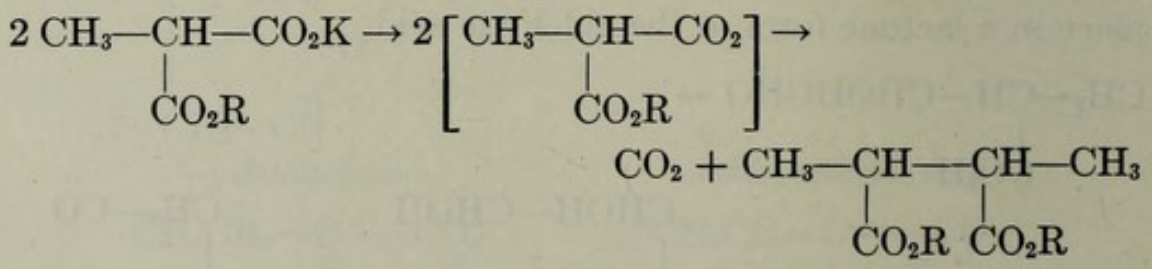
(Rep. 1927, 85). The loss of a methyl group in the process is hard to explain.

*Other methods of preparation.* 1. From propylene dibromide through the dicyanide.

2. From acetoacetic ester or malonic ester by means of a methyl halide and a monohalogen acetic ester.

Its reactions are typically like those of succinic acid. It can be resolved into its optical isomers by means of its salts with the optically active base, strychnine.

**sym-Dimethyl succinic acids,** $HO_2CCH(CH_3)CH(CH_3)CO_2H$, exist in two forms, the "para" acid and the "anti" acid. They are both formed in all methods of preparation and are separated by recrystallizing from water, the anti acid being three times as soluble as the para acid at ordinary temperatures. Since these acids have two similar asymmetric carbons, they would be expected to exist in *d*-, *l*- and *meso*-forms. The "para" acid (m. 192°) is believed to be a *dl*-mixture (racemic) while the "anti" acid (m. 122°) may be the *meso* form. All attempts to separate either acid into optically active forms have failed. The corresponding sym-diphenyl succinic acids have been resolved into optically active forms (Wren). Mixtures of the sym-dialkyl succinic acids are obtained from alpha bromopropionic ester (a) with sodium methyl acetoacetic ester, (b) with sodium methyl malonic ester, (c) with finely divided silver and (d) with KCN. They are also obtained from sodium methyl malonic ester by treatment with halogens or by electrolysis. Another preparation is by the electrolysis of the ester salt of methyl malonic acid.



This is a general method of building up dibasic acids.

**unsym-Dimethylsuccinic acid,** $HO_2CCH_2C(CH_3)_2CO_2H$.

*Preparation.* 1. From isobutylene dibromide through the dicyanide.

2. From ethyl beta-chloroisovalerianate and KCN.

3. From solid sodium malonic ester and alpha-bromoisobutyric ester in xylene at 190°. If the reaction is carried out in refluxing absolute alcohol, part of the desired product is obtained, but a considerable amount of alpha methyl glutaric acid is formed by addition of sodium malonic ester to alpha-methylacrylic ester formed by the alkaline action on the bromo ester (p. 457).

4. From mesityl oxide through mesitonic acid. The potassium salt of the latter is obtained by merely boiling mesityl oxide with KCN solution.

$$CH_3COCH_2C(CH_3)_2CO_2K + 4\ KOH + 3\ Br_2 \rightarrow CHBr_3 + KO_2CCH_2C(CH_3)_2CO_2K + 3\ KBr + 2\ H_2O$$

**Glutaric acid,** $HO_2C(CH_2)_3CO_2H$, is prepared (1) from trimethylene dibromide through the cyanide and (2) from methylene dimalonic ester or methylene diacetoacetic ester prepared from formaldehyde. Glutaric acid resembles succinic acid very closely. It forms a cyclic anhydride and a cyclic imide. Treatment of the silver salts of substituted glutaric acids with $I_2$ gives butyrolactone (Rep. 1923, 91).

$$\begin{matrix} CH_2CH_2CO_2Ag \\ | \\ CH_2CO_2Ag \end{matrix} + I_2 \rightarrow 2\ AgI + CO_2 + \begin{matrix} CH_2CH_2O \\ | \quad | \\ CH_2 — CO \end{matrix}$$

**Higher dibasic acids** are relatively easily available.

(*a*) *Adipic acid,* $HO_2C(CH_2)_4CO_2H$ by oxidation of cyclohexanol (OS).

(*b*) *Pimelic acid,* $HO_2C(CH_2)_5CO_2H$, from pentamethylene dibromide through the cyanide process or from trimethylene dibromide through the malonic ester or acetoacetic ester synthesis. In this process, a cyclic by-product is obtained. The γ-bromopropyl malonic ester first formed reacts with sodium malonic ester to form free malonic ester and its own sodium derivative. This can react internally to give a cyclobutane derivative.

$$\begin{matrix} & & OR \\ & & / \\ BrCH_2CH_2CH_2C = & C — & ONa \\ & | & \\ & CO_2R & \end{matrix} \rightarrow \begin{matrix} CH_2 — C(CO_2R)_2 \\ | \quad | \\ CH_2 — CH_2 \end{matrix} + NaBr$$

(*c*) *Suberic acid*, $HO_2C(CH_2)_6CO_2H$, by the oxidation of cork or castor oil, and by the electrolysis of ethyl potassium glutarate. It is also obtained by the action of trimethylene bromide with magnesium and $CO_2$. This is a combined Wurtz and Grignard reaction.

(*d*) *Azelaic acid*, $HO_2C(CH_2)_7CO_2H$, from the oxidation of oleic acid or from pentamethylene dibromide with Na malonic ester or Na acetoacetic ester. The cyclic by-product is obtained in larger amounts than with trimethylene dibromide.

(*e*) *Sebacic acid*, $HO_2C(CH_2)_8CO_2H$, is obtained by heating a castor oil soap with sodium hydroxide.

$$CH_3(CH_2)_5CHOHCH_2CH{=}CH(CH_2)_7CO_2Na \xrightarrow{NaOH} NaO_2C(CH_2)_8CO_2Na + \underset{\text{capryl alcohol}}{C_6H_{13}CHOHCH_3}$$

Many higher acids of this series are known. *Brassilic* and *thapsic acids* are the $C_{13}$ and $C_{16}$ members. The former is obtained by oxidation of erucic and brassidic acids. *Japanic acid*, nonadecane-1,19-dicarboxylic acid, is obtained from Japan wax (Rep. 1928, 79).

Dibasic acids with an even number of carbons are readily made by Kolbe's electrolytic method from $EtO_2C(CH_2)_nCO_2K$. Other syntheses start with the dibasic acids and involve the following steps (Rep. 1926, 101).

(*a*) $\rightarrow -CO_2Et \rightarrow -CH_2OH \rightarrow -CH_2Br$

(*b*) $-CH_2Br \xrightarrow[\text{ester}]{\text{Na malonic}} -CH_2CH_2CO_2H$ Etc.

(*c*) $-CH_2MgBr \xrightarrow{ClCH_2OMe} -CH_2CH_2OMe \xrightarrow{HBr} -CH_2CH_2Br$ etc.

When the calcium or, better, the thorium salts of the higher dibasic acids ($C_6$ to $C_{19}$) are distilled cyclic ketones result in varying yields (Ruzicka; Rep. 1926, 112). The best yields are obtained with the 5- and 6-ring ketones from adipic and pimelic acids. As usual, substituting groups force the carboxyl groups nearer in space and favor ring closure. Thus $\beta$-Me-adipic acid when heated with CuO gives an 83% yield of 3-Me-cyclopentanone.

The formation of anhydrides from the dibasic acids from $C_6$ to $C_{18}$ has been studied in detail (Hill, Carothers). In addition to rings formed from one and two molecules, higher linear polymers are obtained. Suberic ($C_8$) and the $C_{12}$ acid give anhydrides containing 18- and 26-member rings of m. 57° and 78° which are stable up to the melting points. The polymeric anhydrides, even with adipic acid are the readily obtained forms. Their polymeric nature may be shown by the action of aniline. Thus the ordinary anhydride of adipic acid when treated with aniline gives adipic mono- and di-anilides and adipic acid while the true monomeric 7-ring anhydride, obtained by vacuum distillation of the polymer, reacts with aniline to give only one product, the monoanilide of adipic acid (Hill).

The 15-ring anhydride has a musk odor like the 15-member ketone and lactone (Ruzicka). The effect of alkyl groups on ring closure and stability is again striking. Thus the anhydrides of adipic and $\beta$-Me-adipic acids are readily hydrolyzed while those of the $Me_4$-adipic acids are stable to boiling water (Rep. 1927, 84).

Certain reactions of the derivatives of the dibasic acids differ from those of the monobasic acids because of spatial relations. Thus adipic ester can undergo an internal acetoacetic ester condensation to give cyclopentanone-$\alpha$-carboxylic ester,

$$\begin{array}{l} CH_2CH_2CO \\ | \quad\quad | \\ CH_2 \text{—} CHCO_2Et \end{array}$$

A more remarkable reaction is that of the $\alpha\alpha'$-$Br_2$-adipic ester with NaCN to give 1-cyanocyclobutane-1,2-dicarboxylic ester $\begin{array}{l} CH_2C(CN)CO_2Et \\ | \quad | \\ CH_2CHCO_2Et \end{array}$, which on hydrolysis loses $CO_2$ and give *trans-cyclo*-butane-1,2-dicarboxylic acid (Fuson 1929). This reaction is like that of $\alpha$-Br-propionic ester with KCN which gives mainly a dimolecular product, $EtO_2CCH(Me)C(Me)(CN)CO_2Et$. An even more surprising reaction of this dibromo ester is with secondary amines to give $R_2NCH_2CH_2CO_2Et$ and $CH_3COCO_2Et$ (Fuson 1929, 1930).

The dibasic acids beginning with glutaric can be identified as the phenacyl or *p*-bromophenacyl esters (Kelly 1932).

$$(CH_2)_n(CO_2Na)_2 + 2\,BrCH_2COAr \rightarrow (CH_2)_n(CO_2CH_2COAr).$$

For various values of $n$ the phenacyl esters m. 4, 87°; 5, 72°; 6, 102°; 7, 69°; 8, 80° while the *p*-Br-phenacyl esters m. 3, 136°; 4, 154°; 5, 136°; 6, 144°; 7, 130°. The usual alternation in melting points is striking.

Ionization constants of dicarboxyl compounds and structure. Greenspan, Rev. 1933 I 339–62.

### *B.* Unsaturated Dibasic Acids

**Methylene malonic ester,** $CH_2=C(CO_2Et)_2$, is obtained from methylene iodide or bromide with malonic ester and an excess of sodium ethylate. Hydrolysis gives acrylic acid, decarboxylation taking place spontaneously.

**Alkylidene malonic esters,** $RCH=C(CO_2Et)_2$ are obtained from aldehydes and malonic ester in the presence of acetic anhydride. The acids are also obtained by the action of aldehydes with malonic acid and a secondary amine. Hydrolysis of the esters and decarboxylation of the acids gives $RCH=CHCO_2H$.

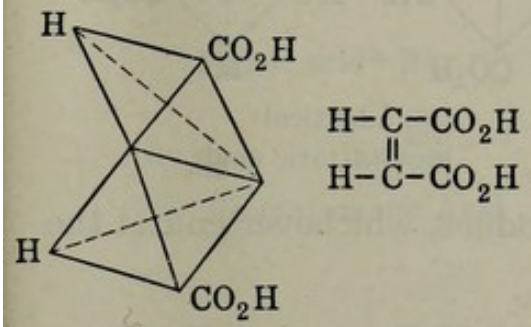
**Maleic acid,** *cis*-butene diacid, $\begin{matrix} H-C-CO_2H \\ \| \\ H-C-CO_2H \end{matrix}$, and **fumaric acid,** *trans*-butene diacid, $\begin{matrix} HO_2C-C-H \\ \| \\ H-C-CO_2H \end{matrix}$, form the most important example of geometrical isomerism. These acids are both obtained from monohalogen succinic acids and by the dehydration of malic acid (hydroxysuccinic acid). By long heating at 150° it gives fumaric acid while at 200° the product is maleic acid. Commercially they are made by the high temperature catalytic oxidation of benzene (EP 916). On reduction they both give succinic acid and with halide acids they give the same monohalogen succinic acids. On mild oxidation with $KMnO_4$, maleic acid gives *meso* or internally compensated tartaric acid while fumaric acid gives racemic acid (*dl*-tartaric acid). Maleic acid, on heating alone, or better, with $P_2O_5$ or acetyl chloride gives maleic anhydride. Fumaric acid, on heating sublimes with a partial change into an anhydride which reacts with water to give maleic acid. Long heating, exposure to light, and treatment with traces of chemical reagents like HCl or $I_2$ convert maleic to fumaric acid, which is thus the more stable form. The change appears to be related to an "activation" of the double bond

(Rep. 1925, 76). Thus a trace of potassium will convert Me maleate to the fumarate. The conversion to fumaric acid may also be induced by chemical reactions in which the acids apparently take no part. Thus, neither $H_2S$ nor $SO_2$ has any effect on maleic acid but the addition of both reagents converts it to fumaric acid. Similarly copper maleate with $H_2S$ gives fumaric acid (Rep. 1925, 109). This effect may be due to "chemical" energy liberated by the reaction or to some specific effect not now understood. The reverse change is brought about by ultraviolet light which converts fumaric acid to maleic acid, the compound richer in energy. The best method for this change is to treat fumaric acid with $P_2O_5$ or acetyl chloride, distill the maleic anhydride formed, and treat it with the calculated amount of water.

The properties of the acids are distinctly different.

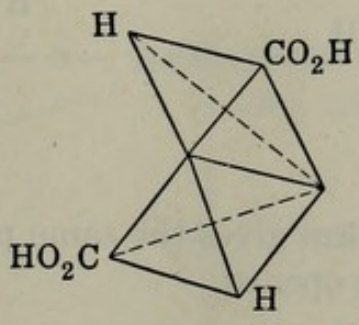
| | Maleic Acid | Fumaric Acid |
|---|---|---|
| m. | 130° | 289° (pressure) |
| b. | 160° | 200° |
| Solubility in cold $H_2O$ | readily soluble | almost insoluble |
| Taste | disagreeable | acid |
| Dissociation K | 1.170 | 0.093 |

The isomerism of maleic and fumaric acids is expressed in the space formulas.




$$\begin{array}{l} H-C-CO_2H \\ \| \\ H-C-CO_2H \end{array}$$

Maleic acid
cis-form

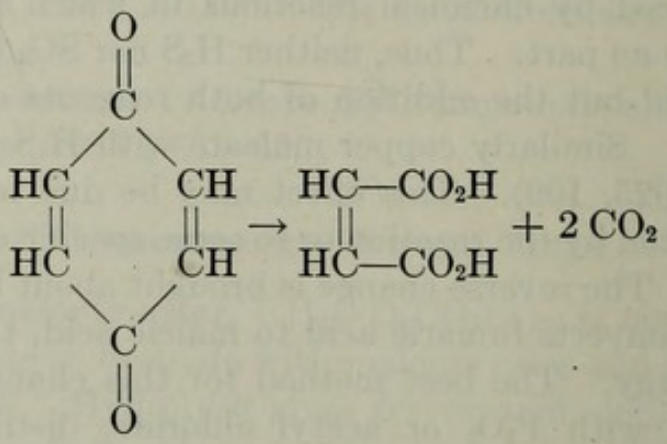



$$\begin{array}{l} H-C-CO_2H \\ \| \\ HO_2C-C-H \end{array}$$

Fumaric acid
trans-form

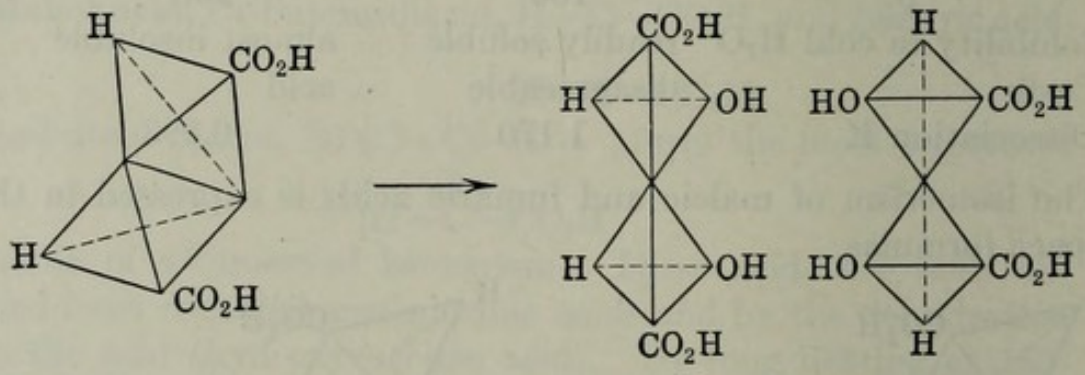
In the *cis* form, it is possible for the carboxyls to approach each other in space. Thus the formation of an anhydride is easy. Another evidence that the assignment of these configurations is correct is that the more stable form should have similar groups as far apart as possible. The formation of maleic

acid directly by the oxidation of quinone also indicates the *cis* configuration for that acid.



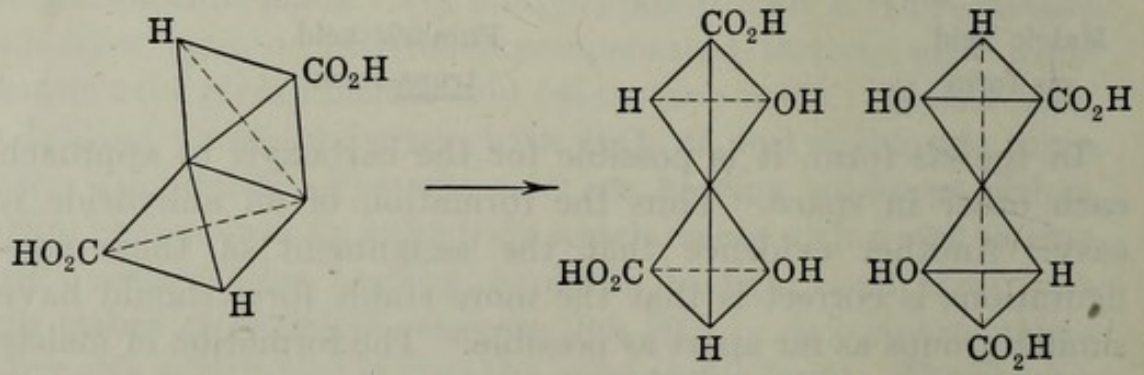

The conversion of the two acids into each other is not understood, largely because we know so little about the true nature of a "double bond."

The action of $KMnO_4$ on maleic and fumaric acids is entirely consistent with the space formulas assigned.




Identical
mesotartaric acid

Thus the *cis* form gives the same product, whichever end of the double bond is opened.



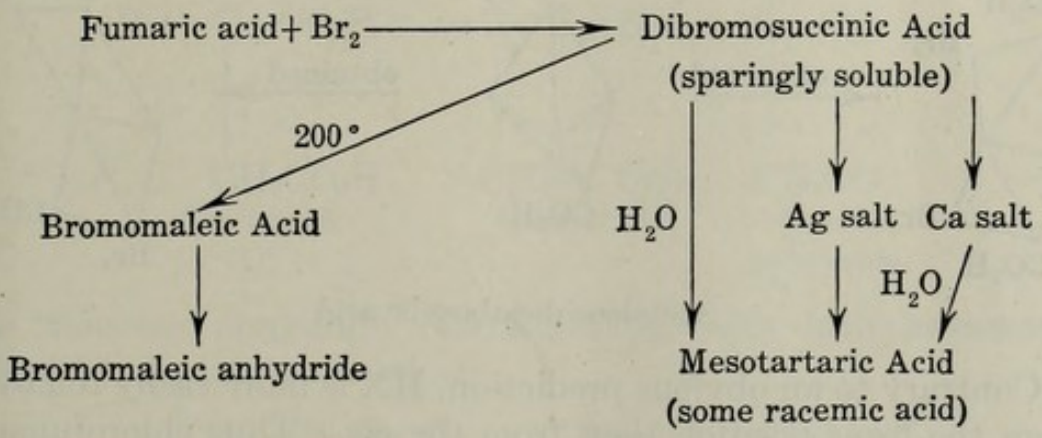

Not identical, enantiomorphs

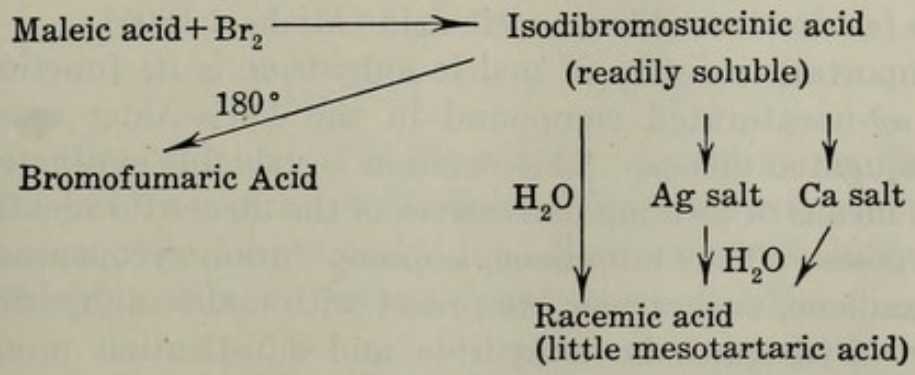
*d*-tartaric acid *l*-tartaric acid

Thus the *trans* form gives *d*- or *l*-tartaric acid depending on the end of the double bond opened.

A similar conversion of maleic and fumaric acids to tartaric acids without optical inversion can be produced by treatment with a chlorate and osmic acid, $OsO_4$ (Milas, Terry, Rep. 1925, 76). By this method fumaric acid gives racemic acid while maleic acid gives mesotartaric acid.

Unfortunately, the whole situation is somewhat more complicated. Just as the interconversions of maleic and fumaric acids are not understood, their addition reactions sometimes give results which are anomolous in the light of present knowledge. These relations are as follows:



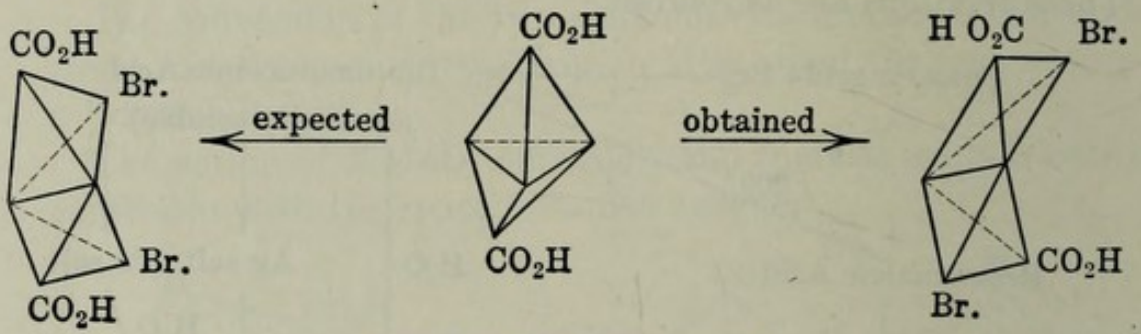

Thus each acid gives mainly the addition product which would be expected from the other one.

If the dibromosuccinic acid from fumaric acid gave *only* mesotartaric acid and the isodibromosuccinic acid from maleic acid gave *only* racemic acid, it would appear that addition of bromine

or its replacement by OH involves a complete inversion of the groups on one of the carbons.

The addition of HOCl to maleic acid gives only *one product*, a chloromalic acid, m. 145°, while fumaric acid gives in addition an isomeric chloromalic acid, m. 153°. Ease of replacement of Cl by OH in the two acids is in the approximate ratio 10,000 : 1 (Rep. 1925, 77).

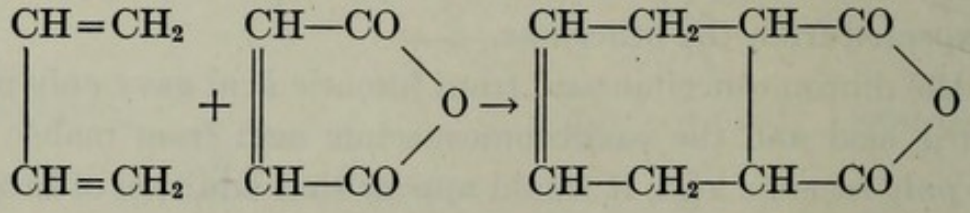
Another fact to show that the formulas used for multiple bonds give only a partial explanation is that acetylene dicarboxylic acid, obtainable from both dibromosuccinic acids, adds halogens and halide acids to give substituted *fumaric* acids instead of the expected *cis* compounds (Michael 1895).




Acetylene dicarboxylic acid

Contrary to an obvious prediction, HX is more easily removed from the *trans* position than from the *cis*. Thus chlorofumaric acid loses HCl to give acetylene dicarboxylic acid about fifty times as fast as does chloromaleic acid (Michael 1895).

An important reaction of maleic anhydride is its functioning as the $\alpha\beta$-unsaturated compound in the Diels-Alder reaction with conjugated dienes. This reaction is valuable synthetically and as a means of forming derivatives of the dienes for identification purposes. Thus butadiene, isoprene, furan, cycopentadiene cyclohexadiene, anthracene, etc., react with maleic anhydride to form tetrahydrophthalic anhydride and substitution products of that substance (Diels, Alder 1931).

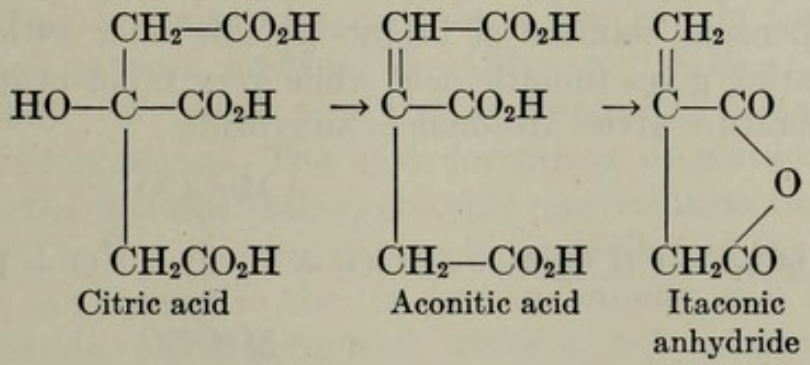


**Citraconic acid,** methyl maleic acid, $CH_3—C(=CH—CO_2H)—CO_2H$

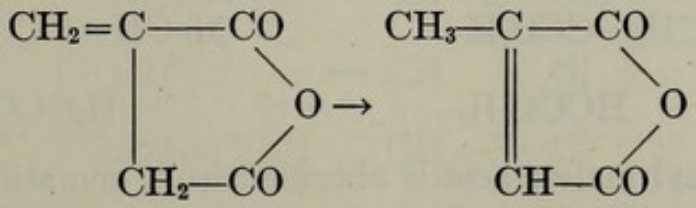
**Mesaconic acid,** methyl fumaric acid, $CH_3—C(=C(CO_2H)—H)—CO_2H$

**Itaconic acid,** methylene succinic acid, $CH_2=C(—CH_2—CO_2H)—CO_2H$

These isomeric acids are obtained by heating citric acid. Careful heating gives itaconic anhydride (OS) (Rep. 1912, 89). Citric acid first loses $H_2O$ giving aconitic acid, which then loses $CO_2$.




The itaconic anhydride rearranges partially into citraconic anhydride during the heating.




The amount of the latter in the mixture obtained from citric acid is increased by protracted heating. When itaconic or citraconic acids or anhydrides are boiled for a long time with 10% NaOH, the chief product is sodium mesaconate, $CH_3—C(=C(CO_2Na)—H)—CO_2Na$.

Citraconic and mesaconic acids can be converted into each other like maleic and fumaric acids but somewhat less readily. The methyl group facilitates the closing of the anhydride ring. Thus mesaconic acid with acetyl chloride readily gives citraconic anhydride.

The equilibrium between these acids is as follows:

$$\underset{16\%}{\text{Itaconic acid}} \rightleftharpoons \underset{15\%}{\text{citraconic acid}} \rightleftharpoons \underset{66\%}{\text{mesaconic acid}}$$

The triad prototropic system is very labile. Thus equilibrium is reached rapidly.

All three acids give methyl succinic acid on reduction.

**Dimethylmaleic acid, pyrocinchoninic acid,** a decomposition product of cinchonine, exists only as the anhydride, another example of the effect of methyl groups on ring closure. A remarkable preparation of this substance is from ethylene tetracarboxylic acid which can be made from its ester obtained by boiling a benzene solution of bromo-malonic ester with $K_2CO_3$. Gentle heating gives fumaric acid while very rapid heating at a high temperature gives $Me_2$-maleic anhydride

$$2\,(HO_2C)_2C{=}C(CO_2H)_2 \rightarrow 6\,CO_2 + \begin{array}{l} MeCCO \\ \| \quad \diagdown \\ \| \quad O \\ \| \quad \diagup \\ MeCCO \end{array} + H_2O$$

**Ethyl maleic acid** is notable for its easy conversion to methyl itaconic acid.

$$\begin{array}{l} MeCH_2{-}CCO_2H \\ \quad\quad\quad\quad \| \\ \quad\quad\quad\quad HCCO_2H \end{array} \rightarrow \begin{array}{l} MeCH{=}CCO_2H \\ \quad\quad\quad\quad\quad | \\ \quad\quad\quad\quad\quad H_2CCO_2H \end{array}$$

**Methyl ethyl maleic acid** is obtained from hematin.

**Diethyl maleic acid, xeronic acid,** is obtained as the anhydride by long heating of citraconic anhydride. Its structure is proved by its preparation from $\alpha\alpha$-$Br_2$-butyric acid and Ag.

**Glutaconic acid,** $HO_2C-CH=CH-CH_2-CO_2H$.

*Preparation.* 1. From citric acid

$$\begin{array}{l} CH_2{-}CO_2H \\ | \\ C(OH)CO_2H \\ | \\ CH_2{-}CO_2H \end{array} \xrightarrow{H_2SO_4} \begin{array}{l} CH_2CO_2H \\ | \\ CO \\ | \\ CH_2{-}CO_2H \end{array} \rightarrow \begin{array}{l} CH_2{-}CO_2H \\ | \\ CHOH \\ | \\ CH_2{-}CO_2H \end{array} \rightarrow \begin{array}{l} CH{-}CO_2H \\ \| \\ CH \\ | \\ CH_2{-}CO_2H \end{array}$$

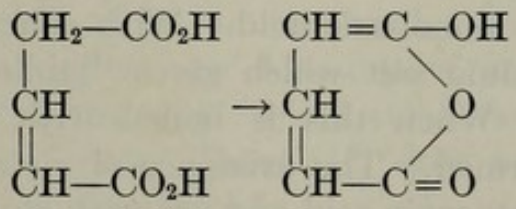
Acetone dicarboxylic acid

2. From malonic ester and chloroform.

$$2\,CH_2(CO_2R)_2 + CHCl_3 + NaOC_2H_5 \rightarrow (RO_2C)_2C{=}CH{-}CH(CO_2R)_2 \downarrow HO_2C{-}CH{=}CH{-}CH_2{-}CO_2H$$

### Isomerism and Structure of Glutaconic Acids

Although glutaconic acid belongs to the same type of ethylenic compounds as maleic and fumaric acids, it is known in only one form. This is apparently because of the mobile three carbon prototropic system, $-CH{=}CH{-}CH_2- \rightleftharpoons -CH_2{-}CH{=}CH-$ The mobility of the H would make impossible a stable *cis-* or *trans-* configuration. The easy formation of glutaconic anhydride by the action of acetyl chloride may indicate the existence of the acid in the *cis-* form or merely the lability of the system by which it can change to the *cis-* form as rapidly as it is removed as anhydride. The anhydride gives a red color with ferric chloride. Consequently it is formulated as having a hydroxyl group.



The methylene group of glutaconic ester reacts with sodium, sodium ethylate and sodamide like the methylene group in acetoacetic ester and similar compounds. Thus the olefin linkage serves the same role as a carbonyl, a cyanide, or a nitro group (Henrich).

$$RO_2C{-}CH{=}CH{-}CH_2{-}CO_2R \rightarrow RO_2C{-}CH{=}CH{-}CH{=}\overset{\displaystyle OR}{\overset{|}{C}}{-}ONa$$

Sodium glutaconic ester with methyl halides gives $\alpha$-methylglutaconic ester. Ozonization shows this to be a mixture of

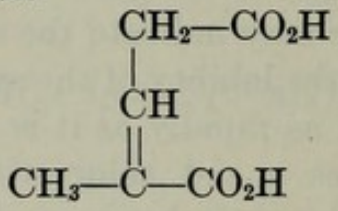
$RO_2C-CH=CH-CHMe-CO_2R$ and

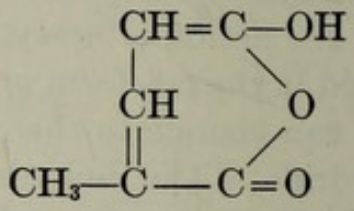
$$RO_2C-CH_2-CH=CMe-CO_2R.$$

This does not indicate that the sodium derivative is a mixture but rather that the H in the 3-carbon system shifts.

$$-CH=CH-CH(CH_3)- \rightleftharpoons -CH_2-CH=C(CH_3)-$$

It should be noted that the H atoms at the ends of the triad system in glutaconic acid and its derivatives are *alpha H* atoms and are correspondingly mobile. When the ester is hydrolyzed, the acid is found by ozonolysis to consist entirely of the second form with the methyl on the unsaturated carbon. $\alpha$-Methylglutaconic acid reacts with acetyl chloride to give a "hydroxy anhydride."





This gives a red coloration with $FeCl_3$ and can be titrated with dilute bases as a monobasic acid. With concentrated KOH it forms a di-potassium salt which gives "labile" (*cis*) $\alpha$-methyl glutaconic acid. When this is boiled with HCl, the stable (*trans*) acid is formed. The existence of *cis* and *trans* isomers with $\alpha$-methyl glutaconic acid and not with glutaconic acid itself is due to the effect of the methyl group in "freezing" the tautomerism of the three carbon system.

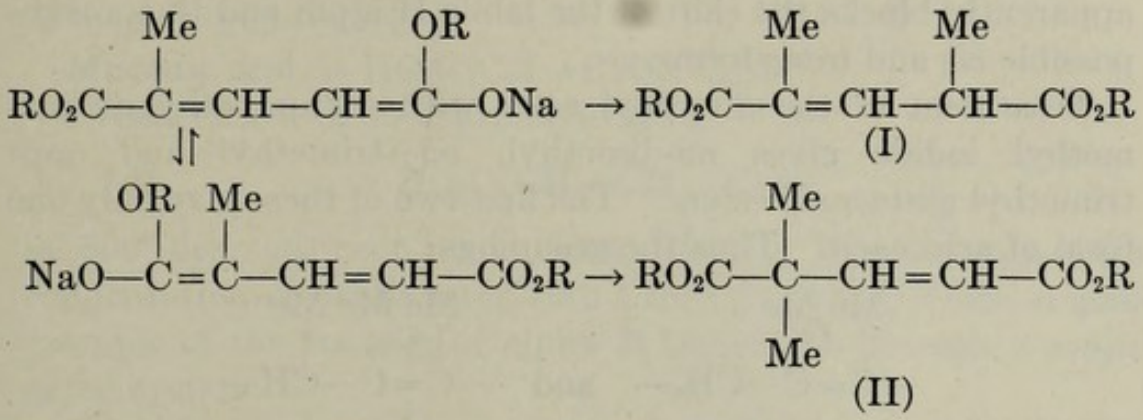
Thus while the system:

$$-CH=CH-CH_2- \rightleftharpoons -CH_2-CH=CH-$$

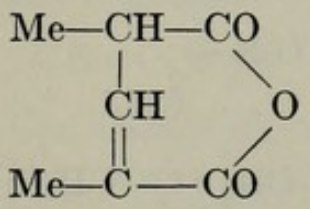
allows the permanent existence of neither a *cis* nor a *trans* form, the system: $-CH=CH-CH(Me)- \rightleftharpoons -CH_2-CH=C(Me)-$ is sufficiently irreversible in the free acid to allow *cis* and *trans* isomers.

When $\alpha$-methylglutaconic ester is treated with more sodium and $CH_3I$, two products are obtained, the $\alpha\alpha'$-dimethyl (I) and the

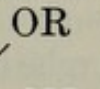
$\alpha\alpha$-dimethyl (II) esters.



Of the two esters, (I) gives an acid which exists in only one form. The symmetrical arrangement of the two methyl groups gives no favored position for the double bond, the two tautomers being identical. The $\alpha\alpha'$-dimethyl acid gives a normal anhydride instead of a hydroxy anhydride.

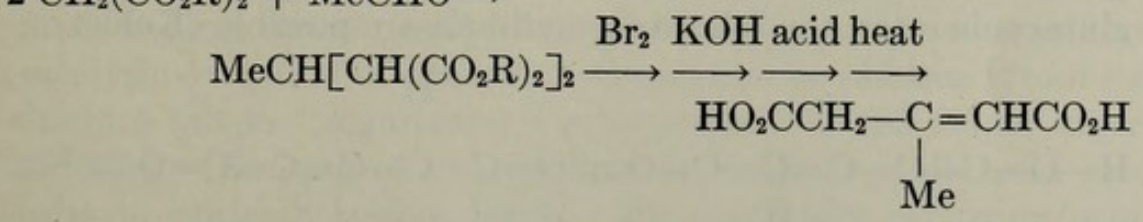


Ester (II) gives an acid with *cis* and *trans* forms. There is no possibility of a shift of its double bond. Ester (I) with more NaOEt and MeI gives $\alpha\alpha\alpha'$-$Me_3$-glutaconic ester. The corresponding acid has the same "blocked" arrangement as in (II) and exists in two forms. Ester (II) does not form a sodium



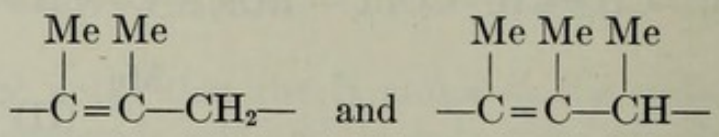
derivative. Apparently the grouping C=C=C−ONa is impossible.

$\beta$-Methyl glutaconic acid is made from malonic ester and acetaldehyde (Knoevenagel).



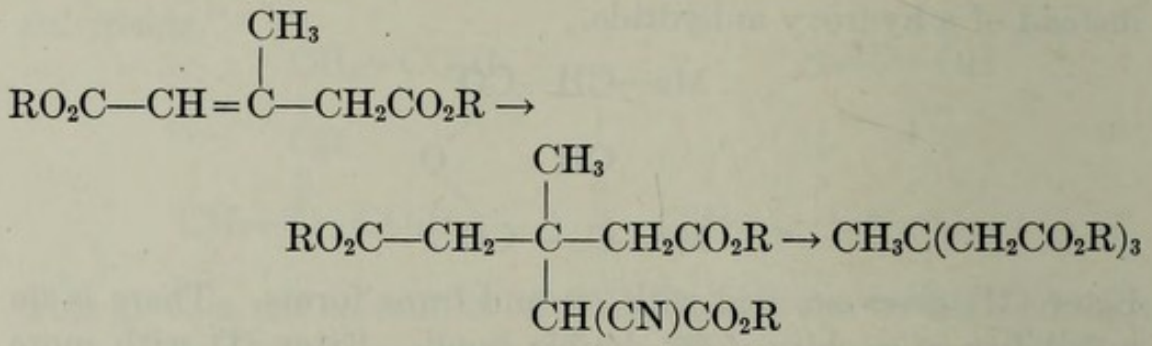
Although the 3-carbon system is symmetrical, the methyl group apparently blocks the shift of the labile H atom and thus makes possible *cis* and *trans* forms.

Treatment of the β-methyl ester with sodium ethylate and methyl iodide gives αβ-dimethyl, αβγ-trimethyl and ααβ-trimethyl glutaconic esters. The first two of these give only one form of acid each. Thus the groupings

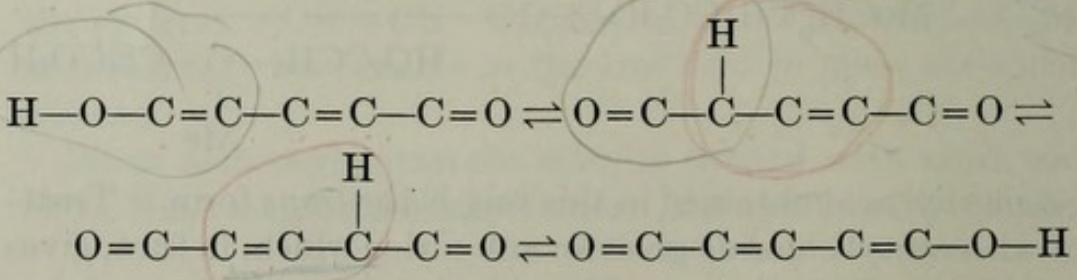


allow a shift of a hydrogen atom. The ααβ-trimethyl acid exists in *cis* and *trans* forms.

Glutaconic ester and both *cis* and *trans* β-methyl glutaconic esters add sodium cyanoacetic ester normally (Kohler).



The failure to obtain this addition, together with other unusual relations of the glutaconic acids, formerly encouraged the use of unorthodox formulas for these substances (Thorpe). Later the use of such formulas has been shown to be unnecessary (Feist). All the relations of the glutaconic acids and their esters can be interpreted in terms of the ordinary conceptions of tautomerism. The unusual property of this type of substance which was not earlier grasped is the combination in a single molecule, of ordinary keto-enol tautomerism and the tautomerism of the "three-carbon" system as found in allyl carbinols and their halides. Thus in a glutaconic ester, the following equilibria are possible (Kohler).



These relations are complicated by the existence of *cis* and *trans* isomers in some cases.

**Muconic acid,** is $HO_2C(CH=CH)_2CO_2H$

Decapentaene-1,10-dicarboxylic acid,

$$HO_2C(CH=CH)_5CO_2H,$$

m. 300° dec., has been made (Kuhn 1936). The first step is the condensation of oxalic ester with $CH_3(CH=CH)_4CO_2Et$, a good example of the transfer of alpha H properties through a conjugated system.

**Crocetin** is a highly unsaturated dibasic acid, probably $HO_2C(CMe=CHCH=CH)_3CMe=CHCO_2H$ (Kuhn 1931).

**Acetylene dicarboxylic acid,** butyne diacid, $HO_2CC\equiv CCO_2H$, m. 179°, is made from $Br_2$-succinic acid and alcoholic KOH and from $Na_2$-acetylide and $CO_2$ (Rep. 1926, 98). It gives the expected reactions. It easily changes to propargylic acid,

$$CH\equiv CCO_2H.$$

Higher acids $HO_2C(C\equiv C)_nCO_2H$ in which $n$ is 2 and 4 have been made (Baeyer 1885). They are explosive.

Acetylene dicarboxylic acid adds bromine to give mainly dibromofumaric acid (Michael 1892). Thus *trans* addition takes place. This recalls the fact that HBr is much more readily removed from bromofumaric acid than from bromomaleic acid.

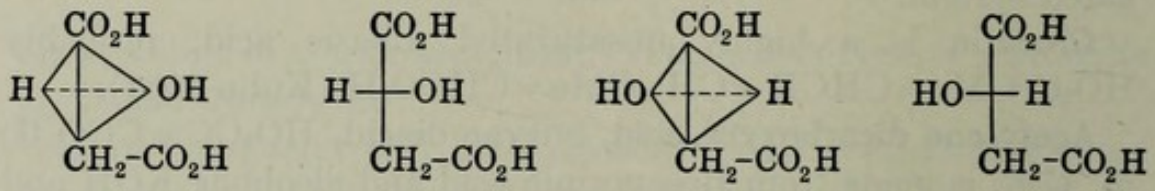
### *C.* Hydroxy Dibasic Acids

**Tartronic acid,** hydroxymalonic acid, $CHOH(CO_2H)_2$, m. 187°, is prepared from bromomalonic acid or from mesoxalic acid, $CO(CO_2H)_2$. It gives the reactions of a secondary alcohol, a dibasic acid and an alpha hydroxy acid. On heating it loses $CO_2$ and forms glycolide.

**Malic acid,** hydroxysuccinic acid, $HO_2CCH_2CHOHCO_2H$, is made in large quantities by the hydration of maleic acid from the catalytic oxidation of benzene. It can also be obtained from its calcium salt in "sugar sand," a by-product of the maple sugar industry. Because of its asymmetric molecule malic acid can exist in optically active forms. The naturally occurring acid shows a most peculiar behavior in this respect. A 34 per cent

solution at 20° is optically inactive. Dilution gives an increasing levo specific rotation while more concentrated solutions show an increasing dextro rotation. Much study has been devoted to this peculiar effect of dilution on the optical activity of malic acid solutions (Bancroft 1930).

Malic acid has been chosen as the standard of comparison for assigning configurations to the glyceric and tartaric acids and to the monose sugars. Of the two possible configurations of malic acid one is arbitrarily chosen as the *d*-form.




d-malic acid l-malic acid

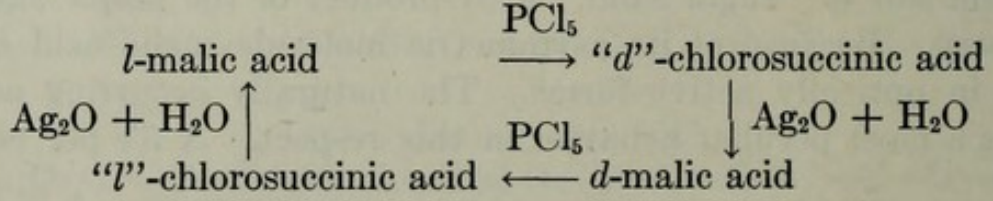
*d*-Malic acid is obtained by reducing *d*-tartaric acid with hydriodic acid (Bremer). Synthetic *dl*-malic acid is best resolved by crystallization of its cinchonine salts. Cinchonine-*d*-malate is less soluble than cinchonine-*l*-malate. When racemic malic acid is crystallized as the ammonium molybdate, the *l*-form separates first (Rep. 1924, 59).

Malic acid gives the reactions which would be expected of its secondary alcohol and two carboxyl groups. Heating gives maleic anhydride and fumaric acid. With urea and $H_2SO_4$, malic acid gives uracil (I). It thus acts like a typical $\alpha$—OH-acid losing CO and $H_2O$ to form an aldehyde which then reacts with the urea.

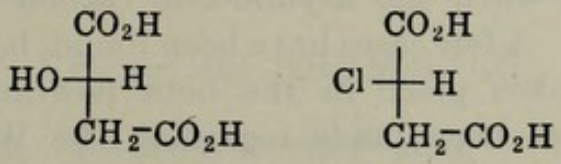
$$HO_2CCH_2CHOHCO_2H \rightarrow HO_2CCH_2CHO \rightarrow$$

$$HO_2CCH_2CH{=}NCONH_2 \rightarrow \begin{matrix} CH{=}N{-}CO \\ | \quad\quad | \\ CH_2{-}CONH \end{matrix} \quad (I)$$

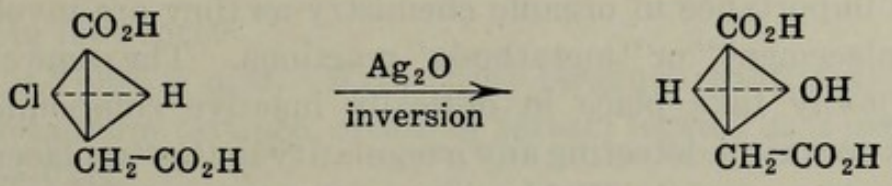
Treatment with $PCl_5$ gives chlorosuccinic acid. When this reaction and the reverse reaction to form malic acid, were carried out with optically active materials, one of the most remarkable changes of organic chemistry was discovered (Walden inversion).



These changes prove that the reactions involved are not simple metathetical reactions since the entering group does not occupy the *same position* on the asymmetric carbon as that occupied by the group which is removed. Extensive studies show that *l*-malic acid and "*d*"-chlorosuccinic acid have the same *configuration.*

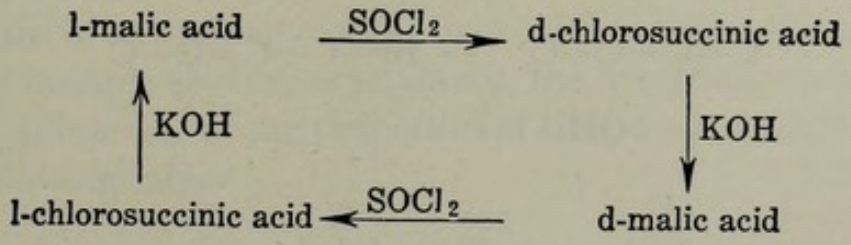



Thus the inversion takes place during the action with silver oxide.

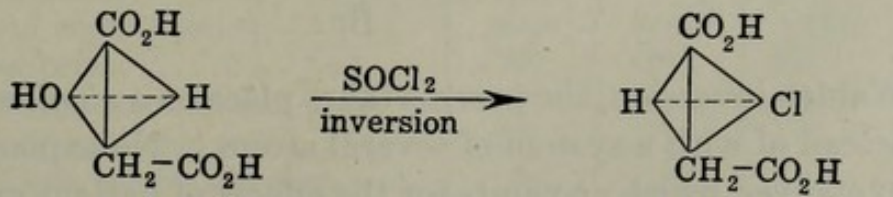



"*d*"-chlorosuccinic acid *d*-malic acid

Thus a more correct name for the first substance would be dextrorotatory-chlorosuccinic acid or *l*-chlorosuccinic acid, the *l*-showing its configurational relationship to the reference substance, malic acid. In the following changes *d*- and *l*- will be used in the latter sense. A different selection of reagents gives the inversion in a different way.



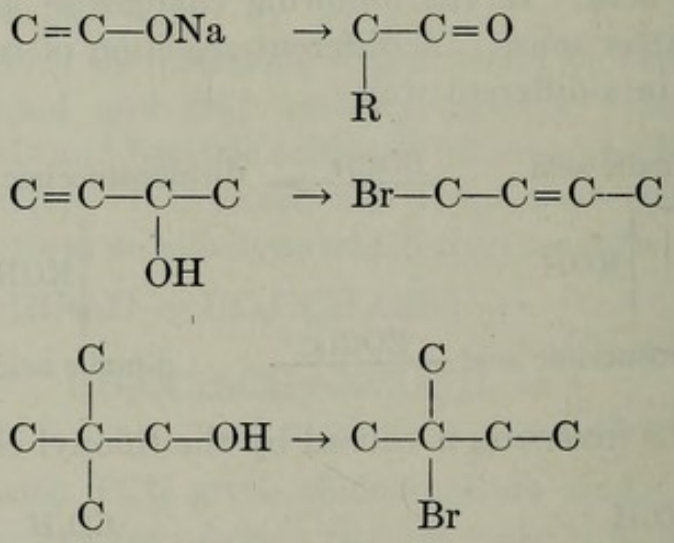

In this case the inversion is caused by the thionyl chloride.




l-malic acid d-chlorosuccinic acid

In this series of changes, $PCl_5$ and KOH produce no inversion and $SOCl_2$ and $Ag_2O$ cause inversion. This generalization holds in reactions with many other optically active materials but not with all. Different results are obtained with the same reagents in different solvents. It was formerly thought that the inversion took place only when the asymmetric carbon was alpha to a carbonyl group. A few cases have been found, however, in which the inversion takes place in the beta position. In fact, no generalization has been made regarding the Walden inversion without the almost immediate discovery of exceptions to it. The processes represented in the Walden inversion are of fundamental importance in organic chemistry as they are involved in all "replacement" or "metathesis" reactions. The same changes undoubtedly take place in optically inactive compounds but there is no way of detecting any irregularity in the "replacement."

The existence of the Walden inversion is less startling now than it was at the time of its discovery. It bears marked similarities to the processes involved in such reactions as those of certain sodium derivatives, of allyl carbinols and of neopentyl alcohol, in which the following abnormal "replacements" take place.



In the Walden inversion, the process takes place on a *single* carbon atom instead of with a system of several atoms. No explanation has been evolved which accounts for the effects of various groups, reagents, solvents and conditions in causing the Walden inversion in some cases or in giving "normal" replacement in others.

*Walden inversion.* Rep. 1911, 60–70.

Sodium malate tastes much like NaCl and is used in conditions under which the latter gives undesirable effects as a condiment ("Ekasalt").

**Citramalic acid** is $\alpha$-hydroxy-$\alpha$-methylsuccinic acid,

$$HO_2CCH_2C(OH)MeCO_2H,$$

**Tartaric acid,** dihydroxysuccinic acid,

$$HO_2CCHOHCHOHCO_2H,$$

exists in four forms.

(*a*) *d-Tartaric acid,* (Weinsäure) obtained from argol (crude acid potassium tartrate, cream of tartar) formed as a precipitate in wine vats.

(*b*) *Racemic acid* (Traubensaure), obtained from the mother liquors of the preparation of *d*-tartaric acid. It is a definite compound of the *d*- and *l*-forms with definite molecules existing even in solution (Rep. 1922, 75).

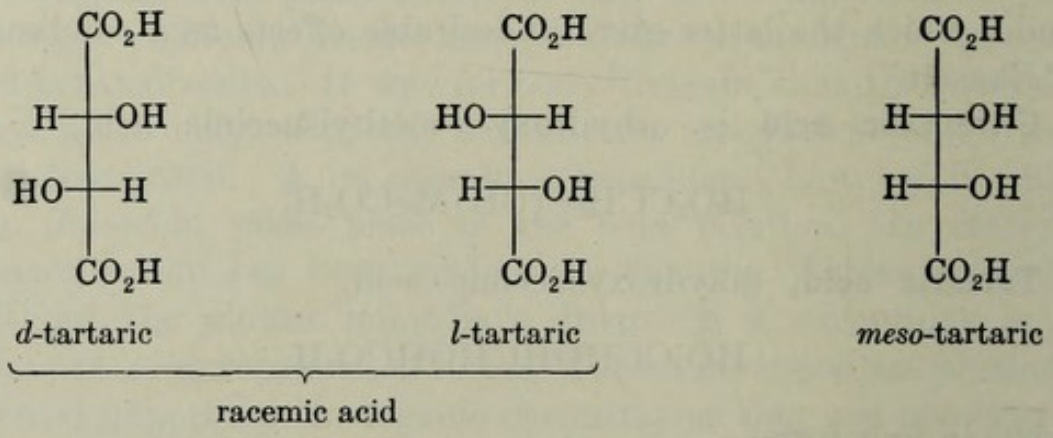
(*c*) *Mesotartaric acid,* obtained along with racemic acid by heating *d*-tartaric acid with dilute alkalies or organic bases like quinoline. Its acid potassium salt is readily soluble in water.

(*d*) *l-Tartaric acid,* obtained by the resolution of racemic acid by means of an optically active base. Thus, when the cinchonine salts of racemic acid are crystallized, the *l*-tartrate separates first.

The differences in the properties of the isomeric acids appear in the following table.

| | *d*-Tartaric | *l*-Tartaric | Racemic | Meso-Tartaric |
|---|---|---|---|---|
| Water of crystallization | none | none | $+H_2O$ | $+H_2O$ |
| Melting point | 170° | 170° | 206° | 140° |
| Solubility in water (cold) | 137 | 137 | 21 | 20 |
| Solubility in alcohol (cold) | 37 | 37 | 2 | 167 |
| Acid K salt, soluble in water | 0.6 | 0.6 | —— | 12.5 |
| Dimethyl ester, m. | 61.5° | 61.5° | 0.85° | 54.0° |
| Diethyl ester, m. | 18.7° | liq. | liq. | —— |
| Ionization constant $\times 10^4$ | 9.7 | 9.7 | 9.7 | 6.0 |

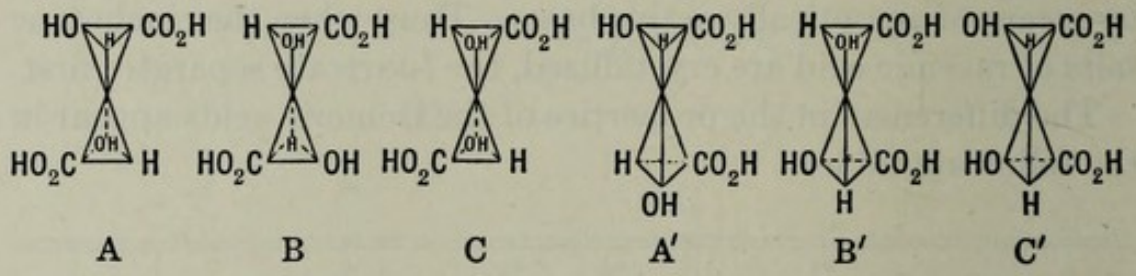
The following configurations are assigned to the tartaric acids.




The configuration of dextrorotatory tartaric acid is based on the fact of its reduction by HI to dextrorotatory malic acid. The reduction of either hydroxyl gives the same product.

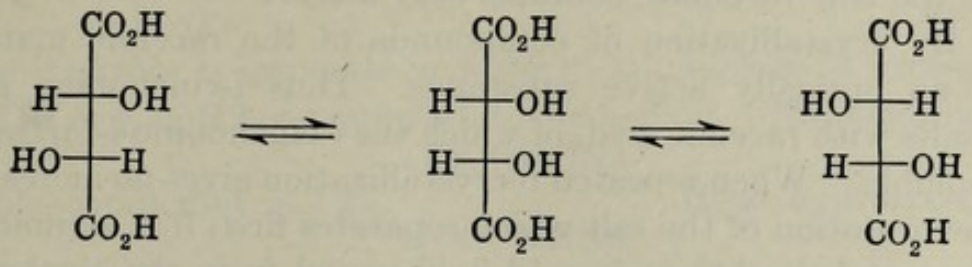
Ordinary solutions of *d*-tartaric acid are dextrorotatory but a cold supersaturated solution is levorotatory.

Studies of the complexes between the tartaric acids and boric acid have lead to the spatial arrangements A, B, and C in which the carboxyl groups are on opposite sides of the molecule. (Rep. 1931, 76.) These will be seen to differ from the ordinary models, A′, B′, C′, by a rotation of one carbon through 180°.




The tartaric acids formed the field in which Pasteur discovered and studied the principles and methods of handling optically active organic compounds. Only modifications of his methods have been introduced since that time. He discovered the phenomenon of racemization, by which heating an optically active substance alone or with a base inverts the asymmetric

arrangement. Thus the optically active tartaric acids become optically inactive.



The result is a mixture of mesotartaric acid with *d*- and *l*-tartaric acids, the latter in equal amounts. Also mesotartaric acid is converted into the same mixture on heating. Heated to a higher temperature, tartaric acid undergoes complex decompositions. The first product is a lactide at about 160°. At 180°, under reduced pressure, CO, $CO_2$, formic, acetic, and pyruvic (pyroracemic) acids are formed (Chattaway 1921). Under other conditions tartaric acid gives as high as a 20% yield of methylsuccinic (pyrotartaric) acid.

Pasteur also discovered and applied the *three methods for resolving a racemic material* into its optical isomers.

1. The mechanical separation of enantiomorphic crystals.

While crystallizing various salts of racemic acid, he noted that a solution of sodium ammonium racemate on slow crystallization deposited crystals which were not symmetrical but had *hemihedral* faces. Moreover, the crystals were of two types, related to each other like the right and left hand or as an object and its mirror image. Pasteur sorted these two kinds of crystals and found that a solution of the dextro hemihedral crystals was levorotatory while a solution of the levo hemihedral crystals of the same concentration gave the same angle of dextrorotation. Treatment of the separate crystals with acids gave *l*-tartaric and *d*-tartaric acids. The mixing of equal amounts of the two acids in solution gave off heat with the formation of racemic acid. It was later found that the hemihedral crystals separate from a solution of sodium ammonium racemate only below 27°. That is a *transition temperature* below which the $NaNH_4$ salts of *d*- and *l*-tartaric acids can exist separately and above which they form

a compound, $NaNH_4$-racemate, which forms symmetrical crystals. The individual tartrates have the formulas, $NaNH_4C_4H_4O_6 . 4\ H_2O$ while the true racemate contains only $2\ H_2O$.

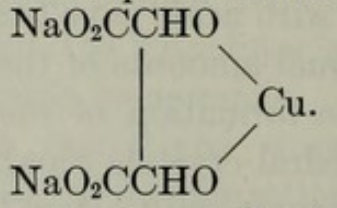
2. By crystallization of compounds of the racemic material with an optically active substance. Thus *l*-cinchonine gives two salts with racemic acid, of which the *l*-cinchonine-*l*-tartrate is less soluble. When repeated recrystallization gives no increase in the levorotation of the salt which separates first, it is assumed to be pure and the *l*-tartaric acid is liberated from the cinchonine salt by careful treatment with an acid or base. If *l*-quinine is used, the *l*-quinine-*d*-tartrate is the less soluble salt. (Ingersoll, 1925, 1928).

3. By biochemical means. Certain lower organisms destroy one optical isomer more rapidly than the other. Thus the *penicillium* of ordinary green mold, grown in ammonium racemate solution, attacks the ammonium *d*-tartrate much more rapidly than the *l*-form. If the process is stopped at the right point practically pure *l*-salt remains.

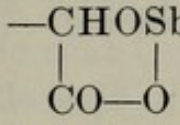
**Rochelle salt** is the dextrorotatory sodium potassium tartrate, $NaKC_4H_4O_6 . 4\ H_2O$. It is a laxative. *Seidlitz powders* contain (1) sodium bicarbonate and Rochelle salt and (2) tartaric acid. When dissolved and mixed $CO_2$ is evolved. Acid potassium tartrate is the acid used with $NaHCO_3$ in tartrate baking powders. It is stable and non-deliquescent.

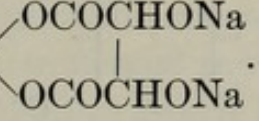
Diethyl tartrate when pure melts at 18.7° (Rep. 1922, 75).

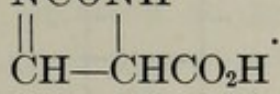
Tartaric acid forms complex salts with various heavy metals. Thus ferric salts cannot be precipitated as ferric hydroxide in a solution containing tartrates. The best known of these complexes is that of copper which is found in Fehling's solution, an alkaline cupric solution from which strong reducing agents precipitate red cuprous oxide. The copper is combined with the hydroxyls,




Tartar emetic is usually formulated as potassium antimonyl tartrate, $KO_2C(CHOH)_2CO_2SbO . \frac{1}{2}\ H_2O$. It is difficult to believe, however, that the hydroxyl groups take no part in the

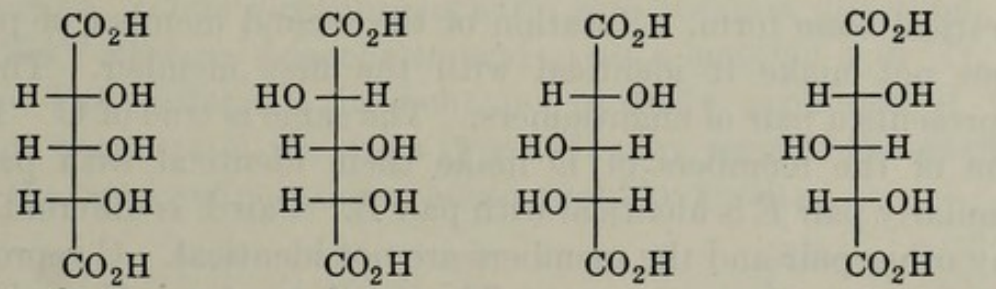
formation of the compound. It would seem more reasonable that a ring  , is involved.

. Calcium tartrate is insoluble in water. It dissolves in excess of cold KOH or NaOH but reprecipitates on boiling. Presumably the soluble compound is  . Heat hydrolyzes the "alcoholate" groupings.

Tartaric acid with urea and $H_2SO_4$ gives 2-imidazolone-4-carboxylic acid,  . It thus acts like the half aldehyde of tartronic acid, $OCHCHOHCO_2H$, a result due to the action of $H_2SO_4$ in converting $-CHOHCO_2H$ to

$$-CHO + CO + H_2O.$$

**Trihydroxy glutaric acid,** $HO_2C(CHOH)_3CO_2H$, exists in the theoretically possible forms, *d*-, *l*-, a racemic and two meso forms. These are related to the aldopentoses and the pentitols.




The first and last are named from their preparation by oxidizing ribose and xylose respectively. The *d*- and *l*-forms are obtained from the corresponding arabinose and lyxose.

**Tetrahydroxy adipic acid,** $HO_2C(CHOH)_4CO_2H$, theoretically can exist in four *d*-, and four *l*-, four racemic, and two meso forms. Most of these possibilities have been realized in the studies on the aldohexoses. Using the symbols ⊢ and ⊣ to indicate the plane

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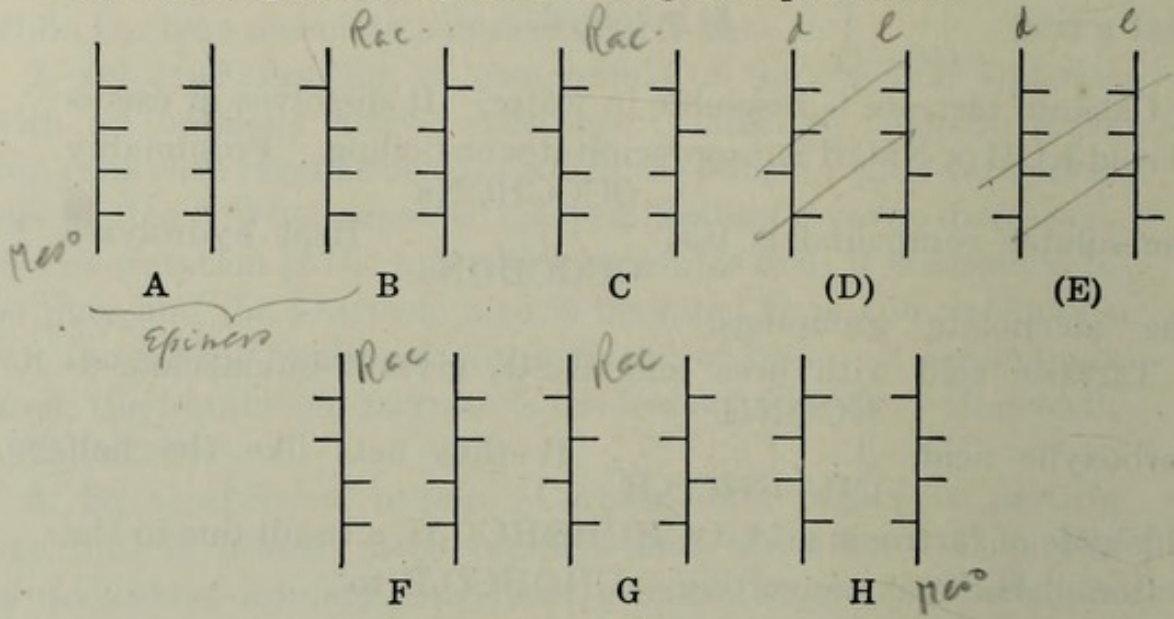
projections H−C−OH and HO−C−H the following pairs of enantiomorphic configurations might be predicted.




Since the ends of the chain are alike any one of these projection formulas can be rotated 180° in the plane of the paper without changing the configuration. By this test the members of pair A are *identical* instead of enantiomorphic and the configuration ++++ represents an internally compensated symmetrical *meso* form. Rotation of the second member of pair B does not make it identical with the first member. Thus B represents a pair of enantiomers. The same is true of C. Rotation of the members of D make them identical with pair C. Similarly pair E is identical with pair B. Pair F is different from any other pair and the members are not identical. G represents another pair of enantiomers. The members of pair H are identical. Thus configurations A and H represent meso forms while B, C, F, and G are racemic forms each consisting of a *d* and an enantiomorphic *l*-form. The following are pairs of *epimers*, A and B, B and H, C and F, C and G.

The commonest of these acids are:

(a) *d*-saccharic acid (*d*-Zuckersäure) which has the configuration C (+−++) and is obtained by the oxidation of sucrose, *d*-glucose, *d*-gulose and substances related to them such as maltose and starch (Rep. 1922, 77). Oxidation of *d*-saccharic acid with $KMnO_4$ gives *d*-tartaric acid (+−) while the Hofmann

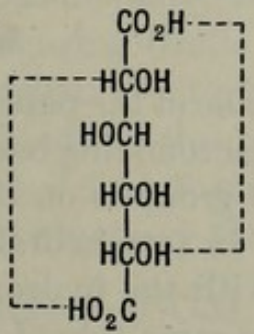
degradation of the diamide gives a dialdehyde which is oxidized to *l*-tartaric acid (−+).

(*b*) **Mucic acid** (Schleimsäure), which is a meso form corresponding to configuration H(+−−+) is obtained by oxidizing lactose, dulcitol and various natural gums related to galactose and galactonic acid. The wood of the mountain larch is rich in galactan gums which form a commercial raw material for galactonic and mucic acids (Acree, 1932). Mucic acid is converted by heating in pyridine at 140° to an equilibrium mixture with *allomucic acid*, also a meso form (Butler 1929). The two $\alpha$-carbons have been inverted to give configuration A(++++). Stronger heating gives *pyromucic acid*, furan-$\alpha$-carboxylic acid.

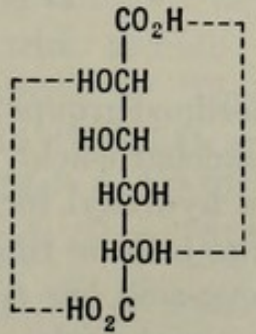
(*c*) **Mannosaccharic, idosaccharic,** and **talomucic acids** exist in *d*-, *l*-, and *r*-forms obtained from the mannoses, idoses, and taloses respectively.

All of these isomers of saccharic acid give adipic acid when reduced with HI.

A difference in the behaviour of *d*-saccharic acid (+−++) and *d*-mannosaccharic acid (−−++), on heating, illustrates the important effect of configuration even on certain chemical properties. Thus *d*-mannosaccharic acid forms a dilactone, m. 180–190°, whereas *d*-saccharic acid gives a lactonic acid (I), m. 132°. This difference in behavior is easily explained if the lactone rings are of the delta type. If they were of the gamma type the two configurations should give like results.



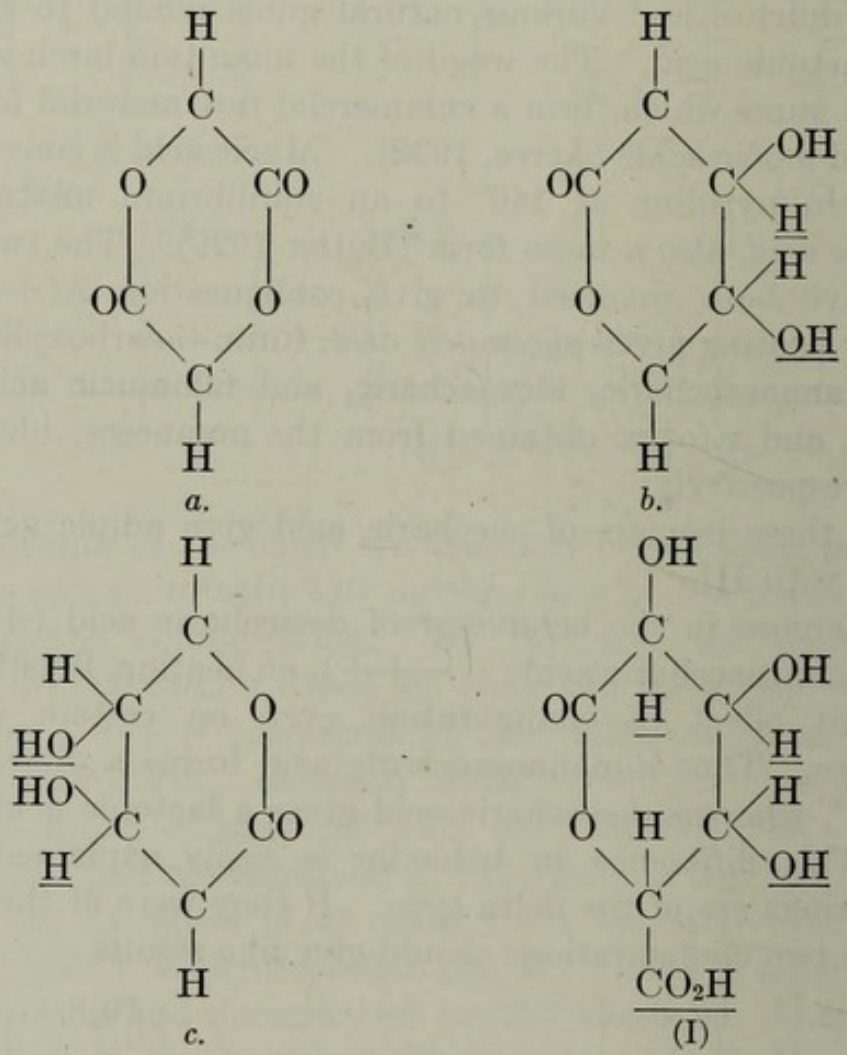

Saccharic acid




Mannosaccharic acid

The dotted lines indicate the relation of the carboxyl group to its delta carbon in each case. In the case of the mannosaccharic acid the hydroxyls delta to the carboxyls are on opposite sides. Thus a dilactone can form readily. When set up in tetrahedral models,

the dilactone forms a cage system consisting of three *cis*-6-membered rings having the $\alpha$- and $\alpha'$-carbons common to all three rings. Thus the three views of the model with the common $\alpha$- and $\alpha'$-carbons at the top and bottom in each are *a*, *b*, and *c*.




The underlined groups are in *front* of the plane of the paper.

With saccharic acid, however, after one lactone ring has formed the delta hydroxyl for the other carboxyl group is on the same side as the lactone ring already formed. In tetrahedral models the lactone-acid has a 6-membered ring with the hydroxyl beta to the free carboxyl as the only one on the same side of the ring as the latter. This is shown in (I). Thus a second lactone ring would have to be in the *beta* position, which is not possible in this type of grouping.

Mannosaccharic acid reduces Fehling's solution on heating while saccharic acid does not. The former does not give a

difficultly soluble acid potassium salt as does the latter.

Two branched chain 6-carbon hydroxy dibasic acids give examples of the unusual *beta type of lactone* (Rep. 1908, 86).

$$CH_2(CO_2H)_2 + Me_2CO \xrightarrow{Ac_2O} Me_2C\!-\!CHCO_2H \quad (O\!-\!CO)$$

$$HO_2CCMe_2CHBrCO_2H \xrightarrow{Ag_2O} Me_2C\!-\!CHCO_2H \quad (CO\!-\!O)$$

The *gem*-dimethyl grouping, as usual, favors ring closure.

### *D.* Dibasic Ketonic Acids

*Mesoxalic acid*, $HO_2CCOCO_2H$, or $HO_2CC(OH)_2CO_2H$, can be made from dibromomalonic acid with $Ba(OH)_2$ or by the hydrolysis of alloxan obtained by the oxidation of uric acid by nitric acid.

$$\begin{matrix} NHCOCO \\ | \quad\quad | \\ CONHCO \end{matrix} \rightarrow CO(NH_2)_2 + (HO)_2C(CO_2H)_2$$

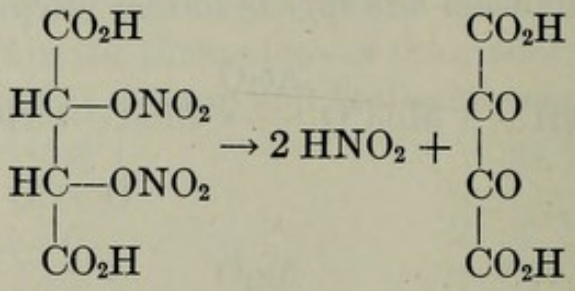
It gives ketone and acid reactions. Esters are known of both the true mesoxalic acid and the dihydroxylmalonic acid form.

**Oxaloacetic acid,** $HO_2CCOCH_2CO_2H$, is obtained as its ester by condensing oxalic and acetic esters with sodium ethylate. It has similar reactions and uses to malonic ester. The acid can also be made by the oxidation of malic acid with $H_2O_2$ and $FeSO_4$ (Fenton). Two forms of the acid, m. 184° and 152°, are described as hydroxy-fumaric and maleic acids (Rep. 1912, 85).

$$HO\!-\!C(\!=\!CH\!-\!CO_2H)\!-\!CO_2H \rightleftharpoons O\!=\!C(\!-\!CH_2\!-\!CO_2H)\!-\!CO_2H \rightleftharpoons HO\!-\!C(\!=\!C\!-\!CO_2H)\!-\!H$$

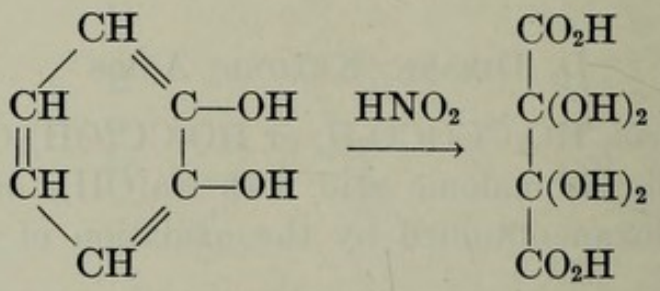
**Dihydroxytartaric acid,** $HO_2CC(OH)_2C(OH)_2CO_2H$, is obtained from tartaric acid dinitrate and from the action of pyro-

catechol with nitrous acid. The first of these processes is an interesting case of intramolecular oxidation.

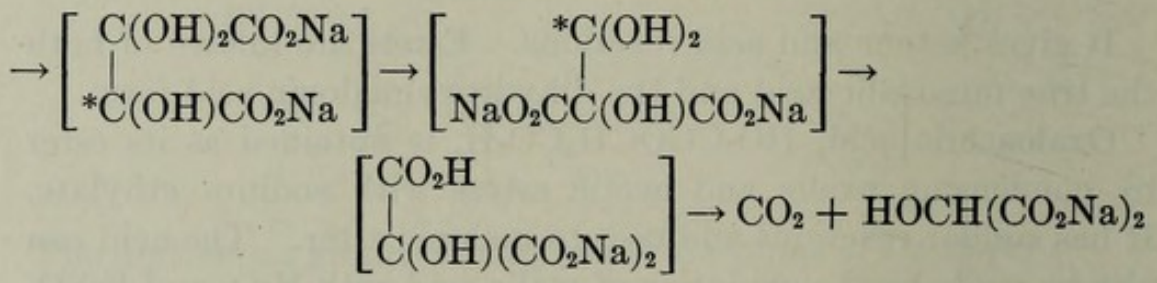


Similar but more complete and violent processes take place when nitroglycerine and related substances are decomposed.

The mechanism of the formation from pyrocatechol is not understood.



The sodium salt of dihydroxy tartaric acid is only slightly soluble. Heat changes it to sodium tartronate. This involves a rearrangement followed by the loss of $CO_2$.



**Acetone dicarboxylic acid,** $HO_2CCH_2COCH_2CO_2H$, is obtained from citric acid by treatment with sulfuric acid, the usual method for removing formic acid from alpha hydroxy acids.

$$(HO_2CCH_2)_2C(OH)CO_2H \rightarrow CO + H_2O + CO(CH_2CO_2H)_2$$

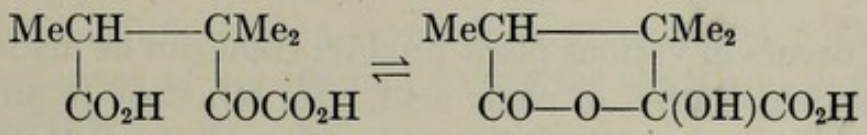
Heat changes it successively to acetoacetic acid and acetone. The reaction cannot be stopped at the intermediate step because acetoacetic acid is less stable to heat than acetone dicarboxylic

acid. It has been proposed as a source of $CO_2$ in baking powders (Wiig 1932).

**αββ-Trimethylketoglutaric acid,** Balbiano's acid,

$$HO_2CCHMeCMe_2COCO_2H,$$

is obtained by oxidation of camphor or camphoric acid. It exists in equilibrium with a lactone form. Formerly a cyclopropane form was assumed (Rep. 1923, 107; 1928, 81–2).



The influence of methyl groups on ring closure can be seen from the fact that its lower homologs, α-ketoglutaric and β-$Me_2$-ketoglutaric acids exist in the open chain form while $Me_4$-α-ketoglutaric acid exists only in the cyclic form (Rep. 1930, 152).

**Dihydroxymaleic acid, ketomalic acid,**

$$HO_2CC(OH)=C(OH)CO_2H \rightleftharpoons HO_2CCHOHCOCO_2H,$$

is obtained by oxidizing tartaric acid with $H_2O_2$ and $FeSO_4$ (Fenton 1895). Bromine water converts it to dihydroxytartaric acid. It decomposes on heating to 50° with water to give glycollic aldehyde (Rep. 1912, 85). Its solution is stabilized by boric acid presumably by the formation of a complex (Rep. 1931, 77).

Penten-1-one-3-dicarboxylic acid-1,5, furonic acid,

$$HO_2CCH=CHCOCH_2CH_2CO_2H,$$

has been obtained from furfural through furylacrylic acid. Reduction by HI gives pimelic acid.

## XXII. POLYBASIC ACIDS

The three chief acids considered here all contain the same carbon skeleton, that of 3-Me-pentane, with the three terminal carbons oxidized to carboxyl groups.

**Tricarballylic acid,** propane-1,2,3-tricarboxylic acid,

$$HO_2CCH_2CH(CO_2H)CH_2CO_2H,$$

m. 166° can be obtained (*a*) from glycerol through the tribromohydrin (1,2,3-tribromopropane) and the corresponding cyanide, (*b*) from citric acid by reduction with HI, and (*c*) by hydrogenation of aconitic acid obtained by dehydrating citric acid.

**Aconitic acid,** propene-1,2,3-tricarboxylic acid,

$$HO_2CCH=C(CO_2H)CH_2CO_2H,$$

m. 191° occurs in various plant products and can be made by the cautious dehydration of citric acid. Its structure is proved by its reduction to tricarballylic acid. Since it is doubly an $\alpha\beta$-unsaturated acid this reduction is easy.

**Citric acid,** hydroxy tricarballylic acid, 2-propanol-1,2,3-tricarboxylic acid, $(HO_2CCH_2)_2C(OH)CO_2H$ is prepared (*a*) from the juice of cull lemons through its insoluble calcium salt and (*b*) by the action of various molds on sugar solutions (molasses). It has been synthesized from *sym*-dichloroacetone through the cyanohydrin and cyanide syntheses. Its triethyl ester has been made by the Reformatzky reaction using ethyl bromoacetate and diethyl oxaloacetate with zinc.

Citric acid gives the reactions of a tribasic acid and a tertiary alcohol. On heating, it gives aconitic acid, itaconic anhydride, citraconic anhydride and acetone. With mineral acids it acts as an $\alpha-OH$ acid, losing CO to form acetone dicarboxylic acid. When heated with urea and $H_2SO_4$ it gives uracil-4-acetic acid (Hilbert 1932). Magnesium citrate is used as a laxative. Ferric ammonium citrate is used with potassium ferricyanide in blue print paper.

Various *complex hydroxy polybasic* acids have been found in lichens. *Protolichesteric acid* is formulated as the lactone of $n$-$C_{13}H_{27}CHOHCH(CO_2H)C(=CH_2)CO_2H$; *agaracinic* acid is $n$-$C_{15}H_{31}CH_2(CO_2H)C(OH)(CO_2H)CH_2CO_2H$; and *caperatic* acid is the monomethyl ester of the tribasic acid, *nor-caperatic acid*, $n$-$C_{14}H_{29}CH(CO_2H)C(OH)(CO_2H)CH_2CO_2H$.

## XXIII. CYANOGEN AND ITS DERIVATIVES

### *A.* Cyanogen and Inorganic Cyanides

**Cyanogen,** $N \equiv CC \equiv N$, is related to its derivatives much as is $Cl_2$. The variety of these is much greater however. It occurs in coal gas in small traces. It is a poisonous colorless gas (b. $-21°$). It is made by heating the cyanides of mercury or silver and by treating a cupric solution with NaCN. The cupric cyanide first formed is hydrolyzed and the resulting HCN reduces the cupric ions and insoluble cuprous cyanide is precipitated. The latter is a component of anti-fouling paints for ships and is available commercially.

$$2\,CuSO_4 + 4\,NaCN \rightarrow \underline{Cu_2(CN)_2} + (CN)_2 + 2\,Na_2SO_4$$

Cyanogen is also formed by the action of $P_2O_5$ on ammonium oxalate or on oxamide. It is readily soluble in water. Even in the cold it readily hydrolyzes giving a brown precipitate of azulmic acid and in the solution oxalic acid, ammonia, HCN, formic acid and urea.

Cyanogen reacts with bases to give cyanides and cyanates (KCNO, etc.).

Paracyanogen, $(CN)_x$, is a brown powder obtained as a by-product in heating $Hg(CN)_2$. It gives cyanogen at a higher temperature. It is also formed by light (Hogness, 1932).

Oxycyanogen has been prepared in polymeric form, $(OCN)_x$ (Hunt 1932).

**Hydrogen cyanide, hydrocyanic acid,** prussic acid, b. 26°, may be made from any cyanide with even dilute acids (OS). This is because it is both a weak acid and volatile. Even carbonic acid (moist air) will react with cyanides. It occurs in various plant products notably as a glucoside with gentiobiose and benzaldehyde in amygdalin of bitter almonds.

Hydrocyanic acid is also obtained from sugar beet residues which contain several per cent of nitrogen as betaine. The steps are as follows:

$$\begin{array}{l} CH_2\text{—}N(CH_3)_3 \\ \quad | \qquad\quad | \\ CO\text{—}O \end{array} \rightarrow (CH_3)_3N \rightarrow 2\,CH_4 + HCN$$

The last step is carried out at 800–1000°.

Hydrogen cyanide is a colorless liquid (m. −14°, b. 26°). It has a peculiar faint odor. Minute amounts cause death. Smaller amounts first paralyze the legs. The poisonous effects are not cumulative. Apparently the animal organism is able to destroy HCN at a certain rate without harm. This fact and the low density of the gas makes it less effective as a war gas than toxic materials which are cumulative in effect.

It is completely miscible with water forming an acid ten thousand times weaker than acetic acid. The solution in water undergoes hydrolysis to a variety of products. It forms a trimer which is probably aminodicyanomethane (Rep. 1922, 69).

Hydrocyanic acid is a tautomeric substance giving reactions and derivatives corresponding to two forms

$$H-C\equiv N \rightleftharpoons H-N=C$$

This apparent shift of a hydrogen ion or proton from one atom to the next is an example of diad prototropy (Ingold), analogous to the triad prototropy of the ketoenol system. Like that process, it is probably bimolecular in nature.

$$O=C-CH \rightleftharpoons H-O-C=C$$

The HNC form contains "bivalent" carbon (Nef.). It is perhaps more accurate and certainly more conservative to say that it contains a carbon which behaves like that in carbon monoxide. Both hydrocyanic acid and carbon monoxide exhibit a type of unsaturation different from that shown by the ethylenic compounds. Here the unsaturation is confined to a *single* atom instead of to an adjacent pair. Thus chlorine will add to these substances to give $Cl_2CO$ and $Cl_2C=NH$. Hydrogen chloride presumably forms unstable compounds, formyl chloride (HCOCl) and iminoformyl chloride (HN=CHCl). Thus benzene reacts in the Friedel-Crafts reaction with HCl and CO or HCN to give PhCHO or PhCH=NH.

The conflict in evidence as to the structure of hydrocyanic acid is well illustrated by two methods of preparations.

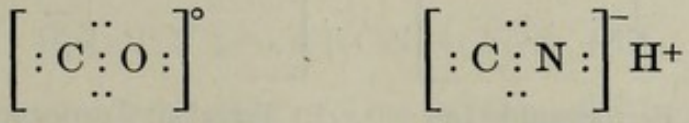
1. That by the dehydration of ammonium formate or of formamide would indicate the $H-C\equiv N$ structure.

2. That from $NH_3$ and $CHCl_3$ and alcoholic KOH would indicate the H—NC form.

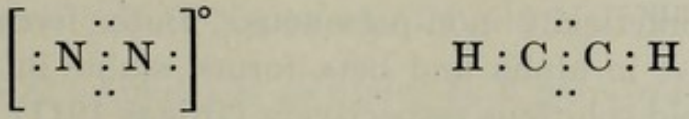
Measurements of the physical properties of hydrocyanic acid show that it exists almost entirely in the HCN form (Reichel 1931, Dadieu, 1931).

Hydrocyanic acid may be regarded as an aldehyde of the ammonia system, as an ammonocarbonous acid, and as the analog of CO in the ammonia system (Franklin, Rep. 1923, 85).

The analogy between carbon monoxide and hydrocyanic acid may be represented electronically:



Analogous structures may be assigned to nitrogen and acetylene.



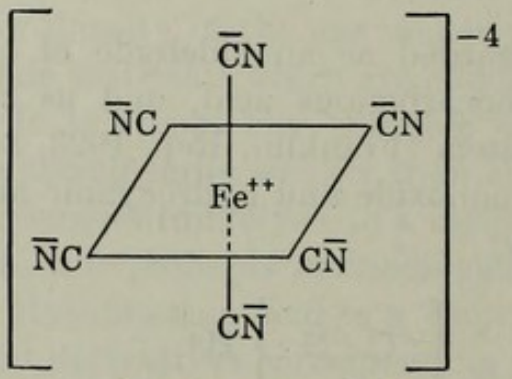
In each case a pair of atoms forms a more or less stable system with ten electrons, the *two* atoms being surrounded by an octet.

The *inorganic cyanides* are obtained in a variety of ways.

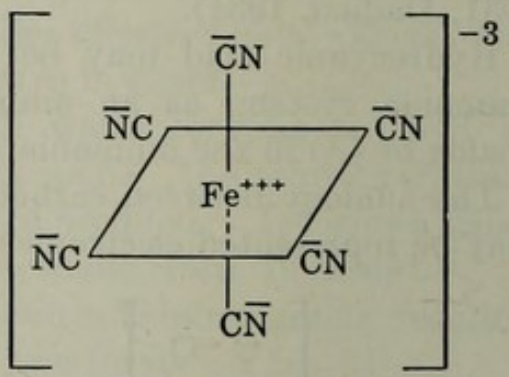
1. The oldest method is the fusion of "organic" nitrogenous material such as leather scraps with iron and potassium hydroxide or carbonate. Leaching the resulting mass with water gives a beautifully crystalline substance, "yellow prussiate of potash," $K_4Fe(CN)_6$, potassium ferrocyanide. The name "Blutlaugensalz" is derived from its preparation by heating dried blood with lye, the blood supplying the C, N and Fe. When this is treated with an oxidizing agent, usually chlorine, it is converted to the "red prussiate of potash," $K_3Fe(CN)_6$, potassium ferricyanide. The modern way of making potassium ferrocyanide is from the iron oxide which has been used to purify illuminating gas. This contains Prussian blue, ferric ferrocyanide. Boiling with milk of lime gives soluble calcium ferrocyanide which is treated with potassium carbonate.

In the ferro- and ferri-cyanides the Fe atom may be regarded as having two and three CN radicals respectively, thus being fer*rous* and fer*ric* iron in the two compounds. In both com-

pounds the "coordination number" of the iron is six (A. Werner). This means that the Fe atom can hold six univalent groups *inside* a complex ion. There is good evidence that these six groups lie four in one plane and one each above and below it.




Tetravalent Ferrocyanide Ion




Trivalent Ferricyanide Ion

These substances do not give iron or cyanide ions in solution. They are practically non-poisonous. Both ferro- and ferricyanides exist in alpha and beta forms, stable in basic and in neutral or acid solutions respectively (Briggs 1911).

The most characteristic reactions of the complex iron cyanides are with iron salts with the formation of characteristic blue precipitates (Prussian Blue and Turnbull's Blue). The formation of Prussian Blue gave the names prussiate and prussic acid. Blue print paper is coated with potassium ferr*i*cyanide and ferr*ic* ammonium citrate. Exposure to light converts the latter to the ferr*ous* salt. Washing with water gives an insoluble blue wherever the light struck.

Heating the complex cyanides with dilute sulfuric acid gives hydrocyanic acid (Rep. 1923, 85).

$$2\ K_4Fe(CN)_6 + 6\ H_2SO_4 \rightarrow FeK_2Fe(CN)_6 + 6\ HCN + 6\ KHSO_4$$

The potassium ferrous ferrocyanide is not acted on by dilute acid. More concentrated acid gives carbon monoxide due to the hydrolysis of HCN to formic acid and the dehydration of the latter.

$$K_4Fe(CN)_6 + 11\ H_2SO_4 + 6\ H_2O \rightarrow 6\ CO + FeSO_4 + 6\ NH_4HSO_4 + 4\ KHSO_4$$

The prussiates do not react with dilute solutions of bases, but with hot concentrated solutions they give precipitates of iron

hydroxides and cyanides in solution. These reactions are of no value in preparing cyanides because of the large excess of base required.

Many other heavy metals form complex cyanides much like the ferrocyanides and the ferricyanides. The commonest coordination number is 6 but some metals have coordination numbers of 2, 4 and 8. Typical examples are $KCu(CN)_2$, $KAg(CN)_2$, $KAu(CN)_2$, $K_2Cd(CN)_4$, $KAu(CN)_4$, $K_4Co(CN)_6$, $K_4Mo(CN)_8$.

2. When prussiates are heated to high temperatures, they decompose.

$$K_4Fe(CN)_6 \rightarrow 4\ KCN + FeC_2 + N_2$$

The yield of cyanide by this process is increased by heating with metallic sodium.

$$2\ Na + K_4Fe(CN)_6 \rightarrow 4\ KCN + 2\ NaCN + Fe$$

The mixture of cyanides is as useful as a pure cyanide for electroplating and for the cyanide process for extracting gold from low grade ores and tailings.

3. Calcium carbide, calcium cyanamide and sodium carbonate at 500° give NaCN.

4. Calcium cyanamide fused with salt gives a mixture of sodium and calcium cyanides. Treatment with sodium carbonate gives NaCN.

5. Nitrogen reacts with a red hot mixture of coal and soda ash to give NaCN (Bucher 1917, EP 293).

$$Na_2CO_3 + 4\ C + N_2 \rightarrow 2\ NaCN + 3\ CO$$

6. Ammonia with red hot coal gives $NH_4CN$.

7. The present commercial method for making sodium cyanide consists in passing $NH_3$ through sodium and charcoal at 600–800°. The steps are probably

$$2\ NH_3 \xrightarrow{Na} 2\ NaNH_2 \xrightarrow{C} Na_2NCN \xrightarrow{C} 2\ NaCN$$

Salts of hydrocyanic acid are often stated to have the isocyanide structure. Mercuric cyanide is remarkable in that it gives no

reactions of either mercury or a cyanide. It behaves like a true organic mercurial having the C—Hg linkage.

Hydrocyanic acid adds to aldehydes and ketones to give cyanohydrins. It also adds to $\alpha\beta$-unsaturated compounds. Potassium cyanide speeds this addition much as the sodium derivative of $\beta$-keto esters does that to the $\alpha\beta$-unsaturated compounds.

$$RCH=CHCOR' + HCN \rightarrow RCHCNCH_2COR'$$

Reduction and hydrolysis convert hydrocyanic acid respectively to methyl amine and formic acid. Diazomethane gives mainly methyl cyanide, $CH_3CN$, with a smaller amount of the isocyanide, $CH_3NC$.

Hydrocyanic acid can be detected as Prussian blue or as the blood-red ferric thiocyanate. The first is obtained by boiling with NaOH and ferric and ferrous salts and acidifying and the second by evaporating with ammonium polysulfide, dissolving in water and adding a ferric salt.

Hydrocyanic acid, as one of the most deadly poisons known, is used as a very effective fumigant especially for orange orchards, holds of ships and for large flour mills. The latter are equipped with permanent piping by means of which the entire mill can be fumigated periodically by simply connecting tanks of liquid HCN to the pipe system. For fumigation, it is available in liquid form and absorbed in porous material (Zyklon). Since its odor in small concentrations is unnoticeable to some individuals, it is often used with *cyanogen chloride*, ClCN, b. 15°, itself a good fumigant and a lachrymater. The latter is prepared from a cyanide solution and chlorine.

Calcium cyanide is so easily hydrolyzed that it cannot be made in the presence of water. It is prepared commercially by the action of anhydrous HCN with calcium carbide. It is a valuable solid fumigant because it acts with the moisture in the air to give HCN (Young 1929).

Soluble cyanides are used for the extraction of gold by dissolving it in the presence of air. The net result is given by the

equation

$$4\,Au + 8\,NaCN + O_2 + 2\,H_2O \rightarrow 4\,NaAu(CN)_2 + 4\,NaOH$$

They are also used for electroplating with gold and silver. Solutions of $NaAu(CN)_2$ and $NaAg(CN)_2$ are used because of the small concentration of $Au^+$ and $Ag^+$ ions which they give. This produces a more compact film of metal.

Sodium nitroprusside, $Na_2[Fe(CN)_5NO]$, formed by the action of nitric acid with potassium ferrocyanide followed by neutralization with $Na_2CO_3$, gives a violet color with inorganic sulfides. In the complex ion the Fe has a valence of +3 and the NO group is neutral, thus leaving a total valence for the ion of −2.

### *B.* Alkyl Cyanides

These are also known as *nitriles*, carbonitriles, or acid nitriles, RCN.

Up to $C_{13}$ these are liquids of peculiar but not unpleasant odor and of only slightly toxic properties as compared with the isomeric isonitriles or carbylamines, RNC, which have most disgusting odors and are highly toxic. Acetonitrile, $CH_3CN$, is soluble in water but the higher members become less soluble.

*Preparation.*

1. From inorganic cyanides.

*a.* KCN or NaCN with alkyl halides in aqueous alcohol solution. As would be expected, the results vary with the halide used. Thus *n*-AmCl gives a 70% yield, *sec*-AmCl a 30% yield and *t*-amyl chloride none (Hass 1931).

*b.* $Cu_2(CN)_2$, AgCN, $Hg(CN)_2$ or $K_2Hg(CN)_4$ with less reactive or more sensitive halides give cyanides and isocyanides. The latter can be removed by heating with *dilute* acid which has no effect on the former.

*c.* Inorganic cyanides heated with solid alkali alkyl sulfates.

$$RKSO_4 + KCN \rightarrow RCN + K_2SO_4$$

Again some isocyanide is formed.

2. From carboxylic acids. The acids are converted to the amides which are then dehydrated.

$$CH_3CO_2H + NH_3 \rightarrow CH_3CO_2NH_4$$

$$CH_3CO_2NH_4 \xrightarrow{\text{Distilled}} CH_3C(=O)-NH_2 + H_2O$$

$$CH_3C(=O)-NH_2 + P_2O_5 \rightarrow CH_3CN + 2\,HPO_3$$

This series of reactions shows the relations between the carboxylic acids, the acid amides and the acid nitriles and proves that the latter have the alkyl group attached to the carbon rather than to the nitrogen of the CN group. A modification of this preparation is the passage of ammonia and the vapors of a carboxylic acid or its ester over alumina at 500°.

3. From primary amines by treatment with bromine and KOH.

$$RCH_2NH_2 + 2\,Br_2 + 4\,KOH \rightarrow 4\,KBr + 4\,H_2O + RCN$$

4. From aldoximes by dehydration with acetic anhydride or thionyl chloride.

$$RCH{=}NOH + Ac_2O \rightarrow RCN + 2\,AcOH$$

5. From Grignard reagents with chlorocyanogen, ClCN.

6. From esters with $NH_3$ passed over hot $Al_2O_3$ or $ThO_2$ (Rep. 1918, 71).

*Reactions.*

1. Hydrolysis ("saponification"). In basic or acid solution the C≡N group is hydrated and then split.

$$RCN + H_2O + NaOH \rightarrow RCO_2Na + NH_3$$
$$RCN + 2\,H_2O + HCl \rightarrow RCO_2H + NH_4Cl$$

The hydrolysis of the higher nitriles becomes increasingly difficult because of the inertness of the corresponding amides. Thus $MeEtCHCH_2CN$, treated with 10 volumes of fuming hydrochloric acid for two days, gave only the amide.

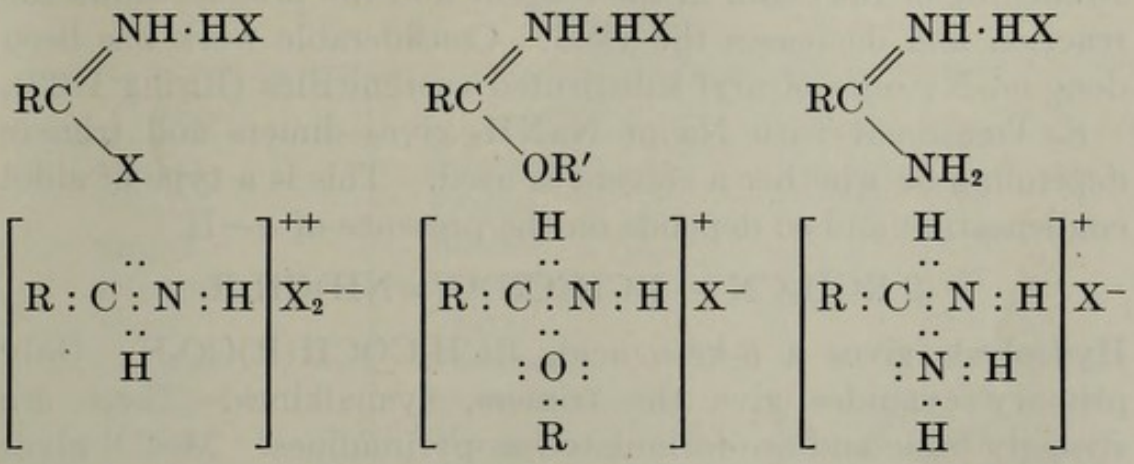
2. Milder addition of water to nitriles gives acid amides. This can be accomplished by heating with water at 180° or by treating with hydrogen peroxide and a base at 40°. Some

nitriles, on solution in conc. sulfuric acid and dilution with water, give the amides.

$$RC{\equiv}N + HOH \rightarrow RC(OH){=}NH \rightarrow RC(=O){-}NH_2$$

Hydrogen sulfide similarly gives thioacid amides, $RCSNH_2$.

3. Dry hydrogen halides form imidohalides. These react with alcohols and mercaptans to give imidoethers and thio-imidoethers. These are stable only as their hydrochlorides. With ammonia they form amidine hydrochlorides. Hydrolysis gives carboxylic acids. All these compounds resemble ammonium compounds which are stable as salts but not as the free hydroxide. They may be formulated as follows:



4. Aliphatic carboxylic acids add to nitriles to form di-acidamides.

$$RCN + RCO_2H \rightarrow (RCO)_2NH$$

This tendency is so great that reactions which would be expected to give $\gamma$-cyanobutyric acid actually give succinimide by internal addition. Aromatic carboxylic acids give an apparent metathesis.

$$ArCO_2H + RCN \rightarrow RCO_2H + ArCN$$

Acid anhydrides form tri-acidamides.

$$RCN + (RCO)_2O \rightarrow (RCO)_3N$$

5. Reduction gives primary amines. Side reactions give secondary and tertiary amines. Best results are obtained with alkaline reduction at moderate temperature. Acid reduction

favors the hydrolysis of the intermediate reduction product, $RCH=NH$ to give an aldehyde which can condense with the primary amine to form a Schiff's base, $RCH=NCH_2R$, which produces a secondary amine on reduction. Catalytic hydrogenation, at relatively high temperatures, eliminates $NH_3$ from two molecules of primary amine to give a secondary amine, etc.

6. Grignard reagents give ketones.

$$RCN + R'MgX \rightarrow RR'C=NMgX \rightarrow RR'C=O.$$

7. Sodium or sodamide with alkyl iodides result in alkylation in the alpha position to give secondary and tertiary alkyl cyanides.

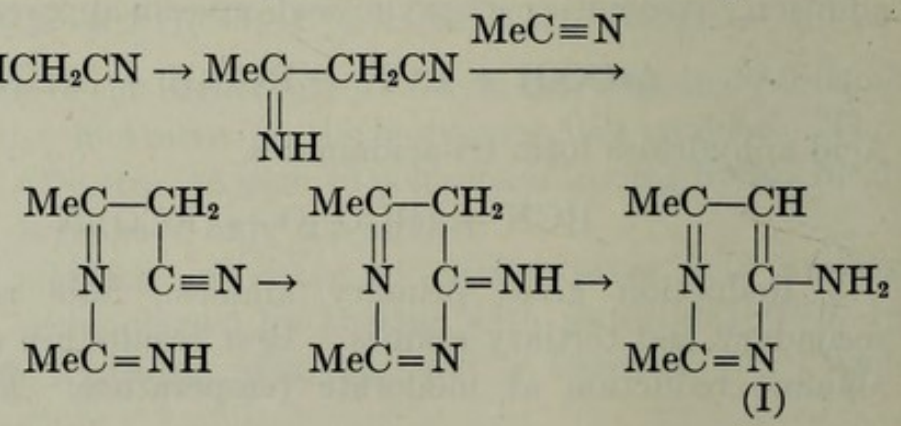
$$RCH_2CN \rightarrow RR'CHCN \rightarrow RR'R''CCN$$

Branching of the chain in the reagent and the product slows the reaction and decreases the yield. Considerable work has been done on Na salts of aryl substituted acetonitriles (Rising 1932).

8. Treatment with Na or $NaNH_2$ gives dimers and trimers depending on whether a solvent is used. This is a type of aldol condensation and so depends on the presence of $\alpha-H$.

$$2\,RCH_2CN \rightarrow RCH(CN)C(=NH)CH_2R.$$

Hydrolysis gives a $\beta$-keto acid, $RCH_2COCH(R)CO_2H$. Only primary cyanides give the trimers, cyanalkines. These are strongly basic and are formulated as pyrimidines. MeCN gives 2,4-dimethyl-6-aminopyrimidine (I). The first step is a condensation involving the $\alpha-H$ of one molecule and the $-C\equiv N$ group of another, the latter functioning like the $C=O$ group in the aldol condensation. Then the NH group reacts with the CN of a third molecule much as $NH_3$ reacts with $C=O$. Finally the NH reacts with the CN in the 5-position to close the 6-ring.




(I)

The final 1,3-shift gives the conjugated system of double linkages characteristic of the pyrimidines.

**Tertiary cyanides** cannot be made from KCN and the halide because the alkaline nature of the former causes the removal of HX. The double compound $Hg(CN)_2.2\,KCN$ is practically neutral and avoids this difficulty.

**Higher nitriles** are made from halides and, in addition, by the action of hypohalites with amines. Thus *n*-butyl amine gives *n*-butyronitrile.

$$C_3H_7CH_2NH_2 + 2\,Br_2 + 4\,NaOH \rightarrow C_3H_7CN + 4\,NaBr + 4\,H_2O$$

This reaction combines with the Hofmann reaction for making amines from acid amides unless the amine formed is volatile

NITRILES

| -cyanide | -nitrile | m. °C | b. °C |
|---|---|---|---|
| Methyl | Acetonitrile | − 44 | 81.5 |
| Ethyl | Propio- | −103 | 98 |
| Propyl | Butyro- | | 116 |
| Isopropyl | Isobutyro- | | 107 |
| Butyl | Valero- | | 141 |
| Isobutyl | Isovalero- | | 129 |
| *sec*-Butyl | Methylethylaceto- | | 125 |
| *t*-Butyl | $Me_3$-aceto- (Pivalo-) | 16 | 106 |
| Amyl | Capro- | | 163 |
| Hexyl | Oenantho- | | 184 |
| Heptyl | Caprylo- | | 199 |
| Octyl | Pelargono- | | 215 |
| Nonyl | Capric- | | 236 |
| Decyl | Undeco- | | 254 |
| Undecyl | Lauro- | 4 | 198 (100 mm.) |
| Dodecyl | Trideco- | | 275 |
| Tridecyl | Myristo- | 19 | 226 (100 mm.) |
| Tetradecyl | Pentadeco- | 23 | 185 (23 mm.) |
| Pentadecyl | Palmito- | 31 | 251 (100 mm.) |
| Cetyl, $C_{16}$ | Margaro- | 29 | 208 (10 mm.) |
| Heptadecyl | Stearo- | 41 | 274 (100 mm.) |
| Pentacosyl, $C_{25}$ | Ceroto- | 58 | |
| Nonacosyl, $C_{29}$ | Mellisso- | 70 | |
| Myricyl, $C_{31}$ | | 75 | |

enough to escape without reacting with excess of hypohalite solution.

$$RCH_2CONH_2 \xrightarrow[NaOH]{Br_2} RCH_2NH_2 \xrightarrow[NaOH]{Br_2} RC{\equiv}N$$

Nitriles can be *identified* by reaction with phloroglucinol in the presence of $ZnCl_2$, followed by hydrolysis to the ketone,

$$RCOC_6H_2(OH)_3\text{-}2,4,6.$$

(Howells 1932). The melting points of such ketones from the first five *n*-alkyl cyanides (°C) are 218, 175, 181, 149, and 120.

**Nitroacetonitrile,** $O_2NCH_2CN$, is obtained from methazoic acid.

$$O_2NCH_2CH{=}NOH + SOCl_2 \rightarrow O_2NCH_2CN + SO_2 + 2\,HCl$$

**Vinyl cyanide,** acrylonitrile, $CH_2{=}CHCN$, b. 78°, is made by dehydrating ethylene cyanohydrin.

**Allyl cyanide,** $CH_2{=}CH{-}CH_2CN$, cannot be made from KCN because the alkaline solution of the latter rearranges the double bond to the $\alpha\beta$-position. The use of cuprous cyanide overcomes this difficulty (OS).

### *C.* Alkyl isocyanides, isonitriles, carbylamines, RNC

These are liquids of penetrating and disgusting odors and of extreme toxicity. They boil somewhat lower than the corresponding cyanides.

*Preparation.*

1. From alkyl iodides and silver cyanide (Gautier 1866). The first product is a double compound RNC.AgCN. The difference in behaviour of AgCN and KCN in giving mainly isonitriles and nitriles respectively is sometimes expressed by giving the formulas as AgNC and KCN. The fact is that this difference is not understood. Electronically the cyanide ion is probably

$$\left[:\ddot{C}:N:\right]^-$$

No information is available as to the factors controlling the attachment of the entering alkyl group to C or to N. From experience with the alkylation of other metal compounds there is no necessary connection between the attachment of the metal (if other than merely ionic) and the attachment of the alkyl group which is not ionic. The clue may lie in the double salt formation with AgCN. This is treated with KCN to liberate the isonitrile

$$RNC.AgCN + KCN \rightarrow KAg(CN)_2 + RNC$$

2. Primary amines with chloroform and a base give the *carbylamine reaction* (Hofmann 1867, Nef 1897).

$$RNH_2 + CHCl_3 + 3\ NaOH \rightarrow RNC + 3\ NaCl + 3\ H_2O$$

It is a delicate test for a primary amine because of the powerful odor of the isocyanides.

Isocyanides are more volatile than the cyanides, MeNC, b. 60°, EtNC, b. 79°.

The *reactions* of the isocyanides depend on a peculiar type of unsaturation located entirely on one atom instead of at two adjacent atoms. Nef concluded that the carbon in the isocyanides is truly bivalent (1899). Gautier, the discoverer of the carbylamines, recognized this peculiarity and formulated them as R−N=C. This may be written as R−N≡C or

$$R : \ddot{N} :: \ddot{C}:$$

1. Halogens add even at low temperatures to give $RN=CX_2$, alkyliminocarbonyl halides. Hydrolysis gives HX, $CO_2$ and $RNH_2$ proving the R−N linkage.

2. Heating with sulfur gives mustard oils, RN=C=S.

3. Water adds to give alkyl formamides, HCONHR, formed from the initial product RN=CHOH. Mineral acids split this product to give formic acid and an amine hydrochloride. Hydrogen sulfide gives a thioformamide, HCSNHR.

4. HCl gas adds to give compounds of the type

$$(RN=CHCl)_2.HCl.$$

5. Acid chlorides add to give alkylimido chlorides of $\alpha$-ketonic acids, RCOC(Cl)=NR.

6. Reduction in alkaline solution or with catalysts gives MeRNH.

7. Oxidation by HgO gives isocyanates, RNCO.

8. The isocyanides give polymers readily.

9. On heating to 250° they rearrange to cyanides.

## XXIV. OTHER COMPOUNDS CONTAINING A SINGLE CARBON ATOM AND THEIR DERIVATIVES

These compounds may be classified according to the stage of oxidation in the series.

| | I | II | III | IV |
|---|---|---|---|---|
| $CH_4$ | $CH_3OH$ | HCHO | $HCO_2H$ | $H_2CO_3$ |

I. As examples of the first stage of oxidation various methyl derivatives have been discussed. These include the alcohol, the amine and related substances, the mercaptan, and the halides.

II. Second stage of oxidation. Formaldehyde, methylene halides, polymers of ($CH_2=NH$) and ($CH_2S$), as well as diazomethane have been discussed.

III. Third stage of oxidation. Formic acid, formamide and hydrocyanic acid have already been covered.

1. Carbon monoxide, CO, is the classical example of a compound of divalent carbon (Nef) (Sidgwick, Rev. *9*, 77). Its similarity to nitrogen in both physical properties and chemical inertness under mild conditions may be shown electronically (Langmuir).

$$:\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}:\overset{\cdot\cdot}{\underset{\cdot\cdot}{N}}: \qquad\qquad :\overset{\cdot\cdot}{\underset{\cdot\cdot}{C}}:\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}:$$

In each case two atoms held by an electron pair are surrounded by an octet of electrons. The catalysts which play so important a role in the chemistry of nitrogen and of carbon monoxide apparently serve to open up this stable arrangement.

*Preparation.*

(1) On the large scale by the action of steam or $CO_2$ on hot coal and of methane with steam.

$$H_2O + C \rightleftharpoons CO + H_2 \quad \text{Water gas}$$
$$CO_2 + C \rightleftharpoons 2\,CO$$
$$H_2O + CH_4 \rightarrow CO + 3\,H_2$$

(2) On the laboratory scale by the action of formic acid with $H_2SO_4$.

*Reactions.*

(1) With oxygen to give $CO_2$.

(2) At high temperatures to give $CO_2$ and C.

(3) With steam and catalysts at high temperatures.

$$CO + H_2O \rightarrow CO_2 + H_2$$

At lower temperatures, $CH_4$ is obtained (Pease 1928, Taylor 1931). With suitable catalysts mixtures of hydrocarbons resembling petroleum can be made (Synthol) (Rep. 1924, 63) (Berl 1930).

(4) With hydrogen to form methanol and higher alcohols (Graves 1931), acids, ketones, etc. This is now the best commercial method for making methanol, *n*-propyl alcohol and isobutyl alcohol. Little isopropyl alcohol is obtained. Higher primary and secondary alcohols to $C_{15}$ with highly branched chains and boiling up to 250° and higher are commercially available from the process (du Pont). Diisopropylcarbinol and *sec*-butylcarbinol are obtained in considerable amounts.

(5) As a high temperature reducing agent in the blast furnace preparation of iron. In this process the finely divided carbon formed by the thermal decomposition of CO plays an important part.

(6) Potassium unites with CO to form a compound $C_6(OK)_6$, the potassium compound of hexahydroxy benzene. The first step is like that in the pinacol reduction of acetone and in the formation of the metal ketyls.

$$CO + K \rightarrow -\overset{|}{\underset{|}{C}}-O-K$$

(7) Carbon monoxide unites with many heavy metals to form metal carbonyls, $M(CO)n$. These are volatile liquids which decompose to the metal and CO at high temperatures. The Mond process for extracting nickel depends on the formation, volatilization and thermal decomposition of nickel carbonyl, $Ni(CO)_4$ (Ahr. 1899). Iron carbonyls, $Fe(CO)_5$ and $[Fe(CO)_4]_3$ are known (Hieber 1931). Carbon monoxide can pass through a red hot iron container by alternate formation and decomposition of iron carbonyls. Iron carbonyl is used as an anti-knock in gasoline.

(8) Carbon monoxide reacts with NaOH under pressure to give sodium formate.

(9) With sodium alcoholates at about 200°, sodium salts of carboxylic acids are formed.

$$RONa + CO \rightarrow RCO_2Na$$

Sodium ethylate with CO at 20° and 80 atm. gives an addition product which reacts with water to give sodium formate and EtOH instead of sodium propionate which is produced at higher temperatures (Scheibler 1931).

(10) With methanol and certain catalysts it gives acetic acid. Other catalysts give methyl formate.

(11) With Grignard reagents, acyloins and olefins are formed.

$$2\,CO + 2\,RMgX \rightarrow 2\,R{-}\underset{\underset{\|}{}}{C}{-}OMgX \rightarrow$$

$$R{-}\underset{\underset{\|}{}}{C}{-}OMgX \quad \underset{R{-}\underset{\underset{\|}{}}{C}{-}OMgX}{\rightarrow} \quad R{-}\underset{\underset{\|}{}}{C}{-}OH \quad \underset{R{-}\underset{\underset{|}{}}{C}{-}OH}{\rightarrow} \quad R{-}\underset{\underset{|}{}}{C}{-}OH$$

(12) The olefin contains $2_{n+1}$ carbons from a Grignard reagent containing $n$ carbons. The double bond is next the middle. Thus ethyl, isopropyl, $n$-butyl and isoamyl Grignard reagents give pentene-2; 2,4-$Me_2$-pentene-2; nonene-4 and 2,8-$Me_2$-nonene-4 in yields up to 70%.

(13) Carbon monoxide forms a more stable compound with hemoglobin than does oxygen. This accounts for its extreme toxic nature even in small amounts. Its presence in automobile

exhaust gases presents a hazard which may have to be eliminated by its catalytic conversion to $CO_2$ (Frazer 1934).

2. **Carbon monoxide acetal,** $C(OC_2H_5)_2$, is said to be obtained by condensing diethoxy acetic ester with sodium ethylate. (Scheibler). The bivalent carbon acetal is described as a liquid, b. p. 77°, stable to bases but readily hydrolyzed by acids. Attempts to prepare it in other laboratories have failed.

The existence of C(ONa) (OEt) a salt of a hemiacetal of CO has not been confirmed (Adickes 1935).

3. **Orthoformates,** $HC(OR)_3$, are obtained from chloroform and sodium alcoholates. They are hydrolyzed by acids to give formic acid and ROH. With Grignard reagents they give acetals of aldehydes.

$$HC(OC_2H_5)_3 + RMgX \rightarrow C_2H_5OMgX + RCH(OC_2H_5)_2$$

4. **Formyl chloride** has never been isolated but undoubtedly exists in equilibrium with CO and HCl.

$$CO + HCl \rightleftharpoons HC(Cl)=O$$

A mixture of CO + HCl gases is used with $AlCl_3$ to introduce the aldehyde group into aromatic compounds.

5. **Formimido chloride** is obtained by the action of dry HCl gas on HCN.

$$HC{\equiv}N + HCl \rightleftharpoons H{-}C(Cl){=}NH$$

It is unstable. With alcohols it gives the corresponding formimido ethers (really esters).

$$HC(Cl){=}NH + ROH \rightarrow HC(OR){=}NH.HCl$$

Formimido chloride is used in another synthesis for aromatic aldehydes (Gattermann). The condensing agent is anhydrous $ZnCl_2$. The needed reagents are conveniently obtained by treat-

ing dry solid zinc cyanide suspended in ether with dry hydrogen chloride gas (Adams).

$$Zn(CN)_2 + 4\,HCl \rightarrow ZnCl_2 + 2\,H{-}\overset{\displaystyle Cl}{\overset{|}{C}}{=}NH$$

6. **Fulminic acid** (Knallsäure), carbon monoxide oxime, $H-O-N=C$, is unstable in the free state. Mercury fulminate was discovered and is still made by the action of mercury, nitric acid and ethyl alcohol (Howard). Mercury fulminate is a detonator for explosives. Silver fulminate is made in the same way and is even more explosive. Mercury fulminate can also be made from sodium nitromethane and mercuric salts.

Fulminic acid can be formed from HCN.

$$HCN + NH_2OH \rightarrow \underset{\displaystyle NHOH}{\overset{|}{HC}}{=}NH \rightleftharpoons \underset{\displaystyle NOH}{\overset{||}{HC}}{-}NH_2 \rightarrow NH_3 + HON{=}C$$

Formamide oxime
Isouretine

*Reactions of fulminic acid.* (1) Polymerization takes place spontaneously even at low temperatures to give a trimer, "meta fulminic acid" which is non-explosive.

(2). Hydrolysis by dilute HCl.

$$H{-}O{-}N{=}C + H_2O \rightarrow \left[HO{-}N{=}\overset{\displaystyle H}{\overset{|}{C}}{-}OH\right] \rightarrow HCO_2H + NH_2OH$$

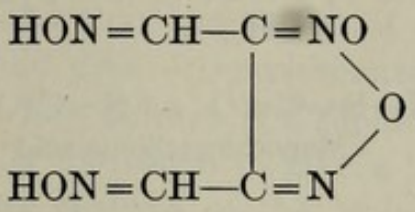
3. Concentrated HCl, nitrous acid and other substances add to the bivalent carbon (Nef).

$$H{-}O{-}N{=}C \rightarrow HO{-}N{=}\overset{\displaystyle H}{\overset{|}{C}}{-}Cl,$$

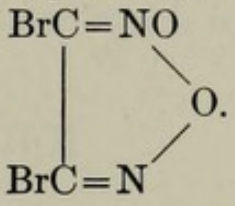
$$HO{-}N{=}\overset{\displaystyle H}{\overset{|}{C}}{-}NO_2, \qquad HO{-}N{=}CCl_2$$

(4) Nitric acid with sodium fulminate gives isocyanilic acid, a

tetramer, the dioxime of furoxandialdehyde (Rep. 1925, 103),



(5) Bromine in acid solution gives $Br_2C=NOH$ while in neutral solution it gives dibromofuroxan,



Fulminic acid, Ahr. 1909, 77 pp.

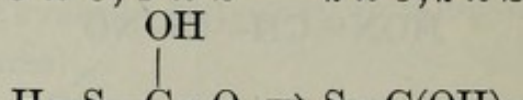
IV. Fourth state of oxidation, all H atoms of methane replaced by OH, $NH_2$, SH or their equivalent. Since about twenty such compounds or the corresponding derivatives are known, some system of classification is necessary. This might be according to the attachment of the carbon valences to O, N and S atoms. The chlorides would fall under the corresponding —OH compounds. In several cases the existence of tautomerism places a given compound in two classes.

### Distribution of Carbon Valences

| (1) *4 to O* | (2) *3 to O, 1 to N* | (3) *2 to O, 2 to N* | (4) *1 to O, 3 to N* |
|---|---|---|---|
| $C(OH)_4$ Orthocarbonic acid | $NH_2CO_2H$ Carbamic acid | $O=C(NH_2)_2$ Urea | $\rightleftharpoons$ $HO-C(NH_2)=NH$ |
| $O=C(OH)_2$ Carbonic acid | $NH_2COCl$ | $O=C=N-H$ Isocyanic acid | $\rightleftharpoons$ $H-O-C\equiv N$ Cyanic acid |
| $CO_2$ | | | $Cl-C\equiv N$ |
| $CCl_4$ | | | |
| $COCl_2$ | | | |

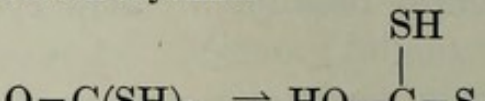
(5) *4 to N* (6) *3 to O, 1 to S* (7) *2 to O, 2 to S* (8) *1 to O, 3 to S*

$HN=C(NH_2)_2$
Guanidine


Monothiocarbonic acid

$NH_2—C\equiv N$
Cyanamide

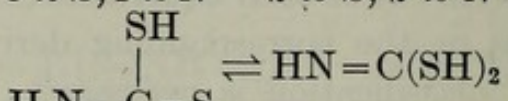
$O=C=S$
Carbon oxysulfide


Dithiocarbonic acid
Xanthic acid

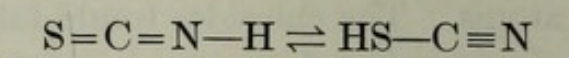
$CSCl_2$

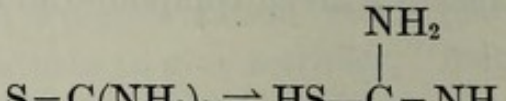
(9) *4 to S* (10) *3 to S, 1 to N* (11) *2 to S, 2 to N* (12) *1 to S, 3 to N*

$S=C(SH)_2$
Trithiocarbonic acid

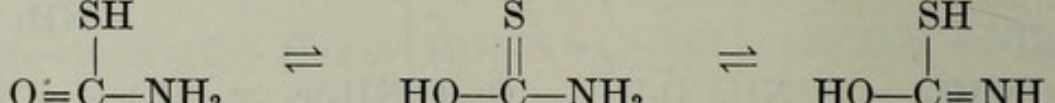

Dithiocarbamic acid

$CS_2$
Carbon disulfide


Isothiocyanic acid Thiocyanic acid


Thioruea

(13) *2 to O, 1 to N, 1 to S* (14) *1 to O, 1 to N, 2 to S* (15) *1 to O, 2 to N, 1 to S*


Monothiocarbamic acid

### *A.* Carbonic Acid and Its Derivatives

1. **Ortho carbonic acid,** $C(OH)_4$, is incapable of existence. Orthocarbonates, $C(OR)_4$, are obtained from sodium alcoholates and chloropicrin.

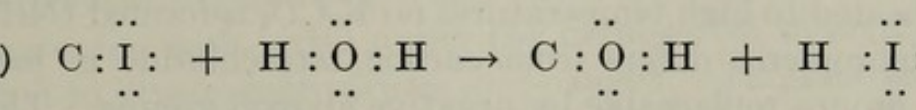
$$4\,RONa + Cl_3CNO_2 \rightarrow C(OR)_4 + 3\,NaCl + NaNO_2$$

$C(OEt)_4$, b. 159°.

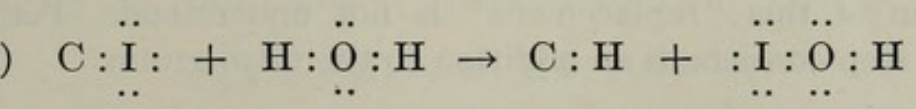
It might be expected that the action of carbon tetrachloride with alcoholates would give orthocarbonates. Such is not the case, however. The first change is a replacement of one of the four halogen atoms by hydrogen to give a haloform which then gives an orthoformate instead of the expected orthocarbonate (Nef). The replacement of one halogen atom by a hydrogen is most marked in the case of tetraiodomethane which reacts with boiling water to give iodoform.

$$CI_4 + H_2O \rightarrow CHI_3 + HOI$$

In this case the iodine replaced is said to be "positive" because it combines with the negative OH of the water. Expressed in another way, the iodine is removed without taking with it the electron pair which held it to the carbon. This is unusual because halogens tend to keep a complete octet of electrons and give ordinary metathetical reactions

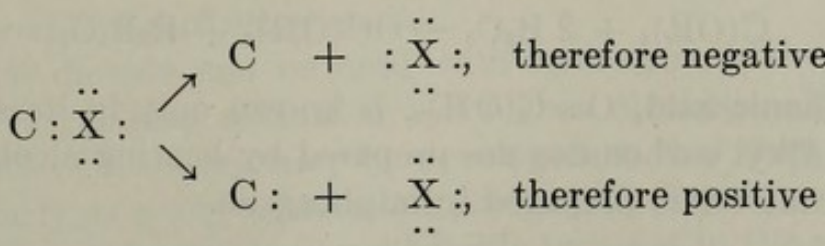


(*a*)



(*b*)

Looked at in this way, the "abnormal" replacement of halogen by hydrogen (b) is seen to be a metathesis also, one in which a *positive* hydrogen replaces a *positive* halogen instead of a *negative* hydroxyl replacing a *negative* halogen, the difference between a positive and a negative halogen depending on the fate of the electron pair which holds it to another atom.



The second type of change is naturally favored by a reducing agent as a *giver* of electrons, thus changing the abnormal positive

halogen into the normal negative halide ion. Thus:

$$C : \underset{\cdot\cdot}{\overset{\cdot\cdot}{X}} : \; + \; : \text{(from reducer)} \; \rightarrow \; C : \; + \; : \underset{\cdot\cdot}{\overset{\cdot\cdot}{X}} :$$

This process is the reverse of halogenation.

$$C : H \; + \; : \underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}} : \underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}} : \; \rightarrow \; C : \underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}} : \; + \; H : \underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}} :$$

When carbon tetrachloride is heated with a sodium alcoholate the first step is:

$$CCl_4 + NaOCH_3 \rightarrow CHCl_3 + NaCl + CH_2O$$

The three remaining Cl atoms then react metathetically to give $HC(OCH_3)_3$.

Even when $CCl_4$, $CBr_4$ or $CI_4$ and an excess of alcoholic KOH are heated to high temperatures no $K_2CO_3$ is formed (Nef).

Chloropicrin differs from carbon tetrachloride in having all four groups replaceable by negative alkoxyl groups. The mechanism of this "replacement" is not understood. Perhaps its first step consists in an addition to the nitro group.

$$Cl_3C{-}\overset{\overset{O}{\|}}{N}O \rightarrow Cl_3C{-}\overset{\overset{ONa}{|}}{\underset{\underset{OR}{|}}{N}}O \rightarrow NaNO_2 + Cl_3C{-}OR$$

Ortho carbonates on heating with boric anhydride give ordinary carbonates.

$$C(OR)_4 + 2\,B_2O_3 \rightarrow OC(OR)_2 + R_2B_4O_7$$

2. **Carbonic acid,** $O{=}C(OH)_2$, is known only in its salts and esters. Alkyl carbonates are prepared by heating alcohols with chloroformic esters prepared from phosgene.

$$ClCO_2R + R'OH \rightarrow HCl + RR'CO_3$$

If different alkyl groups are used the heating must be kept to a

minimum to avoid the change

$$RR'CO_3 + R'OH \rightarrow R_2'CO_3 + ROH$$

in which ROH represents the more volatile alcohol.

The alkyl carbonates give the ordinary ester reactions but are less readily reactive than the corresponding esters of the carboxylic acids. Thus ethyl carbonate is not easily hydrolyzed to alcohol and $CO_2$.

Ethyl carbonate reacts with Grignard reagents to give esters or tertiary alcohols, depending on the proportions of reagents used and the nature of the groups involved.

$$RMgX + O{=}C(OC_2H_5)_2 \rightarrow RCO_2C_2H_5 + C_2H_5OMgX$$
$$3\ RMgX + O{=}C(OC_2H_5)_2 \rightarrow R_3COMgX + 2\ C_2H_5OMgX$$

In the case of groups like naphthyl and tertiary butyl, the reaction is relatively slow and stops at the ester stage.

3. **Carbon dioxide,** carbonic anhydride, $CO_2$, is involved in many important organic reactions. The most important reaction is its union with water under the influence of sunlight and chlorophyl to give carbohydrates and oxygen. The first step is undoubtedly the production of formaldehyde.

$$CO_2 + H_2O \rightarrow HCHO + O_2$$

Starting with this formaldehyde, plants and animals elaborate the countless carbon compounds necessary to their existence. The production of formaldehyde from $CO_2$ and $H_2O$ and the conversion of the formaldehyde to simple sugars has been achieved by the use of ultraviolet light (Rep. 1924, 66–9).

One of the most important sources of carbon dioxide is the action of ferments in which they decarboxylate organic acids as in the production of ethyl alcohol.

Carbon dioxide can be used with hydrogen in the catalytic process for making methanol and higher alcohols. Eventually this series of reactions may be developed so that man may produce nearly as many materials from carbon dioxide as does Nature. He will probably never be able to use it in the concentration of 4 parts in 10,000, however.

Carbon dioxide enters into a number of ordinary organic reactions. Thus it adds sodium-carbon compounds, Grignard reagents, sodium alcoholates sodium mercaptides and ammonia to give $RCO_2Na$, $RCO_2MgX$, $ROCO_2Na$, $RSCO_2Na$, $NH_2CO_2NH_4$ and $NH_2CONH_2$.

4. **Carbon tetrachloride,** as has been seen, does not act as the acid chloride of orthocarbonic acid. First of all, it is unexpectedly unreactive. Secondly, when it does react, it does not give derivatives of carbonic acid. With alcoholic KOH at 100° it gives KCl, CO and $H(COC_2H_5)_3$ but no trace of $K_2CO_3$.

5. **Carbonyl chloride,** phosgene, $O=CCl_2$, b. 8°, is a true acid chloride of carbonic acid. It is very poisonous. On a small scale it is made from carbon tetrachloride and 80 per cent oleum (fuming sulfuric acid containing 80 parts $SO_3$ added to 100 parts of pure $H_2SO_4$)

$$CCl_4 + SO_3 \rightarrow COCl_2 + S_2O_5Cl_2, \text{ pyrosulfuryl chloride}$$

Commercially it is made from CO and $Cl_2$ with a catalyst such as activated carbon.

$$CO + Cl_2 \rightarrow COCl_2$$

Sunlight hastens the reaction. (Hence the name phosgene, Davy).

Phosgene gives the ordinary acid chloride reactions: (1) with alcohols in the cold only one Cl reacts.

$$ClCOCl + ROH \rightarrow HCl + ClCO_2R$$

The resulting chloroformic esters are themselves acid chlorides.

(2) On warming with alcohols, phosgene gives alkyl carbonates.

$$COCl_2 + 2\,ROH \rightarrow 2\,HCl + R_2CO_3$$

(3) With $NH_3$ and primary and secondary amines it gives urea and N-substituted areas. With primary amines an excess of phosgene gives isocyanates.

$$COCl_2 + RNH_2 \rightarrow (RNH{-}\underset{\displaystyle Cl}{\underset{|}{C}}{=}O) \rightarrow HCl + R{-}N{=}C{=}O$$

(4) Heated with $NH_4Cl$, it gives carbamyl chloride.

$$COCl_2 + NH_4Cl \rightarrow NH_2COCl + 2\,HCl$$

(5) It reacts in the Friedel-Crafts reaction with aromatic compounds to give acid chlorides and ketones. In one important case, it reacts even without $AlCl_3$. This is the reaction with dimethylaniline to give Michler's ketone, an important intermediate in the making of triphenyl methane dyes.

$$2\,Me_2NC_6H_5 + COCl_2 \rightarrow 2\,HCl + (Me_2NC_6H_4)_2CO$$

It was this commercial use for phosgene which first made it available as a war gas. Because of its slow reactions with most substances, it was difficult to protect troops against this gas until it was found to react readily, even in small concentrations, with sodium phenolate, $C_6H_5ONa$, to give diphenyl carbonate.

Phosgene, Dyson, Rev. *4*, 109–166.

In general, the derivatives of carbonic acid react much less rapidly than the corresponding derivatives of the fatty acids. This is true of the following:

$$\left.\begin{matrix} EtOCO_2Et \\ NH_2CO_2Et \end{matrix}\right\} RCO_2Et$$

$$\left.\begin{matrix} NH_2CO_2Et \\ NH_2CONH_2 \end{matrix}\right\} RCONH_2$$

$$\left.\begin{matrix} ClCOCl \\ NH_2COCl \\ EtOCOCl \end{matrix}\right\} RCOCl$$

6. **Chloroformic acid, "chlorocarbonic" acid,** $ClCO_2H$, is known only in its derivatives. Chloroformic esters are made by treating primary or secondary alcohols in the cold with phosgene. The chloroformic esters, as acid chlorides, react with all active H compounds such as water, alcohols, ammonia, primary and secondary amines, etc. Ethyl and methyl chloroformate have proved very useful in "protecting" phenolic hydroxyl groups (E. Fischer, Depsides).

$$-OH + ClCO_2CH_3 \rightarrow -OCO_2CH_3$$

The resulting carbonate is fairly stable to acid reagents but is readily eliminated by alcoholic ammonia.

### *B.* Amides of Carbonic Acid

1. **Carbamic acid,** aminoformic acid, $NH_2CO_2H$ is known only in its derivatives.

(*a*) *Ammonium carbamate* is formed directly from $NH_3$ and $CO_2$

$$2\,NH_3 + CO_2 \rightarrow NH_2CO_2NH_4$$

This is a very soluble white crystalline compound. The carbamates of the alkaline earth metals are soluble. In this they resemble the bicarbonates.

$NH_2—CO—OCaO—CO—NH_2$ $\qquad$ $HO—CO—OCaO—CO—OH$

Ca carbamate $\qquad$ Ca bicarbonate

Ammonium carbamate is hydrolyzed to ammonium carbonate by water at 60°.

(*b*) Alkyl carbamates are the *urethanes*, $NH_2CO_2R$. They may be prepared (1) by treating chloroformic esters with ammonia or primary or secondary amines (2) by treating carbamyl chloride, $NH_2COCl$, with an alcohol or, (3) by heating urea to a high temperature with an alcohol,

$$CO(NH_2)_2 + ROH \rightarrow NH_2CO_2R + NH_3$$

(4) by adding alcohols to isocyanic acid or isocyanates.

$$C_6H_5N{=}C{=}O + ROH \rightarrow C_6H_5N{=}\underset{\displaystyle OR}{\underset{|}{C}}{-}OH \rightarrow C_6H_5NH{-}\underset{\displaystyle OR}{\underset{|}{C}}{=}O$$

Phenyl isocyanate $\qquad$ A phenyl urethane

The phenyl and naphthyl urethanes are readily purified crystalline substances very useful in identifying alcohols. The urethanes give the reactions of esters and acid amides. They form stable sodium derivatives which react with alkyl and acyl halides to give N-substituted urethanes. In this way ethyl chlorocarbonate gives ethyl imidodicarboxylate, $NH(CO_2Et)_2$, m. 50°. The N-alkylated urethanes react with nitrous acid and with nitric acid to give N-nitroso and N-nitro compounds. The reduction of these give mono-substituted hydrazines. As has been seen, diazomethane is made by the action of alkali on nitroso-N-methyl urethane, $MeN(NO)CO_2Et$.

*Urethane,* $NH_2CO_2Et$, m. 50°, b. 180°, is a hypnotic.

2. **Carbamic acid chloride,** carbamyl chloride, $NH_2CO-Cl$, m. 50°, b. 62°, is obtained by adding dry HCl to cyanic acid and by heating phosgene with ammonium chloride to 400°. It reacts vigorously as an acid chloride even in the Friedel and Crafts reaction. On standing it changes to cyamelide.

3. **Urea, carbamide,** $NH_2-CO-NH_2$, m. 132°, is the chief nitrogenous product of protein metabolism. A human adult excretes about 30 g. per day. It is obtained from urine by evaporation and addition of nitric acid to precipitate the slightly soluble urea nitrate. Historically, the most important synthesis is from a cyanate and an ammonium salt (Woehler 1828).

$$NH_4—O—C\equiv N \rightarrow NH_2—\overset{\overset{O}{\|}}{C}—NH_2$$

In the laboratory, it is formed in varying yields by the action of ammonia on phosgene, alkyl carbonates, alkyl chloroformates, urethanes and carbamyl chloride.

*Commercial Syntheses.*

(1) From $CO_2 + NH_3$. The ammonium carbamate first formed is heated under pressure.

$$NH_2CO_2NH_4 \rightarrow H_2O + NH_2-CO-NH_2$$

This is like the ordinary formation of an acid amide from its ammonium salt.

(2) By the partial hydrolysis of cyanamide from calcium cyanamide.

$$NH_2—C\equiv N + H_2O \rightarrow NH_2—\underset{\underset{OH}{|}}{CNH} \rightleftharpoons NH_2—CO—NH_2$$

*Formula of Urea.* There has been much discussion on this subject. The best evidence indicates it to be a tautomeric substance.

$$\begin{matrix} NH_2 & & NH_2 & & NH_3\oplus \\ | & & | & & | \\ NH_2—C=O & \rightleftharpoons & HN=C—OH & \rightleftharpoons & HN=C—O\ominus \end{matrix}$$

The last formula has been proposed because of the ease with which urea loses $NH_3$ to form cyanic acid (E. A. Werner, 1923). Such

an assumption is hardly necessary in view of the ease with which substances containing the grouping $C(OH)NH_2$ lose $NH_3$ to give a C=O group. The reactions are different in many respects from those of ordinary acid amides. Consequently, the OH formula has been favored by some. On the other hand X-ray and crystallographic evidence indicate the carbamide formula (Hendricks 1928). The mass of evidence bearing on the structure of urea includes peculiarities in the following reactions (Werner): (*a*) phosgene + $NH_3$; (*b*) urethane, $NH_2CO_2Et$, with $NH_3$: (*c*) effect of heat on alkylated ammonium carbamates; (*d*) the reaction of urea with nitrous acid; and (*e*) the formation of nitroso ureas from monosubstituted ureas and nitrous acid instead of primary amines or alcohols.

$$[MeNHCONH_2 + HNO_2 \rightarrow MeNHCO_2H \rightarrow MeNH_2 \rightarrow MeOH]$$

$$MeNHC(OH)NH + HNO_2 \rightarrow MeN(NO)C(OH)NH \text{ (90\% yield)}$$

(*f*) Action of $Me_2SO_4$ to give $HN=C(OMe)NH_2$ instead of an N–Me compound. The exact significance of these facts in the structure of urea has been questioned by many.

*Reactions.* (1) Slow heating removes $NH_3$ from two molecules to give *biuret*, $NH_2-CO-NH-CO-NH_2$. Biuret reacts in basic solution with copper salts to give an intense violet color ("biuret reaction"). More rapid heating gives cyanic acid, $H-O-C\equiv N$ which immediately polymerizes.

(2) Acids form salts, for instance, the difficultly soluble nitrate $NH_2CONH_2.HNO_3$. The chloride, phosphate and oxalate are also known. It also forms crystalline compounds with various inorganic salts including NaCl and $AgNO_3$.

(3) It gives salts with metals such as mercury.

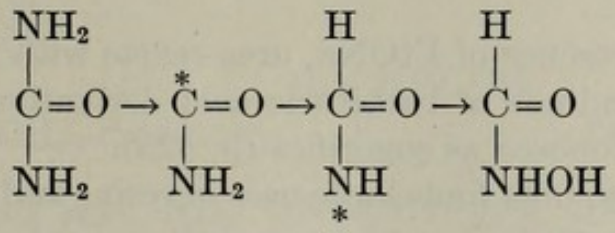
(4) Treatment with aqueous acids or alkalies gives $NH_3$ and $CO_2$ or their reaction products. An enzyme (*urease*, Sumner) found in soybeans and jackbeans produces the same change at room temperature.

(5) Nitrous acid reacts with urea

$$CO(NH_2)_2 + 2\,HNO_2 \rightarrow CO_2 + 2\,N_2 + 3\,H_2O$$

This reaction never gives the calculated amount of gaseous products.

This is not surprising when it is recalled that the "replacement" of $-NH_2$ by $-OH$ often involves rearrangements. In this case the following changes might take place.

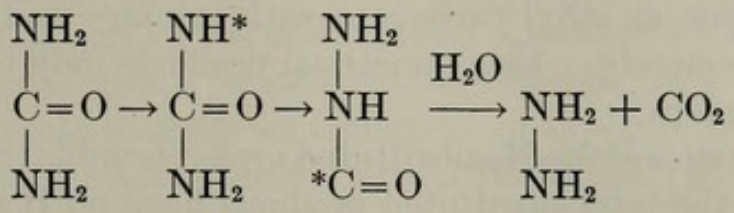


If formhydroxamic acid or some similar rearrangement product resulted, it would behave quite differently from urea.

(6) Hypohalite solutions or bases and halogens react nearly according to the following equation

$$CO(NH_2)_2 + 3\ KOBr + 2\ KOH \rightarrow K_2CO_3 + N_2 + 3\ KBr + 3\ H_2O$$

In this case a rearrangement (Hofmann) is known to take place.



The hydrazine can be obtained as an insoluble product by adding benzaldehyde. If the reaction is carried out at 0° with only one equivalent of hypohalite, hydrazine is the chief product.

(7) Urea reacts with chlorine and water at 0° to give mono- and di-N-chloroureas (EP 502).

$$CO(NH_2)_2 + Cl_2 \rightarrow NH_2CONHCl + HCl$$

The chlorine in this compound is "positive." It liberates iodine from iodides. With acids it gives explosive nitrogen chloride.

$$3\ NH_2CONHCl + 8\ HCl + 3\ H_2O \rightarrow 3\ CO_2 + 5\ NH_4Cl + NCl_3$$

The dichloro compound, $CO(NHCl)_2$, has similar properties. With $NH_3$ it gives para-urazine, $CO(NHNH)_2CO$, a structure proved by hydrolysis by sulfuric acid to $CO_2$ and hydrazine sulfate.

(8) Formaldehyde condenses with urea to give *methylol ureas*, $NH_2CONHCH_2OH$ etc. The methylol groups can combine with

more urea to form more and more complex molecules until a resin is formed. Urea-formaldehyde resins can be made colorless and transparent. They are of increasing importance in the resin industry.

(9) In the presence of EtONa, urea reacts with malonic esters to give the hundreds of barbituric acid derivatives which have been used or proposed as soporifics (p. 525).

Commercially, urea finds large uses in resins and as a stabilizer in nitrocellulose products such as smokeless powder and celluloid. In these it combines with the small amounts of nitric acid formed by their gradual decomposition. A crude ammonia urea solution is used with acid phosphates in mixed fertilizers.

The action of hydroxylamine and HCN gives $HN=CHNHOH$, formamidoxime, *isuret*, an isomer of urea.

4. **Alkyl ureas** are known corresponding to the two usual formulas for urea $(NH_2)_2CO \rightleftharpoons HN=C(NH_2)OH$.

Symmetrical di- and tetra-alkylated ureas may be obtained from phosgene or ethyl carbonate with primary and secondary amines respectively. Unsymmetrical products may be obtained by suitable steps.

The properties of the N-substituted ureas resemble those of urea except that the tetrasubstituted products have no H replaceable by the action of $HNO_2$ or $HNO_3$.

O-Substituted ureas or "isoureas" are obtained from cyanamide (Stieglitz)

$$NH_2-C\equiv N+ROH+HCl \rightarrow NH_2(RO)C=NH.HCl.$$

5. **Ureides,** acyl ureas, are so numerous and important as to deserve a separate classification. As substituted acid amides they can be prepared in a variety of ways either starting with urea and a suitable acid or its derivative such as the chloride, anhydride or ester or with an acid amide and cyanic acid.

**Allophanic** acid, $NH_2CONHCO_2H$, the ureide of carbonic acid is known only as the esters obtained from (1) urethanes and cyanic acid and (2) chloroformates and urea and as its amide (biuret) obtained by heating urea. The allophanates of alcohols may be used for identification purposes. Thus the Me, Et and Pr esters melt at 208°, 191° and 160°.

*Hydantoin*, glycolyl urea, 2,4-diketotetrahydroimidazole, m. 216°, $CONHCH_2$ is related to glycollic acid. Its tautomeric
$NH—CO$
form is 2,4-$(OH)_2$-imidazole, $\begin{matrix} HOCNHCOH \\ \| \quad\quad \| \\ CH—N \end{matrix}$. Partial hydrolysis gives *hydantoic acid*, $NH_2CONHCH_2CO_2H$, glycoluric acid, m. 156° dec., which on further hydrolysis forms $NH_3$, $CO_2$ and glycine. Hundreds of substituted hydantoins have been studied (T. B. Johnson).

Nirvanol is phenyl ethyl hydantoin.

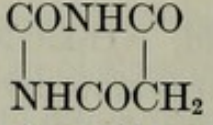
**Lactyl urea,** is a 5-Me-hydantoin related to lactic acid while 1-Me-hydantoin is obtained by the partial hydrolysis of creatinine (1-Me-2-iminohydantoin). Hydrolysis of these gives α-aminopropionic acid, and N-Me-glycine respectively. 4,4-Dialkylhydantoins are formed from the diamides of dialkylmalonic esters. The first step is undoubtedly a Hofmann rearrangement. The isocyano group formed reacts with the $NH_2$ group in the same molecule to close the 5-ring.

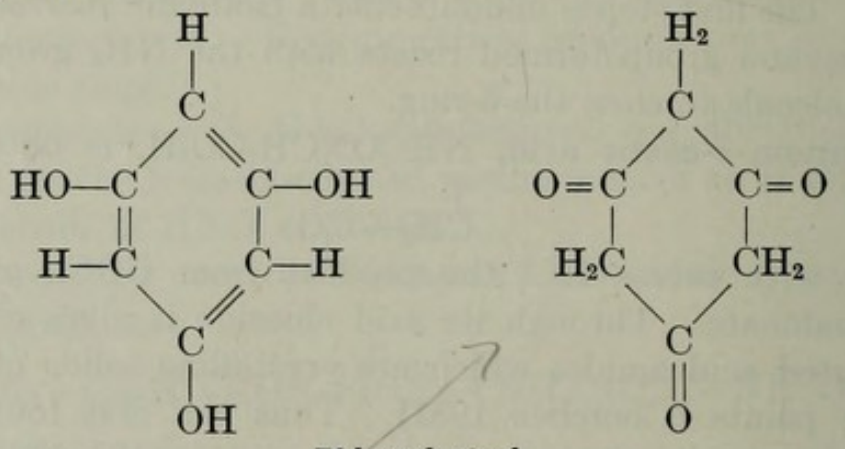
**Hydantoin-3-acetic acid,** $\begin{matrix} NHCONCH_2CO_2H \\ | \quad\quad | \\ CH_2—CO \end{matrix}$, is obtained by heating with excess HCl the product from $COCl_2$ and ethyl aminomalonate. Through its acid chloride it gives esters and substituted acid amides which are crystalline solids of definite melting points (Cherchez 1931). Thus the first four normal esters of hydantoin-3-acetic acid melt at 91°, 119°, 116° and 95° while the isobutyl, sec-butyl and isoamyl esters melt at 124°, 142° and 100°.

**Cyclic ureides,** related to dibasic acids, are readily obtained both synthetically and from certain natural products.

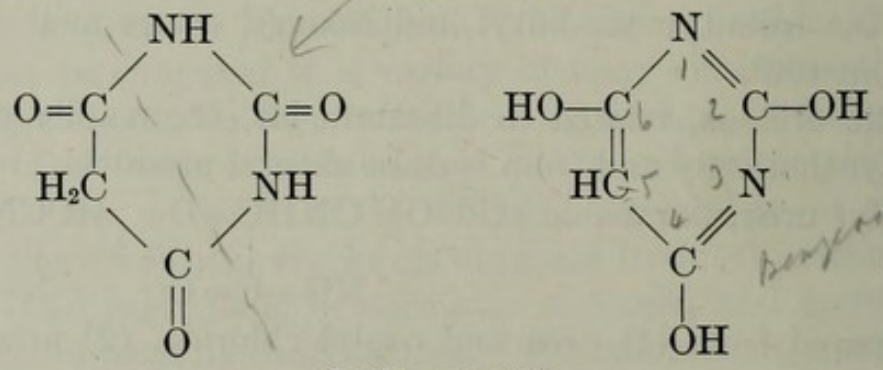
**Oxalyl urea,** parabanic acid $\begin{matrix} O=CNHC=O \\ | \quad\quad | \\ NH—C=O \end{matrix} \rightleftharpoons \begin{matrix} HOCN=COH \\ \| \quad\quad | \\ N—C=O \end{matrix}$
is prepared from (1) urea and oxalyl chloride, (2) urea, oxalic acid and $POCl_3$, or (3) by oxidation of uric acid with nitric acid. It forms mono and dibasic salts undoubtedly related to the $-OH$ form. Water converts the salts into those of *oxaluric* acid,

$NH_2CONHCOCO_2H$, a *ureido acid*. Methylparabanic acid and di-Me-parabanic acid are obtained by oxidation of methyl uric acid and caffeine respectively. The latter can be made by methylating the di-silver salt of parabanic acid with methyl iodide. As usual, the fact that the alkyl attaches itself to N does not prove that the metal had that attachment.

**Barbituric acid,** malonyl urea,  can be made from urea, malonic acid and $POCl_3$. It gives nitro, nitroso (isonitroso), bromo and metallo derivatives. By means of the latter, two alkyl groups can be introduced. Hydrolysis to dialkyl malonic acids proves their attachment to the methylene carbon. Barbituric acid contains several possibilities of triad tautomerism. Its formula will be seen to resemble the keto form of phloroglucinol. It probably exists in equilibrium with a benzenoid form, 2,4,6-$(OH)_3$-pyrimidine.



Phloroglucinol



Barbituric acid

The ease of reaction with nitric acid, nitrous acid, bromine and active metals combine to favor the benzenoid ("phenolic")

structure. The pyrimidine ring, a benzene ring with two meta CH groups replaced by N, occurs as such or in tautomeric form in the purines, uric acid and its derivatives.

**Diethylbarbituric acid,** Veronal, Barbital, $Et_2C\begin{matrix}CO—NH\\ |\quad\quad |\\ CONHCO\end{matrix}$, is an important soporific made by condensing urea with diethylmalonic ester in presence of NaOEt. It is the prototype of over five hundred 5,5-disubstituted barbituric acids which have soporific power in varying degree and with varying objectionable or dangerous reactions. The sodium salts of the disubstituted barbituric acids are soluble in water and act more rapidly as soporifics than do the free acids. Among the widely used barbituric acid derivatives are the following, the substituents being 5,5- in each case.

| | |
|---|---|
| Luminal, Phenobarbital (Gardenal) | Ethyl, Phenyl |
| Amytal | Ethyl, isoamyl |
| Neonal | Ethyl, *n*-butyl |
| Ortal | Ethyl, *n*-hexyl |
| Rutonal | Methyl, Phenyl |
| Dial | Diallyl |
| Allonal | Isopropyl, Allyl |
| Propanal | Di-*n*-propyl |
| Ipral | Ethyl, Isopropyl |
| Noctal | Isopropyl, β-Br-Allyl |
| Pernocton | *sec*-Butyl, β-Br-Allyl |
| Sandoptal | Isobutyl, Allyl |
| Phanodorn | Ethyl, Δ′-cyclohexenyl |
| Nembutal (Pentobarbital) | Ethyl, 2-sec-Amyl |

Because of pathological complications from their continued use, the sale of the barbituric acids is usually controlled by legal safeguards. The corresponding thio and N-alkyl compounds are replacing some of the simpler substances.

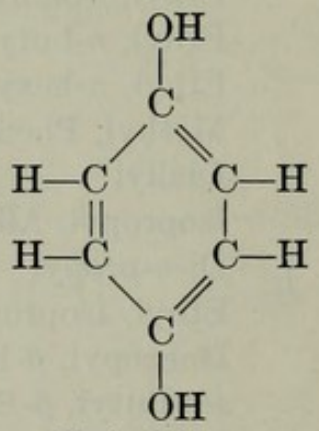
**Violuric acid,** 5-isonitrosobarbituric acid, $\begin{matrix}NHCOC=NOH\\ |\quad\quad |\\ CONHCO\end{matrix}$, is obtained by action of nitrous acid on barbituric acid or of hydroxylamine with alloxan. Reduction of it or of the 5-nitro

compound gives 5-aminobarbituric acid, *uramil*, from which uric acid has been synthesized.

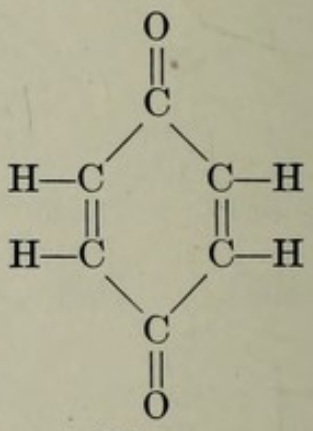
Isovioluric acid, alloxan-6-oxime is known (Bogert 1932).

**Dialuric acid,** tartronylurea, $\begin{matrix}\text{NHCOCHOH}\\ \quad|\quad\quad|\\ \text{CONHCO}\end{matrix}$, is a colorless crystalline compound which readily undergoes oxidation even in air. As 2,4,5,6-$(OH)_4$-pyrimidine, this behavior would be expected. Oxidation gives alloxantin and then alloxan. It is a strong dibasic acid.

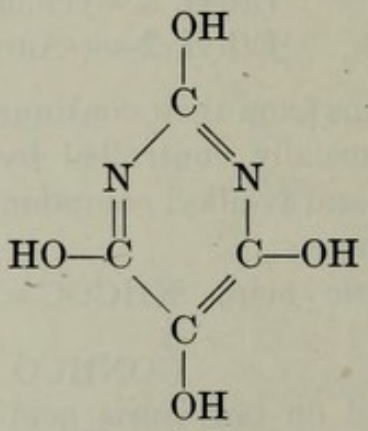
**Alloxan,** mesoxalylurea, $\begin{matrix}\text{NHCOCO}\\ \quad|\quad\quad|\\ \text{CONHCO}\end{matrix}$, is formed from uric acid by oxidation. It is strongly acid. With ferrous sulfate it gives an indigo-blue color. The completely tautomerized form of alloxan is not benzenoid but quinoid. It bears the same relation to tartronyl urea that hydroquinone does to quinone.



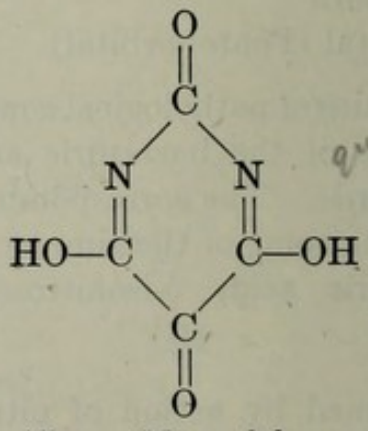
Hydroquinone



Quinone

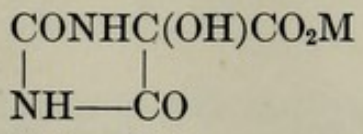


Tartronylurea



Alloxan, Mesoxalylurea

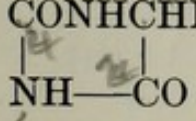
Alloxan combines with $NaHSO_3$. It crystallizes with 4 $H_2O$, one molecule of which is not removed at 100°. This is presumably combined in the hydrated form of the middle carbonyl group. Reduction converts alloxan to alloxantin and then to tartronyl urea. Alloxan is a good oxidizer, liberating iodine from iodides and converting indigo white to blue. With bases it undergoes the benzilic acid rearrangement to give an alloxanate,



These reactions resemble those of quinones.

**Alloxantin,** $C_8H_6O_8N_4$, bears a relation to tartronylurea and mesoxalylurea similar to that which quinhydrone bears to hydroquinone and quinone. It can be formed by mixing the two or by mild oxidation of the one or reduction of the other. It was originally obtained by the oxidation of uric acid with nitric acid. Tetramethylalloxantin, *amalic acid,* is obtained from caffeine and chlorine water.

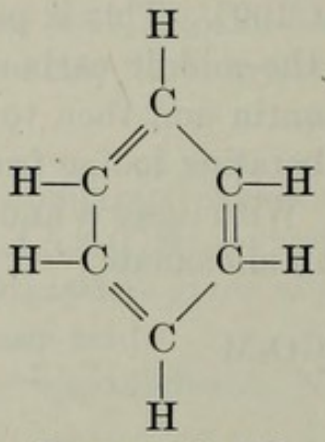
Alloxantin, heated with ammonia, gives *murexide,* an ammonium salt of *purpuric acid,* soluble in water to a purple red solution, which turns blue with bases. An alkaline solution of alloxantin gives a blue color with traces of iron salts (Deniges 1925). Citrates and tartrates do not interfere.

*Allantoin,* 4-carbamidohydantoin,  m. 231° dec., is found in various animal products. It is also formed from uric acid by $KMnO_4$.

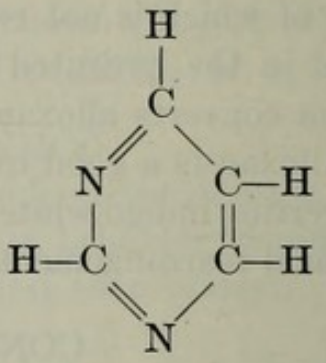
### *Purines and Their Derivatives*

Purine is the parent substance for a series of cyclic diureides of which uric acid is the best known. The relation of purine to

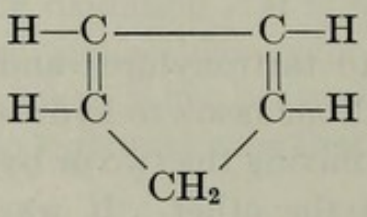
other important compounds is shown in the following formulas:



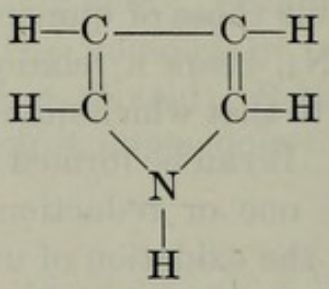
Benzene—b. 80°



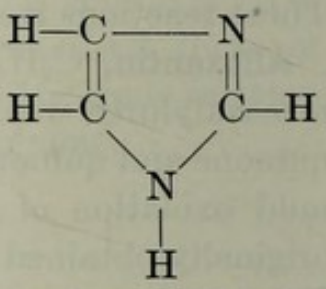
Pyrimidine—m. 22°, b. 124°



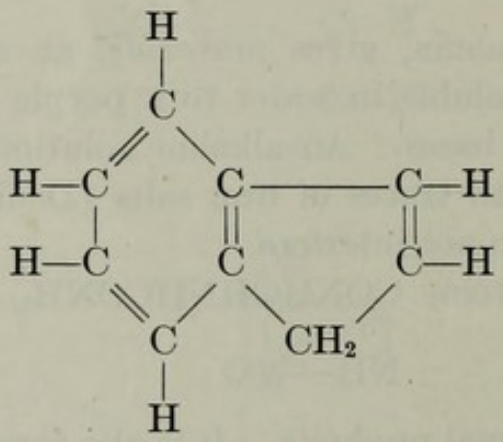
Cyclopentadiene—b. 41°



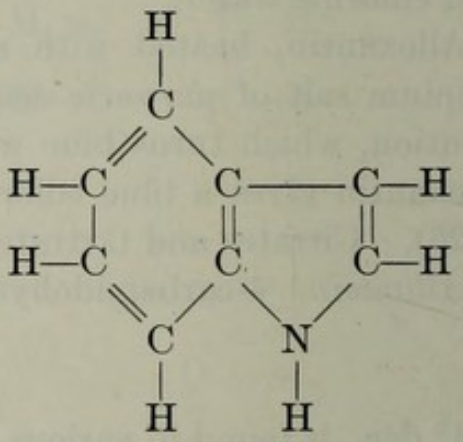
Pyrrole—b. 131°



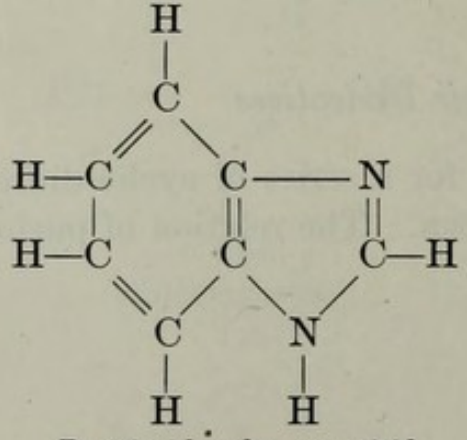
Imidazole—m. 89°, b. 255°



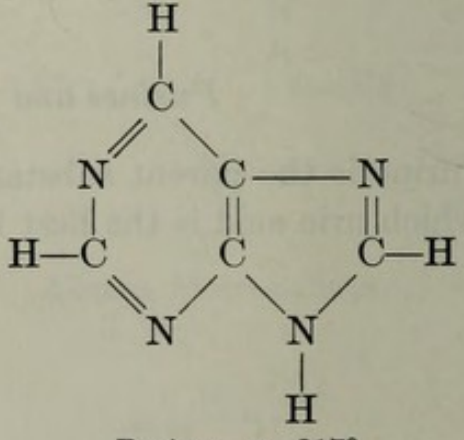
Indene—b. 180°



Indole—m. 52°, b. 254°



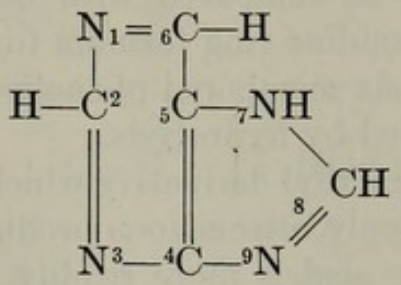
Benzimidazole—m. 170°



Purine—m. 217°

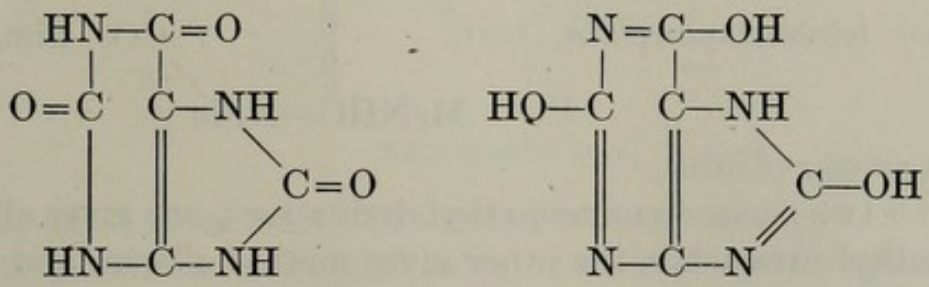
All of the rings involved have conjugated linkages and resulting peculiarities in properties.

Another formulation of purine is commonly used:



This emphasizes the relation to two molecules of urea but conceals the aromatic analogy. Purine is tautomeric with a substance having H in position 9 instead of 7.

**Uric acid** is usually written as the tri-keto form of 2,6,8-trihydroxypurine but is actually a tautomeric substance corresponding to the formulas:



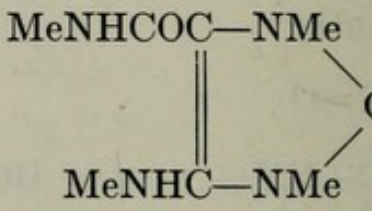
Uric acid occurs as ammonium urate in the excreta of carnivorous animals, in large amount in those of snakes and birds and in traces in those of mammals. It is usually prepared from guano or from snake excrement. It is practically insoluble in water and organic solvents. It is a weak dibasic acid. The common salts are the acid ones. Even alkali salts are only slightly soluble. The acid lithium salt is most soluble (1 part in about 400 of water). This fact was responsible for the popularity of "lithia water" as a supposed solvent for uric acid in various diseases.

Uric acid gives a blue color with tungstic acid and a base (Frabot 1904).

The determination of the structure of uric acid formed a most important chapter in early structural chemistry (1863–1883). Looking backward, the essential facts appear as follows:

(1) Careful oxidation gives alloxan and urea. The ready oxidation of uric acid, in contrast to the fact that the parent substance (purine) is difficult to oxidize, is reminiscent of the ease of oxidation of phenols as compared with benzene. It is added evidence for the pyrimidine ring formula for uric acid. Careful oxidation breaks the six membered phenolic ring while the other urea residue is removed by hydrolysis.

(2) It gives a tetramethyl derivative which on hydrolysis gives methyl amine as the only nitrogenous product. It is significant that tetramethyl uric acid is more readily hydrolyzed and less readily oxidized than uric acid itself. The tetra N—Me compound necessarily has the O=C—NMe grouping which should add water more readily than the HO—C=N grouping which probably predominates in the unmethylated acid. $Me_4$-uric acid, on careful treatment with dilute bases, loses the No. 2 carbon to give *tetramethylureidin*,




Similarly caffein gives *caffeidin*.

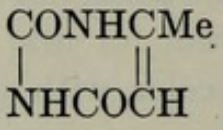
(3) Of two isomeric monomethyl derivatives, one gives alloxan and methyl urea while the other gives methyl alloxan and urea.

The first two facts indicate the presence of two urea residues and a three carbon chain while the last shows that the molecule is not symmetrical.

The *synthesis* of uric acid has been achieved in many ways. Two of these will be given because of their instructive steps.

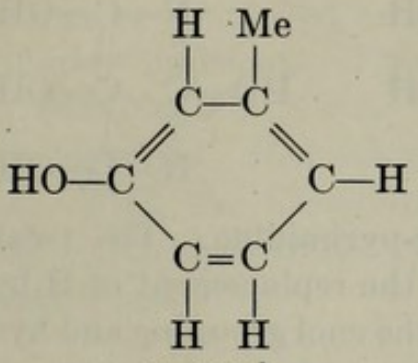
*A. Synthesis of Behrend and Roosen.*

(1) Urea heated with acetoacetic ester gives *methyl uracil* which, from its method of formation is naturally represented as

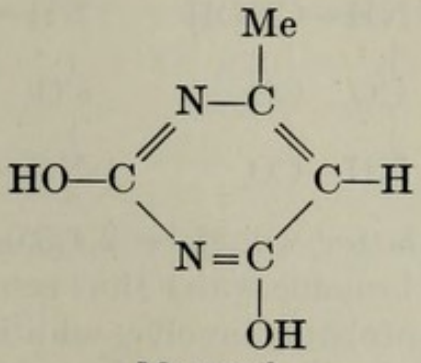



(2) Treatment with nitric acid introduces a nitro group and converts the methyl to carboxyl. Both these changes suggest the properties of an aromatic substance like meta-cresol. On this

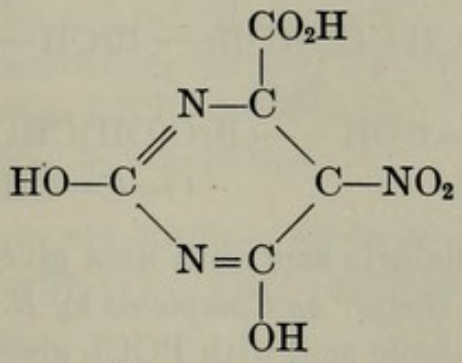
basis methyl uracil can be regarded as 2,4-dihydroxy-6-methyl-pyrimidine




*m*-cresol



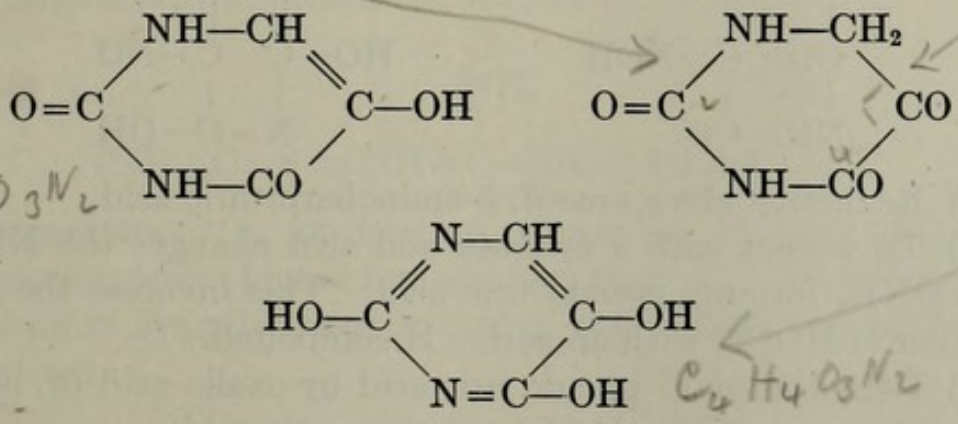

Me-uracil




Nitrouracilic acid

(3) Heat eliminates $CO_2$ leaving nitrouracil.

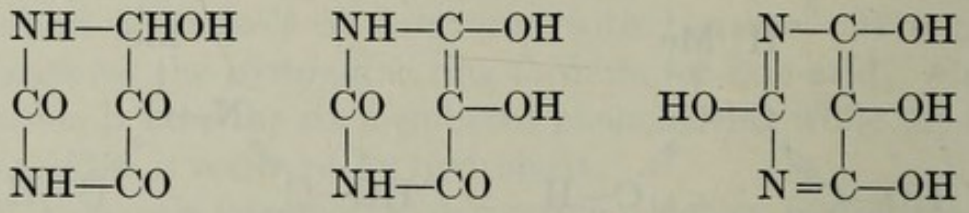
(4) Reduction and hydrolysis give the corresponding amino and hydroxyl compounds. The latter may be regarded as hydroxy uracil, isobarbituric acid or 2,4,5-trihydroxypyrimidine.




The ready hydrolysis of the $NH_2$ to OH is reminiscent of the behavior of the groupings:

$$C{=}C{-}NH_2 \rightleftharpoons CH{-}C{=}NH \xrightarrow{H_2O} CH{-}C(OH)NH_2 \rightarrow CH{-}C{=}O \rightleftharpoons C{=}C{-}OH$$

(5) Treatment of hydroxy-uracil with bromine water gives *isodialuric acid* which corresponds to the following formulas



The latter would be 2,4,5,6-$(OH)_4$-pyrimidine. The treatment with bromine water thus results in the replacement of H by OH. This probably involves addition to the enol grouping and hydrolysis of the resulting alpha bromo compound.

$$CH=C(OH) \rightarrow BrCH—C(OH)Br \rightarrow BrCH—C=O \rightleftharpoons$$

$$BrC=COH \xrightarrow{H_2O} BrC(OH)CHOH \rightarrow$$

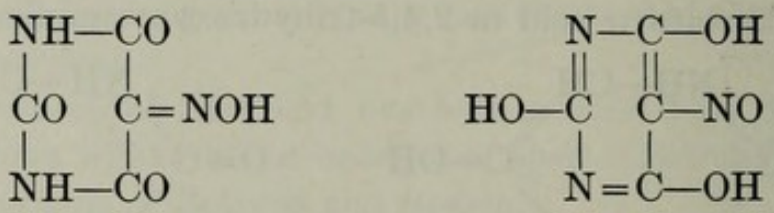
$$O=C—CHOH \rightleftharpoons HOC=COH$$

(6) Heating isodialuric acid with urea gives uric acid.

*B. Synthesis of Baeyer as Completed by E. Fischer.*

(1) Urea and malonic acid with $POCl_3$ give barbituric acid.

(2) Treatment with nitrous acid gives *violuric acid*, isonitroso-barbituric acid, the 5-oxime of mesoxalylurea, which may also be regarded as a nitroso derivative of the phenolic pyrimidine form of barbituric acid.



(3) Reduction gives *uramil*, 5-aminobarbituric acid.

(4) Treatment with a cyanate and acid changes the $NH_2$ to $NHCONH_2$ forming pseudo uric acid. This involves the usual reaction of HOCN with an active H compound.

(5) Dehydration of pseudo uric acid by oxalic acid or, better, by heating with hydrochloric acid gives uric acid.

With $POCl_3$ uric acid reacts in the OH form giving 2,6-dichloro-8-hydroxypurine and 2,6,8-trichloropurine. The chlorine atoms are very reactive in contrast to aromatic chlorides. This is probably due to the grouping N=C−Cl which behaves like the

active grouping in acid chlorides, O=C−Cl, in contrast to the inactive grouping C=C−Cl in the inactive aromatic and vinyl chlorides. To a certain extent the replacement of the chlorine atoms can be controlled because of a difference in reactivity in the different positions. This range in activity may be indicated as No. 6 ≫ No. 2 > No. 8. Thus HI with trichloropurine gives 2,8-diiodopurine. Reduction of the latter with zinc dust gives purine. With the $Cl_3$-compound, bases and $NH_3$ replace the 6-Cl by −OH and $-NH_2$. NaOEt introduces ethoxy groups in positions 6 and 2.

Important substances related to uric acid are:

Xanthine, 2,6-$(OH)_2$-purine
Hypoxanthine, Sarcine, 6-OH-purine
Guanine, 2-$NH_2$-6-OH-purine
Adenine, 6-$NH_2$-purine

These four substances are obtained by hydrolysis of nucleic acids from cell nuclei (Pryde 77). They can be made from uric acid through $Cl_3$-purine.

Caffeine (theine), 1,3,7-$Me_3$-2,6-$(OH)_2$-purine
Theobromine, 3,7-$Me_2$-2,6$(OH)_2$-purine
Theophylline, 1,3-$Me_2$-2,6-$(OH)_2$-purine

These are found in plant products such as tea, coffee and cocoa.

8. **Thiourea,** thiocarbamide, m. 172°,

$$(NH_2)_2C{=}S \rightleftharpoons NH{=}\overset{\overset{NH_2}{|}}{C}{-}SH \rightleftharpoons HN{=}\overset{\overset{\oplus NH_3}{|}}{C}{-}S^{\ominus}$$

*Preparation.* (1) By heating ammonium thiocyanate. This process requires a higher temperature than the rearrangement of ammonium cyanate to urea. Also, the reaction is less readily completed.

$$\underset{75\%}{NH_4SCN} \overset{170°}{\rightleftharpoons} NH_3 + HN{=}C{=}S \rightleftharpoons \underbrace{HN{=}\overset{\overset{NH_2}{|}}{C}{-}SH \rightleftharpoons (NH_2)_2C{=}S}_{25\%}$$

(2) By treating cyanamide with ammonium sulfide.

$$NH_2—CN + H_2S \rightarrow NH_2—\overset{\overset{SH}{|}}{C}=NH \rightleftharpoons (NH_2)_2C=S$$

Thiourea is a much weaker base than urea. It forms stable complex ions with heavy metals. For this reason a solution of thiourea in mineral acid will dissolve even gold.

*Reactions.* (1) Mercuric oxide removes $H_2S$ to give cyanamide.

(2) Careful oxidation by $KMnO_4$ gives urea.

$$(NH_2)_2C=S + [O] \rightarrow (NH_2)_2C=O + S$$

(3) Oxidation with acid $KMnO_4$ solution or with halogens gives a disulfide, as usual with $-SH$ compounds.

$$2\,NH_2—\overset{\overset{NH}{\|}}{C}—SH + [O] \rightarrow NH_2—\overset{\overset{NH}{\|}}{C}—S—S—\overset{\overset{NH}{\|}}{C}—NH_2,$$ formamidine disulfide.

(4) Oxidation by hydrogen peroxide gives a sulfinic acid.

$$NH_2—\overset{\overset{NH}{\|}}{C}—SH + 2\,[O] \rightarrow NH_2—\overset{\overset{NH}{\|}}{C}—SO_2H$$

(5) Alkyl halides react readily to give S-alkyl compounds, as proved by their hydrolysis to mercaptans.

$$(NH_2)_2C=S + RI \rightarrow (NH_2)_2\overset{\overset{I}{|}}{C}—S—R \rightarrow HI + NH=\overset{\overset{NH_2}{|}}{C}—SR$$

(6) Aldehydes give no action in neutral solution but with a trace of acid form $RCH=NCSNH_2$ instantly.

The tendency for thiourea to react in the $-SH$ form is most pronounced (Werner 1923) but the solid apparently exists in the symmetrical form (Hendricks 1928). With diazomethane, thiourea gives $MeSC(NH_2)NH$ whereas urea is unchanged (Rep. 1919, 87).

**Substituted thioureas** are obtained as follows:

(1) By heating the thiocyanates of primary or secondary amines.

(2) By adding $H_2S$ to a disubstituted cyanamide.

(3) By adding $NH_3$ or primary or secondary amines to mustard oils (isothiocyanates), RNCS.

$$R{-}N{=}C{=}S + NH_3 \rightarrow RN{=}\overset{\overset{NH_2}{|}}{C}{-}SH \rightleftharpoons$$

$$RNH{-}\overset{\overset{NH_2}{|}}{C}{=}S \rightleftharpoons RNH{-}\overset{\overset{NH}{\|}}{C}{-}SH$$

(4) By heating primary amines with carbon disulfide.

$$RNH_2 + CS_2 \rightarrow RNH{-}\overset{\overset{S}{\|}}{C}{-}S{-}NH_3R \rightleftharpoons$$

$$RNH{-}\overset{\overset{S}{\|}}{C}{-}SH + RNH_2$$

$$\downarrow\uparrow$$

$$(RNH)_2C(SH)_2 \rightarrow H_2S + (RNH)_2C{=}S$$

(5) By heating thiophosgene with amines.

$$CSCl_2 + 2\,RNH_2 \rightarrow (RNH)_2C{=}S$$
$$+ 2\,RR'NH \rightarrow (RR'N)_2C{=}S$$

### *C.* Amidines of Carbonic Acid and Related Compounds

**Guanidine,** carbamidine, iminourea, $(NH_2)_2C{=}NH$.

*Preparation.* (1) Heating ammonium thiocyanate at 180°, presumably with the formation of thiourea and cyanamide as intermediates.

(2) Heating cyanamide with $NH_4Cl$ to give guanidine hydrochloride.

(3) Ammonolysis of orthocarbonates.

$$C(OEt)_4 + 3\,NH_3 \rightarrow (NH_2)_2C{=}NH + 4\,EtOH$$

(4) Ammonolysis of chloropicrin.

$$Cl_3CNO_2 + 7\,NH_3 \rightarrow (NH_2)_2C{=}NH + 3\,NH_4Cl + N_2 + 2\,H_2O$$

It might be thought that carbon tetrachloride would also give guanidine with $NH_3$ but it gives formamidine instead.

(5) Ammonolysis of cyanogen chloride.

$$Cl{-}C{\equiv}N \xrightarrow{NH_3} NH_2CN \xrightarrow{NH_3} (NH_2)_2C{=}NH$$

Guanidine is a white crystalline hygroscopic substance. It is a *strong* monoacid base, even forming carbonates. It unites with hydrogen ions to form the stable "strong" ion $[C(NH_2)_3]^+$.

Partial hydrolysis gives urea. It can be nitrated and finally converted to hydrazine by the following steps.

$$NH{=}C(NH_2)_2 \rightarrow NH{=}\underset{\displaystyle NH_2}{\overset{|}{C}}{-}NH.NO_2 \rightarrow$$

$$NH{=}\underset{\displaystyle NH_2}{\overset{|}{C}}{-}NH{-}NH_2 \rightarrow 2\,NH_3 + CO_2 + NH_2NH_2$$

With nitrous acid, guanidine gives an 80–90% yield of cyanamide (Bancroft 1932).

$$\begin{matrix} & NH_2 \\ & / \\ C{=}NH & \\ & \backslash \\ & NH_2 \end{matrix} \rightarrow \begin{matrix} & NH_2 \\ & / \\ C{=}NH & \\ & \backslash \\ & OH \end{matrix} \rightarrow H_2O + HN{=}C{=}NH \rightleftharpoons H_2NC{\equiv}N$$

Cyanamide with amines gives substituted guanidines. Thus glycine and its N–Me derivative, sarcosine, give

$H_2NC(NH)NHCH_2CO_2H$ and $H_2NC(NH)NMe{-}CH_2CO_2H$

Glycocyamine (Guanidine acetic acid) — Creatine

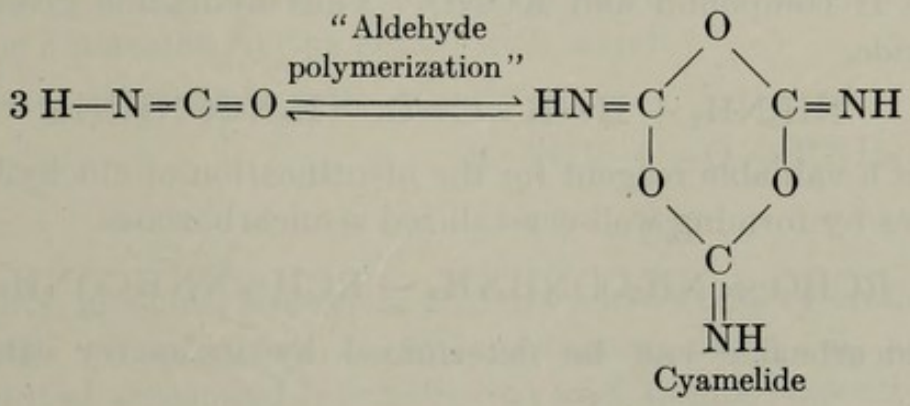
Creatine is found in muscle and is obtained from beef extract. These substances contain OH and $NH_2$ in the 1,5-position and are easily dehydrated by heating with acids to give imino-hydantoins. The product from creatine is *creatinine*, $HN{=}\underset{\displaystyle MeN}{\overset{|}{C}}NH\underset{\displaystyle CH_2}{\overset{|}{C}}O$. It is a strong base and forms well-defined salts with acids. It also reacts slowly with bases to give salts of creatine by opening of the amide linkage.

### *D.* Cyanic Acid and Related Compounds

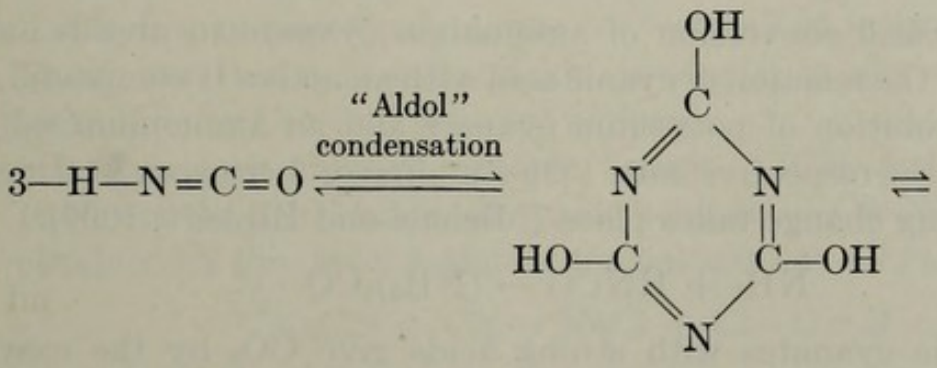
1. Cyanic acid, $H-O-C\equiv N$, and isocyanic acid $H-N=C=O$, have no independent existence. The dry distillation of urea gives cyanuric acid, $H_3C_3O_3N_3$, (Scheele). When this is heated and the vapors are condensed below 0° a volatile liquid, HCON, is obtained which is unstable above 0°. Its reactions show it to be tautomeric.

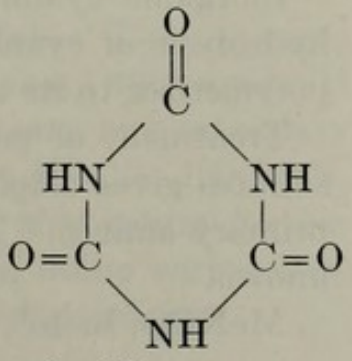
$$H-O-C\equiv N \quad \rightleftharpoons \quad O=C=N-H$$

Cyanic acid thus offers an example of triad prototropy (Ingold). Above 0°, it polymerizes to cyanuric acid and an isomeric substance, cyamelide. Cyamelide can be converted to salts of cyanuric acid by alkalies. The relations between these substances are as follows:




Cyamelide




Cyanuric acid

The fact that diazomethane gives the tri-N-methyl compound from cyanuric acid has been given as evidence for the NH formula. This may merely be an example of the easier methylation of NH as compared with OH. The cyanurates are related to the OH formula. O—Hg and N—Hg compounds are known. O-Alkyl compounds are obtained from alkyl iodides and silver cyanurates at low temperatures while the N-alkyl compounds are formed by the polymerization of RNCO or by heating the O-alkyl compounds. The O- and N-compounds are identified by their hydrolysis to ROH and $RNH_2$.

Potassium cyanate is made by oxidizing KCN with PbO or $PbO_2$.

Cyanic acid is useful in replacing an active H by the $-CO-NH_2$ group. This is done by acidifying a mixture of the active H compound and KCNO. Thus hydrazine gives *semicarbazide.*

$$NH_2NH_2 + H-N=C=O \rightarrow H_2NCONHNH_2$$

This is a valuable reagent for the identification of aldehydes and ketones by forming well-crystallized semicarbazones.

$$RCHO + NH_2CONHNH_2 \rightarrow RCH=NNHCONH_2$$

Semicarbazide can be determined by iodimetry (Bartlett, 1932).

The classical conversion of ammonium cyanate to urea is an example of the reaction of cyanic acid with an active H compound. The cold solution of potassium cyanate and an ammonium salt consists of the respective ions. On standing or, better, on heating the following change takes place (Michael and Hibbert, 1909).

$$NH_3 + HNCO \rightarrow (NH_2)_2CO$$

Inorganic cyanates with strong acids give $CO_2$ by the easy hydrolysis of cyanic acid. Weak acids give cyanic acid which polymerizes to its trimer, cyanuric acid.

Treatment of potassium cyanate with alkyl halides or alkyl sulfates gives *alkyl isocyanates* as proved by their hydrolysis to primary amines. True organic cyanates, $R-O-C\equiv N$, are not known.

MeNCO, b. 45°, EtNCO, b. 60°.

Isocyanates are also made by passing phosgene over heated primary amine hydrochlorides and then distilling the resulting substituted carbamyl chlorides or treating them with the calculated amount of alkali.

$$RNH_2.HCl + COCl_2 \rightarrow RNHCOCl + 2\,HCl$$
$$RNHCOCl \rightarrow HCl + R-N=C=O$$

In this way phenyl isocyanate and alpha naphthyl isocyanate are made from aniline and $\alpha$-naphthylamine respectively. They are valuable reagents for the identification of alcohols and primary and secondary amines because they form well-crystallized urethanes and substituted ureas.

Isocyanates react with active H compounds and with Grignard reagents, the addition taking place on the carbonyl group. A keto shift usually follows as the second step of the reaction. This may be illustrated by the action with water.

$$R{-}N=C=O + H_2O \rightarrow R{-}N=C(OH)_2 \rightarrow$$
$$R{-}NH{-}\underset{\displaystyle OH}{\underset{|}{C}}=O \rightarrow RNH_2 + CO_2$$

Similarly, alcohols, ammonia, primary and secondary amines and Grignard reagents give N-alkyl urethanes, mono- di- and trisubstituted ureas, and N-substituted acid amides respectively.

Alkyl isocyanates polymerize to "esters" of isocyanuric acid. These are really N-substitution products as shown by their hydrolysis to $CO_2$ and primary amines.

2. **Cyanogen chloride,** chlorocyanogen, ClCN, and BrCN and ICN, are the acid halides of cyanic acid, $HO-C\equiv N$. They are obtained by the direct action of the halogens on a cyanide.

$$NaCN + Cl_2 \rightarrow NaCl + Cl-C\equiv N$$

ClCN, b. 15°, BrCN and ICN, volatile crystals. The cyanogen halides give the ordinary reactions of acid halides with active H compounds like $H_2O$, alcohols, $NH_3$ and primary and secondary amines. The products first formed, namely, HOCN, $ROC\equiv N$, $NH_2-C\equiv N$, $RNH-CN$, etc. are capable of reacting further with the active H compounds to give $NH_3$, imino carbonates, $(RO)_2C=NH.HCl$, guanidine and substituted guanidines.

Cyanogen bromide gives an unusual reaction with tertiary amines (v. Braun). It forms an addition compound which decomposes with the loss of one of the organic groups on heating.

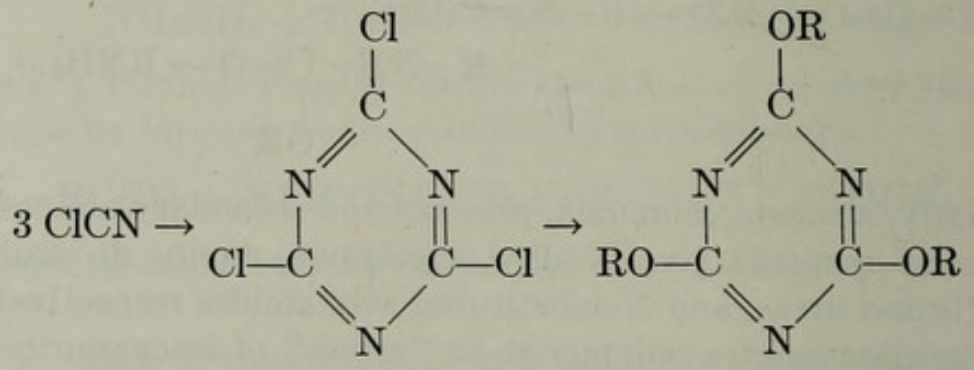
$$R_3N \rightarrow R_3NCN(Br) \rightarrow RBr + R_2N-CN$$

The disubstituted cyanamide can readily be converted to a secondary amine.

$$R_2NCN \xrightarrow{H_2O} R_2N-CO_2H \rightarrow CO_2 + R_2NH$$

With a cyclic amine the ring is opened. Thus N-methyl piperidine gives first $Br(CH_2)_5N(CN)Me$ and then $Br(CH_2)_5NHMe$.

Cyanogen chloride polymerizes on standing to give the acid chloride of cyanuric acid, *cyanuric chloride*, m. 145°, b. 190°. This reacts with alcohols to give true esters of cyanuric acid which hydrolyze to give cyanuric acid and alcohols.




Cyanuric chloride reacts with $NH_3$ to give the corresponding acid amide, *melamine*. If one $NH_2$ of melamine is hydrolyzed off, *ammeline* results, if two $NH_2$ groups are replaced by OH, the product is *ammelide*, while replacement of all three $NH_2$ groups in melamine by OH groups gives cyanuric acid.

3. **Cyanamide,** $NH_2-C\equiv N$.

*Preparation.* (1) As the calcium salt ("Lime Nitrogen," Kalkstickstoff), from calcium carbide and nitrogen at 1000°.

$$CaC_2 + N_2 \rightarrow CaN-CN + C$$

This product is used as a fertilizer on slightly acid soils because of its gradual conversion to cyanamide, urea, ammonium carbamate and ammonium carbonate.

(2) As the sodium salt in the manufacture of cyanides.

$$2\,NaNH_2 + C \xrightarrow{400^\circ} Na_2N{-}CN + 2\,H_2$$

The sodium salt may also be obtained by treating calcium cyanamide with $Na_2CO_3$ solution.

From the sodium salt, free cyanamide may be obtained by means of sulfuric acid.

$$Na_2NCN + 10\,H_2O + H_2SO_4 \rightarrow Na_2SO_4.10\,H_2O + NH_2CN$$

The cyanamide is extracted from the crystalline mass with ether or alcohol.

(3) From cyanogen chloride and the calculated amount of ammonia.

$$ClCN + 2\,NH_3 \rightarrow NH_4Cl + NH_2CN$$

(4) By desulfurizing thiourea by heating with HgO.

$$CS(NH_2)_2 + HgO \rightarrow HgS + H_2O + NH_2CN$$

Cyanamide is a colorless soluble crystalline substance, m. 40°. When melted it gives a dimer, "dicyandiamide," cyanoguanidine, $H_2N(HN)CNHCN$. At higher temperatures it gives a trimer, melamine, the triamide of cyanuric acid. Cyanamide is a weak base and a weak acid. It adds water, ammonia and hydrogen sulfide to give urea, guanidine and thiourea respectively. Its salts react with alkyl halides to give dialkyl cyanamides which are readily converted to secondary amines.

$$Na_2NCN + 2\,RX \rightarrow R_2NCN \rightarrow R_2NCO_2H \rightarrow R_2NH$$

Cyanamide exhibits tautomerism (Rep. 1915, 85).

$$\underset{\text{Basic}}{N{\equiv}C{-}NH_2} \rightleftharpoons \underset{\text{Acidic}}{HN{=}C{=}NH}$$

Calcium cyanamide, Ahr. 1931, 213 pp.

4. **Thiocyanic acid,** rhodanic acid, (Rhodanwasserstoffsäure), $H{-}S{-}C{\equiv}N$ and isothiocyanic acid, $H{-}N{=}C{=}S$, are tautomeric. Thiocyanic acid is a crystalline solid, stable below 0° and in dilute solution, in which it shows the properties of a strong acid. At ordinary temperature it polymerizes to a yellow insoluble compound.

Potassium thiocyanate is made by melting KCN with sulfur. Ammonium thiocyanate is obtained as a by-product from the purification of illuminating gas. It is formed from the $CS_2$ and $NH_3$ in the gas.

$$CS_2 + 4\,NH_3 \rightarrow NH_4-S-C\equiv N + (NH_4)_2S$$

Organic thiocyanates are obtained from KSCN with alkyl halides or alkyl sulfates. Their structure is proved by their formation from cyanogen chloride and mercaptides. A more conclusive proof is their oxidation by nitric acid to alkyl sulfonic acids. Still another proof is that with sodium malonic ester they give cyanomalonic ester and alkyl disulfides (Kohler).

MeSCN, b. 133°; EtSCN, b. 142°.

At high temperatures the thiocyanates rearrange to give isothiocyanates (mustard oils). $R-S-C\equiv N \rightarrow R-N=C=S$.

**Mustard oils,** RNCS, are obtained from primary amines, carbon disulfide and lead nitrate or some similar salt which can give an insoluble sulfide.

$$RNH_2 + CS_2 \rightarrow [RNH-CS_2H] \xrightarrow{Pb(NO_3)_2} PbS + RN=C=S$$

*sym*-Disubstituted thioureas react with acids to give mustard oils.

$$RNH-CS-NHR + HCl \rightarrow RN=C=S + RNH_3Cl$$

The Raman spectra of mustard oils give no indications of double bonds. On the other hand, alkyl isocyanates show Raman lines for double bonds. Parachor measurements, however, indicate that mustard oils contain true double bonds (Sidgwick 127).

*Reactions of Mustard Oils.* The carbon-sulfur linkage is very reactive. Water under the influence of acids can give the following reactions:

$$R-N=CS \rightarrow RN=\underset{\displaystyle OH}{\overset{\displaystyle |}{C}}-SH \rightleftharpoons RNH-\underset{\displaystyle OH}{\overset{\displaystyle |}{CS}} \rightleftharpoons RNH_2 + COS$$

$$\Downarrow\Uparrow$$

$$RNH-\underset{\displaystyle O}{\overset{\displaystyle ||}{C}}-SH \rightleftharpoons H_2S + R-N=C=O \rightarrow$$

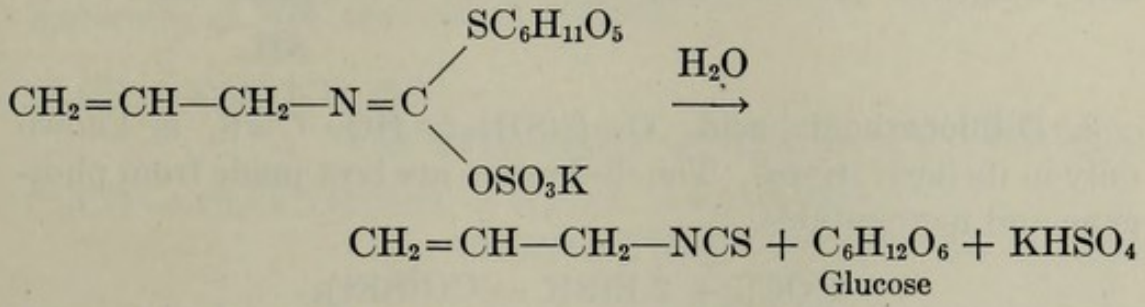
$$RNH_2 + CO_2$$

The products formed depend on the acid used and the conditions.

Anhydrous alcohols, $NH_3$ and primary and secondary amines give thiourethanes, and substituted thioureas.

MeNCS, m. 34°, b. 119°; EtNCS, b. 132°

Allyl mustard oil occurs as a glucoside, potassium myronate, in mustard seeds. This can be hydrolyzed by acids or by the enzyme myrosin found in mustard seeds.



$$CH_2=CH-CH_2-N=C(SC_6H_{11}O_5)(OSO_3K) \xrightarrow{H_2O} CH_2=CH-CH_2-NCS + C_6H_{12}O_6 + KHSO_4$$

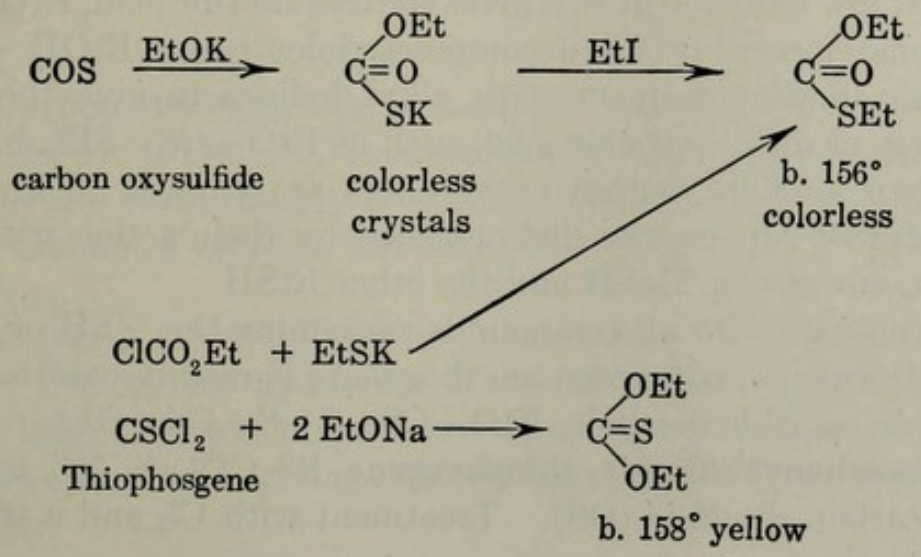
Glucose

Many other mustard oils occur in plant products.

*Thiocyanogen*, $(SCN)_2$, is obtainable from lead or mercury thiocyanate and bromine. It resembles bromine in its action with aromatic compounds and unsaturated compounds (Söderbäck, 1925, Bruson 1928).

### *E.* Thiocarbonic Acids

1. **Monothiocarbonic acid,** $HS-C(OH)=O \rightleftharpoons S=C(OH)_2$, is not known in the free state. Derivatives may be prepared as follows:



2. **Carbon oxysulfide,** COS, is made (1) from CO and S at red heat, (2) by potassium thiocyanate and 1:1 sulfuric acid

$$H{-}N{=}C{=}S + H_2O \rightarrow \underset{\underset{H}{|}}{H{-}N{-}}\underset{\underset{OH}{|}}{C{=}S} \rightarrow O{=}C{=}S + NH_4HSO_4$$

It is a colorless combustible gas with a faint odor, b. −47°. It reacts like $CS_2$ with alcoholates, mercaptides, amines and Grignard reagents. It is readily hydrolyzed to $CO_2$ and $H_2S$.

3. **Dithiocarbonic acid,** $O{=}C(SH)_2 \rightleftharpoons HO{-}\overset{\overset{SH}{|}}{C}{=}S$, is known only in its derivatives. The di-S esters are best made from phosgene and mercaptides.

$$COCl_2 + 2\ EtSK \rightarrow \underset{\text{b. 196°}}{CO(SEt)_2}$$

The S, O derivatives are readily obtained from $CS_2$ and alcoholic potash.

$$CS_2 + C_2H_5OH + KOH \rightarrow C{=}S \quad \begin{matrix} OEt \\ SK \end{matrix}$$

Potassium ethyl xanthogenate

This is a stable crystalline product. With copper compounds, *yellow* precipitates are obtained (hence the name). With mineral acids at low temperatures, it gives the free xanthic acid, $EtOCS_2H$. At room temperature this decomposes violently into $EtOH + CS_2$. The xanthogenates react with alkyl halides to give the S, O di-esters of dithiocarbonic acid, such as EtO−CS−SEt, b. 200°. The two possible methyl ethyl esters are known. They both boil at 184° but can be distinguished by their action with ammonia, one giving MeSH and the other EtSH.

In common with all compounds containing the −SH or −SM (metal) linkage, potassium xanthogenate is readily oxidized to a disulfide, xanthic disulfide, EtO−CS−S−S−CS−OEt.

**Thiocarbonyl chloride, thiophosgene,** $S{=}CCl_2$, b. 33°, is made from carbon disulfide (OS). Treatment with $Cl_2$ and a trace of

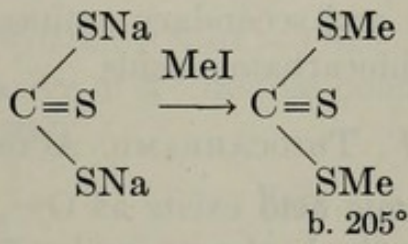
iodine gives $Cl_3CSCl$, perchloro methyl mercaptan. Reduction with Fe gives $CSCl_2$, an orange liquid of penetrating odor. Its reactions resemble those of phosgene except that it is much less reactive. Thus it is only slowly decomposed by boiling water. With $NH_3$ it gives $NH_4SCN$ instead of thiourea or $NH_2CSCl$. The process may depend on the greater acidic properties of the $-SH$ group as compared to the $-OH$ group formed by the initial addition of $NH_3$ to the CS and CO groups. Thus successive molecules of $NH_3$ may act as follows:

$$Cl_2CS \rightarrow Cl_2C(NH_2)SH \rightarrow Cl_2C(NH_2)SNH_4 \rightarrow 2\,NH_4Cl + N{\equiv}C{-}SNH_4$$

$$Cl_2CO \rightarrow Cl_2C(NH_2)OH \rightarrow NH_4Cl + ClCONH_2 \rightarrow ClC(OH)(NH_2)_2 \rightarrow NH_4Cl + CO(NH_2)_2$$

With primary amines the reaction is readily stopped at the mustard oil, RNCS. Thiophósgene is polymerized by light.

4. **Thiocarbonic acid, trithiocarbonic acid,** $S{=}C(SH)_2$, is an unstable red oil. Its soluble salts are readily obtained from alkali sulfides and $CS_2$. With heavy metal solutions highly colored precipitates are obtained. The alkali salts react readily with alkyl halides to give esters.




b. 205°

5. **Carbon disulfide,** $CS_2$, is made by heating carbon and sulfur in an electric furnace. When purified by distilling over mercuric chloride, its usual disagreeable odor is largely removed. It boils at 47° and has a very low kindling point (below 100°). It is very reactive.

*Reactions.* (1) With water, under special conditions it gives COS. Usually the hydrolysis is complete to $CO_2$ and $H_2S$.

(2) With chlorine in presence of iodine, a complex series of changes takes place, giving $Cl_3CSCl$ and finally $CCl_4$ and chlorides of sulfur.

(3) With sulfur monochloride, in the presence of iron as a catalyst it gives carbon tetrachloride.

$$CS_2 + 2\,S_2Cl_2 \rightarrow CCl_4 + 6\,S$$

The sulfur is converted to $S_2Cl_2$ and used again. This is the commercial method for making $CCl_4$.

(4) Reduction by zinc and acid gives trithiomethylene, trimer of thioformaldehyde.

(5) With alkalies and alcohols, it gives xanthogenates. This is the basis of the commercial viscose process for converting cellulose (a poly hydroxyl compound) into rayon. The cellulose is treated with sodium hydroxide and $CS_2$ to make viscose. This is then forced through minute openings into a dilute acid solution to regenerate the cellulose in fine silky fibers which can be spun into thread and yarn.

$$ROH + CS_2 + KOH \rightarrow ROCS_2K \xrightarrow{\text{acid}} ROCS_2H \rightarrow ROH + CS_2$$

(6) With ammonia it gives the ammonium salt of dithiocarbamic acid.

$$CS_2 \xrightarrow{NH_3} \left[\begin{array}{l} NH_2 \\ | \\ S{=}C{-}SH \end{array}\right] \rightarrow \begin{array}{l} NH_2 \\ | \\ S{=}C{-}SNH_4 \end{array}$$

(7) With primary and secondary amines it gives amine salts of N-substituted dithiocarbamic acids.

### *F.* Thiocarbamic Acids

**1. Monothiocarbamic acid** exists as O−, N−, and S− alkyl derivatives. The methods of preparation follow:

(*a*) O-Derivatives

$$\underset{\substack{\text{Unsym. diethyl}\\ \text{dithiocarbonate}}}{EtO{-}CS{-}SEt} + NH_3 \rightarrow \underset{\substack{\text{O-Ethyl thiocarbamate}\\ \text{m. 58°}}}{EtO{-}CS{-}NH_2} + C_2H_5SH$$

(*b*) S-Derivatives. The S-esters may be made from the O–esters by heating with a trace of alkyl halide (Wheeler).

$$NH_2{-}CS{-}OEt \xrightarrow{EtI} \left[\begin{array}{l} SEt \\ | \\ NH_2{-}C{-}OEt \\ | \\ I \end{array}\right] \rightarrow EtI + \begin{array}{l} SEt \\ | \\ NH_2{-}C{=}O \end{array}$$

They may also be obtained by the careful hydrolysis of a thiocyanate with dilute acid.

$$Et{-}S{-}C{\equiv}N + H_2O \rightarrow Et{-}S{-}\overset{\overset{NH_2}{|}}{C}{=}O$$

S-Ethyl thiocarbamate
m. 109°

The S-esters decompose at 150° to give mercaptans and cyanuric acid.

(*c*) N-Alkyl derivatives are made (1) from carbon oxysulfide and amines and (2) from thiophosgene and amines followed by treatment with alkyl halides or alcoholates.

$$COS + RNH_2 \rightarrow RNH{-}CO{-}SNH_3R \xrightarrow{RI} RNH{-}CO{-}SR'$$

$$CSCl_2 + R_2NH \rightarrow R_2N{-}CS{-}Cl \xrightarrow{NaOR'} R_2N{-}CS{-}OR'$$

The compounds containing the C=S grouping with no free H on the adjacent atoms are orange or red in color and oxidize spontaneously showing phosphorescence. Since the compound RNH−CS−OR′ does not show these phenomena its formula probably should be written $RN{=}\overset{\overset{SH}{|}}{C}{-}OR'$. This is another indication of the peculiarity of a "double bond" attached to sulfur (pp. 163, 240, 253, 362).

2. **Dithiocarbamic acid,** $NH_2{-}\overset{\overset{SH}{|}}{C}{=}S \rightleftharpoons NH{=}C(SH)_2$, is obtained as colorless needles by treating its ammonium salt with HCl. The salt is made by cold alcoholic ammonia and $CS_2$.

$$CS_2 \xrightarrow{NH_3} [NH_2{-}CS_2H] \xrightarrow{NH_3} NH_2{-}CS_2NH_4$$

Ammonium
dithiocarbamate

The ammonium salt decomposes on heating to give

$$H_2S + NH_4SCN.$$

Oxidizing agents such as $FeCl_3$ and the halogens form a disulfide.

$$2\,NH_2{-}\overset{\overset{S}{\|}}{C}{-}SH + [O] \rightarrow H_2O + \underset{\text{Thiuram disulfide}}{NH_2{-}\overset{\overset{S}{\|}}{C}{-}SS{-}\overset{\overset{S}{\|}}{C}{-}NH_2}$$

Alkyl halides give a series of reactions ending with the formation of dithiocarbonates.

$$NH_2{-}CS{-}SNH_4 \xrightarrow{RI} \underset{\text{Alkyl dithiocarbamate}}{NH_2{-}CS{-}SR} \xrightarrow{RI}$$

$$\underset{\substack{\text{Dialkyl dithio-}\\ \text{carbamate}\\ \text{hydroiodide}}}{NH{=}C(SR)_2.HI} \xrightarrow[H_2O]{\text{heat}} NH_4I + (RS)_2CO$$

Primary and secondary amines can be used in place of ammonia to give the corresponding substituted thiocarbamates. Dimethylamine gives the rubber accelerator, *TUADS*, tetramethyl thiuram disulfide.

$$Me_2NH + CS_2 \rightarrow S{=}C(NMe_2)SNH_2Et_2^{\cdot} \rightarrow$$

$$S{=}C(NMe_2)SH \xrightarrow{[O]} S{=}C(NMe_2)S{-}SC(NMe_2){=}S$$

Sodium diethyl dithiocarbamate, $Et_2NCS_2Na$, gives a characteristic golden brown color with very dilute ammoniacal cupric solutions (Callan 1930).

## XXV. CARBOHYDRATES, GLUCIDES (GLYCIDES), SACCHARIDES

The sugars, starches and celluloses form this important group. The original name, carbohydrate, was based on the fact that all of these substances then known had formulas which could be written as $C_m(H_2O)_n$. Even on this basis the name was unsatisfactory because many substances such as formaldehyde and acetic acid could be written as "hydrates" of carbon but were not carbo-

hydrates. It is now known that some sugars deviate from this formula. Thus rhamnose is $C_6H_{12}O_5$. Carbohydrates are also defined as hydroxyaldehydes or hydroxyketones or substances which give those on hydrolysis. This definition is not wholly satisfactory. While glycollic aldehyde, $HOCH_2CHO$, gives the *reactions characteristic of a simple sugar*, namely, (*a*) reduction of ammoniacal silver solution to give a mirror, (*b*) reduction of alkaline cupric solution (Fehling's solution) to give a precipitate of cuprous oxide, (*c*) formation of a yellow-brown color on heating with strong alkalies, (*d*) the development of a violet color when a solution with alpha naphthol is underlayed with concentrated sulfuric acid, Molisch Test (Foulger 1931), and (*e*) the formation of a crystalline osazone (di-phenylhydrazone) when treated with an excess of phenylhydrazine, other hydroxy aldehydes and ketones fail to give some or all of these characteristic reactions. Simple sugars contain either the equivalent of the $-CHOHCHO$ or $-COCH_2OH$ grouping usually in cyclic combination. Thus simple sugars could be defined as substances which contain an alpha hydroxy aldehyde or an alpha keto primary alcohol. Even this definition fails. Thus ribodesose obtained from thymus nucleic acid (Levene) contains the $-CH_2CHO$ grouping as does also digitoxose.

## Classification of Carbohydrates

1. Simple sugars usually contain the grouping $-CHOHCHO$ or $-COCH_2OH$ or their equivalent. They cannot be hydrolyzed to smaller molecules. They are known as *monosaccharides*, *monosaccharoses*, *monoses*, or *oses*. They are either aldoses or ketoses. It should be remembered that in these substances the aldehyde or ketone group usually does not exist free but in some union with a hydroxyl group of the same molecule if a 5- or 6-membered ring can be formed within the molecule (glucose) or of another molecule if that is the only way a ring can be formed (glycollic aldehyde).

Oses containing 5 to 10 carbon atoms are indicated as pentoses to decoses. The terms diose, triose and tetrose are ambiguous as they can mean (*a*) monosaccharoses containing 2, 3 or 4 carbon

atoms or (*b*) polysaccharoses which can be hydrolyzed to 2, 3 or 4 mols of monose. The first meaning would apply to glycolose, $C_2H_4O_2$, glycerose, $C_3H_6O_3$, and erythrose, $C_4H_8O_4$, while the second would apply to sucrose, $C_{12}H_{22}O_{11}$, raffinose, $C_{18}H_{32}O_{16}$, and stachyose, $C_{24}H_{42}O_{21}$. Glucose is an aldohexose, dihydroxyacetone is a ketotriose, raffinose a hexotriose (it gives 3 mols of hexose on hydrolysis) etc.

2. Substances which on hydrolysis give simple sugars. These are called *osides*.

*a*. *Osides* which give only *oses* on hydrolysis are *holosides*, more commonly called *polysaccharides*, *polysaccharoses*, or *polyoses*. Such are the higher sugars like sucrose and the starches and celluloses.

*b*. *Osides* which give *oses* and other types of compounds are *heterosides*, usually known as *glucosides*. Amygdalin on hydrolysis gives glucose, HCN and benzaldehyde.

Carbohydrate classification, Gortner, 487.

## *A*. Monoses

The simplest monose, the aldodiose, *glycollic aldehyde*, has already been described. Its reactions are characteristic of the simple sugars except that the smallness of its molecule causes its dimerization in the reaction of hydroxyl and carbonyl group. It contains no asymmetric carbon atom and, consequently, cannot exist in optically active form as do all natural monoses.

**Glyceric aldehyde,** glyceraldehyde, propandiolal,

$$HOCH_2CHOHCHO,$$

can be obtained in the racemic forms by the following steps (OS).

$$HOCH_2CHOHCH_2OH \rightarrow CH_2{=}CHCHO \rightarrow ClCH_2CH_2CH(OEt)_2 \rightarrow CH_2{=}CHCH(OEt)_2 \rightarrow HOCH_2CHOHCH(OEt)_2 \rightarrow HOCH_2CHOHCHO.$$

It is interesting that it is probably easier to carry out these steps than to oxidize one of the primary alcohol groups in glycerol although that oxidation has been carried out by hydrogen peroxide and $FeSO_4$ (Witzemann 1914). When the aldehyde is liberated from its acetal, an oily enolic compound is obtained as a by-product, $HOCH_2C(OH){=}CHOH$. Dimolecular glyceraldehyde

boiled with pyridine gives as much as 49% dihydroxyacetone, apparently through this enediol which is common to both substances (Rep. 1927, 64).

Glyceraldehyde exists as a crystalline dimer, m. 138°. In solution this gradually changes to the monomer.

It forms an osazone, m. 132°.

It acts like a true aldehyde in giving the Angeli-Rimini hydroxamic acid reaction. In this respect it differs from the higher aldoses which show no true aldehyde group in this reaction due to cyclic hemiacetal formation.

Its oxime when acetylated and treated with ammoniacal silver solution loses HCN. This is a *general method for going from one aldose to the next lower one* (Wohl 1893). The net result is as follows:

$$HOCH_2CHOHCH{=}NOH \rightarrow HCN + H_2O + HOCH_2CHO$$

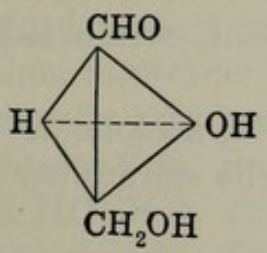
*d*- and *l*-Glyceraldehyde have been obtained as syrups. *dl*-β-Amino-lactic aldehyde dimethyl acetal,

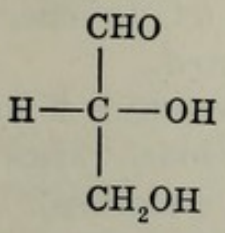
$$NH_2CH_2CHOHCH(OMe)_2,$$

was treated with *l*-menthyl isocyanate, $C_{10}H_{19}NCO$, to give substituted ureas, *l*-$C_{10}H_{19}NHCONHCH_2CHOHCH(OMe)_2(l)$ and the *l*-*d* isomer. The stereomers were separated and hydrolyzed and the $NH_2$ group was replaced by OH by means of nitrous acid. Hydrolysis by excess of dilute acid gave the optically active glyceraldehydes (Rep. 1915, 66).

Glyceraldehyde can be slowly fermented by yeast.

*d*-Glyceraldehyde is assigned the configuration (Rosanoff 1906).




All monoses with the same arrangement of the H, OH and $CH_2OH$ on the optically active carbon farthest from the aldehyde or ketone group (the active group) are classed as *d*- regardless of whether their rotations are actually dextro- or levo-. The ar-

rangement H—C—OH when the active group and the $CH_2OH$ are at the top and bottom of the formula and in the plane of the paper so that the H and OH are back of this plane is the *d*-form, and is indicated as + regardless of the actual sign of rotation.

**Dihydroxyacetone,** propandiolone, $HOCH_2COCH_2OH$, is best obtained from glycerol by means of the Sorbose-bacterium. It crystallizes as a dimer, m. 80°. On standing in water solution, this becomes monomeric. With excess phenylhydrazine it gives the osazone of glyceraldehyde, m. 132°. Oxime, m. 84°.

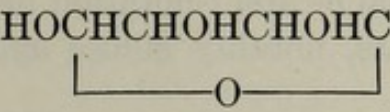
It can be made from glyceraldehyde through the common enediol.

When the semicarbazone of the monoacetate of dihydroxy acetone is boiled with glacial acetic acid, the disemicarbazone of pyruvic aldehyde is produced (Evans).

$$HOCH_2C{=}NNHCONH_2 \quad \rightarrow \quad CH_3C{=}NNHCONH_2$$
$$\quad\quad\quad

## Tetroses, $C_4H_8O_4$

**Aldotetroses.** In common with the higher aldoses these fail to give certain typical aldehyde reactions such as the hydroxamic acid test of Angeli. They are cyclic hemiacetals (Tollens 1883).



These, because of their similarity to the lactones formed by hydroxy acids, are called *lactols.*

There are four possible configurations of carbons 2 and 3 (counting the active group as 1 in the aldotetroses).

| *a* | *b* | *c* | *e* |
|---|---|---|---|
| + | − | + | − |
| + | − | − | + |

Four aldotetroses are known.

If the aldotetroses were true aldehydes these four would be the only possible isomers. Inspection of the cyclic formula will show, however, that the aldehyde carbon in the cyclic form is also asymmetric. Thus there can be two forms of the cyclic hemiacetal, HOCH−O− and −O−CHOH, in the usual projection formulas. These two forms of the cyclic hemiacetals have been isolated with the higher monoses (notably glucose) and are called the $\alpha$ and $\beta$ forms of the sugars. In solution they are interconvertible and finally form an equilibrium mixture. Since the $\alpha$ and $\beta$ forms differ sterically they differ in optical activity. Thus if either form or a mixture other than the equilibrium mixture is dissolved, the optical rotation of the solution gradually changes until the equilibrium mixture is reached. This change is *mutarotation* (multirotation, birotation).

A word may be said here as to the physical reality of the conception contained in Emil Fischer's distinction between the HCOH and HOCH or the + and − arrangement of hydroxyl groups in the sugars. The best proof of its reality is its agreement with a multitude of facts in the sugar field discovered long after Fischer's formulation of these principles. The significance of the *sides* on which hydroxyl groups are located becomes doubly important because the ring structure of the sugars keeps these

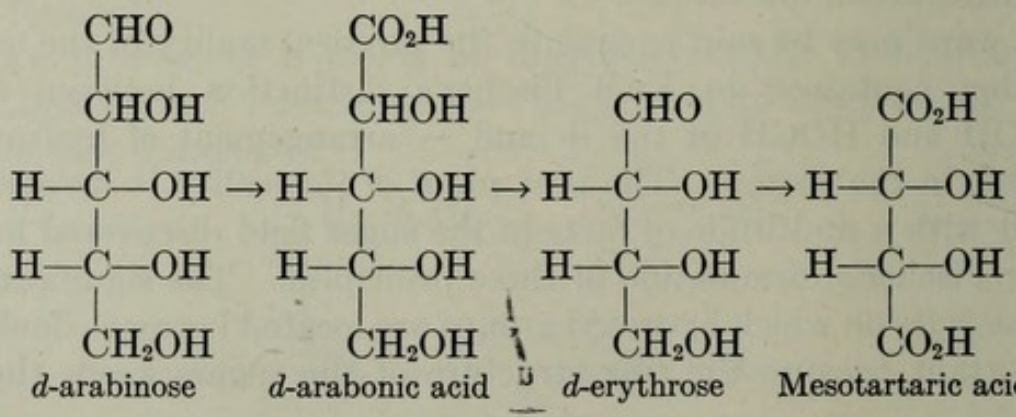
positions definite in relation to each other in a way which would not be possible in open chain compounds in which there is free rotation about each single bond. The ring has the same effect as a double linkage in restricting rotation.

Emil Fischer's original *d*- and *l*-notation had to be modified in the case of a few sugars, notably gulose and idose and related sugars (Rosanoff 1906).

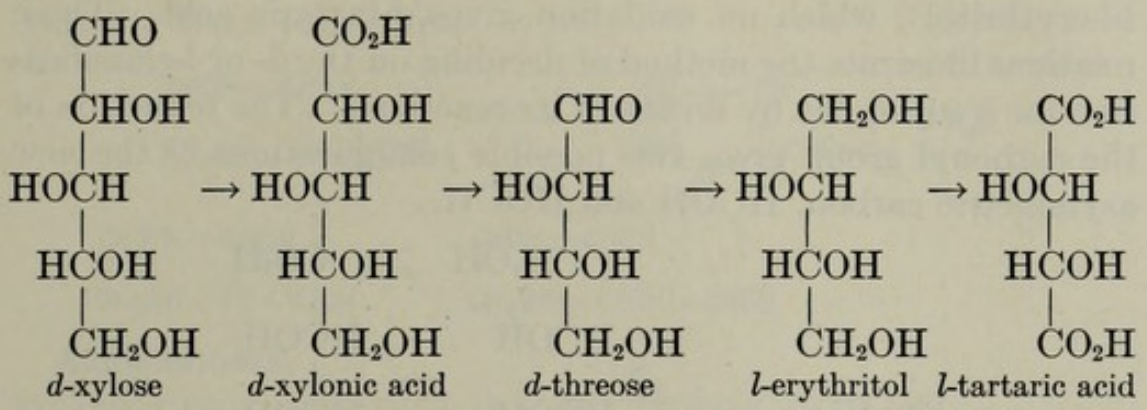
*d*-Erythrose is obtained by the degradation of *d*-arabonic acid by the method of Ruff (1898–1902). This consists in treating the calcium salt with hydrogen peroxide and ferric acetate. The net result is

$$-\mathrm{CHOH}-\mathrm{CO_2H} + [\mathrm{O}] \rightarrow \mathrm{H_2O} + \mathrm{CO_2} + -\mathrm{CHO}$$

This is an *important general method for going from one aldose to a lower one.* On reduction *d*-erythrose gives meso-erythritol whose structure also follows from its oxidation to mesotartaric acid. *l*-Erythrose is obtained similarly from *l*-arabinose and is similarly related to mesotartaric acid. Since, of the possible configurations of tartaric acid, ++, +−, −+, only the first is symmetrical, that must correspond to the internally compensated or meso compound. Thus the configurations *a* and *b* must correspond to the two erythroses. Since the ++ configuration corresponds to that of *d*-glyceraldehyde, that is assigned to *d*-erythrose and the other to its enantiomorph, *l*-erythrose. Following are the processes related to *d*-erythrose, with the formulas written as those of aldehydes instead of the true cyclic lactols and lactones. This procedure is often followed with the sugars but it must be carefully remembered that the cyclic forms are the actual ones unless the hydroxyl groups are protected by groups such as methyl or acetyl.



***d*-Threose** can be obtained by degrading the aldopentose, *d*-xylose. On reduction it gives *l*-erythritol which on oxidation with nitric acid gives *l*-tartaric acid. Since *l*-tartaric acid has the $-+$ configuration the configurations thus determined follow:




From the $+$ configuration of its lowest C it might have been expected that *l*-erythritol would have been classed as *d* on the same basis as the monoses. It is classified as *l*- because of its relation to *l*-tartaric acid. Configuration c $(+-)$ belongs to *l*-threose.

*d*-Erythrose and *d*-threose differ only in the configuration of the No. 2 carbon. One has the configuration $++$ and the other $-+$. Pairs of substances differing in this way are *epimers*. Thus meso-tartaric acid is epimeric to both *d*- and *l*-tartaric acid. This relation is important because it is possible to change one epimer to the other.

Bromine water converts the aldotetroses to *d*- and *l*-erythronic and *d*- and *l*-threonic acids.

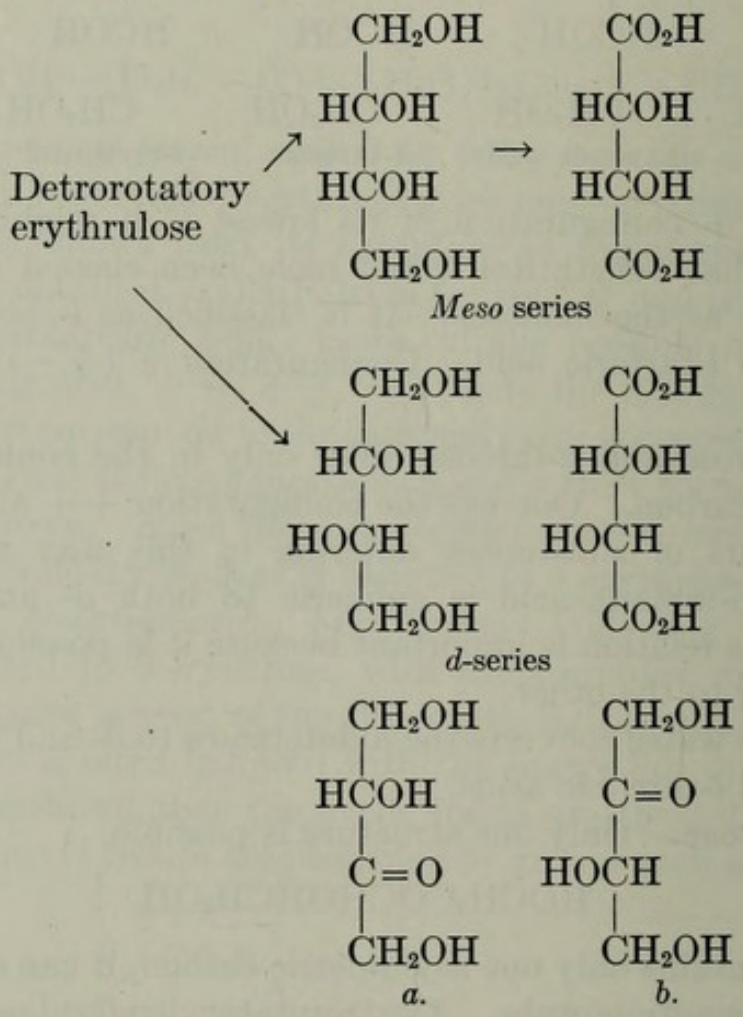
**Ketotetrose.** Only one structure is possible,

$$HOCH_2COCHOHCH_2OH.$$

Since it contains only one asymmetric carbon, it can exist only in one set of enantiomorphs. Dextrorotatory *erythrulose* is obtained by the action of the Sorbose-bacterium on *meso*-erythritol. This production of optically active material is characteristic of biochemical reactions involving asymmetric carbon atoms. Ordinary oxidation of a secondary carbinol grouping in meso-erythritol would be expected to attack both of these indiscriminately. The attack of one would give *d*- and of the other, *l*-erythrulose. The

mechanism by which the biochemical "reagents" accomplish one process exclusively is one of the major unsolved problems of chemistry and biology.

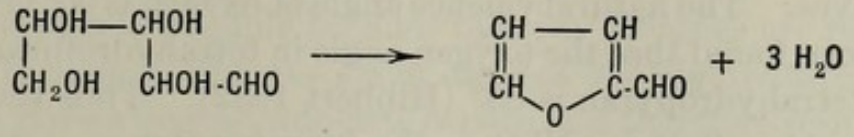
On reduction, the dextrorotatory erythrulose gives a mixture of two tetritols, meso-erythritol and levorotatory erythritol (*d*-erythritol), which on oxidation gives *d*-tartaric acid. These relations illustrate the method of deciding on the *d*- or *l*-classification for a substance by means of its reactions. The reduction of the carbonyl group gives two possible configurations of the new asymmetric carbon, HCOH and HOCH.

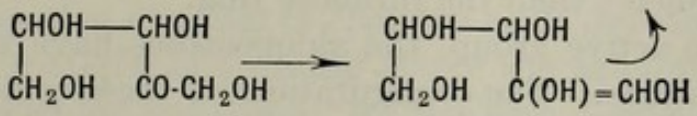



In order to give these results, the erythrulose must have the configuration *a*. Turning this 180° in the plane of the paper gives *b*, which is identical but has the active group at the top of the formula. Thus it is evident that the asymmetric carbon in the dextrorotatory erythrulose is related to that in *l*-glycerose and it must therefore be classed as *l-erythrulose.*

Erythrulose, like other ketoses, differs from aldoses in not being attacked by dilute bromine water which converts the aldoses to the corresponding acids.

**Pentoses,** $C_5H_{10}O_5$, in contrast to the lower monosaccharides, are widely distributed in nature. Treatment with dilute acid converts them to furfural



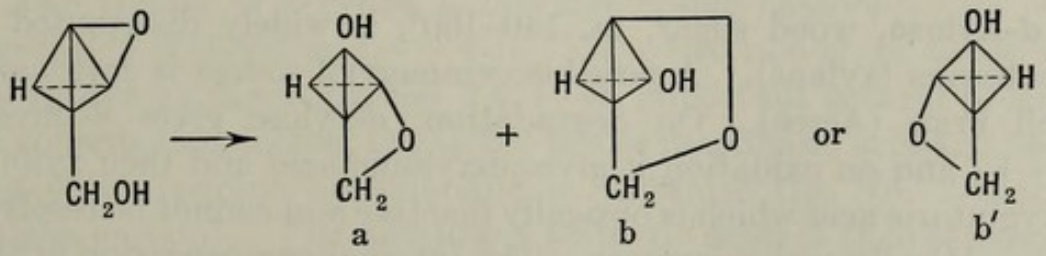


**Aldopentoses,**

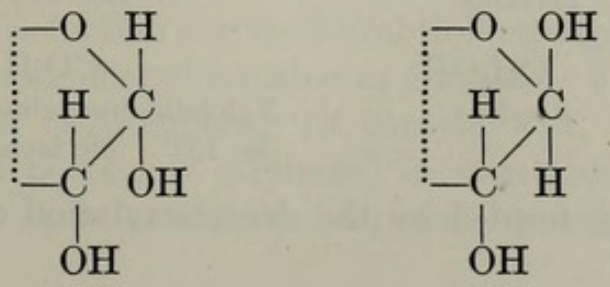
$HOCH(CHOH)_3CH_2$ and $HOCH(CHOH)_2CHCH_2OH$.

(gamma form)

Each can exist in $\alpha$ and $\beta$ form depending on the type of ring closure. This may be illustrated as follows:



The difference depends on which bond of the carbonyl linkage opens to add the H from the hydroxyl. Forms *b* and *b′* are identical. The latter can be seen to be the enantiomer of *a*. They may be regarded as having the projected configurations − and + or HOCH and HCOH with the ring oxygen as the point of reference as to "right" and "left." The relation between the alpha and beta forms of the lactols can better be shown by perspective formulas (Haworth).



In this method of representation the ring lies in the plane of the paper and groups written *below* a given atom are in *front* of it and vice versa.

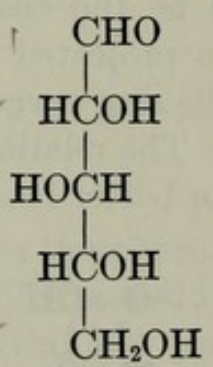
The ordinary 6-ring form (amylene oxide, pyranose) is the more stable and less reactive form. The 5-ring form (butylene oxide, furanose) is very reactive and can be isolated only in the form of derivatives. The natural valence angle of oxygen is 90° (Pauling). It has been found that the oxygen angle in tetrahydrofuran is 105° and in tetrahydropyran is 88° (Hibbert 1932). Thus the pyranose ring is less "strained" than the furanose ring.

In addition to the active group, the aldopentoses have three asymmetric carbon atoms. The configurations of these could be

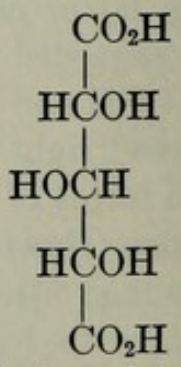
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| + | − | + | − | + | − | − | + |
| + | − | + | − | − | + | + | − |
| + | − | − | + | + | − | + | − |
| *a* | *b* | *c* | *e* | *f* | *g* | *h* | *j* |

Seven optically active aldopentoses are known corresponding to seven of these configurations.

***d*-Xylose,** wood sugar, m. 140–160°, is widely distributed as pentosans (xylans). A possible commercial source is cottonseed hull bran (Acree). On degradation, *d*-xylose gives *d*-threose (−+) and on oxidation it gives *d*-xylonic acid and then xylotrioxyglutaric acid which is optically inactive and cannot be resolved into optically active isomers. The internal compensation of this acid shows that its third C must have the HCOH or + configuration. Thus *d*-xylose has configuration (+−+).




*d*-xylose




Xylotrihydroxyglutaric acid, m. 152°. No lactonic acid

*d*-Xylose is also formed by the decarboxylation of *d*-glucuronic

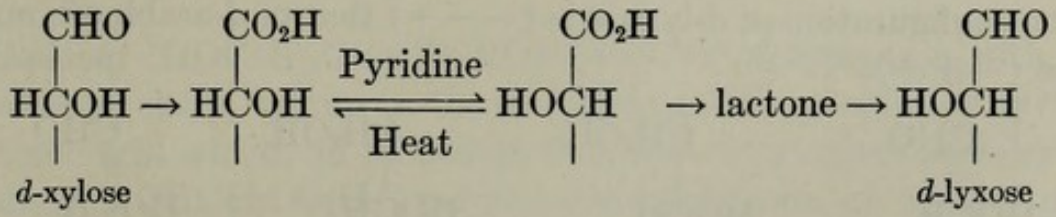
acid. *d*-Xylose, by the cyanohydrin synthesis, yields *d*-gulonic acid and *d*-idonic acid. *This process is valuable for going from one aldose to the next higher one* (Kiliani).

$$-CHO \rightarrow -CH(OH)CN \rightarrow -CH(OH)CO_2H \rightarrow \text{lactone} \rightarrow -CHOHCHO$$

The last step is possible because hydroxy lactones are readily reduced to lactols whereas acids are not readily reducible. The process gives a new asymmetric carbon and therefore results in the formation of a pair of epimeric acids (lactones). Since the starting material is optically active the amounts of the two epimers formed are not equal. In this case *d*-gulonic acid predominates. Reduction gives xylitol, an optically inactive non-resolvable syrup. The phenylosazone of *d*-xylose, m. 161°, is different from that of *l*-arabinose, m. 160°, but is identical with that formed by *d*-lyxose.

*l*-Xylose can be obtained from the hexonic acid, *l*-gulonic acid. It has the configuration (− + −).

The epimer of *d*-xylose is *d*-lyxose (same osazone). Its configuration is therefore (− − +). The *conversion of an aldose into its epimer* by inverting No. 2 C is an important general process. It consists in oxidizing the aldose to the monobasic acid and heating with pyridine or quinoline to racemize the No. 2 carbon (alpha carbon). The mixture of epimeric acids is then separated by suitable means and the new lactone is reduced to the new aldose by sodium amalgam.

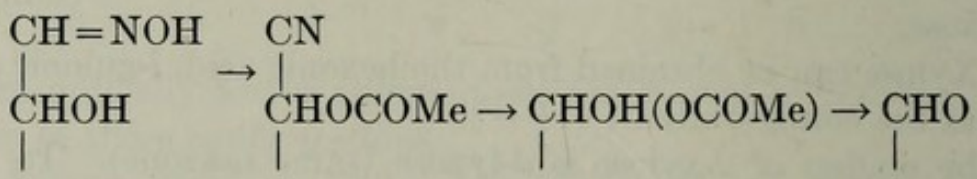



*d*-Lyxose, m. 101°, shows mutarotation to a value of $[\alpha]_D = -13.9°$. On reduction it gives *d*-arabitol (configuration − − +). It gives the same phenyl osazone as *d*-xylose. *l*-Lyxose has not been obtained. *l*-Arabinose, "*Arabinose*," m. 160°, is widely distributed as pentosans (arabans) in vegetable gums such as gum Arabic. It is ordinarily prepared by acid hydrolysis of

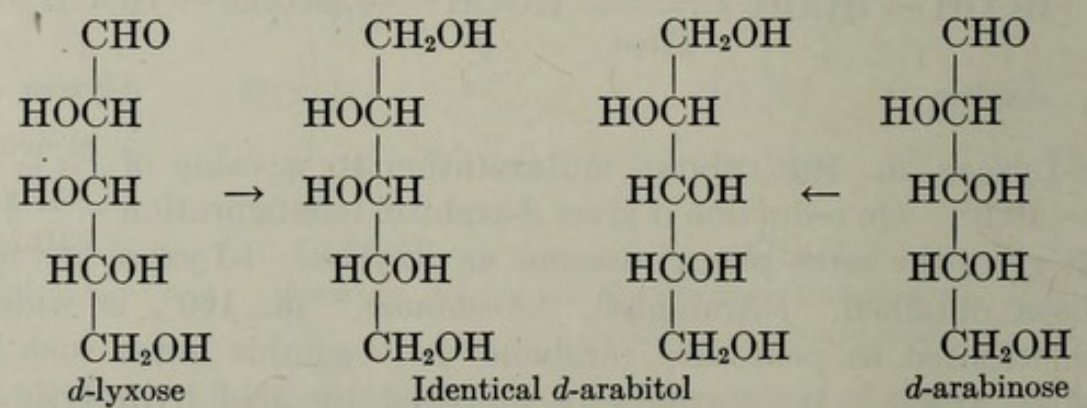
cherry gum or mesquite gum (Anderson 1925, 1930). It is also found in sugar beet residues. *l*-Arabinose is strongly dextrorotatory and shows mutarotation, the equilibrium value for a 10% solution being $[\alpha]_D = +105°$. *p*-Bromophenylhydrazone, m. 162°, phenylosazone, m. 160°. This same osazone is formed by *l*-ribose.

Reduction of *l*-arabinose gives *l*-arabitol. Bromine water gives *l*-arabonic acid. Further oxidation with nitric acid gives *l*-trihydroxyglutaric acid.

*d*-Arabinose occurs in certain glucosides and has been made by degrading the oxime of *d*-glucose (Wohl), the *general method for forming a lower aldose from a higher one.* The oxime is prepared and treated with acetic anhydride to form the acetylated cyanide. This, with ammoniacal silver solution, gives the acetate of the next lower aldose.




*d*-Arabinose, on reduction, gives *d*-arabitol which is also obtained by the reduction of *d*-lyxose. Thus *d*-arabinose and *d*-lyxose differ only in the relation of the end groups to the three central carbon atoms. Interchanging the active group and the $CH_2OH$ group in the formula of one would give the formula of the other. This would not be true of configurations *a*, *b*, *f* and *g* because such an interchange would make no difference. Since the configuration of *d*-lyxose is $(--+)$ that of *d*-arabinose must be $(-++)$.



*dl*-Arabinose is probably the pentose found in urine during pentosuria.

*dl*-Arabinose has been resolved by means of *d*-amyl mercaptan. The mercaptal of *d*-arabinose is less soluble in alcohol than that of the *l*-form. The aldose is regenerated by HgO.

*l*-Ribose is the epimer of *l*-arabinose (same osazone). As such it can be obtained by epimerization of the latter by conversion to *l*-arabonic acid and racemization of the alpha carbon followed by separation and reduction of the lactone to *l*-ribose (− − −). On reduction it gives adonitol, optically inactive by internal compensation (− − −), m. 102°. The properties of this substance are in sharp contrast to those of the closely related xylitol (− + −). On oxidation *l*-ribose gives *l*-ribonic acid and then ribotrihydroxy glutaric acid (− − −) which forms a hydroxylactonic acid, m. 170°. This is in contrast to xylotrihydroxy glutaric acid (− + −) which gives no lactonic acid.

*d*-Ribose is the characteristic sugar of plant nucleic acid (yeast) (Levene, Jacobs 1908–11).

Thyminose, *d*-2-desoxyribose is the sugar of animal nucleic acid (Levene, Rep. 1930, 265).

The configurations of the aldopentoses may be summarized.

*d*- and *l*-Arabinose, − + + and + − −.
*d*- and *l*-Xylose, + − + and − + −.
*d*- and *l*-Lyxose, − − + and + + −.
*d*- and *l*-Ribose, + + + and − − −.

**Apiose,** $(HOCH_2)_2C(OH)CHOHCHO$, an aldopentose with a branched chain, occurs in the glucoside apiin. Oxidation gives apionic acid which, on reduction with HI and P, gives isovaleric acid, $Me_2CHCH_2CO_2H$. *p*-Bromophenylosazone of apiose, m. 212°. It does not give furfural with acids.

**Ketopentoses** are unknown in nature. Probably one of the by-products of the condensation of formaldehyde in the presence of $CaCO_3$ to give formose (a hexose) is a ketone pentose. This gives the phenylosazone of *dl*-arabinose.

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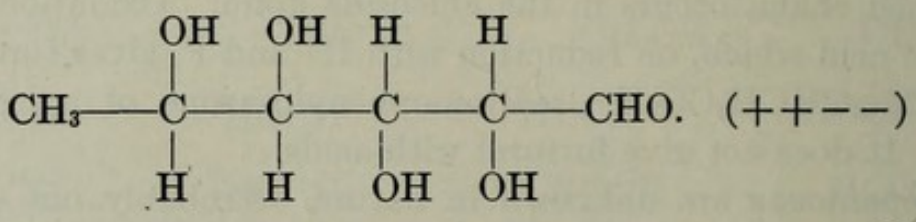
## Methyl Aldopentoses, $CH_3CH(CHOH)_3CH$ (with O bridge)

These are found as glucosides and methyl pentosans in various plant products.

***l*-Rhamnose,** *l*-mannomethylose, "isodulcite," m. 124°, monohydrate, m. 93°, is found in many glucosides including xanthorhamnin, quercitrin, strophanthin, ouabain and solanin. The freshly prepared water solution of the hydrate is levorotatory but gradually becomes dextrorotatory (mutarotation). At equilibrium in a 10% solution $[\alpha]_D = +8.4°$. The anhydrous rhamnose starts with a dextrorotation of about + 30° and drops to the equilibrium value.

Phenylosazone, m. 187°.

Reduction gives rhamnitol, treatment with acids gives methyl furfural, with bromine water gives rhamnonic acid and with nitric acid gives *l*-trihydroxyglutaric acid, $HO_2C(CHOH)_3CO_2H$ (++−). This settles the configuration of carbons Nos. 2–4 as a group but leaves undecided whether the alpha carbon is + or − and leaves carbon No. 5 uncertain. Both these questions are settled by applications of Hudson's Lactone Rule (1910). This states that, with the projection formulas arranged in the usual way, the lactones having the gamma OH on the right will be dextrorotatory and vice versa. The lactone of rhamnonic acid is levorotatory. Therefore, carbon No. 4 has the − configuration and No. 2 and No. 3 are ++. On treatment with $H_2O_2$ and ferric acetate (Ruff), rhamnonic acid gives a methyl tetronic acid, whose lactone is levorotatory, thus showing that carbon No. 5 in rhamnose is −. The configuration of rhamnose is thus




Rhamnose can be epimerized through its lactone to give *isorhamnose* with the configuration −+−− (starting from the active group as usual). *Isorhamnose*, *l*-epirhamnose, is identified by its ethyl mercaptal, $-CH(SEt)_2$, m. 98°. Such derivatives obtained

from the simple sugars and mercaptans (both aliphatic and aromatic) have proved valuable for identification and to stabilize the aldehyde group. The mercaptal grouping is stable to ordinary reagents but is readily removed by HgO or $HgCl_2$

$$-CH(SEt)_2 + HgO \rightarrow -CHO + (EtS)_2Hg$$

**Fucose** (galactomethylose), **quinovose** (chinovose, isorhamnose, isorhodeose, *d*-glucomethylose), **epi-rhodeose, gulomethylose, talomethylose** and **altromethylose** are stereomers of rhamnose (Rep. 1929, 98).

**Digitoxose,** $Me(CHOH)_3CH_2CHO$, is a 2,6-desoxyhexose (Rep. 1930, 106).

## Hexoses, $C_6H_{12}O_6$

These are the most important natural sugars. They are most widely distributed in nature both in the free state and in combination as heterosides (glucosides) and holosides ("polymeric" forms like the polysaccharides). They are fermented by various organisms. With acids they give first 5-hydroxymethyl furfural and then levulinic acid, $MeCO(CH_2)_2CO_2H$. There are sixteen theoretically possible aldohexoses and eight 2-ketohexoses. Fourteen of the former and six of the latter are actually known. A large portion of the work on the hexoses was done by Emil Fischer and his many students.

Aldohexoses, $CH_2OHCH(CHOH)_3CHOH$ and $CH_2OHCHOHCH(CHOH)_2CHOH$

The first is the normal form and the second the *gamma* form. One has a pyran ring and the other a furan ring. Thus the two forms are also called pyranoses and furanoses (Haworth). Each can exist in alpha and beta forms depending on the configuration of the active carbon in relation to the lactol ring.

The *pyranose ring* contains the five C atoms in one plane with nearly the normal angles and the oxygen in a different plane with its normal valence angle of about 90°. The *furanose ring* is a

strained ring of four carbons and one oxygen in a plane with all of the angles distorted (Hibbert 1932).

The number of stereoisomers of a given structure can be calculated by simple formulas. If $n$ is the number of asymmetric carbon atoms, $a$ the number of optically active forms, and $m$ the number of meso forms (optically inactive by internal compensation); then

1. If the molecule contains no two carbons attached to identical groups, $a = 2^n$; $m = 0$.
2. If $n$ is even and the molecule can be divided into two equal halves, $a = 2^{n-1}$; $m = 2^{\left(\frac{n-1}{2}\right)}$.
3. If $n$ is odd and the molecule can be divided into two equal halves by a plane through the middle carbon, $a = 2^{n-1} - 2^{\left(\frac{n-1}{2}\right)}$; $m = 2^{\left(\frac{n-1}{2}\right)}$.

The configurations of the aldohexoses have been determined by the principles already outlined with the lower monoses. Each aldohexose has four asymmetric carbon atoms besides the active or aldehyde carbon which is responsible for alpha and beta forms. Since each of these carbons is different (the two ends of the molecule are different), there are $2^4$ or 16 possible configurations. Arranging the models in the usual way with the active group at the top and the $CH_2OH$ at the bottom with both in the plane of the paper and the H and OH groups back of this plane and then projecting the formula on paper and finally indicating the HCOH and HOCH arrangements as + and − respectively, we have the sixteen possible combinations:

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| +− | −+ | +− | +− | −+ | −+ | +− | −+ |
| +− | +− | −+ | +− | −+ | −+ | −+ | +− |
| +− | +− | +− | −+ | −+ | +− | −+ | −+ |
| +− | +− | +− | +− | +− | +− | +− | +− |

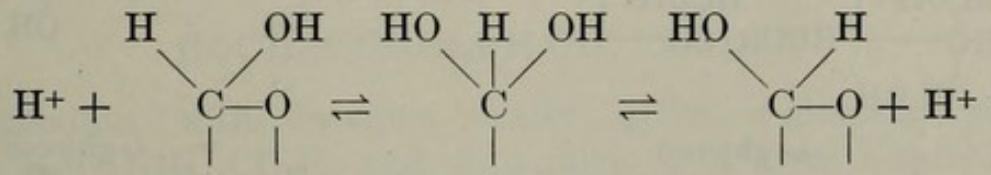
In each pair, the first represents a member of the *d*-series, related to *d*-glucose and *d*-glyceraldehyde and the second the enantiomorph belonging to the *l*-series.

The methods of assigning these configurations will be indicated only briefly as the principles have already been developed.

### *d*-Glucose, Dextrose, Grape Sugar, (+−++)

This monose is widely distributed in plants. In animals it is a normal constituent of the blood and is related to the development of muscular energy. In diabetes mellitus it occurs in the blood and urine in large amounts. It occurs as the sole constituent of the polysaccharides, maltose, cellobiose, trehalose, starch and cellulose and with other monoses in lactose, turanose and sucrose. It is the commonest sugar in natural glucosides (heterosides) and gives the name to these substances.

Ordinary dextrose is mainly $\alpha$-glucose, m. 146°, $[\alpha]_D = +109.6°$. $\beta$-Glucose can be obtained by crystallizing glucose from hot pyridine, m. 148–150°, $[\alpha]_D = +20.5°$. Both forms show mutarotation (multirotation, birotation), the optical activity of the solutions changing until the value for the equilibrium mixture, + 52.7°, is reached. This corresponds to about 37% $\alpha$- and 63% $\beta$-glucose. The change of one form into the other is catalyzed by hydrogen ions or hydroxyl ions near the neutral point but is stopped by as weak a base as pyridine or as weak an acid as cresol (Lowry 1925). On the other hand, a mixture of these two solvents makes mutarotation about twenty times as fast as in water. The change consists of the addition and removal of $H^+$ as in the bimolecular mechanism of keto-enol isomerization.



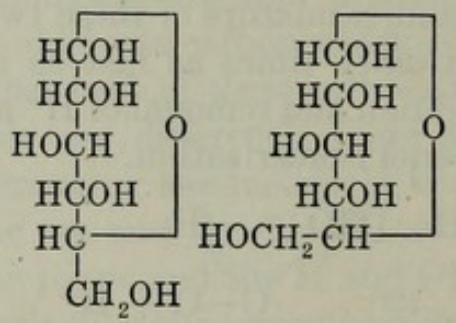
The determination of the configuration of the two glucoses depends on an application of Boeseken's discovery of the effect of 1,2-dihydroxy compounds in increasing the conductivity of a boric acid solution as in the case of glycol and glycerol.

$\alpha$-Glucose, with boric acid, gives a solution of higher conductivity than a similar solution of $\beta$-glucose and boric acid. The conductivity of the former falls and of the latter rises until the same value is attained. That this is due to the formation of the equilibrium mixture of $\alpha$ and $\beta$ sugars is shown by the fact that the velocity constants for the changes in conductivity and in optical activity are the same (Rep. 1913, 79). Thus $\alpha$-glucose

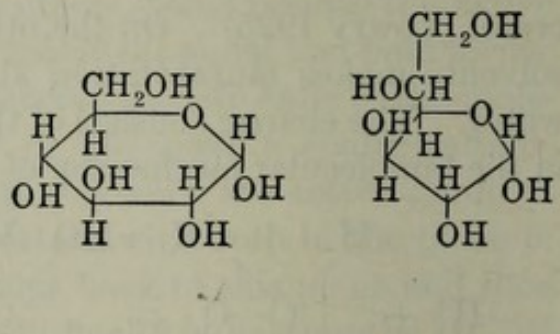
must have two hydroxyl groups in the favorable position while $\beta$-glucose does not. In view of the pyranose structure of glucose, the only way to achieve this condition is for the active (aldehydic) asymmetric carbon to have the + or HCOH configuration to match that of the No. 2 carbon. $\beta$-Glucose correspondingly has the configuration $-+--++$, starting with the No. 1 carbon. The No. 5 carbon being in ring combination, no two adjacent OH groups are in the same plane. The convincing nature of Boeseken's results is lessened somewhat by the unexplained fact that the glucosides of tetramethyl glucose (with no OH on $C_2$) give similar results with boric acid. The same configurations for alpha and beta glucose are obtained by Hudson's rule (1909) (Rep. 1910, 87).

That the intermediate in the process of mutarotation may be the aldehyde form is indicated by data on the mutarotation in chloroform solution of the penta-acetate of *aldehydo*-galactose (Wolfrom 1932).

Various ways of indicating the configuration of the forms of glucose follow (Rep. 1929, 94).




$\alpha$- glucose




$\gamma$-glucose

The last, *gamma* glucose, is a very reactive form which has only been isolated as derivatives (Levene, Rev. 1928, 1–16). The gamma sugars are probably of the utmost importance in natural processes. Before they were recognized as furanose forms of the ordinary pyranoses they were called *heteros* or *h*-sugars (Rep. 1925, 88). The $\gamma$-glucose illustrated above is really an alpha form (No. 1 and 2 hydroxyls *cis*). Reversal of the H and OH on the No. 1 carbon would give the beta form of the gamma sugar. Four isomeric ethyl glucosides have actually been prepared.

Glucose, in solution, behaves as a tautomeric mixture of the following forms: alpha and beta *d*-glucopyranose, the hydrated

aldehyde form, the 1,2-enediol, alpha and beta *d*-glucofuranose, and perhaps a minute amount of the free aldehyde form.

Glucose is not as sweet as sucrose. It is made in enormous amounts by the hydrolysis of starch (about one billion pounds per year). Depending on its purity it appears as corn syrup, yellow chip glucose, corn sugar, cerelose (a very pure crystalline monohydrate), etc.

Pure dextrose solution is used intravenously in conditions which lower the natural blood sugar content.

On heating, glucose loses water and becomes glucosan, $C_6H_{10}O_5$.

*d*-Glucose gives the same osazone, m. 205°, as *d*-mannose and *d*-fructose. Thus carbons Nos. 3–5 in these three monoses have the same configuration. Since the degradation of *d*-glucose gives *d*-arabinose the configuration of these carbons is (−++). In addition to the methods of Wohl (p. 551) and of Ruff (p. 554) the following method gives excellent yields of arabinose. *d*-Gluconic anhydride with $NH_3$ gives the amide which reacts with hypochlorite solution to give *d*-arabinose (Weerman, Rep. 1915, 74). The hydroxyisocyanate, $-CH(OH)NCO$, formed as an intermediate may be assumed to lose HNCO or to be hydrolyzed to $-CH(OH)NH_2$, the $NH_3$ addition compound of the lower aldose which readily forms the aldose by reaction with the hypochlorite.

Reduction of *d*-glucose gives *d*-sorbitol,

$$HOCH_2(CHOH)_4CH_2OH, \quad \text{m. } 111°.$$

Oxidation with bromine water gives *d*-gluconic acid, $HOCH_2(CHOH)_4CO_2H$, and with nitric acid gives *d*-saccharic acid, $HO_2C(CHOH)_4CO_2H$. The latter gives a characteristic difficultly soluble acid potassium salt. Permanganate oxidation of *d*-saccharic acid gives oxalic and *d*-tartaric acid, configuration (+−). Since carbon No. 3 is − like No. 2 in arabinose, carbon No. 2 in glucose must be +.

Glucose is an excellent reducing agent, especially in alkaline solution, and is used as such with ammoniacal silver solution for silvering mirrors and in the vat process for converting insoluble indigo to indigo white.

The oxidation of glucose and the other monoses is a most complex and important problem (Evans, Rev. 1929, 281–316).

In the presence of dilute bases, *d*-glucose gives an equilibrium mixture with its epimer, *d*-mannose, and *d*-fructose, the related ketohexose (Lobry de Bruyn 1895). The same mixture is obtained from any one of the three sugars. At equilibrium 63.4% glucose, 30.9% fructose and 2.4% mannose are obtained (Wolfrom, 1928).

The process goes through the enediol, $-C(OH)=CHOH$, common to the three sugars. At the same time, a small amount of *d*-glutose, probably a 3-ketohexose (osazone, m. 165°), is formed. This would result from the enolization of the fructose involving carbon No. 3 (Benedict, Dakin 1926).

Stronger bases (8N) give *i*-lactic acid, $\alpha,\gamma$-dihydroxybutyric acid and saccharinic acids (Nef 1910, Glattfeld 1927, Nicolet 1932). These are not to be confused with saccharic acid (Zuckersäure) obtained by oxidizing glucose and gulose. The saccharinic acids (Saccharinsäure) are the results of rearrangements much like the benzilic acid rearrangement. If only H rearranges the result is a metasaccharinic acid such as $HOCH_2(CHOH)_2CH_2CHOHCO_2H$ while if a carbon rearranges the result is an isosaccharinic acid such as

$$HOCH_2CHOHCH_2C(OH)(CH_2OH)CO_2H.$$

Glucose and other sugars dissolve calcium oxide and related substances to form glucosates, etc.

Glucose with an ammoniacal zinc solution gives methyl glyoxalin, indicating splitting by the mild alkali to give glyoxal, MeCOCHO, and formaldehyde.

### Derivatives of *d*-Glucose

$\alpha$-Methyl glucoside, $HOCH_2\overset{\textstyle O}{\overset{\frown}{C}}H(CHOH)_3CHOMe$ (configuration $++-++$), m. 166°, is the chief product from the action of dilute methyl alcoholic HCl on glucose. It is strongly dextrorotatory without *mutarotation*. Thus the lactol ring is definitely fixed. It is converted to *d*-glucose by maltase, an enzyme which splits alpha glucosides. $\beta$-Methyl glucoside ($-+-++$), m. 108°, is made from aqueous glucose and dimethyl sulfate (poison)

and alkali, the reagents being added gradually in equivalent amounts. It is levorotatory without mutarotation. It is more easily hydrolyzed than the α-form. Thus treatment of the glucoside with alcoholic HCl gives the α-form

$$\begin{array}{ccc} \alpha\text{-glucose} + \text{MeOH} & \rightleftharpoons & \alpha\text{-glucoside} \\ \Updownarrow & & \\ \beta\text{-glucose} + \text{MeOH} & \rightleftharpoons & \beta\text{-glucoside} \end{array}$$

β-Methyl glucoside gives β-glucose with emulsin, a typical β-glucoside-splitting enzyme.

A mixture of the α- and β-methyl glucosides can be treated with yeast to give the β-form alone. The α-form is hydrolyzed by the maltase in the yeast which only splits alpha glucosides. The resulting glucose is fermented by the zymase of the yeast. γ-Methyl glucoside is a furanose (butylene oxide ring) (Rep. 1927, 70). It was first made by Emil Fischer by allowing glucose to stand with 1% methyl alcoholic HCl at room temperature. It is much more reactive to acids and oxidizing agents than the α- and β-glucosides.

Four ethyl glucosides have been prepared. These are known as alpha, beta, gamma and delta. The last two are derivatives of the reactive gamma glucose. They are better called α- and β-glucopyranosides and α- and β-glucofuranosides. Their mps. and specific rotations are 114°, +150°; 73°, −33°; 83°, +98°; 60°, −86°.

Treatment of the methyl glucosides with MeI and $Ag_2O$ (Purdie, Irvine 1903) or with $Me_2SO_4$ and NaOH (Lewis, Gustus 1927) gives tetramethyl methyl glucosides which can be distilled under reduced pressure. Hydrolysis gives $Me_4$-glucose, $b_{20}$ 182–5°. This has a bitter taste and reduces Fehling's solution on heating but with the formation of only one-fifth as much cuprous oxide as given by glucose itself. The presence of the methoxyl group evidently blocks the continued oxidation of the carbohydrate chain. $Me_4$-glucose can be obtained in α- and β-forms which show mutarotation.

Methylated sugars with acetic anhydride and HBr give the corresponding acetylated bromo-sugars (Hess 1935). Thus 2,3,6-$Me_3$-glucose gives 1-α-Br-tetra-acetyl-glucose from which glucose can be obtained by hydrolysis.

The various partly methylated glucoses have been made and are important in relation to the structures of the polysaccharides. The other methylated monoses are similarly important. In all such substances the methoxyl determination of Zeisel is most useful (Hewitt, Moore 1902; Rigakos 1931; Bruckner 1932).

Pentamethyl aldehydo glucose, $MeOCH_2(CHOMe)_4CHO$, has been made by methylating diethylmercaptoglucose and then removing the mercaptal groups with $HgCl_2$ (Levene 1926). This reacts readily with methanol to give the acetal, $-CH(OMe)_2$.

Tetra-allyl $\alpha$-methyl glucoside has been prepared using allyl bromide in place of MeI (Adams 1924).

Alkali salts of glucose and other sugars can be made with the alkali metals in liquid ammonia (Muskat 1934). These are useful for introducing alkyl and other groups into the sugars.

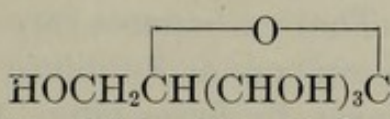
$\alpha$- and $\beta$-penta-acetyl glucoses, m. 112° and 134°, of the formula $MeOCOCH_2CH(CHOCOMe)_3CHOCOMe$ have been prepared. One of the acetyl groups is more easily removed than the rest. The penta-acetate of the true aldehyde formula, $MeOCOCH_2(CHOCOMe)_4CHO$, has been made by acetylating the mercaptal of glucose, $-CH(SR)_2$, and treating with HgO (Wolfrom 1929).

Acetobromoglucose, $MeOCOCH_2CH(CHOCOMe)_3CHBr$, m. 89°, is made from the penta-acetate and HBr in glacial acetic acid. Treatment with zinc and acetic acid, followed by hydrolysis, gives *d*-glucal, $HOCH_2CHCHOHCHOHCH=CH$. This is identical with *d*-mannal. It is a typical *saccharal* (Rep. 1931, 98). More highly unsaturated monose derivatives such as glucose-ene are known.

Hydrochloric and hydrofluoric acids also react with acetylated monoses (Brauns 1931).

Among the acyl derivatives of the sugars are those obtained with *p*-toluene sulfonyl chloride. The grouping, $-SO_2C_6H_4CH_3$, is called the *tosyl* group (Ohle).

$\alpha$- and $\beta$-forms, m. 160° and 141°, of the *phenylhydrazone* of *d-glucose* can be obtained. These show mutarotation. Thus they are cyclic forms subject to the same type of isomerization as $\alpha$- and $\beta$-glucose,



$$HOCH_2CH(CHOH)_3CHNHNHC_6H_5$$

Glucose reacts with one mol of methylphenylhydrazine, $C_6H_5(Me)NNH_2$, but is not oxidized by an excess of the reagent (difference from ketoses). Excess phenylhydrazine gives the well-known osazone formation.

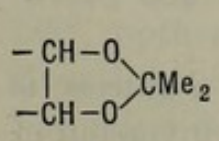
**Phenylglucosazone** (A), m. 205° (Butler, Cretcher 1929). On hydrolysis or, better, on treating with another aldehyde, the phenylhydrazone groups can be removed leaving an alpha keto aldehyde, an *osone*.

$$\text{(A)}\quad HOCH_2(CHOH)_3C(=NNHC_6H_5)CH=NNHC_6H_5 \xrightarrow{RCHO} HOCH_2(CHOH)_3COCHO$$

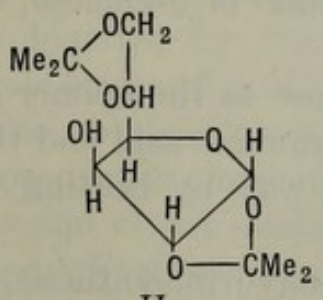
Reduction of the osones gives ketoses. In this case *d*-fructose.

Glucose reacts with one or two mols of acetone, adjacent *cis* hydroxyl groups reacting to give isopropylidene derivatives (I). The acetone cpds. of the sugars are valuable in blocking certain positions so that others can be methylated (Rep. 1927, 74). When only one acetone is introduced it reacts in the 1,2-position of the pyranose form. When a second molecule of acetone reacts with glucose, it involves the 5,6-hydroxyls, thus forcing a change to a furanose ring (II).

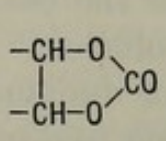
Similarly carbonates (III) can be formed by chloroformic ester, $ClCO_2Et$, and a base or pyridine (Rep. 1924, 71). 1,2-Isopropylidene-$\alpha$-glucofuranose-5,6-carbonate can be split by acids to



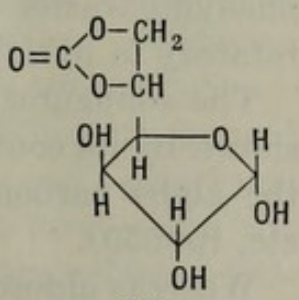
I



II



III



IV

give the 5,6-carbonate of gamma glucose (IV) (Rep. 1929, 96). This has the characteristic high reactivity of the gamma sugars such as the reduction of a cold permanganate solution and the practically instantaneous union with methanol in the presence of HCl (Haworth 1926). The carbonates are less readily hydrolyzed than the acetone compounds by dilute acids but are immediately converted to glucose by bases (Rep. 1930, 102).

**Glucose-6-phosphate** (Rep. 1931, 98) is an example of the hexose-phosphates which are probably important in fermentation processes.

**Glucosamine** has $NH_2$ in place of the $\alpha$-OH of glucose. It is obtained by the hydrolysis of *chitin*, the bony material of crustacea. It also occurs in *chondroitic acid* in cartilage combined with glucuronic acid, acetic acid and sulfuric acid.

### Other Aldohexoses

***l*-Glucose,** $(-+--)$, is obtained from *l*-arabinose by the cyanohydrin synthesis (Kiliani). This gives a mixture of *l*-mannonic acid and *l*-gluconic acids. The lactone of the former crystallizes first. The latter is purified as the calcium salt. Reduction of the *l*-gluconic lactone gives *l*-glucose. *l*-Glucose is not fermented by yeast.

***d*-Mannose,** $(--++)$, m. 132°, occurs in glucosides (mannosides) and in polyoses (mannans) in a great variety of natural products. One of the chief of these is the ivory nut from which buttons are made. The waste material from this manufacture is readily hydrolyzed by dilute acid to give mannose.

*d*-Mannose is readily fermented by yeast. Its phenylhydrazone, m. 205°, is very insoluble in water. In pyridine solution it is dextrorotatory but shows no mutarotation. Excess of phenylhydrazine gives the osazone of *d*-glucose, m. 205°, levorotatory in pyridine solution.

The configuration of *d*-mannose as the epimer of *d*-glucose is shown by its conversion to *d*-mannonic acid and the inversion of the alpha carbon in the usual way by heating with pyridine, etc. (p. 559).

Whereas aldoses, by the cyanohydrin synthesis, usually give a pair of epimeric acids, *d*-mannose gives only *one* acid and that in

nearly quantitative yield, *d*-mannoheptonic acid. This is a true *asymmetric synthesis* in which an optically active molecule influences the configuration of a newly formed asymmetric carbon.

Mannose reacts with diphenylmethane-dimethyl-dihydrazine also called bis-[(N$\alpha$-methylhydrazine)-4-phenyl]-methane to give $CH_2(C_6H_4NMeN=C_6H_{12}O_5)_2$ (v. Braun 1917). This reagent shows a peculiar selectivity in the sugars with which it reacts. It does not act with fructose or the disaccharides. It acts only with aldoses in which carbons Nos. 2, 3 and 4 have at least two adjacent hydroxyls of the same "sign." Thus it reacts with mannose (− − + +), galactose (+ − − +), arabinose (− + +) and ribose (+ + +) while it does not act with glucose (+ − + +) or xylose (+ − +). Because it can be used to separate epimers in some cases (glucose and mannose), it has been called von Braun's epimer reagent.

*d*-Mannose forms a di-acetone compound which reduces Fehling's solution and shows mutarotation. Thus the active group is free and the acetone residues are combined in the 2,3- and 5,6-positions.

*l*-Mannose is obtainable from *l*-mannonic lactone which crystallizes first from the mixture with *l*-gluconic lactone in the Kiliani synthesis from *l*-arabinose. It is not fermented by yeast.

***d*-Galactose,** (+ − − +), m. 168°, occurs in galactans, in glucosides and in lactose, raffinose and stachyose and in certain cerebrosides. It is best obtained by hydrolyzing lactose and crystallizing out the galactose leaving the glucose in solution. A potential commercial source is found in the galactans of the mountain larch (Acree). It shows mutarotation. It is more slowly fermented than the other natural monoses. Its methylphenyl hydrazone, $HOCH_2(CHOH)_4CH=NN(Me)C_6H_5$, m. 191°, is only slightly soluble in water. Reduction gives dulcitol, m. 188°, optically inactive by internal compensation. Oxidation gives *d*-galactonic acid and finally mucic acid, a meso compound. The latter is also obtained from *l*-galactose. When mucic acid is reduced the product is a racemic mixture of *d*- and *l*-galactonic acids, the reduction of one carboxyl giving the former and the other the latter. Further reduction gives *dl*-galactose. Fermentation destroys the *d*-form leaving *l*-galactose.

Studies of the mutarotation of solutions of galactose indicate that they contain the $\alpha$- and $\beta$-pyranose and $\alpha$- and $\beta$-furanose sugars (Rep. 1929, 92).

Penta-acetyl aldehydogalactose can be made from the ethyl mercaptal, $-CH(SEt)_2$. The free aldehyde shows no mutarotation in chloroform. Its crystalline hydrate and its ethyl hemiacetal show mutarotation (Wolfrom 1931).

*dl*-Galactose is obtained by the careful oxidation of dulcitol. Fermentation destroys the *d*-form. The *dl*-mixture can be separated by making the *d*-amylphenylhydrazine (Neuberg 1905) by means of $C_6H_5(C_5H_{11})NNH_2$, separating the two compounds *dd* and *dl* and removing the hydrazine by treating with benzaldehyde.

***l*-Idose,** (+−+−), m. 156°, is obtained in the usual way from the *l*-idonic acid which is formed with *l*-gulonic acid from *l*-xylose by the cyanohydrin synthesis. *d*-Gulonic acid can be epimerized to *d*-idonic acid which can be reduced to *d*-idose. Reduction and oxidation give iditol, m. 74°, and idosaccharic acid. The latter gives a difficultly soluble copper salt. The idoses are not attacked by yeast.

***l*-Gulose,** m. 156°, (configuration −−+−), can be made from *l*-xylose by the cyanohydrin synthesis. It gives sorbitol and saccharic acid. Thus it resembles glucose except that the aldehydo and primary carbinol groups are reversed with respect to the four central carbons. This reversal of the ends can be carried out experimentally in the following steps:

*d*-Glucose → *d*-gluconic acid → *d*-saccharic acid →

| | | | | |
|---|---|---|---|---|
| | +−++ | −−+− | −−+− |
| ↗ | *d*-glucuronic acid → | *l*-gulonic acid | → | *l*-gulose |
| ↘ | (*l*-guluronic acid) → | (*d*-gluconic acid) | → | (*d*-glucose) |
| | −−+− | +−++ | +−++ |

***d*-Talose,** m. 188°, (−−−+), can be made by epimerizing *d*-galactonic acid, separating and reducing the *d*-talonic lactone formed. Methylphenylhydrazone, m. 154°. It gives talitol, m. 86°, and talomucic acid, m. 158°.

***d*-Altrose,** m. 184°, (−+++), and *d-allose*, m. 184°, (++++), are obtainable from *d*-ribose (+++) by the Kiliani synthesis.

The configurations are settled by the fact that *d*-altrose gives an optically active dibasic acid, *d*-talomucic acid, m. 158°, while *d*-allose gives a meso acid, allomucic acid, m. 170°.

**Hamamelose,**

$$HOCH_2(CHOH)_2C(OH)(CH_2OH)CHO,$$

a branched chain aldohexose, is found as a glucoside in hamameli tannin (Rep. 1930, 106).

2-Ketohexoses, $HOCH_2\overset{\overset{\textstyle O}{\frown}}{C}(OH)(CHOH)_3CH_2$ and $HOCH_2\overset{\overset{\textstyle O}{\frown}}{C}(OH)(CHOH)_2CHCH_2OH$

The second is the furanose or gamma form. The configurations are determined by reference to those of the aldohexoses which give the same osazones, that is, the aldohexoses which have the same configurations for carbons 3–5. The ketohexoses exist in alpha and beta form and show mutarotation.

***d*-Fructose,** levulose, fruit sugar, (− + +), occurs in the sweet juices of fruits and in honey, in sucrose and in inulin. It is best prepared from the latter source as found in the roots of the dahlia and the Jerusalem artichoke (Jackson). *Invert sugar* is the equimolar mixture of fructose and glucose obtained by hydrolyzing sucrose. It is levorotatory since *d*-fructose has a stronger levo rotation than *d*-glucose has dextro.

*d*-Fructose can be made from *d*-glucose by the usual reaction for *converting an aldose into the related ketose*, that is, through the gluosazone which, on treatment with benzaldehyde, gives *d*-glucosone, $HOCH_2(CHOH)_3COCHO$. This can be reduced to *d*-fructose.

*d*-Fructose reduces Fehling's solution more rapidly than the aldohexoses but does not react with alkaline iodine solution whereas the aldoses do. It gives the same osazone as *d*-glucose and *d*-mannose. With methylphenylhydrazine it gives both a hydrazone and an osazone (difference from glucose and other aldoses). Evidently the carbonyl group in the 2-position condenses readily and No. 1 carbinol group is oxidized even by so

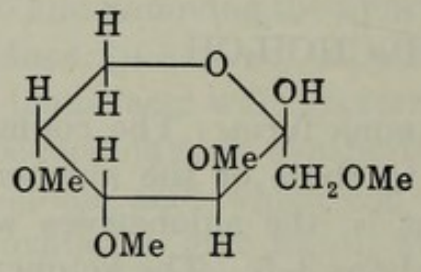
mild an agent. On the other hand, if the $C_6H_5(Me)NN=$ group is on the No. 1 carbon, the No. 2 carbinol group is not oxidized and no osazone can be formed.

Reduction of *d*-fructose gives *d*-mannitol (− − + +) and *d*-sorbitol (+ − + +).

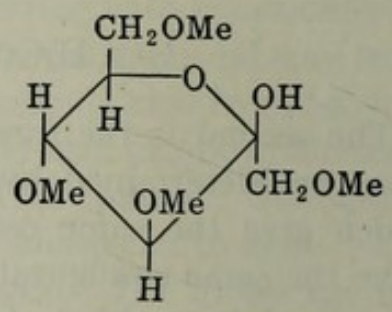
It is fermented by yeast. It is sweeter than sucrose and can be used by diabetics in place of carbohydrates which give glucose in the body.

Treatment with mild alkaline reagents partly converts *d*-fructose to *d*-glucose and *d*-mannose (and some glutose).

Methylated fructoses are important in sugar studies.




Tetramethyl-α-fructose
Reacts slowly with HCl + MeOH
No reaction with cold $KMnO_4$
Dextrorotatory




Tetramethyl-γ-fructose
Rapid reaction with
HCl + MeOH and with $KMnO_4$
Levorotatory

The fact that the furanose or gamma form of levulose is found in sucrose, inulin, etc., is related to its greater reactivity which enables it to unite with other monose molecules.

$Me_4$-γ-fructose, with dilute acid, changes readily to ω-methoxymethylfurfural (Rep. 1927, 71).

*d*-Fructose gives two isomeric di-acetone compounds which are non-reducing but are furanose derivatives, the combination taking place in the 1,2,4,5- and 2,3,4,5-positions respectively.

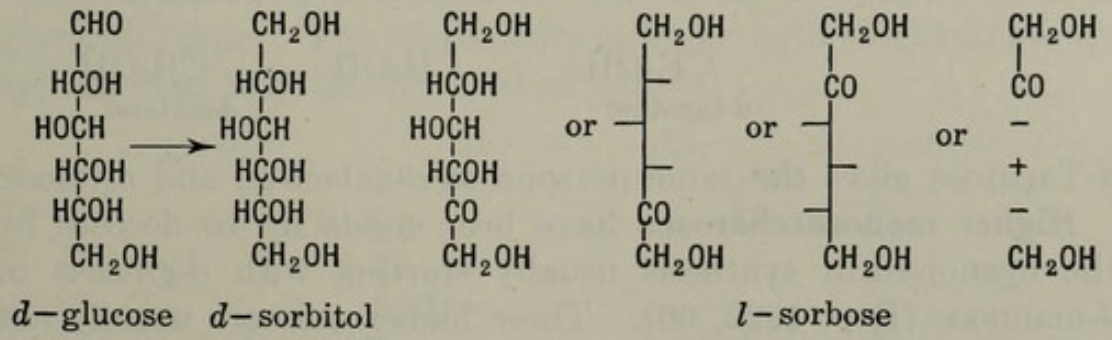
γ-Fructose-1,6-diphosphoric acid is found in yeast (Robinson 1928).

*dl*-Fructose, alpha acrose, formose, has been obtained artificially by polymerizing through aldol condensation, the following, *a*. formaldehyde, *b*. glycollic aldehyde, *c*. glycerose obtained by careful oxidation of glycerol and consisting of glyceraldehyde and dihydroxyacetone, *d*. the same mixture obtained from acrolein dibromide, $BrCH_2CHBrCHO$, with barium hydroxide.

Several osazones have been obtained from the mixture of sugars formed in this way. The most important is phenyl-$\alpha$-acrosazone, m. 219°, identical with the osazone obtained from *dl*-glucose and *dl*-mannose. The sugar shows the reactions of *d*-fructose except for its optical inactivity. By the regular monose reactions this synthetic sugar has been converted to *d*-glucose, *d*-fructose, *d*-mannose, *d*-galactose, *l*-xylose, etc.

Formose (Butlerow 1861) obtained from formaldehyde also contains small amounts of sorbose (*β-acrose*) and a ketopentose (Rep. 1925, 82). The formation of carbohydrates in nature probably involves a process much like that of the conversion of formaldehyde to formose.

*l*-Sorbose, m. 165°, (− + −), occurs in various plant products. It is formed from *d*-sorbitol (+ − + +) by the Sorbose-bacterium. It might be thought that this action would give two products, one by the oxidation of the No. 2 carbon and the other by that of the No. 5 carbon, but only the latter is attacked. The Sorbose-bacterium like most biological reagents is highly specific. It can oxidize only a No. 2 carbon in a system $++CH_2OH$ or $--CH_2OH$. That is, it oxidizes a No. 2 carbon in a system where the No. 2 and No. 3 carbons have their OH groups on the same side. Thus it does not oxidize *l*-iditol (+ − + −). The relations of *l*-sorbose are instructive in showing configurational relations:

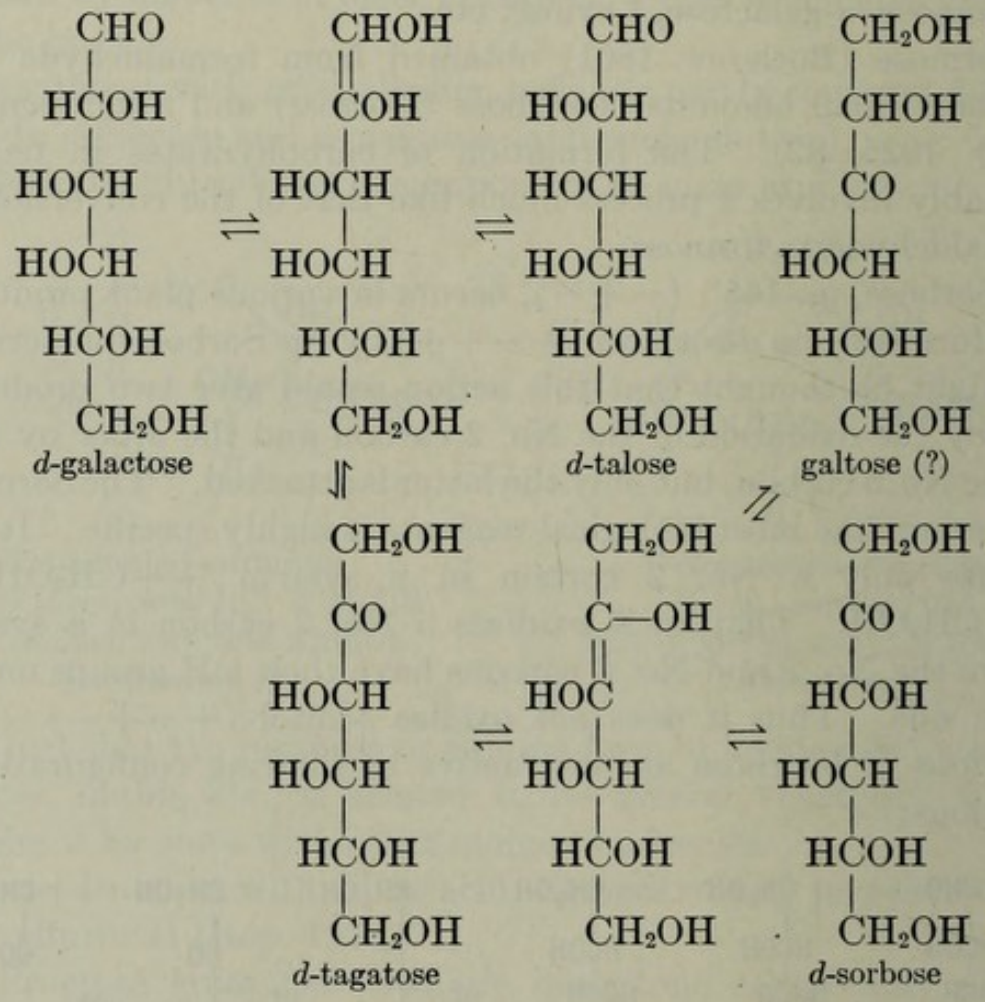



*l*-Sorbose on reduction gives *l*-sorbitol and *l*-iditol. It gives the same osazone as *l*-gulose and *l*-idose. It is not fermented by yeast.

*d*-Sorbose is obtained by the action of dilute bases on *d*-galac-

tose (see under tagatose). Its properties, except its dextrorotation, are like those of its *l*-enantiomers.

*d*-Tagatose, m. 124°, (configuration $--+$), is formed in small amounts in the action of dilute bases with *d*-galactose. This is a most complex process involving also *d*-talose, *d*-sorbose and *galtose* (possibly a 3-ketohexose, phenylosazone, m. 183°).




*d*-Tagatose gives the same osazone as *d*-galactose and *d*-talose.

**Higher monosaccharoses** have been made up to decoses by the cyanohydrin synthesis usually starting with *d*-glucose or *d*-mannose (Rep. 1922, 66). These higher oses are usually not fermentable. An exception is manno-nonose. *Sedoheptose* is obtained from *Sedum spectabile*, osazone, m. 197°. A manno-ketoheptose is obtained from the avocado pear.

**Amino sugars** and related polyoses are important in various animal products. Glucosamine (chitosamine) has an $NH_2$ group in place of the alpha hydroxyl of glucose. It exists in $\alpha$ and $\beta$

forms (Rep. 1922, 78). Chitin, found in various marine animals, gives glucosamine on acid hydrolysis. A *thiosugar* has been found in the adenine nucleoside of yeast (Levene 1925).

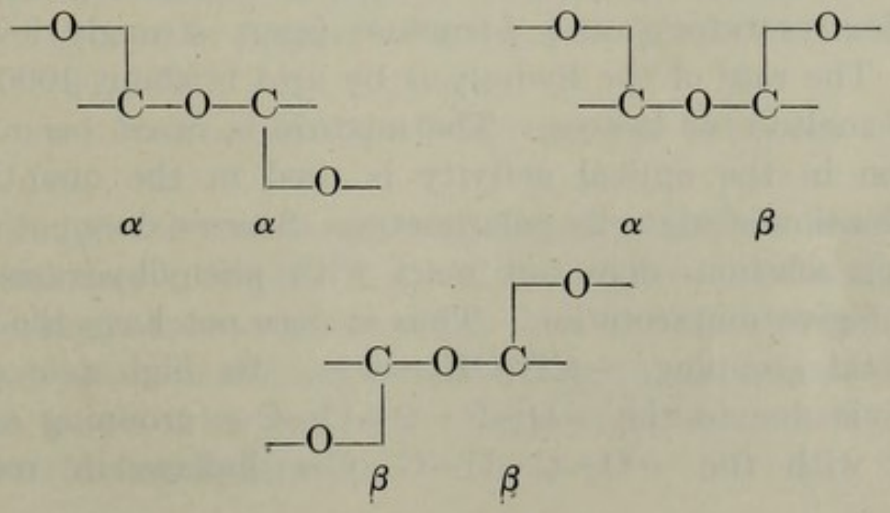
### *B.* Polyoses, Polysaccharides, Polysaccharoses, Holosides

These give only simple sugars on hydrolysis. They may be divided into substances which are sweet and readily soluble like ordinary sugar (sucrose), and those which are not, like the starches and celluloses.

**Sugar-like polyoses, oligosaccharides.** Just as methyl alcohol can unite with glucose to give methyl glucosides other hydroxy compounds can form similar unions with monoses. This includes the monoses themselves. If the second monose forms the glucoside of the first by means of its own aldehydo hydroxyl, the resulting biose has no active group and cannot reduce Fehling's solution. Such a case is that of sucrose. If, however, the glucoside is formed through any other OH of the second monose, the active group of the latter is left free and the resulting biose is a reducing sugar like maltose. Such a sugar can also form an osazone and can give mutarotation.

Sucrose and turanose both give glucose and fructose on hydrolysis but turanose reduces Fehling's solution and acts with phenylhydrazine while sucrose does neither.

Union between two monoses can be of the alpha or beta glucosidic type. The possibilities in which both aldehydo groups are involved may be indicated as follows:



These are all non-reducing forms. These three possibilities are realized in trehalose, isotrehalose and neotrehalose each of which consists of two molecules of *d*-glucose united through both aldehyde groups. If only one aldehyde group is involved only the $\alpha$- and $\beta$-forms of the glucoside linkage are possible. The free aldehydo group can, however, exist as alpha or beta form.

What may be regarded as the simplest *biose* is the compound, $CH_2OHCHOH-O-CH_2OH$, m. 148°, isolated from cabbage leaves (Buston 1923). It is faintly sweet and is soluble in water. It is not hydrolyzed by acids, does not reduce Fehling's solution and does not form an osazone. These properties are due to the fact that aldehyde groups of the component parts glycollic aldehyde and formaldehyde are masked in the "glucoside" union.

**Bioses,** $C_{11}H_{20}O_{10}$. *Vicianose,* on hydrolysis, gives *d*-glucose and *l*-arabinose while *primaverose* gives *d*-glucose and *d*-xylose.

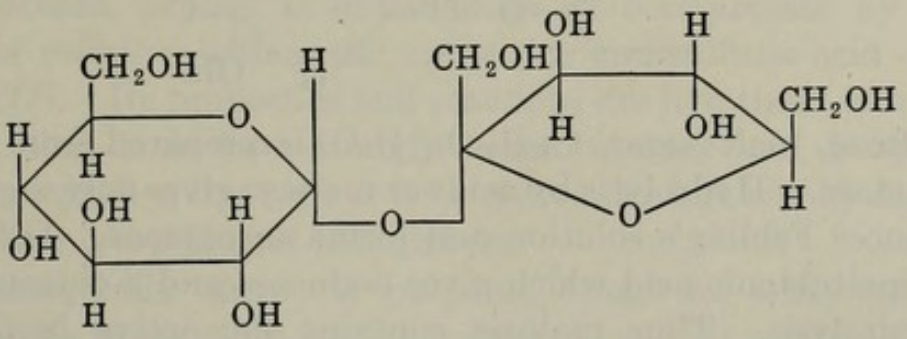
## Bioses, $C_{12}H_{22}O_{11}$

The natural and related members on hydrolysis by acid or by specific enzymes, all give glucose either alone or with other hexoses. *Maltose, gentiobiose, cellobiose* and the three *trehaloses* all give glucose alone. *Sucrose* and *turanose* give also *d*-fructose, while *lactose* and *melibiose* give also *d*-galactose and *apiobiose* gives also apiose. The artificial biose, 4-glucosido-mannose gives also mannose (Isbell 1931).

**Sucrose,** cane sugar, saccharose, saccharobiose, "sugar," m. 160°, is obtained from the sugar cane and the sugar beet. $[\alpha]_D^{20} = +66.5°$. Hydrolysis by acid or invertase gives *d*-glucose (dextrorotatory) and *d*-fructose (more strongly levorotatory). The rate of the hydrolysis by acid is about 1000 times that of maltose or lactose. The mixture is *invert sugar.* The inversion in the optical activity is used in the quantitative determination of sugar by polarimetry. Sucrose does not reduce Fehling's solution, does not react with phenylhydrazine and does not give mutarotation. Thus it does not have the active hemiacetal grouping, $-CH(OH)-O-$. Its high rate of hydrolysis is due to the $-O-C-O-C-O-$ grouping as contrasted with the $-O-C-O-C-C-$ linkage in reducing

bioses. Vigorous oxidation converts sucrose mainly to oxalic and saccharic acids.

The structure of sucrose has been determined by methylation of the hydroxyl groups and hydrolysis to tetramethyl-*d*-glucose and 1,3,4,6-tetramethyl-*d*-fructose (Haworth). This is different from ordinary tetramethylfructose which is 1,3,4,5. Thus the fructose in sucrose has a furanose ring (gamma) instead of the ordinary pyranose ring. The structure of sucrose is




Sucrose is thus 2-glucosido-$\gamma$-fructose or 2-glucosido-fructofuranose. The glucosido group is introduced in place of the 2—OH group in gamma fructose. It can also be regarded as 1-($\gamma$-fructosido)-glucose. Hudson gives the full designation of sucrose as 2-[alpha-*d*-glucosido(1,5)]-beta-*d*-fructose(2,5). Another possible name is 1-$\alpha$-*d*-glucopyranosyl-$\beta$-*d*-fructofuranoside.

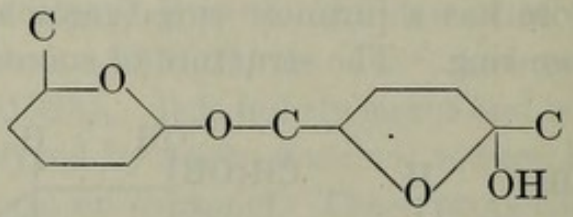
Sucrose forms several definite compounds with lime (calcium sucrates or, less correctly, saccharates). These are sometimes used for recovering an additional amount of sucrose from molasses. They can be decomposed by treatment with $CO_2$.

Triphenylchloromethane, trityl chloride, reacts with *primary* alcohol groups in sugars. Thus sucrose gives a tri-trityl ether (Rep. 1929, 100).

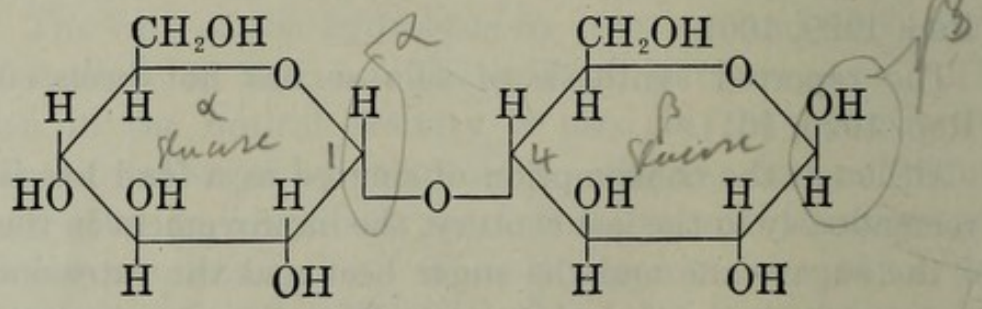
The reported synthesis of sucrose has not been confirmed (Rep. 1929, 101).

Although the consumption of sucrose as a food has increased tremendously in the last century, the improvement in the culture of the sugar cane and the sugar beet and the extension of the former culture in tropical countries has given a potential production in excess of its food uses. Industrial uses are actively being sought (Mellon Institute).

**Turanose,** m. 157°, gives glucose and levulose on hydrolysis but differs from sucrose in reducing Fehling's solution, and in showing mutarotation, indications of the free hemiacetal grouping. It is a 5-glucosidofructose unless the fructose has the furanose structure as in sucrose in which case it is 6-glucosido-$\gamma$-fructose. The skeleton structure of turanose would then be




**Maltose,** malt sugar, $C_{12}H_{22}O_{11}.H_2O$, is prepared from starch by diastase. Hydrolysis by acids or maltase gives only *d*-glucose. It reduces Fehling's solution and forms an osazone. Oxidation gives maltobionic acid which gives *d*-glucose and *d*-gluconic acid on hydrolysis. Thus maltose contains the active hemiacetal group $-CH(OH)-O-$. Since maltase, which splits maltose, is found to split only alpha glucosides and not the beta forms, maltose is concluded to be an alpha glucoside. Maltose solution shows an increasing dextrorotation on standing. Since this is characteristic of the mutarotation of $\beta$-glucose, the free glucose lactol ring in maltose is probably of that type. Methylation of maltose followed by hydrolysis gives tetramethylglucose and 2,3,6-trimethylglucose. The latter indicates that the linkage with the second molecule of glucose is through the 4-position since the 5-position is part of the pyranose ring. On the basis of this experimental evidence, maltose is described as 4-$\alpha$-glucosido-$\beta$-glucose and the corresponding formula is




The name indicates that an alpha glucose molecule has been attached through its active OH to the 4-carbon of a beta glucose

molecule with elimination of water between the two OH groups. Another descriptive name for maltose is 4-*d*-glucopyranosyl-α-*d*-glucopyranoside.

As would be expected from its two primary alcohol groups, maltose forms a di-trityl ether with triphenylmethyl chloride.

**Isomaltose** is a more or less indefinite material prepared from starch and by synthesis from glucose. *Revertose* is a biose obtained from *d*-glucose by maltase, osazone, m. 173°.

**Cellobiose,** cellose, is obtained as its octa-acetate by treatment of cellulose with acetic anhydride and sulfuric acid (Peterson 1927). Its properties and reactions are like those of maltose except that it is less strongly dextrorotatory and is split by emulsin which splits typical beta glucosides but not by maltase. Cellobiose is 4-β-glucosido-β-glucose.

**Lactose,** milk sugar, is prepared from the whey of milk. Hydrolysis gives *d*-glucose and *d*-galactose. It contains a free active group as shown by oxidation by Fehling's solution, its action with phenylhydrazine and its mutarotation. Bromine water gives lactobionic acid which, on hydrolysis, becomes *d*-galactose and *d*-gluconic acid showing that the free active group is in the glucose part. The oxidation of bioses to bionic acids by bromine is best carried out in the presence of a benzoate which reacts with the HBr and prevents the breaking of the biose linking (Rep. 1929, 94). Since methylation and hydrolysis give $Me_4$-galactose and 2,3,6-$Me_3$-glucose, lactose is 4-β-*d*-galactosido-*d*-glucose. It exists in α- and β-forms whose rotations fall and rise respectively until the equilibrium value of +55° is reached.

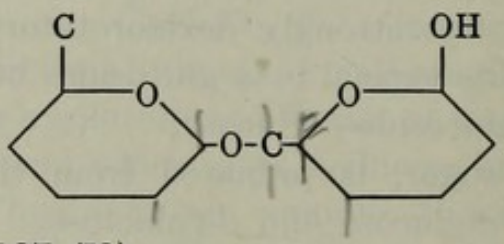
Lactose, with dilute bases, gives a ketose, *lactulose* which gives *d*-fructose and *d*-galactose on hydrolysis. It is 4-β-*d*-galactosido-α-*d*-fructose (Rep. 1930, 109).

Lactose octa-acetate, with $AlCl_3$, gives the chloroacetyl derivative of *neolactose*, a galactosido-*d*-altrose. This inversion of both the α- and β-carbons is very unusual (Hudson 1926). This artificial biose differs from those occurring in nature by not containing glucose. Cellobiose and lactose have the same skeleton structure as maltose (Haworth, Rep. 1927, 78).

Lactose, Whittier, Rev. 1925, 85–126.

**Gentiobiose,** obtained from gentianose, a triose, gives glucose on hydrolysis, is split by emulsin and gives tetramethylglucose and 2,3,4-trimethylglucose on methylation and hydrolysis. It is thus 6-$\beta$-glucosido-glucose. The enzymes are true catalysts in that they speed up the reverse process as well as the direct one. Thus emulsin converts *d*-glucose to gentiobiose. It reduces Fehling's solution and shows mutarotation.

**Melibiose,** is obtained from raffinose. It is 6-$\alpha$-galactosido-$\alpha$-glucose and the corresponding -$\beta$-glucose. The equilibrium value $[\alpha]_D = +143°$. The skeletons of gentiobiose and melibiose are




(Haworth, Rep. 1927, 78).

**Trehalose,** isotrehalose and neotrehalose are glucosido-glucoses containing no free active group. They presumably represent the three possible forms: 1-$\alpha$-glucosido-$\alpha$-glucose, 1-$\alpha$-glucosido-$\beta$-glucose and 1-$\beta$-glucosido-$\beta$-glucose (Rep. 1925, 88). Trehalose appears as a reserve carbohydrate in many fungi which are unable to form starch.

**Rutinose** is a biose, $\beta$-1-*l*-rhamnosido-6-*d*-glucose (Zemplén 1935).

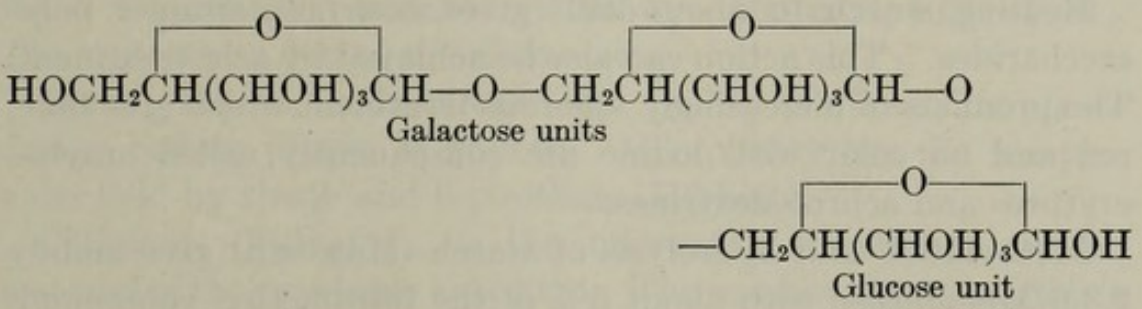
## Trioses, $C_{18}H_{32}O_{16}$

**Raffinose,** melitriose, the most important trisaccharide, is found in small amounts in nature. It is present in cottonseed meal to about 8% and in beet molasses. It is tasteless. Careful hydrolysis by acids or by raffinase gives *d*-fructose and melibiose while hydrolysis by emulsin gives sucrose and galactose. Thus the two enzymes attack different glucoside linkages. It does not reduce Fehling's solution. Thus there is no free active group. It is probably 1-($\gamma$-fructosido)-6-galactosido-glucose.

**Gentianose,** with dilute acids or invertase gives fructose and gentiobiose which can be further hydrolyzed to glucose. It contains no free active group. Thus it is probably 1-fructosido-6-glucosido-glucose.

**Melezitose,** melecitose, can be hydrolyzed to glucose and turanose. Since it does not reduce Fehling's solution it contains no free active group and is probably 2,5- or 2,6-diglucosido-fructose.

**Mannotriose,** manninotriose, gives 2 molecules of *d*-galactose and 1 of *d*-glucose. It reduces Fehling's solution and may be 6-(6-galactosido-galactosido)-glucose,




TETROSE

**Stachyose,** $C_{24}H_{42}O_{21}$, is the only definite tetrasaccharide. It does not reduce Fehling's solution. Careful hydrolysis gives mannotriose and *d*-fructose. Thus it is possibly 1-fructosido-6-(6-galactosido-galactosido)-glucose.

Haworth, "Constitution of the Sugars," Arnold and Company, London, 1929.

*Polyoses unlike sugar.*

These form important sources of reserve carbohydrates in animals and in plants (glycogen, inulin, starch) and material for the cell walls in plants (cellulose). Most of them are of very high molecular complexity and are insoluble. Under certain conditions, they give colloidal solutions. They undergo hydrolysis to monoses with varying degrees of ease. Polysaccharides related to nearly all the types of monoses are known although those derived from glucose are by far the most plentiful.

**Starch.** The starches obtained from different vegetable sources differ in physical properties but all give glucose on complete hydrolysis. Partial hydrolysis of starch gives simpler polysaccharides such as the dextrins. Many enzymes, such as diastase, hydrolyze starch to maltose. Such enzymes are widely distributed in plants and animals.

Alpha and beta amylose have been separated from the outside and inside of starch granules, the former amounting to over 80% of the total. They differ in optical activities (Rep. 1930, 112).

Starch gives a characteristic blue color with free iodine.

Starch does not reduce Fehling's solution. With hypobromite it gives maltobionic acid which on hydrolysis gives *d*-glucose and *d*-gluconic acid.

Heating starch to about 250° gives *dextrines*, simpler polysaccharides. This action can also be achieved by acid treatment. The products of increasingly vigorous treatment which give blue, red and no color with iodine are consequently called amylo-, erythro- and achroo-dextrines.

Methylation and hydrolysis of starch (Haworth) give mainly 2,3,6-$Me_3$-glucose with about 5% of the tetramethyl compound. On this basis starch is regarded as a polyglucosidic alpha combination of about 20 glucose units combined by the 1- and 4-positions as in maltose (Rep. 1931, 102; 1933, 127).

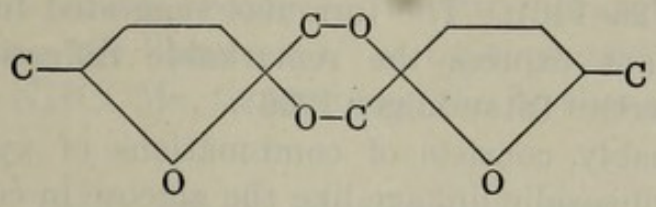
Starch, Gray and Staud, Rev. 1927, 355–74.

**Glycogen,** liver starch, is the means used by the animal body to store glucose. It is more soluble in hot water than other polysaccharides. It does not reduce Fehling's solution. With iodine it gives a violet red color. Hydrolysis gives amyloses, maltose and finally glucose.

**Inulin** is a reserve polysaccharide in many plants. It does not reduce Fehling's solution. It is soluble in hot water and is levorotatory. Acids or inulase convert it entirely to *d*-fructose. Methylation and splitting gives 3,4,6-$Me_3$-$\gamma$-fructose (Haworth). Thus the fructose in inulin is fructofuranose the same as in sucrose. Hydrolysis converts it to the more stable fructopyranose, ordinary *d*-fructose. The fructose units in inulin are held in glucosidic linkage probably through the 2- and 1-positions of successive units in the chain molecule. Inulin undergoes "depolymerization" to smaller combinations of fructose units with great ease (Rep. 1929, 101–3).

Treatment of inulin with nitric acid in chloroform gives a very stable difructose anhydride (Irvine, Rep. 1932, 130). Its

skeleton is




Three isomeric forms have been obtained corresponding to the three theoretically possible stereomers (Jackson 1929, 1931). The stability is due to the dioxan ring.

**Levan,** laevan, a levulosan like inulin, is found in plants during certain phases of growth. It probably has the fructose units held by the 2- and 6-positions (Hibbert).

**Cellulose,** $(C_6H_{10}O_5)_x$, is the important structural building material of the vegetable kingdom. The amount of it in existence at any one time corresponds to about half the amount of $CO_2$ in the atmosphere. It is constantly being built up from that source and being broken down to it again by various microorganisms.

Cotton is nearly pure cellulose. A very high grade of alpha cellulose is now obtained from wood by removing all other materials by physical and chemical treatment.

Cellulose is insoluble in most solvents but dissolves in ammoniacal copper solution (Schweitzer's reagent).

Hydrolysis gives glucose in almost quantitative yield. Acetolysis of cellulose gives about 40% yield of cellobiose octa-acetate. Cellotriose, m. 238°, cellotetraose, m. 251°, and cellohexaose, m. 266°, have been prepared (Willstätter) (Rep. 1931, 104).

Cellulose may be regarded as consisting of long chains of glucose molecules linked in glucosidic (beta) combination. (Rep. 1924, 88–91; 1932, 126). These chains orient themselves in the fibers of cellulose. It is experimentally known that there are three hydroxy groups for each glucose unit in cellulose. The nitrates, acetates and xanthogenates of these groups are of the utmost importance in the industries based on nitrocellulose (explosives, lacquers), and in the manufacture of artificial fibers (Rayon, acetate silk, etc.). The ethers of cellulose are also industrially important.

The polysaccharides have received much attention in recent years and many of the difficult problems in the field including

that of their molecular complexity are approaching solution. (Rep. 1932, 126–136). The formulas suggested for starch and cellulose do not express the remarkable differences in their physical properties (Staudinger 1936).

**Xylan** probably consists of combinations of xylose residues held in beta glucosidic linkage like the glucose in cellulose (Rep. 1929, 105).

**Pentosans,** arabans, etc. bear similar relations to the pentoses that starch and cellulose bear to glucose.

**Lichenin,** moss starch, is found in lichens and seeds. It is a typical hemicellulose or reserve cellulose such as are stored in plants as ready sources of carbohydrate energy. They are readily hydrolyzed by acids and enzymes. Rep. 1925, 100; Hawley 1932.

**Pectins** are complex compounds of polygalacturonic acid and related compounds combined with methanol and monoses in glucosidic combination (Link 1934).

Lignin. Phillips, Rev. 1934 I, 103–165.

## XXVI. AMINO ACIDS

These substances are of the utmost importance since those in which the amino group is alpha to the carboxyl group are the building stones of the proteins of animals and plants. These have been obtained by hydrolysis of proteins and have been built up in the laboratory to form polypeptides which resemble some of the simpler protein compounds (E. Fischer 1906).

The amino acids show the reactions of both their characteristic groups. They are thus amphoteric, forming, for example, either hydrochlorides or sodium salts. In the neutral condition they exist as ammonium salts formed between the amino and carboxyl groups, either of the same or different molecules. As ammonium salts, the amino acids are non-volatile, crystalline solids, very soluble in water but practically insoluble in organic liquids.

Amino acids form phosphotungstates which are useful in their isolation (Drummond 1918).

In utilizing the reactions of either of the groups in the amino acids the presence of the other must be remembered. Thus an

attempt to make an acid chloride by means of any of the ordinary reagents causes trouble because of the active H atoms of the $NH_2$ group. If these are "protected" as by conversion to an acetyl derivative, $-NHCOMe$, the carboxyl can be changed to $-COCl$ satisfactorily.

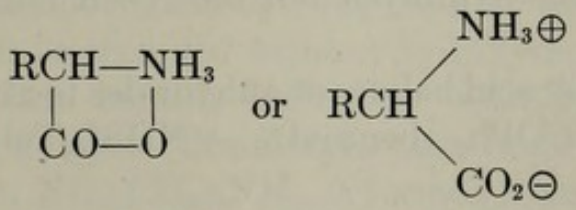
*Preparation of Alpha Amino Acids.*

1. By hydrolysis of proteins either by heating with dilute acid or by proteolytic enzymes. Methods of separation for the thirty-one amino acids which have been isolated from various proteins are still inadequate.

2. By hydrolysis of alpha amino nitriles obtained by treating aldehydes with KCN and $NH_4Cl$ (Strecker, Zelinsky). This process is assumed to go through the cyanohydrins.

$$RCHO \rightarrow RCH(OH)CN \rightarrow RCH(NH_2)CN \rightarrow RCH(NH_2)CO_2H$$

The amino acids will be represented as in the "free" form although they exist as an ammonium salt such as:




3. By the usual methods for making amines from halogen compounds. The action of $NH_3$ with alpha halogen acids gives the desired product but also di- and even tri-substitution products of ammonia. On the other hand, the Gabriel phthalimide synthesis is successful with alpha bromo esters (see Method 6).

4. By the reduction of oximes and hydrazone derivatives of alpha keto acids.

5. From aldehydes by condensation with hippuric acid (benzoyl glycine) followed by reduction and hydrolysis

$$RCHO + PhCONHCH_2CO_2H \rightarrow RCH{=}C(NHCOPh)CO_2H \rightarrow RCH_2CH(NHCOPh)CO_2H \rightarrow RCH_2CH(NH_2)CO_2H$$

The reduction step is easy because of the $\alpha\beta$-position of the double bond.

6. Treatment of an alkyl halide of Class 1 (p. 71) with sodium phthalimidomalonic ester, obtained from bromomalonic ester and

potassium phthalimide, followed by hydrolysis and heating, has the net effect of adding the grouping $-CH(NH_2)CO_2H$ to the original organic residue

$$RX \rightarrow RC(CO_2Et)_2N(CO)_2C_6H_4 \rightarrow$$
$$C_6H_4(CO_2H)_2 + RC(NH_2)(CO_2H)_2 \rightarrow$$
$$CO_2 + RCH(NH_2)CO_2H.$$

The history of the discovery of amino acids including methionine has been given by Vickery, Rev. 1931, 169–318. Gortner, 291–308.

*Reactions of Alpha Amino Acids.*

*A. Reactions due to the $-NH_2$ Group.*

1. Formation of hydrochlorides, $RCH(NH_3Cl)CO_2H$.

2. Alkylation to give $-NHR$ and $-NR_2$. This sometimes involves the formation of a betaine, or internal quarternary ammonium salt, $\oplus R_3NCH(R')CO_2\ominus$. This, on heating, gives an ester such as $R'CH(NR_2)CO_2R$. The ester alkyl can be removed by acid or alkaline hydrolysis but the $N-R$ linkage is not thus broken.

3. Acylation by acid halides or anhydrides to give $-NHCOMe$ (acetyl), $-NHCOPh$ (benzoyl), $-NHSO_2Tol$ (*p*-toluenesulfonyl, tosyl) etc.

4. With nitrous acid to give $N_2$ and hydroxy acids and related products. The measurement of the $N_2$ gas is a method for determining $NH_2$ groups (Van Slyke). Conversion of the $NH_2$ group to hydroxyl is also produced by various microorganisms.

Treatment of the *esters* with nitrous acid gives diazo esters, $RC(N_2)CO_2H$, which resemble diazomethane in reactions.

5. Hydriodic acid at 200° removes the amino group leaving unsubstituted acids.

6. Treatment with formaldehyde converts the $-NH_2$ groups to $-NHCH_2OH$ groups. This leaves the carboxyl group free so that it can be titrated with indicators. This is the basis of the "formol titration" of amino acids.

7. They give characteristic crystalline compounds with Reinecke's solution, $H[Cr(NH_3)_2(SCN)_4]$. Thus lysine Reineckate has the formula $C_6H_{14}O_2N_2.2\,HR,4\,H_2O$, m. 235° dec.

*B. Reactions due to the $-CO_2H$ Group.*

1. Formation of metal salts, $RCH(NH_2)CO_2Na$ etc.

2. Formation of esters, $RCH(NH_2)CO_2R'$, from the acid, alcohol and HCl. This gives the ester hydrochloride which, with mild alkaline treatment, gives the free ester. These compounds are volatile and have been used in separating amino acids (E. Fischer).

3. Formation of acyl halides, etc. For this reaction the amino group must be acetylated or benzoylated before treatment with $SOCl_2$, $PCl_5$, etc., to give RCH(NHCOMe)COCl, etc. After the acid chloride has been used for the desired purpose, the protecting group can be removed by vigorous treatment with HCl to give the hydrochloride of the free $NH_2$ compound. Since the chief use of acyl halides of amino acids is in making peptides this process is of limited value because the hydrolysis of the protecting group also breaks the peptide linkage. Acetyl-glycyl-glycine has the formula $CH_3CONHCH_2CONHCH_2CO_2H$. Thus the protecting group is held by a "peptide linkage" also. This difficulty has been overcome by Bergmann by using a protecting group which can be removed without hydrolysis (p. 605).

4. Heating with barium hydroxide solution removes $CO_2$ leaving primary amines. Similar processes occur in putrefaction. Thus putrescine, $NH_2(CH_2)_4NH_2$, is formed from ornithine.

5. Treatment with acetic anhydride and pyridine removes $CO_2$ and forms an $\alpha$-acetamidoketone (Rep. 1928, 91).

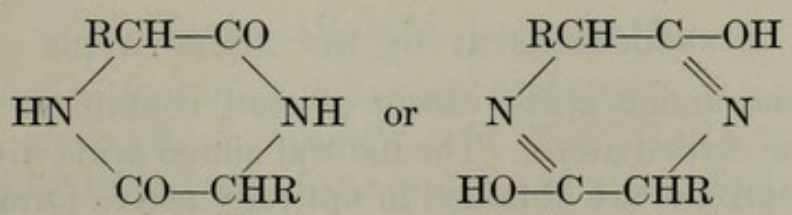
$$RCH(NH_2)CO_2H + (MeCO)_2O \rightarrow CO_2 + RCH(NHCOMe)COMe$$

6. Reduction of esters of amino acids with Na and absolute alcohol gives homologs of ethanolamine, $RCH(NH_2)CH_2OH$.

*C. Reactions involving both $-NH_2$ and $-CO_2H$.*

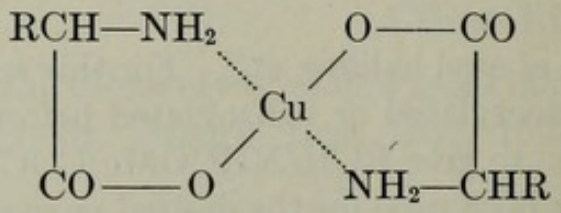
1. Formation of inner salts or dipolar ions (Zwitter ions) as already outlined.

2. Dehydration to give diketopiperazines.



This type of grouping is also formed in the partial hydrolysis of proteins.

3. Amino acids dissolve CuO on heating and give deep blue salts which show the properties of cuprammonium complex salts. They give no precipitate with bases. They may be formulated as



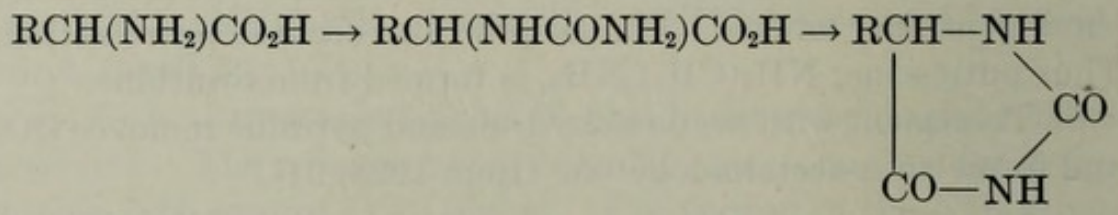
Dilute $FeCl_3$ solution gives a red color with many amino acids. This is undoubtedly due to a complex formation involving both groups.

4. Various biological processes remove both groups with the formation of primary alcohols.

$$RCH(NH_2)CO_2H + H_2O \rightarrow CO_2 + NH_3 + ROH.$$

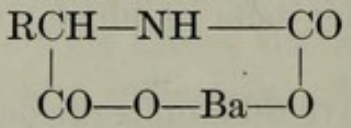
This is the source of the alcohols of fusel oil.

5. Treatment with potassium isocyanate and HCl gives *hydantoins*.



$NH_4SCN$ in acetic anhydride gives *thiohydantoins*.

6. Carbon dioxide in the presence of bases adds to the $NH_2$ group giving carbamino acids which form stable soluble salts with alkaline earth metals. Thus solutions of the amino acids in barium hydroxide give no precipitate with $CO_2$ but form soluble salts of the type



### Stereochemistry of the Amino Acids

The alpha amino acids, except glycine, contain at least one asymmetric carbon atom. The natural amino acids with the exception of glycine are obtained in optically active forms. They

all belong to the *l*-series as can be shown by their configurational relation to the *l*-malic acid. The optical activity of the amino acids depends on the specificity of the enzymes which tear down and build up proteins. If they can combine with one configuration they cannot combine with its mirror image. They literally have to be "hand in glove" with their substrates and a right hand cannot fit a left glove.

Introduction and replacement of the $NH_2$ group in the optically active amino acids give many examples of the Walden inversion. The following changes are illustrative.

1. Dextrorotatory (*l*-) alanine $\xrightarrow{NOBr}$ *l*-Br-propionic acid.
2. Levorotatory (*d*-) alanine $\xrightarrow{NOBr}$ *d*-Br-propionic acid.
3. Treatment of the optically active bromopropionic acids with $NH_3$ gives the alanines of the *same* sign of rotation as the starting material. Thus *l*-alanine can be converted to *d*-alanine and vice versa by apparently simple metathetical processes. In spite of an enormous amount of work and much speculation, these changes are still not understood.

The racemic synthetic amino acids are readily resolved by means of active bases such as brucine after protecting the $NH_2$ by the formyl group (Fischer 1905).

## Classification of Amino Acids

The individual amino acids related to proteins may be classified in various ways. Some have the same number of acid and basic groups while others have an excess of one or the other. While most contain the basic and acid groups in aliphatic chains, with or without aromatic substituents, proline and hydroxy proline have these groups in heterocyclic combination. As will be seen these are closely related to the aliphatic diamines just as the parent pyrrolidine is related to 1,4-diaminobutane.

### *A. Purely Aliphatic Amino Acids*

1. *Simple amino derivatives of the acetic acid series.*

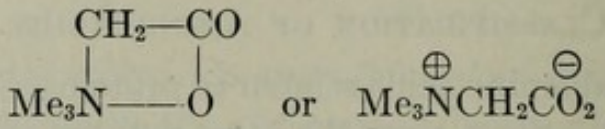
**Glycine,** glycocoll, aminoacetic acid, $H_2NCH_2CO_2H$, m. 232°, is obtained by hydrolysis of the proteins of glue, gelatin and silk

fibroin. Treatment of chloroacetic acid with ammonia gives glycine together with iminodiacetic acid, $NH(CH_2CO_2H)_2$ and nitrilotriacetic acid, $N(CH_2CO_2H)_3$. By modifications of the process, the yield can be raised to 50% (Robertson 1927). Glycine is obtained by treating Cu, Co, Ni or Zn salts of chloroacetic acid with $NH_3$. The action of NaCN, $NH_4Cl$ and formaldehyde give $C_9H_{12}N_6$ (Johnson, Rinehart, 1924) a trimer of methyleneamino acetonitrile, $CH_2=N-CH_2CN$, which can be converted to glycine by hydrolysis (OS).

Four types of complex copper salts of glycine are known (Borsook 1932).

A solution of glycine in barium hydroxide gives no precipitate with $CO_2$ but forms a soluble salt of a carbamino acid.

Acetyl glycine, $CH_3CONHCH_2CO_2H$, is called *aceturic acid*. *Hippuric acid*, benzoylglycine, $C_6H_5CONHCH_2CO_2H$, m. 187°, occurs in urine of the herbivora. It can be made from glycine and benzoic acid or benzoyl chloride. It condenses with aldehydes to give $\alpha$-benzamido-$\alpha\beta$-unsaturated acids which can be reduced and hydrolyzed to give higher $\alpha$-amino acids. **Sarcosine,** N-methylglycine, $CH_3NHCH_2CO_2H$, is formed by the decomposition of creatine and caffeine. It occurs in muscle and is found in meat extract. **Betaine,** completely methylated glycine, gives its name to similar internal quaternary ammonium salts of amino acids



Betaines are found in plants probably as end-products of nitrogen metabolism (Barger). Betaine itself occurs in sugar beets and can be obtained from beet molasses. It can be made from $Me_3N$ and chloroacetic acid. When heated to 293° it becomes methyl-N-dimethylaminoacetate, $Me_2NCH_2CO_2Me$. At higher temperatures it gives $Me_3N$.

The physiological activity of *-onium compounds* of the betaine type has been extensively studied by Renshaw and his students.

**Alanine,** $\alpha$-aminopropionic acid, $CH_3CH(NH_2)CO_2H$, m. 298°, exists in practically all proteins. It constitutes over 20% of the fibroin of silk. It was first synthesized by Strecker

from acetaldehyde. It can be prepared from pyruvic acid, $MeCOCO_2H$, with $H_2$ and $NH_3$ in the presence of palladium catalyst. Similar results are obtained when cysteine is used as the catalyst. It is possible that the formation of amino acids in organisms may go through the keto acids.

**α-Aminobutyric acid,** $C_2H_5CH(NH_2)CO_2H$, is found in very small amounts in a few proteins.

**Valine,** α-aminoisovaleric acid, $(CH_3)_2CHCH(NH_2)CO_2H$, m. 315°, is found in small amounts in many proteins and to about 5% in edestin and casein. Yeast converts it to isobutyl alcohol. **Norvaline** is α-amino-*n*-valeric acid, $CH_3CH_2CH_2CH(NH_2)CO_2H$.

**Leucine,** α-aminoisocaproic acid,

$$(CH_3)_2CHCH_2CH(NH_2)CO_2H,$$

m. 295°, is widely distributed among proteins and makes up a large part of such important ones as the globin of hemoglobin, serum albumen, serum globulin, blood fibrin, keratin of horn, hair, etc. and vegetable proteins such as edestin and zein. It is fermented by yeast to isoamyl alcohol. **Isoleucine,** α-amino-β-methylvaleric acid, $C_2H_5(CH_3)CHCH(NH_2)CO_2H$, m. 280°, makes up 1–2% of the amino acids of casein. Its molecule contains two asymmetric carbon atoms. The natural material is bitter and is fermented by yeast to optically active amyl alcohol. Mild treatment with barium hydroxide solution racemizes the alpha carbon giving *allo-isoleucine* which is sweet and is not attacked by yeast. Allo-isoleucine can also be made from *d*-valeraldehyde by the Strecker synthesis, the new asymmetric carbon being obtained in both stereoisomeric forms. **Norleucine,** caprine, α-amino-*n*-caproic acid, $CH_3(CH_2)_3CH(NH_2)CO_2H$, m. 285°, is found in traces in certain proteins. It is found along with leucine in the proteins from the spinal cords of cattle.

**Beta-amino acids** can be made from β-halogenated acids and by the addition of ammonia to αβ-unsaturated acids. Heat reverses this process, converting the β-$NH_2$ to αβ-unsaturated acids. *Betaines* of beta amino acids on heating give the $R_3N$ salts of αβ-unsaturated acids. Betaines of alpha amino acids decompose on heating to give $R_3N$ and αβ-unsaturated acid, thus giving a simple way of removing the amino group by exhaustive methylation.

**Gamma- and delta-amino acids** can be made from the corresponding halogen acids. On heating they lose water and form gamma lactams analogous to the lactones. The betaines of gamma amino acids, on heating, give $R_3N$ and gamma lactones (Rep. 1904, 101).

**Amino acids** with more carbons between the active groups are known. These show reactions of both groups. A method of producing the $\omega$-amino caproic and heptylic acids involves the following changes (v. Braun 1907).

$$\text{Benzoyl piperidine} \xrightarrow{PCl_5} C_6H_5CONH(CH_2)_5Cl \xrightarrow[\text{Na malonic ester}]{\text{KCN etc.}} \xrightarrow[\text{etc.}]{}$$

Reduction of the phenylhydrazones of keto acids gives the corresponding amino acids (Fischer 1911).

$\epsilon$-Aminocaproic acid when heated gives 20–30% of the 7-membered lactam and 80–70% of a polymer probably containing at least ten molecules of the acid. On the other hand $\gamma$-aminobutyric acid and $\delta$-aminovaleric acid, on heating, give the 5- and 6-membered lactams without the formation of any polymers. $\zeta$-Aminoheptoic acid gives only polymeric products and none of the 8-membered lactam (Carothers 1930). Thus if the distance between the $NH_2$ and $CO_2H$ groups is favorable for ring formation, the action of heat is intramolecular. Otherwise, there is an increasing tendency to have the elimination of water take place between different molecules.

2. *Amino derivatives of aliphatic acids containing an additional basic group.*

**Ornithine,** $\alpha\delta$-diaminovaleric acid, $H_2N(CH_2)_3CH(NH_2)CO_2H$, is obtained as a syrup by the hydrolysis of arginine

$$-CH_2NHC(NH)NH_2 + 2\,H_2O \rightarrow -CH_2NH_2 + CO_2 \rightarrow 2\,NH_3.$$

The extra $NH_2$ group makes this substance an amine as well as an internal ammonium salt. Putrefaction decarboxylates it to putrescine, $H_2N(CH_2)_4NH_2$. Proline may be regarded as the inner cyclic imine of ornithine.

**Lysine,** $\alpha\epsilon$-diaminocaproic acid, $H_2N(CH_2)_4CH(NH_2)CO_2H$, m. 224°. The presence of the free amino group lowers the m.p.

60° as compared with norleucine. Lysine occurs in all the important classes of proteins except the prolamines. It occurs to about 10% in serum albumen and in fibrin from clotted blood. Decarboxylation by the bacteria of putrefaction gives cadaverine, $H_2N(CH_2)_5NH_2$. Lysine is an essential for nutrition.

**Arginine,** $\alpha$-amino-$\delta$-guanidylvaleric acid,

$$H_2NC(NH)NH(CH_2)_3CH(NH_2)CO_2H,$$

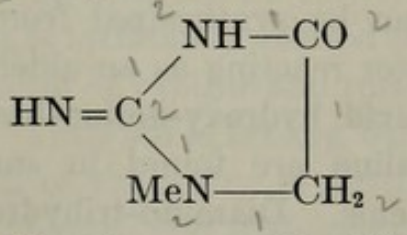
m. 238° dec., is best prepared from gelatine (Bergmann 1927). It is a strong enough base to give a stable carbonate. Clupeine and salmine, proteins of the sperm of herring and salmon contain arginine to the extent of two-thirds of their amino acid residues. In smaller amounts it occurs in nearly all proteins. It apparently contributes their basic properties. In the same way that a 1,4-diamine can lose $NH_3$ to form a cyclic imine, a 1,4-amino-guanadino compound such as arginine might lose a molecule of guanidine to give *proline*, pyrrolidine-$\alpha$-carboxylic acid. The parallel occurrence of arginine and proline in most proteins may indicate such a relation.

Suberyl arginine is a constituent of the bufotoxins from toad venom.

**Creatine,** N-methylguanidylacetic acid,

$$H_2NC(NH)N(CH_3)CH_2CO_2H,$$

is present in muscle and, as creatine phosphoric acid, is intimately connected with muscular activity. An inner anhydride, *creatinine*, is found in plants and in beef extract.



The hydrolysis of creatine gives sarcosine, $MeNHCH_2CO_2H$.

3. *Amino derivatives of dibasic acids.*

**Aspartic acid,** aminosuccinic acid, $HO_2CCH_2CH(NH_2)CO_2H$, m. 251°, an acid as well as an ammonium salt, is widely distributed among proteins. Its synthesis from malic acid through chlorosuccinic acid is easy. With optically active materials, these

changes have given many important examples of the Walden inversion. **Asparagin,** $HO_2CCH(NH_2)CH_2CONH_2$, the half amide of aspartic acid is found in asparagus.

**Glutamic acid,** $\alpha$-aminoglutaric acid,

$$HO_2C(CH_2)_2CH(NH_2)CO_2H,$$

m. 206°, is found in most proteins. It gives acid properties because of its free carboxyl group. It is the most plentiful single component of the hydrolytic products of casein, amounting to 15–20%. It forms over 40% of the gliadin from wheat gluten. Sodium glutamate (Ajinomoto, Aji, Chuyu, Gluta, Ve-tze-sin) is used as a condiment in Japan and China to give a meatlike taste to vegetable foods (Han 1929). It can be tasted in 1 : 3000 dilution whereas the limits for sucrose and NaCl are 1 : 200 and 1 : 400. Yeast converts glutamic acid to succinic acid, a product found in small amounts in fermentation residues. **Glutamine,** $HO_2CCH(NH_2)CH_2CH_2CONH_2$, is the half amide of glutamic acid. Insulin is believed to contain glutamine combined with cystine (Jensen 1932).

4. *Hydroxy aliphatic amino acids.*

**Serine,** $\alpha$-amino-$\beta$-hydroxypropionic acid

$$HOCH_2CH_2(NH_2)CO_2H,$$

m. 228° dec., is obtained by acid hydrolysis of silk gum, which consists mainly of the protein, *sericin* (Shelton 1925). It occurs in small amounts in other proteins. With nitrous acid it gives glyceric acid. It can be synthesized from hippuric ester and formic ester, the latter reacting as an aldehyde.

**Hydroxyglutamic acid, hydroxy-amino-butyric acid, hydroxylysine** and **hydroxyvaline** are found in small amounts in the hydrolysis of proteins. **Diamino-trihydroxydodecanoic acid,** $C_{12}H_{26}N_2O_5$, and **diamino-dihydroxysuberic acid,** $C_8H_{16}N_2O_6$, have been obtained from casein.

5. *Aliphatic amino acids containing sulfur.*

**Cysteine,** $\alpha$-amino-$\beta$-mercaptopropionic acid,

$$HSCH_2CH(NH_2)CO_2H,$$

is readily oxidized to its disulfide *cystine*. The oxidation-reduction system $-S-S-$ and $-SH$ represented by these two compounds is of the utmost importance in biological processes. The oxidation of cysteine is catalyzed by even minute amounts of metals like Fe, Cu, and Mn. The sulfhydryl group (mercapto group) in cysteine has important growth stimulating properties (Hammett 1933). Other mercapto compounds such as thioglycollic acid, $HSCH_2CO_2H$, thioglucose, and thiocresols have similar effects when applied to seedlings and to wounds in animals (Hammett 1930). Cysteine hydrochloride solution buffered with sodium borate is recommended as an aid to the healing of wounds (Squibb).

While cysteine has not been found in proteins it is the active part of the tripeptide glutathione which is widely distributed in cells.

Cysteine cannot be considered separately from cystine. The two probably form a biological unit involved in all processes of oxidation and growth. Naturally the material from dead tissues is found mainly in the oxidized form, cystine.

**Cystine,** bis-[$\alpha$-aminopropionic acid]-$\beta$-disulfide,

$$[-S-CH_2CH(NH_2)CO_2H]_2,$$

m. 260° dec., occurs plentifully in hair, wool and horn. This occurrence is probably related to the growth promoting effect of cysteine which on oxidation gives cystine, the ordinary change from a sulfhydryl compound to a disulfide. It is similarly found in hemoglobin and in insulin, the hormone of the pancreas. In both these proteins it is intimately related to oxidizing function. The activity of the sulfur in cystine and related proteins presents a complex problem. Thus while boiling with 0.1 N sodium carbonate liberates 2.8% of the sulfur in cystine as $H_2S$, the same treatment of dialanylcystine and dialanylcystine anhydride give 18.6% and 91.8% respectively (Sheppard 1930).

Cystine with excess iodine solution gives *cysteic acid*,

$$HO_3SCH_2CH(NH_2)CO_2H.$$

Cystine is essential for nutrition.

**Methionine,** $\alpha$-amino-$\gamma$-methylmercapto-butyric acid,

$$CH_3SCH_2CH_2CH(NH_2)CO_2H,$$

is found in casein in small amounts and in ovalbumin and edestin to the extent of 4.5 and 2%. It has been synthesized in several ways (Rep. 1931, 234). One preparation is by the phthalimido-malonic ester synthesis from 1-chloro-2-methylmercaptoethane, $ClCH_2CH_2SMe$, obtainable from ethylene chloride and NaSMe. Synthetic methionine has been resolved by means of the brucine salts (Marvel 1931). The *l*-isomer is identical with the natural material. Methionine may act like cystine in metabolism. Although *taurine,* aminoethyl sulfonic acid, $H_2NCH_2CH_2SO_3H$, does not belong in this series it may be mentioned here because of its occurrence in bile and its possible relation to methionine from which it might be obtained by oxidation and decarboxylation. It is readily synthesized by standard reactions.

*B. $\alpha$-Aminopropionic Acid (Alanine) with Cyclic Substituents in the Beta Position*

1. *With purely aromatic substituents.*

**Phenylalanine,** $\alpha$-amino-$\beta$-phenylpropionic acid,

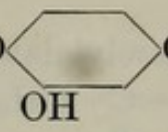
$$C_6H_5CH_2CH(NH_2)CO_2H,$$

m. 280° ±, is found in all classes of proteins except the protamines. It gives the xanthoproteic reaction with nitric acid.

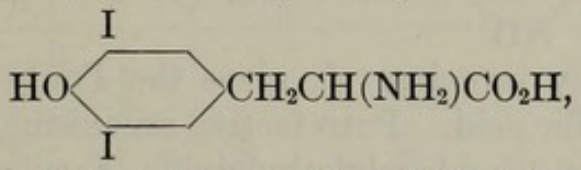
**Tyrosine,** *p*-hydroxy-phenylalanine, $\alpha$-amino-$\beta$-*p*-hydroxy-phenylpropionic acid, $p$-$HOC_6H_4CH_2CH(NH_2)CO_2H$, m. 318°, occurs in all types of proteins except the protamines. It gives the xanthoproteic test with $HNO_3$. With Millon's reagent (mercuric nitrate in nitric acid containing nitrous acid), it gives a red brown precipitate. With diazotized sulfanilic acid (benzene *p*-diazonium sulfonate) it gives a red color due to formation of an azo dye (Pauly reaction). Decarboxylation gives *tyramine,* $\beta$-*p*-hydroxyphenyl-ethyl amine. The ethyl ester of tyrosine is used as an anti-oxidant in edible fats. N-Dimethyltyramine is *hordenine.*

**Surinamine,** ratanhine, is N-methyltyrosine,

$$p\text{-}HOC_6H_4CH_2CH(NHCH_3)CO_2H.$$

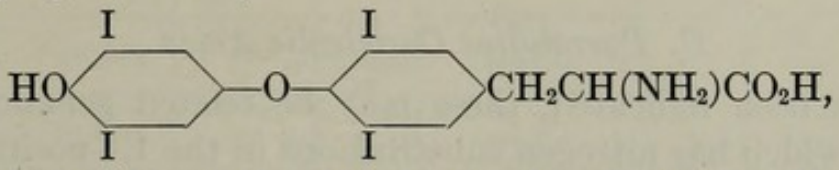
3,4-Dihydroxyphenylalanine,  , is found in only a few proteins.

**Iodogorgoic acid,** 3,5-diiodotyrosine,



has been obtained from the protein of the thyroid gland (Rep. 1931, 234).

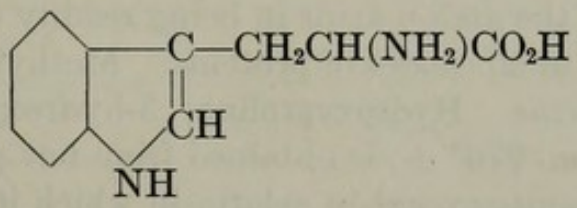
**Thyroxine,** 3,5-diiodo-4-(3,5-diiodo-4-hydroxyphenoxy)-phenylalanine, $\alpha$-amino-$\beta$-4-(2,6,3′,5′-tetraiodo-4′-hydroxy-diphenyloxidyl)-propionic acid,



was first isolated from the thyroid gland by Kendall. Harington, in Barger's laboratory, proved its structure and synthesized it (Rep. 1926, 234; 1928, 261; 1930, 274; 1931, 234).

2. *With heterocyclic substituents.*

**Tryptophane,** $\beta$-indolylalanine, $\alpha$-amino-$\beta$-3-indolypropionic acid, m. 290° ±.

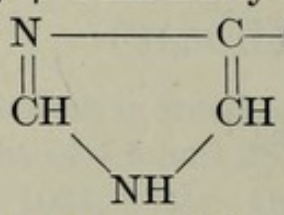


It is one of the essential amino acids. Zein (corn) and gliadin (wheat) contain no tryptophane and will not support life. It can be synthesized from $\beta$-aldehydo-indol and hippuric acid.

The betaine of tryptophane, *hypophorine*, is found in some seeds.

With concentrated nitric acid, tryptophane gives a yellow color which changes to orange with ammonia (xanthoproteic reaction). With glyoxylic acid and conc. sulfuric acid, it gives a blue violet color (Adamkiewicz).

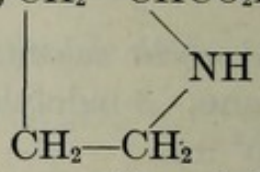
Tryptophane gives rise to the growth-hormone, hetero-auxin, indole-3-acetic acid (Kögl, Rep. 1935, 426).

**Histidine,** β-4-imidazolylalanine, α-amino-β-4-imidazolylpropionic acid,  , m. 235°, is obtained from many proteins. It gives the Pauly reaction with diazotized sulfanilic acid. Putrefactive organisms decarboxylate it to *histamine*, β-4-imidazolylethylamine, a substance of high physiological activity. Histidine is essential for life.

The *betaine of histidine* is found in certain edible mushrooms. **Ergothioneine** (thiozine), the betaine of 2-mercaptohistidine, is found in ergot and in blood. (Eagles 1928.)

### *C. Pyrrolidine Carboxylic Acids*

As has been indicated, these may be related genetically to arginine which has nitrogen substitutions in the 1,4-position in a saturated ring and is consequently closely related to these 1,4-cyclic imines.

*Proline,* pyrrolidine-α-carboxylic acid,  , m. 220°, is unique among the amino acids in being readily soluble in alcohol. It is found in all classes of proteins. Methylation gives the betaine, *stachydrine.* **Hydroxyproline,** 3-hydroxypyrrolidine-2-carboxylic acid, m. 270° ±, is obtained from few proteins and in only minute amounts except in gelatin in which it is reported to the extent of 15%. The position of the hydroxyl group is not definitely settled. If hydroxyproline is related to a hypothetical hydroxyarginine, the 3-position seems more probable than the 4-position which is usually assigned to the hydroxyl.

### *Amino Acids Formed from Individual Proteins*

The methods of separation and identification of amino acids are still so inadequate that the following figures are merely indications of the order of magnitude of the occurrence of various amino acids and of the fact that the compositions of different

APPROXIMATE PERCENTAGES OF THE COMMONER AMINO ACIDS IN REPRESENTATIVE PROTEINS

| | Alanine | Arginine | Aspartic acid | Cystine | Glutamic acid | Glycine | Histidine | Hydroxyproline | Leucine | Lysine | Methionine | Phenylalanine | Proline | Serine | Tryptophane | Tyrosine | Valine | Ammonia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Protamines* | | | | | | | | | | | | | | | | | | |
| Salmine | | 89 | | | | | | | | | | | 4 | 3 | | | 1.6 | |
| *Histones* | | | | | | | | | | | | | | | | | | |
| Globin | 4 | 5 | 4 | 0.3 | 1.7 | | 11 | 1 | 29 | 4 | | 5 | 3 | 0.6 | 3 | 2 | | |
| *Albumins* | | | | | | | | | | | | | | | | | | |
| Serum | 4 | 5 | 4 | 7 | 8 | | 4 | 1 | 30 | 11 | | 4 | 4 | 0.6 | 1 | 5 | | |
| Egg | 2 | 3 | 2 | 0.3 | 9 | | 1 | | 8 | 3 | 4 | 4 | 2 | | 2 | 1 | 2 | |
| *Globulins* | | | | | | | | | | | | | | | | | | |
| Animal | | | | | | | | | | | | | | | | | | |
| Serum | 2 | 4 | 2.5 | 4 | 8 | 3 | 2 | | 19 | 7 | | 2.5 | 2.5 | | 4 | 7 | | 2 |
| Fibrin | 4 | 7 | 2 | 1 | 10 | 3 | 3 | | 15 | 10 | | 2.5 | 4 | 0.8 | 5 | 7 | 1 | |
| Miosin | 4 | 5 | 0.5 | | 14 | 0.5 | 3 | | 8 | 3 | | 2.5 | 3 | | | 2 | 1 | |
| Vegetable | | | | | | | | | | | | | | | | | | |
| Edestin | 4 | 16 | 4 | 0.2 | 14 | 4 | 4 | 2 | 14 | 4 | 2 | 2.5 | 2 | | | 2 | 6 | 2 |
| *Prolamines* | | | | | | | | | | | | | | | | | | |
| Gliadin | 3.5 | 3 | 0.6 | 1.8 | 44 | | 2 | | 7 | | | 2 | 13 | | 1 | 1 | 2 | 5 |
| Zein | 3.8 | 1.5 | 2 | | 31 | | 0.8 | | 25 | | | 8 | 9 | | | 5 | | 4 |
| *Scleroproteins* | | | | | | | | | | | | | | | | | | |
| Keratin | 1.5 | 3 | 1 | 8 | 7 | 2 | 0.5 | | 10 | 0.5 | | 1 | 3 | 1 | | 3 | 2 | |
| Fibroin (silk) | 23 | 1.5 | | | | 40 | 1 | | 1.5 | 1 | | 1 | 1 | 2 | | 10 | | |
| Gelatin | 5 | 8 | 2 | | 4 | 20 | 0.5 | 15 | 5 | 4 | | 1 | 7 | 0.4 | | | | 0.4 |
| *Phosphoproteides* | | | | | | | | | | | | | | | | | | |
| Casein | 1.5 | 3 | 1 | 0.2 | 15 | | 4 | | 8 | 7 | 0.2 | 3 | 7 | 0.5 | | 4 | 7 | |

proteins vary over wide ranges. In most cases the numbers given are averages of those reported by various authorities.

### Polypeptides

These contain two or more amino acids held by the amido linkage $-NH-CO-$ or $-N=C(OH)-$. They are obtained by cautious hydrolysis of proteins and by synthetic means (Gortner, 309–21).

The simplest dipeptide, glycylglycine,

$$H_2NCH_2CONHCH_2CO_2H,$$

can be made in a variety of ways which illustrate the methods of linking amino acids together:

1. By action of bases on the bimolecular anhydride, diketopiperazine.

2. By action of $NH_3$ on the product of the action of chloroacetyl chloride with the amino group of glycine. For the preparation of higher peptides, the chloroacetyl glycine can be converted to its acid chloride and treated with another amino acid, etc. The final step is the replacement of the chlorine in the chloroacetyl group by means of ammonia.

A natural tripeptide, *glutathione*, glutamylcysteinylglycine,

$$HO_2CCH(NH_2)CH_2CH_2CONHCH(CH_2SH)CONHCH_2CO_2H$$

(Rep. 1930, 254), is a constituent of practically all cells. It is intimately involved in cell growth.

The polypeptides containing a large number of amino acid units have many properties resembling the simpler proteins.

E. Fischer (1907) and E. Abderhalden (1916) have built up polypeptides containing 18 and 19 amino acid residues respectively. Unfortunately these differ from natural proteins in many important ways besides their smaller molecules. They contain:

1. Only the simplest amino acids.

2. No free amino, carboxyl or guanidyl groups which characterize the important proteins. The methods used in their preparation had distinct limitations including the difficulty of removing the protecting group from the $NH_2$ without hydrolyzing peptide linkages and even racemizing the asymmetric alpha carbon.

These difficulties have been overcome by Bergmann and Zervas (1933) who have achieved two advances which open up tremendous new possibilities in the study of polypeptides, proteins and the related enzymes.

1. A method of protecting the amino group and removing the protecting group without using any hydrolytic process, thus avoiding the breaking of the peptide linkages.

2. A method of degrading a polypeptide by removing one amino acid residue at a time and identifying it, instead of using the old method of vigorous hydrolysis which gave all the amino acid molecules with no clue as to the order in which they were linked.

A most inspiring aspect of these two spectacular advances in one of the most difficult fields of organic chemistry is that they are based on relatively simple and long known reactions.

Bergmann's method of protecting the amino group is by the carbobenzoxy group, introduced by $C_6H_5CH_2OCOCl$, which is readily formed from phosgene and benzyl alcohol. After the acid chloride or acid azide has been formed and has been combined with the desired amino acid the protecting group is removed by catalytic *hydrogenation* with palladium black.

$$-NHCO_2CH_2C_6H_5 \rightarrow -NH_2 + CO_2 + C_6H_5CH_3$$

This involves no attack on any other linkage in the peptide. Optically active amino acids and peptides protected by the carbobenzoxy group are remarkably stable to racemizing influences. The catalytic reduction fails with cystine compounds. In the case of guanidine derivatives the strongly basic group is masked by nitration. The nitroguanidine compound then behaves like an ordinary amino acid. During the catalytic reduction the nitro group is removed.

$$O_2NNHC(NH)NH- \rightarrow NH_2C(NH)NH-$$

By the improved methods, dipeptides of the natural amino acids (levorotatory) have been made as follows: glutamyl- and lysyl-glutamic acids, lysyl-glycine, lysyl-histidine, lysyl- and tyrosyl-aspartic acids, glutamyl- and tyrosyl-tyrosine, and glycyl-arginine.

Bergmann's method of degrading the polypeptides is even more brilliant. The free amino group is first blocked by treatment with phenyl isocyanate to give a phenyl ureide.

$$H_2N- \rightarrow C_6H_5NHCONH-$$

The free carboxyl group of the protected peptide is now methylated by diazomethane. Treatment of the ester with hydrazine gives the hydrazide, which, with nitrous acid, gives the azide. Treatment of the azide with benzyl alcohol gives the benzylurethane by rearrangement. This has two $-NH-$ groups on the same carbon. On catalytic reduction both of the $N-C$ linkages are broken giving toluene, ammonia, an aldehyde and the amide of a peptide containing one less amino acid residue than the starting material. This amide can be treated with hydrazine and nitrous acid and the resulting azide can be rearranged, etc., etc., until only a single amino acid remains. The important steps follow:

$$Q-CONHCHRCO_2H \rightarrow -CO_2Me \rightarrow -CONHNH_2 \rightarrow -CON_3 \rightarrow Q-CONHCHR-NHCO_2CH_2C_6H_5 \rightarrow Q-CONH_2 + RCHO + NH_3 + CO_2 + C_6H_5CH_3$$

Identification of aldehyde, RCHO, gives the constitution of the terminal amino acid of the peptide. Thus the formation of isovaleraldehyde or the half aldehydes of succinic and malonic acids would indicate respectively as the end component leucine, glutamic or aspartic acid.

*Splitting of Peptides by Enzymes*

While Emil Fischer used the enzymes as tools in studying the proteins, later workers, starting with R. Willstätter and continuing with Waldschmidt-Leitz (1925–) and his students and collaborators such as A. K. Balls (1931), have used the peptides as tools in studying enzymes. By this means it has been possible to diagnose the results of the fractionations of enzymes by adsorbents. Thus erepsin (from intestines) contains several enzymes, among others a dipeptidase which carries on the last step of the splitting of a protein and an amino-polypeptidase which attacks higher peptides by first attaching itself to the amino group. Trypsin (from pancreas) gives a carboxylpolypeptidase

which is specific for peptides of the proper degree of acidity (Balls). Just as papainase can combine with isoelectric (neutral) protein molecules and split them there is a dipeptidase which can split neutral "dipeptides" like chloroacetyl-*o*-nitroaniline (Balls). Apparently the enzyme, in this case, combines directly with the peptide linkage.

Many of the earlier polypeptides cast little light on the action of the enzymes because of their inertness to these enzymes. The work of Bergmann and Zervas in making available peptides more nearly resembling the natural proteins has opened new possibilities in this field (1933). By studying the action of dipeptidase on dipeptides of all significant types they find:

1. The nine dipeptides listed on p. 605 are split. These all contain levorotatory amino acids with the exception of the glycyl group in the last one which is, of course, symmetrical. They also contain what may be called a normal peptide linkage,

$$H_2N-CHR-CONH-CHR'-CO_2H$$

This includes, between the free amino and carboxyl groups an alpha H, a $-CONH-$ grouping and another alpha H.

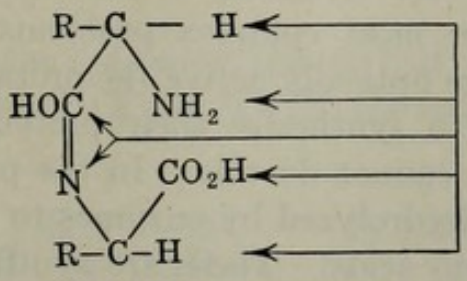
2. Dipeptidase fails to react with

a. *β-l*-Asparagyl-*l*-tyrosine which has an extra $CH_2$ between the free $NH_2$ and $CO_2H$ groups.

b. Substances like glycyl-sarcosine and *l*-alanyl-*l*-proline which have no free imido H.

c. Substances like *l*-alanyl-*α*-aminoisobutyric acid and aminoisobutyryl-glycine in which one or other of the two alpha H atoms is lacking.

d. Dipeptides containing one or both amino acids of the dextrorotatory instead of the natural levorotatory form. These facts are summarized in diagrammatic illustration (Bergmann 1934).

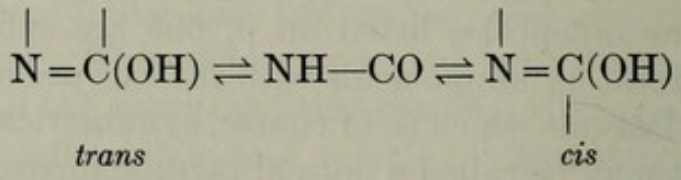



Dipeptide Enzyme

The enzyme is pictured as fitting spatially the peptide according to Emil Fischer's lock and key analogy. The hand and glove analogy is probably more accurate because a key has a *plane of symmetry* whereas an enzyme apparently has none.

The necessary contact in space between the enzyme and the peptide would fail:

1. If there were no imino H and the $-N=C(OH)-$ grouping were thus impossible. In that case the $NH_2$ and $CO_2H$ groups could not approach each other closely enough to unite with the enzyme. The *trans* form of the above structure cannot be attacked for similar reasons. It can change to the *cis* form, however.




2. If another atom lay between the $NH_2$ and $CO_2H$ and thus changed the size of the ring.

3. If one or other of the two alpha H atoms is missing or is interchanged in space with R or R′.

## Proteins

These are found universally distributed in larger or smaller amounts in both animal and vegetable organisms. They are complex combinations of relatively simple amino acids. The form of combination of these units is only partly known. While they undoubtedly include polypeptide linkages there are also other more labile linkages (Gortner, 318; Klarmann, Rev. 1927, 51–108).

The molecular weights of most proteins are 34,000 or higher (Svedberg). They are colloidal in character. Consequently their solutions offer most complex problems (Sörenson 1925). Protein solutions are optically active (levorotatory).

Plants are able to synthesize their proteins from inorganic material. Animals cannot do this. In the processes of metabolism, proteins are hydrolyzed by enzymes to give simpler products including amino acids. These are synthesized to give the specific proteins needed by the species involved. The animal

body is unable to build up certain amino acids such as cystine, histidine, lysine, and tryptophane.

Combinations of proteins with non-protein materials form the *proteides* such as hemoglobin of blood, nucleoproteins of the cell nuclei and mucins of the mucous membranes. The proteides are also called *conjugated proteins.*

The proteins usually contain about the following percentages: carbon 50, hydrogen 7, oxygen 20, nitrogen 17, sulfur 0.2. Many contain other elements such as phosphorus, iron and iodine. Some of the simplest contain no sulfur.

*Acidic and basic properties of proteins. Isoelectric point.*

The amino acids of which proteins are composed are of three types as to acid or basic properties.

1. Truly amphoteric substances having an equal number of $-NH_2$ and $-CO_2H$ groups as in glycine and cystine.
2. Substances with more basic tendencies because of an extra $-NH_2$ group as in arginine and lysine.
3. Those with acidic tendencies because of an extra carboxyl group as in glutamic and aspartic acids.

Depending on their amino acid content, proteins have varying acidic or basic properties. Thus zein forms salts only with bases and on hydrolysis gives no basic amino acids. The protamines, however, are strongly basic and yield an excess of basic amino acids on hydrolysis.

A thorough study of the addition of gaseous HCl to all types of organic nitrogen compounds (Bancroft 1930) has led to the conclusion that a true peptide linkage, $-CONH-$, should add HCl stoichiometrically. It is found that 30% and 92% of the nitrogen in gliadin and edestin add HCl in this way while zein does not add HCl at all, thus indicating that it contains no true peptide linkages.

When the hydrogen ion concentration (pH) of a protein solution is changed by adding HCl and NaOH, the following equilibria are involved:

$$H_3\overset{\oplus}{N}-Q-CO_2H \underset{OH^\ominus}{\overset{H^\oplus}{\leftrightarrows}} H_3\overset{\oplus}{N}-Q-CO_2^\ominus \underset{H^\oplus}{\overset{OH^\ominus}{\rightleftarrows}} H_2N-Q-CO_2^\ominus$$

The pH at which the dipolar ions are at a maximum is the *isoelectric point* of the protein. At this point the solution shows minimum conductivity, osmotic pressure and viscosity. At this pH the protein shows the least swelling with water and does not undergo cataphoresis (Michaelis). That is, the colloidal particles move toward neither electrode. Proteins coagulate best and contain the least amount of inorganic matter at their isoelectric points.

The isoelectric points (in pH units, neutrality = 7, with acids below and bases above this value) are as follows: glutenin 4.5, gelatin 4.7, egg albumin 4.8, serum albumin 5.4, edestin 5.7, oxyhemoglobin 6.8, gliadin 9.2, clupeine 12.1.

*Classification of the Proteins*

1. **Protamines.** These are the simplest proteins and contain no sulfur. They are strongly basic, have low molecular weights (about 3000), are readily soluble in water and do not coagulate on heating. They occur in the sperm of fish: clupeine in herring, cypreine in carp, salmine in salmon and trout, and sturine in sturgeon. These apparently all contain diamino and monoamino acids in the ratio 2 : 1 (Waldschmitz-Leitz). Thus the probable molecular proportions of amino acids in clupeine is arginine 10, proline 1, alanine 1, serine 2, valine 1, and in salmine it is arginine 14, proline 3, serine 3, valine 1.

2. **Histones** resemble the protamines but are more complicated and contain sulfur. They are obtained from hemoglobin, from the white blood corpuscles, from nucleoproteides and from the sperm of animals. They are coagulated by heat but the coagulum is soluble in dilute acid. Their solutions give precipitates with solutions of many other proteins.

3. **Albumins** are amphoteric with no excess of acid or basic properties. They are soluble in water and are coagulated by heat. The albumins of egg, serum and milk are characteristic. Leucosin is a vegetable albumin from wheat. They are difficultly precipitated by salt solutions. Hydrolysis gives no glycine. Myogen forms 80% of muscle protein.

4. **Globulins** are weakly acidic. They are insoluble in water and soluble in dilute salt solutions but are precipitated by higher

salt concentrations. This definition is highly incomplete because different salts and the same salts at different concentrations have markedly different effects (Gortner, 365). Heat coagulates the globulins.

Animal globulins are found in the body fluids while plant globulins occur as solids in seeds, etc. *Myosin* of muscle is a typical globulin. Its coagulation produces *rigor mortis*. Edestin is found in hemp seeds and ovoglobulin in egg yolk.

5. **Prolamines** (gliadins) are vegetable proteins soluble in 70–80% alcohol but insoluble in absolute alcohol and in water. Their hydrolysis gives much proline, no glycine, lysine or tryptophane. Thus they cannot support life without other proteins. Examples are *gliadin* from wheat and other cereals, *hordein* from barley and *zein* from corn. Milk also gives an alcohol-soluble prolamine.

6. **Glutelins** are insoluble in neutral solvents but dissolve in very dilute acids and bases. Examples are glutenin from wheat and oryzein from rice.

7. **Scleroproteins,** (albuminoids) of skin and related structures, are insoluble in water and solvents in general. They contain much sulfur and resist hydrolysis especially by the ordinary proteolytic enzymes. Examples are collagen (glue and gelatine), keratin (horn, wool, etc.), fibroin (silk), and elastin (animal ligaments).

*Classification of the Proteides (Conjugated Proteins)*

The first three classes contain phosphoric acid in various combinations:

1. **Phosphoproteides** are weak polybasic acids. They are not coagulated by heat. On hydrolysis with HCl in the presence of pepsin they give proteoses and a complex phosphoric acid derivative, *paranucleic acid,* which is different from animal and plant nucleic acids in that it contains no xanthines, pyrimidines nor pentoses.

Examples are *vitelline* of egg yolk and *casein* of milk.

2. **Nucleoproteides** from cell nuclei contain proteins combined with nucleic acid. The latter is of two kinds typified by plant nucleic acid from yeast cells and animal nucleic acid from the

pancreas. The nucleoproteides are soluble in bases and insoluble in acids.

3. **Lecithoproteides** are soluble in such solvents as ether. They include complex compounds of phosphoric acid (lecithines, phosphatides, phospholides) and occur in cytoplasm and cell membranes.

4. **Chromoproteides** are combinations such as hemoglobin and its oxidation product oxyhemoglobin. The action of glacial acetic acid and NaCl gives the hydrochloride of hematin, the red pigment combined with the globin. Other examples of chromoproteides are hemocyanin of the blood of marine animals, and *phycoerythrin* and *phycocyan* of seaweeds. Black hair, wool, etc., contain a protein combined with *melanin*.

5. **Glucoproteides**, glycoproteides or mucins contain proteins combined with carbohydrate derivatives such as glucosamine and glucuronic acid. They include the proteins of the various mucous fluids of animals and probably part of egg white. The mucins are acid and insoluble in neutral solution but soluble in slightly basic solution.

6. **Lipoproteins** (Mathews) contain as the prosthetic (additional) group a higher fatty acid.

*Classification of Protein Cleavage Products (Derived Proteins)*

1. **Proteans.** Insoluble in water. First products of cleavage.

2. **Metaproteins,** products formed by further action of acids, or enzymes. Soluble in dilute acids and bases. Insoluble in neutral solvents.

3. **Proteoses,** albuminoses, soluble hydrolysis products of proteins. Not coagulated by heat. Precipitated by excess solid ammonium sulfate.

4. **Peptones,** hydrolysis products. Soluble, not coagulated by heat, not precipitated by ammonium sulfate.

5. **Peptides,** definite compounds consisting of two or more amino acids united through the $-NHCO-$ or $-N=C(OH)-$ linkage.

The proteolytic enzymes give different degrees of cleavage: pepsin gives proteoses and peptones; trypsin gives proteoses,

peptones and amino acids; and erepsin changes peptones to amino acids and $NH_3$.

### *Molecular Weights of Proteins*

From his studies of the rates of sedimentation in the supercentrifuge, Svedberg concludes that the molecular weights of typical proteins are about as follows: egg albumin, 34,000; hemoglobin, 66,000; casein, 98,000; gelatine, 150,000; and the blood pigments of certain lower marine animals, as high as a million. Values even approaching five million have been indicated (Rep. 1931, 231). The order of magnitude of these values is confirmed by purely chemical means. Thus hemoglobin with its 0.4% of Fe would have a molecular weight of 14,000 if its molecule contained only *one atom* of iron, which is rather improbable. If there is *only one cystine* unit in hemoglobin the molecular weight is 16,000. The value of 75,000 to 100,000 for casein, obtained with the ultracentrifuge taken in conjunction with the percentages of sulfur, phosphorus, cystine, tryptophane, tyrosine, and histidine of 0.78, 0.86, 0.49, 1.24, 5.55 and 1.78 respectively, gives the value 98,000 cited above (Carpenter 1931).

### *Protein Reactions*

These are very complex but a few are of general importance.

1. Many proteins form soluble alkali salts. A typical example is casein, which has at least five potassium salts containing from one to sixteen potassium atoms per molecule of casein (Robertson).

2. Proteins form salts with acids. Varying amounts of HCl will unite with proteins. This salt formation is not limited by the number of free $-NH_2$ groups (Bancroft 1930).

3. Free amino groups in protein liberate nitrogen when treated with nitrous acid (Van Slyke). The amount of $NH_2$ groups varies widely, the percentage of the total nitrogen existing as $NH_2$ groups being: zein, 0; gliadin, 1.1; edestin, 1.8; gelatine, 3.1; casein, 5.5.

4. Heating with bases in the presence of a trace of copper salt gives a red violet color. This is called the *biuret reaction* because it was first noted with biuret, $NH_2CONHCONH_2$. It is also given by other nitrogen compounds but not by amino acids.

Thus the completeness of protein hydrolysis can be detected by the failure of the biuret test.

5. Nitric acid gives a yellow color which turns orange with ammonia (xanthoproteic reaction). When a solution of a protein is underlayed with nitric acid, the protein is precipitated in a white ring at the junction of the two liquids (Heller's test for albumin in urine).

6. Millon's reaction. Mercury dissolved in twice its weight of conc. nitric acid and diluted with two volumes of water gives a red color when heated with a solid protein.

7. Potassium ferrocyanide and acetic acid give hydroferrocyanic acid which gives precipitates with many proteins.

8. Salts of heavy metals such as Cu, Hg and Pb give precipitates.

9. Reagents for alkaloids give precipitates with most proteins.

Cyclo-aliphatic

# PART II

## ALICYCLIC OR POLYMETHYLENE COMPOUNDS

### I. GENERAL

#### *A.* Occurrence

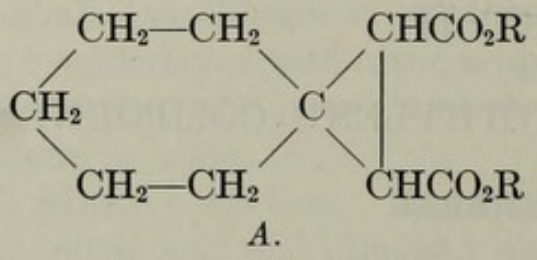
The alicyclic compounds, as the name indicates, are cyclic compounds having aliphatic properties. Many with 6- and 5-membered rings occur very widely in nature in various plant products and in crude petroleums. Most petroleums with the exception of Appalachian (Pennsylvania grade) and Michigan crudes contain large amounts of naphthenes or complicated alicyclic compounds. The terpenes and camphors of plants are mainly alicyclic in nature.

Many alicyclic compounds have been synthesized by applying the ordinary synthetic processes in such a way that they take place *intramolecularly* with the formation of rings instead of *intermolecularly* to form larger molecules. Up to 1926 rings of 3 to 9 carbons had been made.

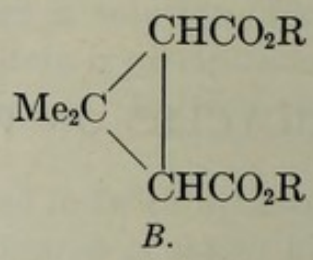
#### *B.* Baeyer Strain Theory

Baeyer in 1885 first noted that the angle subtended by the corners and center of a regular tetrahedron, namely about 109.5°, lies between the value for the angles in the regular pentagon and hexagon, namely 108° and 120°. On this was based the Baeyer Strain Theory that 5- and 6-membered rings form most readily and are most stable. Qualitatively this conception has been most helpful. That other factors are involved is shown by the greater occurrence of 6-membered rings as compared with 5-membered rings although the latter have practically the "natural" angle for a tetrahedral carbon atom. Influences which tend to give the normal angle between the carbon valences give easier formation and greater stability. Thus the *spiro*

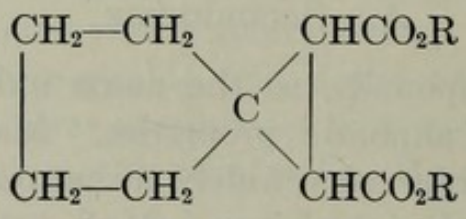
*compound A* containing a 6- and a 3-ring with one carbon in common is more easily made and is more stable than the cyclopropane compound *B* (Rep. 1915, 109).




*A.*




*B.*




*C.*

The increased angle in the 6-ring (120°) tends to force together the other valences of the spiro carbon and thus stabilize the 3-ring. Thus *A* is not opened by conc. HCl at 240° whereas *B* is opened by 5% acid at 200°. Further support to this reasoning is given by the fact that compound *C* has the same stability as *B* (Rep. 1921, 94). The 5-ring does not change the natural angle.

Large strainless rings (Sachse-Mohr, Rep. 1924, 92) have been found in nature and have been synthesized (Ruzicka 1926–1934; Rep. 1926, 112; 1928, 111; Carothers 1933). These have been made with as many as 32 carbon atoms. In these compounds the atoms of the ring do not lie in one plane. Thus the natural angle of the carbon atoms is not strained to equal the angle of a large plane polygon.

The most common phenomenon involving the Baeyer strain conception is the fact that suitably reactive groups in the 1,5 of 1,6 position tend to react *intramolecularly* with ring closure.

The presence of substituent groups greatly changes the ease of closing rings and the stability of the rings (Rep. 1922, 126; 1925, 129).

### *C.* Reactions for Forming Alicyclic Compounds

These are mainly familiar aliphatic reactions. Among these are the Wurtz reaction, acetoacetic ester and malonic ester

syntheses with dihalides, and *intramolecular* examples of the aldol and acetoacetic ester condensations and pinacol reductions. Probably the oldest and most general reaction is the production of a cyclic ketone by heating the salt of a dibasic acid.

### *D.* Methods for Opening Alicyclic Rings to Give Aliphatic Compounds

These also involve familiar reactions such as oxidation of olefinic or ketonic compounds. The 3- and 4-membered ring compounds are exceptional in that they can be converted to propane and butane derivatives by catalytic hydrogenation and to propylene and butylene derivatives by heating with catalysts like $Al_2O_3$.

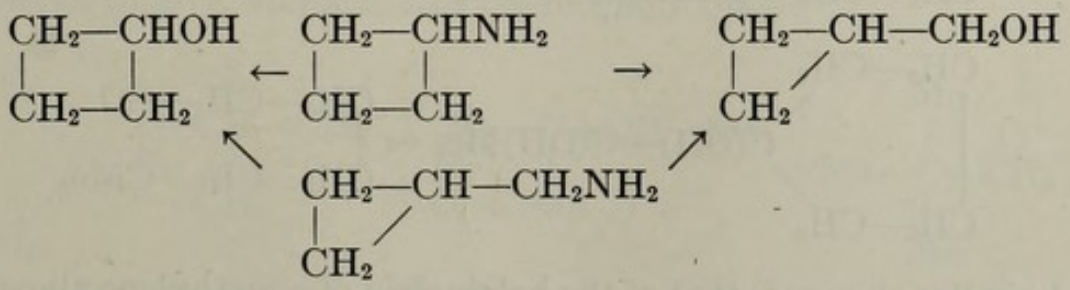
### *E.* Change in Size of Rings

Just as rearrangements in the aliphatic series involve the shift of a C—C linkage, so in the alicyclic series such rearrangements result in the formation of larger or smaller rings.

1. Treatment of aliphatic amines with nitrous acid produces rearranged products in practically all cases.

$$Me_3CCH_2NH_2 \rightarrow Me_2C(OH)CH_2Me$$

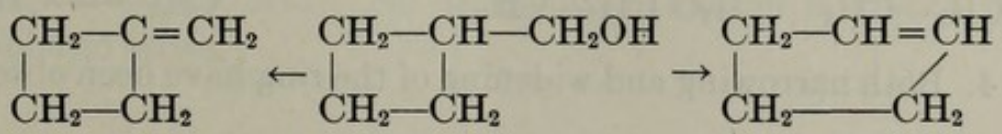
Similarly alicyclic amines give rearranged products with different rings as well as the normal products of replacement of $NH_2$ by OH.



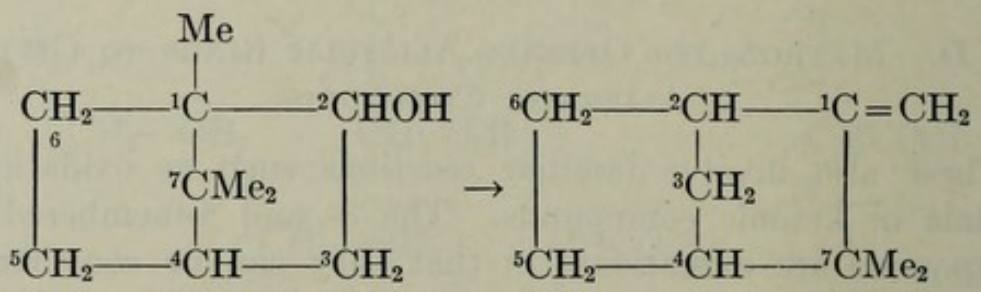
2. Dehydration of alcohols often gives rearrangements.

$$Me_3CCHOHMe \rightarrow Me_2C{=}CMe_2$$

Similarly



An analogous narrowing of the ring has not been produced with alicyclic alcohols. The dehydration of borneol to give camphene instead of bornylene involves a similar conversion of one ring into another, in this case without changing the size of the ring.



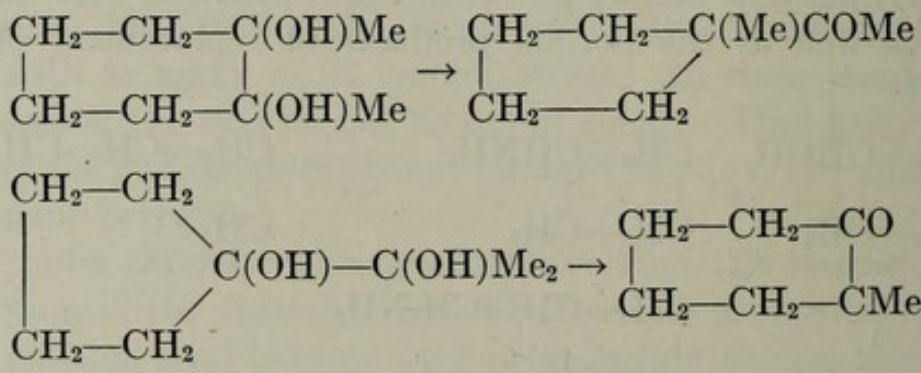
Thus one 6-ring was broken at linkage 1 : 6 and a new 6-ring formed by linkage of atoms 2 and 6.

To obtain a narrowing of the ring by dehydration, a grouping such as 2,2-$Me_2$-cycloheptanol would be necessary. This should give olefins with the skeleton of isopropylcyclohexane.

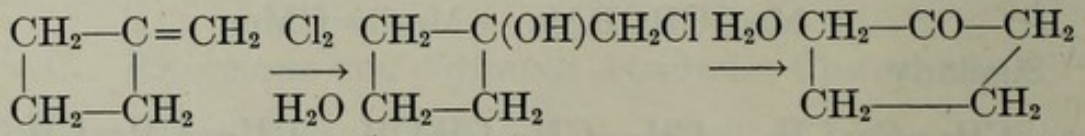
3. Probably the oldest authentic rearrangement is that of pinacol to pinacolone.

$$Me_2C(OH)C(OH)Me_2 \rightarrow Me_3CCOMe$$

In the alicyclic series the pinacolone rearrangement produces both narrowing and widening of the ring.

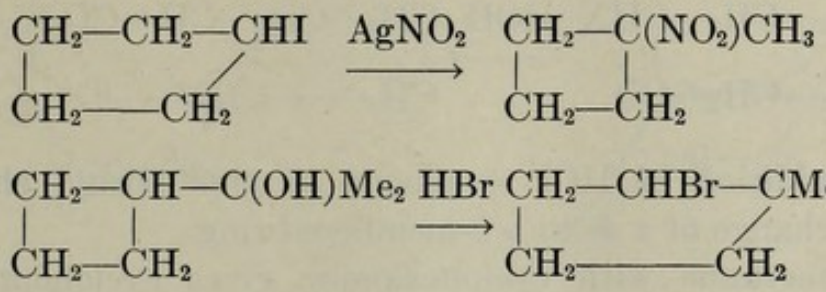


A similar change is that of the halohydrin of a methylene alicyclic compound to give the ketone of the next larger ring.



4. Both narrowing and widening of the ring have been observed

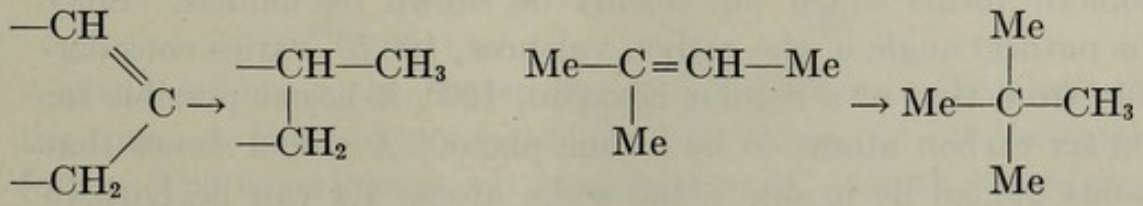
in addition to the normal reactions in supposedly metathetical processes.



Cyclopropylcarbinol with HBr gives the normal product and some cyclobutyl bromide. Likewise cyclobutylcarbinol gives largely cyclopentyl bromide. No entirely analogous reactions are known in the aliphatic series.

5. Reduction decreases the size of the ring in some cases. Benzene with HI at 300° gives cyclohexane and methylcyclopentane. Cyclohexane is partially converted to Me-cyclopentane by similar treatment with HI while cycloheptane gives Me-cyclohexane and $Me_2$-cyclopentane. Similar changes are undoubtedly involved in the action of HI with cyclohexyl and cycloheptyl iodides to give Me-cyclopentane and Me-cyclohexane respectively.

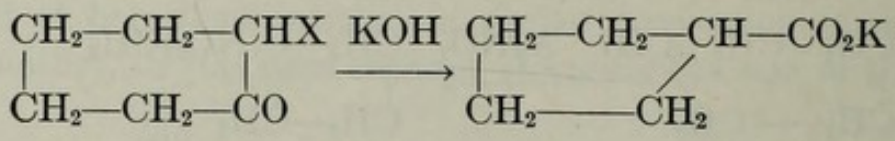
Cycloheptadiene-1,3 with $H_2$ and Ni gives cycloheptane or Me-cyclohexane depending on the temperature. An analogous change takes place with $Me_3$-ethylene and $H_2$ in a dark electric discharge to give $Me_4$-methane (Meneghini 1933).



Cyclohexane can be isomerized to Me-cyclopentane by an alumina catalyst (Ipatief 1911).

6. The oxidation of cyclobutanol is reported to give cyclopropane carboxylic acid. No analogous oxidation is known in the aliphatic series.

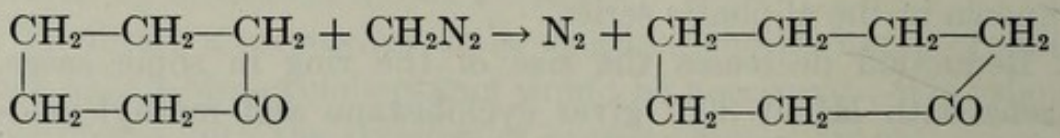
7. $\alpha$-Halogencycloketones with bases give carboxylic acids of the next lower ring.



8. The addition of HCl to pinene to give bornyl chloride involves a change of a 4- to a 5-membered ring.

9. Diazomethane with cyclohexanone gives cycloheptanone (Mosettig 1930). This is analogous to the action with an acid chloride.

$$RCOCl + CH_2N_2 \rightarrow N_2 + RCOCH_2Cl$$

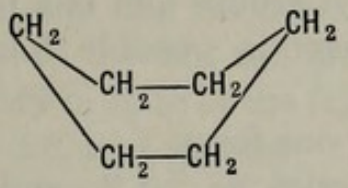


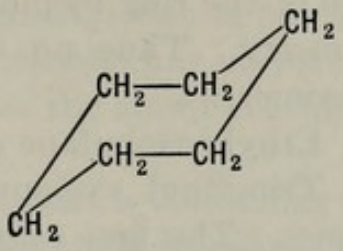
## II. ISOMERISM OF ALICYCLIC COMPOUNDS

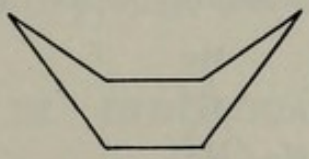
This is more complex than that of the aliphatic compounds. It may be illustrated by the cyclic isomers, $C_6H_{12}$. As will be recalled, this formula represents 13 olefins with 5 possible in *cis* and *trans* forms and one in *d*- and *l*-forms, a total of 19 isomers of all kinds. It also represents polymethylene compounds as follows:

1. Cyclohexane. Theoretically this should exist in two stereoisomeric forms which can readily be shown by models. Since the natural angle of the carbon valences, 109.5°, varies considerably from that of a regular hexagon, 120°, it is not possible for the six carbon atoms to lie in one plane. A model shows that atoms 2,3,5,6 lie in one plane while atoms 1,4 can lie both in one other plane (*cis*) or each in a separate plane, one above and one below the plane of the four middle atoms (*trans*). Actually only one form of cyclohexane is known. This is probably the *trans* form. Models built accurately to scale according to the best X-ray data (Organospheres, Steiger) indicate the *trans* form

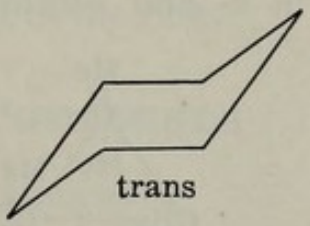
as very stable whereas the *cis* form is very labile. Derivatives of cyclohexane are known in both forms.







cis

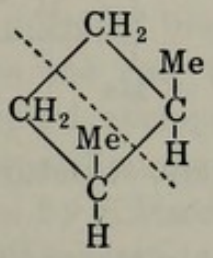


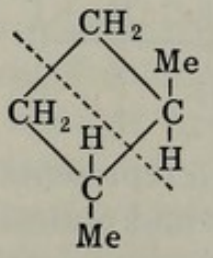
trans

The *cis* and *trans* forms are sometimes called the "*boat*" and "*seat*" forms.

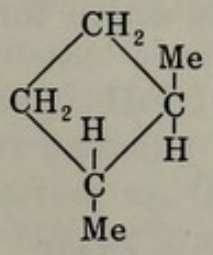
2. Methylcyclopentane offers no possibilities for isomerism.

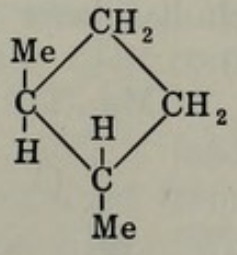
3. Dimethylcyclobutanes can exist as 1,1-; 1,2-, and 1,3-isomers. The four carbon ring occupies one plane. In the 1,1-isomer one methyl is above and the other below this plane. The 1,2-compound can have both methyls in one plane (*cis*) or one above and one below the plane of the ring (*trans*).





A plane following the dotted line perpendicular to the plane of the ring is a plane of symmetry for the *cis* but not for the *trans* form. The latter has no plane of symmetry. It can, therefore, exist in enantiomorphic forms (*d*- and *l*-).

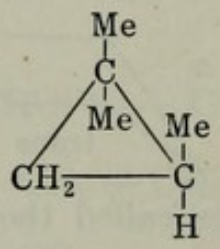


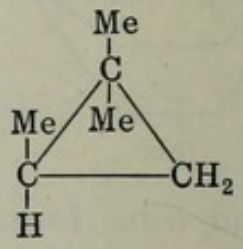


The 1,3-isomer can also exist in *cis* and *trans* forms. In this case a plane through the 1,3-corners and at right angles to the plane of the ring includes both methyl groups and is a plane of symmetry. Thus no enantiomorphism is possible for either 1,3-isomer.

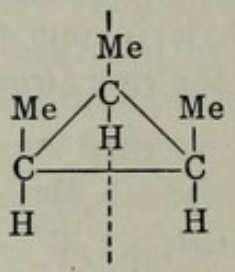
4. Ethylcyclobutane can have only one form.

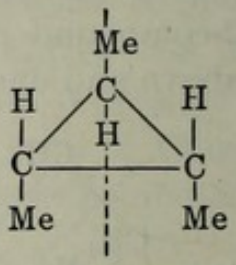
5. Trimethyl cyclopropanes can exist as 1,1,2- and 1,2,3-isomers. The first cannot exist in *cis* and *trans* forms but can exist in *d*- and *l*-forms because the molecule is asymmetric.



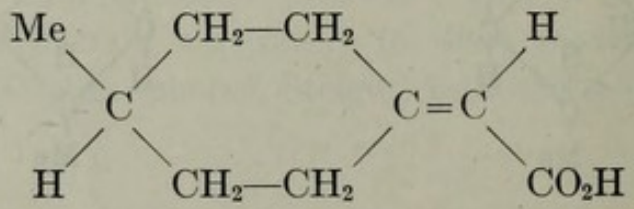

On the other hand the 1,2,3-isomer exists in *cis* and *trans* forms but optical isomers are impossible because both forms have at least one plane of symmetry through one corner bisecting the opposite side, making enantiomorphs impossible.




Thus $C_6H_{12}$ represents 14 alicyclic isomers, structural and stereo (geometric and optical).

All of the asymmetric molecules noted in the optically isomeric alicyclic compounds cited above contain at least one asymmetric carbon (attached to four different groups). The alicyclic series provides an example of an asymmetric optically active molecule containing *no asymmetric atom*, 1,4-methylcyclohexylideneacetic acid, which has been resolved into its active forms (Perkin, Pope 1909)

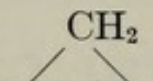


Models show that a plane including the Me and H bisects the ring but is not symmetrical to the H and carboxyl, while the plane of the ring includes the H and carboxyl but is not symmetrical to the Me and H. Thus the molecule has no plane of symmetry in spite of the fact that no one of the atoms is attached to four different groups.

*Unsaturated alicyclic compounds.* Substances containing one or more double bonds in the ring are known but it has never been possible to prepare one with a triple bond in the ring.

## III. INDIVIDUAL ALICYCLIC COMPOUNDS

### *A.* Cyclopropane Compounds



**Cyclopropane,** trimethylene, $CH_2 — CH_2$, m. −127°, b. −34°, is made from trimethylene halides and sodium or zinc. Because of its value as an inhalation anesthetic, attempts are being made to cheapen its preparation (Hass 1935). At high temperatures alone, or with catalysts (Pt, etc.) at lower temperatures, it isomerizes to propylene. With $H_2$ and Ni at 80° it gives propane. $Br_2$ and HBr react even in the cold to form trimethylene dibromide and *n*-propyl bromide respectively. Strangely, chlorine does not open the ring but forms *cyclopropyl* chloride, b. 43°. Alkyl substituted cyclopropanes usually undergo ring opening more easily even than does the parent substance. Cyclopropane is not oxidized by $KMnO_4$, thus differing from propylene.

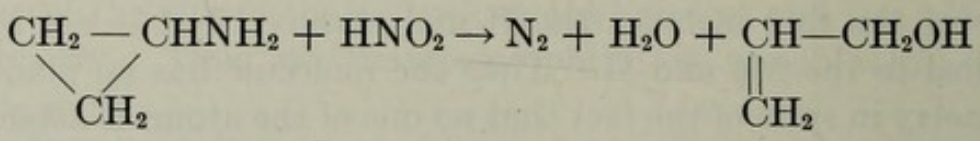
Homologs of cyclopropane are made from 1,3-dibromides and zinc. Me-cyclopropane, b. 5°, 1,1-$Me_2$-, b. 21°.

All attempts to make *methylene cyclopropane* have failed. This recalls the failure to prepare pure cyclopropanone (p. 624).

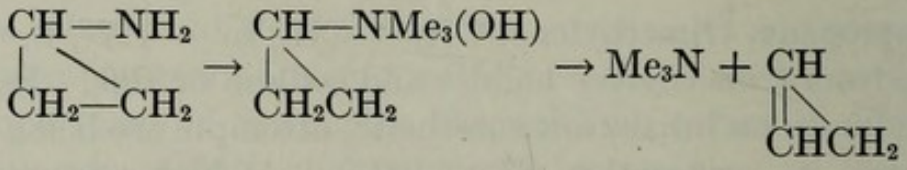
**Cyclopropyl alcohol** is not known. A great variety of methods have failed to give it (Lipp 1932–3). Glycerol-1,3-dibromohydrin with Zn gives allyl alcohol (Aschan 1890). The corresponding esters with Na give allyl esters (Sattler 1932).

**Cyclopropyl amine,** $(CH_2)_2CHNH_2$, b. 50°, is made by the Hofmann reaction on the acid amide obtained from the acid chloride and $NH_3$ or from the cyanide and $H_2O_2$. With nitrous

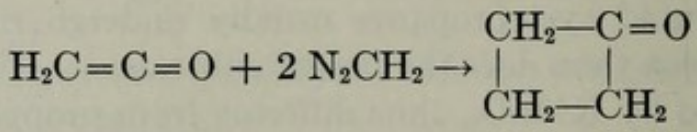
acid, it gives allyl alcohol instead of cyclopropyl alcohol (Kishner 1905).



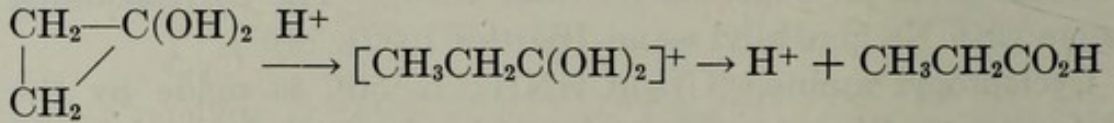
The change is analogous to the action of nitrous acid on neopentylamine except that the transfer of electrons within the electronically deficient cyclopropyl residue breaks a C—C linkage without forming a new one. The resulting allyl fragment combines with hydroxyl ion to give allyl alcohol. Cyclopropylamine can be completely methylated. Its quaternary hydroxide decomposes to give cyclopropene, b. −80°, a substance very reactive with oxygen and bromine and readily subject to polymerization.



**Cyclopropanone** has not been prepared in the free state in spite of many attempts (Lipp 1932–3). Apparently a doubly linked oxygen attached to a cyclopropane ring involves great strain. The reaction of ketene with diazomethane gives cyclobutanone instead of the expected product



With excess ketene and a little water or methanol the product is the hydrate or hemiacetal, $(CH_2)_2C(OH)_2$ or $(CH_2)_2C(OH)OMe$, in which the strain of the doubly linked oxygen is avoided. The crystalline hydrate gradually changes to propionic acid. This is not an ordinary rearrangement but probably a splitting of the cyclopropane ring as in the action of HBr.



The hemiacetal, when shaken with a dilute base, evolves heat

and changes to methyl propionate. The stability of the hydrate as compared with the free ketone recalls the great stability of 1,1-$Cl_2$-cyclopropane (Gustavson 1890).

**Cyclopropylcarbinol,** $(CH_2)_2CHCH_2OH$, can be made by reducing the corresponding ester. The corresponding bromide, *trimethylenyl bromide*, b. 106°, is best made by von Braun's substituted benzamide method (von Braun 1925, Adams 1928). The corresponding amine is made by reducing cyclopropyl cyanide obtained from γ-bromobutyronitrile and a solid base.

$$BrCH_2CH_2CH_2CN \xrightarrow{KOH} (CH_2)_2CHCN \xrightarrow{[4H]} (CH_2)_2CHCH_2NH_2$$

$$(CH_2)_2CHCH_2NH_2 \xrightarrow{PhCOCl} \xrightarrow{PBr_5} (CH_2)_2CHCH_2Br + PhCN$$

**Cyclopropyl methyl ketone,** b. 112°, is made from ethylene dibromide, acetoacetic ester and an excess of NaOEt. The first product, $BrCH_2CH_2CH(COMe)CO_2Et$, can react with sodioacetoacetic ester to give $EtO_2C(MeCO)CHCH_2CH_2CH(COMe)CO_2Et$, or with NaOEt to give a Na derivative which can react internally to give $CH_2{-}C(COMe)CO_2Et$ (with $CH_2$ bridging) which can be split like other acetoacetic esters to give either cyclopropyl methyl ketone or cyclopropane carboxylic acid. The ketone is split by HBr to give $Br(CH_2)_3COMe$.

### *Cyclopropane Carboxylic Acids*

These will be discussed rather fully because they illustrate principles important in this series.

1. The **monocarboxylic acid,** ethyleneacetic acid, m. 17°, b. 181°, is made by heating the 1,1-dicarboxylic acid. It is also obtained from trimethylene glycol, through the dibromide, and the bromocyanide.

$$Br(CH_2)_3CN \xrightarrow{KOH} CH_2{-}CHCN \rightarrow (CH_2)_2CHCO_2H$$

($CH_2$ bridging)

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The removal of HX takes place better in liquid $NH_3$-ether solution with $NaNH_2$ (Cloke 1931). The carboxyl group stabilizes the ring. Thus bromine replaces the alpha H instead of opening the ring. Fuming HBr acts only at 175° to give $\gamma$-Br-butyric acid. The acid chloride and Et ester b. 119° and 133°.

2. The **1,1-dicarboxylic acid,** ethylenemalonic acid, vinaconic acid, m. 140°, is made from ethylene bromide, malonic ester and excess NaOEt. The by-product is ethylene dimalonic ester, $(RO_2C)_2CHCH_2CH_2CH(CO_2R)_2$. Heat converts the dibasic acid to cyclopropane carboxylic acid.

3. The **1,2-dicarboxylic acids** are obtained by decarboxylating the 1,1,2-tricarboxylic acid made from malonic ester, $\alpha\beta$-$Br_2$-propionic ester and NaOEt. The *cis* or *maleinoid* form of the 1,2-acid is obtained as its anhydride, m. 59°, by heating the 1,1,2-acid above 200° or by treating it with acetyl chloride. The anhydride unites with $H_2O$ at 140° to give the 1,2-acid, m. 139°. It corresponds not only to maleic acid with a ring in place of a double bond but also to mesotartaric acid because it contains two asymmetric carbon atoms which compensate each other. When the *cis*-1,2-acid or its anhydride is heated a short time at 240° with fused KOH, cooled and acidified, the *trans* or *fumaroid* 1,2-acid, m. 175°, is obtained. This corresponds to racemic acid and can be resolved through the brucine salts into the *d*- and *l-trans* cyclopropane-1,2-dicarboxylic acids, m. 175°, $[\alpha]^D = \pm 84.8°$. The silver salt of the *trans* acid, on heating, gives the anhydride of the *cis* acid. Another preparation of the *trans* acid is from acrylic ester and diazoacetic ester through pyrazolin-3,5-dicarboxylic ester.

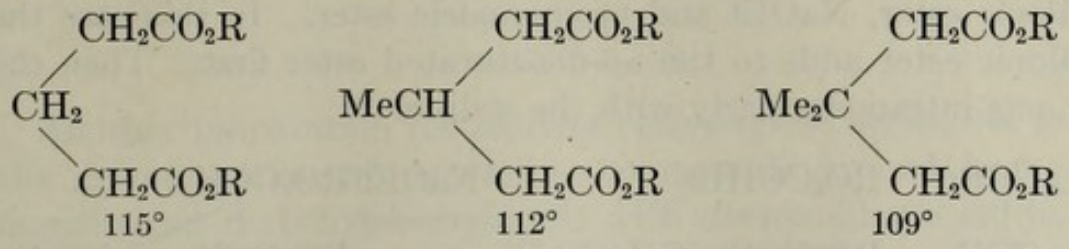
$$CH_2{=}CHCO_2R + N_2CHCO_2R \xrightarrow{50°}$$

$$RO_2CCHN{=}N \xrightarrow{180°} RO_2CCH(CH_2)CHCO_2R$$

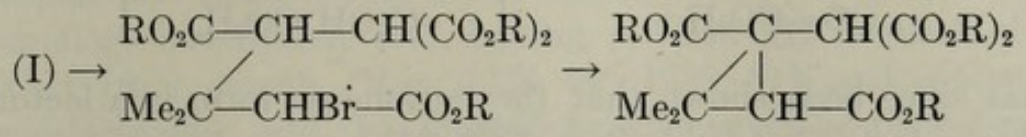
It is notable that the 1,2-dicarboxyethyl cyclopropane is stable to HBr whereas the 1,1-compound is split by this reagent (Rep. 1914, 117).

The ease of closing the cyclopropane ring depends on the valence angles as determined by the volumes of the attached

groups. Thus the calculated angles in the open-chain compounds are as follows:

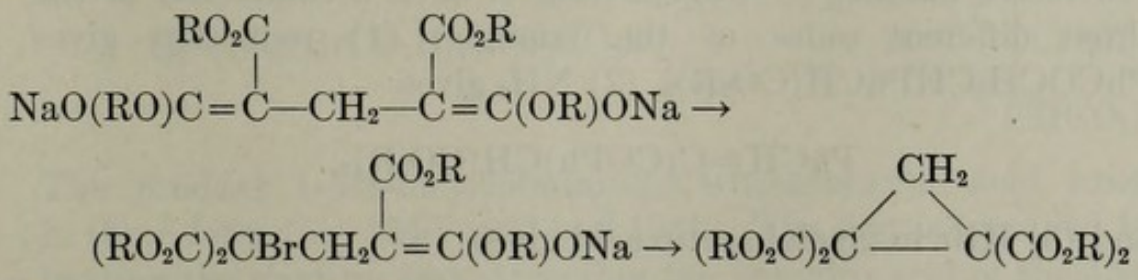



As the angle decreases the ease of 3-ring formation increases (Rep. 1922, 115). A good example of this effect is found in the action of 1,3-dibromides with sodio-malonic ester. Whereas $Br(CH_2)_3Br$ gives the expected cyclobutane compound, $Me_2C(CHBrCO_2R)_2$ (I) gives a cyclopropane derivative and $\alpha\alpha'$-$Br_2$-glutaric ester gives both types of products (Rep. 1925, 126–8). In (I) the arrangement of the groups evidently favors 3-ring closure.




4. The **cis-1,2,3-tricarboxylic acid,** m. 153°, is obtained by heating the tetracarboxylic acid made from malonic ester, NaOEt and dibromosuccinic ester. The *trans*-1,2,3-acid, m. 220°, is obtained by heating pyrazolin-3,4,5-tricarboxylic esters obtained from diazoacetic ester and fumaric ester.

5. The **1,1,2,2-tetracarboxylic acid,** m. 200° dec., is obtained by the action of bromine on the disodio derivative of propane-1,1,3,3-tetracarboxylic ester made from methylene chloride and sodiomalonic ester. The first action of the bromine is to substitute on one of the alpha carbons. The resulting bromo compound then reacts internally to give the 3-ring.




The **cis-1,2,3-trans-1-acid,** m. 100° dec., is made from malonic

ester, NaOEt and $Br_2$-succinic ester. Heat converts it to the *cis-1,2,3-acid.* The *cis-1,2-trans-1,3-acid,* m. 198°, is made from malonic ester, NaOEt and bromomaleic ester. In this case the malonic ester adds to the $\alpha\beta$-unsaturated ester first. Then the Br acts intramolecularly with the sodium.

$$\begin{array}{l} RO_2CCBr \\ \| \\ RO_2CCH \end{array} \rightarrow \begin{array}{l} RO_2CCHBr \\ | \\ RO_2CCH{-}CH(CO_2R)_2 \end{array} \xrightarrow{NaOEt} \begin{array}{l} RO_2CCH \\ | \quad \diagdown \\ RO_2CCH{-}C(CO_2R)_2 \end{array}$$

The acid loses $CO_2$ to give the trans-1,2,3-acid.

The ring-chain tautomeric formula formerly assigned to Balbianos' acid, obtained by the oxidation of camphoric acid, was 1,3,3-$Me_2$-2-OH-cyclopropane-1,2-dicarboxylic acid (Rep. 1922, 114).

$$\begin{array}{l} Me_2C{-}CH(Me)CO_2H \\ | \\ CO{-}CO_2H \end{array} \rightleftharpoons \left[ \begin{array}{l} Me_2C{-}C(Me)CO_2H \\ | \quad / \\ C(OH)CO_2H \end{array} \right]$$

It has since been shown that the tautomeric form is a lactone of the hydrated ketoacid (Rep. 1928, 81).

Many *complex cyclopropane derivatives* have been made by processes such as the addition of malonic ester to benzalacetophenone, bromination and removal of HBr from the $\alpha\gamma$-positions (Kohler 1917–).

$$PhCH{=}CHCOPh \rightarrow \begin{array}{l} PhCH{-}CH_2COPh \\ | \\ CH(CO_2R)_2 \end{array} \xrightarrow{Br_2} \xrightarrow{Base} \begin{array}{l} PhCH{-}CHCOPh \\ | \quad / \\ C(CO_2R)_2 \end{array}$$

The actual existence of a 3-membered ring is proven in a conclusive manner by the splitting of such a compound at the three different sides of the triangle: (1) reduction gives $PhCOCH_2CHPhCH(CO_2R)_2$, (2) $NH_3$ gives

$$PhCH{=}C(COPh)CH(CO_2R)_2,$$

and (3) HBr in glacial acetic acid gives

$$PhCOCH_2C(CO_2H)_2CHBrPh,$$

which loses $CO_2$ and HBr to give

$$PhCH=CCH=CPh$$
$$\quad\quad\;|\quad\quad|$$
$$\quad\;CO\text{——}O$$

Another preparation for *complex cyclopropane derivatives* is by the decomposition of pyrazoline compounds formed from $\alpha\beta$-unsaturated carbonyl compounds with diazomethane or diazoacetic ester. These have been illustrated in the preparation of some of the cyclopropane carboxylic acids.

**Natural cyclopropane derivatives** are the thujenes and carenes which have internal and external 3-membered rings attached to the 6-membered terpene rings. Similar compounds have been synthesized. The stability of the cyclopropane ring is surprisingly illustrated by the oxidation of such substances containing CO or C=C in the 6-ring to give 1,1-$Me_2$-cyclopropane-2,3-dicarboxylic acid, *caronic acid*, from carone, its homolog, *homocaronic acid*, having $-CH_2CO_2H$ in place of one $CO_2H$ from carene, (Rep. 1923, 99; 1928, 81), and *α-tanacetogendicarboxylic acid*, 1-isopropyl-2-carboxycyclopropane-1-acetic acid from thujone. One of the acids from the insecticide pyrethrum is pyrethronic acid (Rep. 1923, 98).

$$Me_2C\text{—}CHCO_2H$$
$$\quad\;|\;/$$
$$\quad CHCH=CHEt$$

Oxidation gives a glycol and then *trans*-caronic acid.

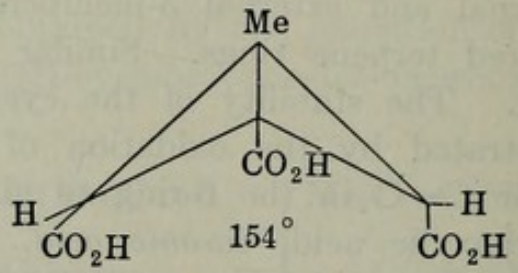
Derivatives of *bicyclobutane* and *tricyclobutane* have been prepared (Rep. 1920, 87–9).

$$MeCH_2CHO + 4\,HCHO \rightarrow MeC(CH_2OH)_3 \rightarrow MeC(CH_2CO_2R)_3 \rightarrow$$

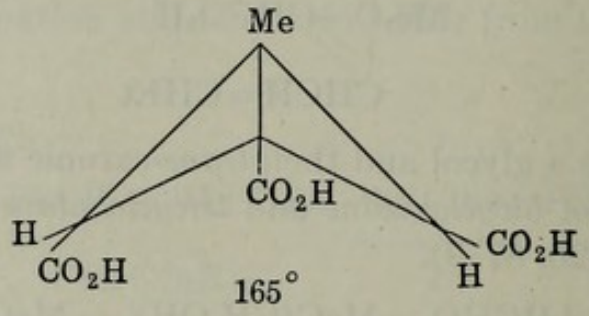
$$MeC(CHBrCO_2R)_2(CH_2CO_2R) \xrightarrow[\text{heat}]{\text{KOH}} \xrightarrow{\text{acid}} MeC(CH_2CO_2H)_3$$

The product 1-Me-bicyclobutan-2,3,4-tricarboxylic acid exists in three forms, m. 154°, 165° and 193°. The first is removed by heating the mixture and extracting the anhydro acid of the 154° isomer with ether. Treatment with acetic anhydride converts

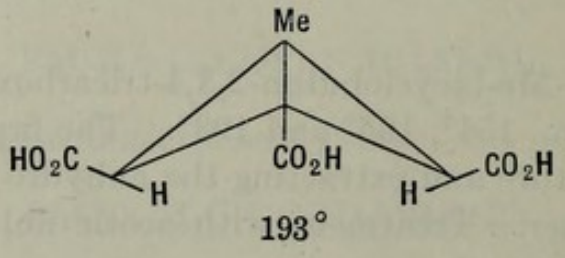
the 165° isomer to the anhydro compound which is removed by ether. The residue is the 193° isomer which does not form an anhydro acid. Bromination of the three acids proceeds very differently: the 154° acid giving a stable bromo acid; the 165° acid giving a lactonic acid free of bromine; and the 193° acid giving methyl-tricyclobutane-tricarboxylic acid. In harmony with their reactions the acids are assigned the following configurations. A study of the models shows that the 2,3,4-carbons, the 3-carboxyl and the two H atoms are in one plane while the 2,4-carboxyls lie near each other slightly below this plane.



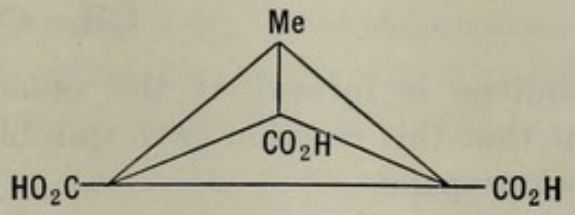

Anhydride formation should be easy. The monobromide gives no opportunity for reaction either with a carboxyl or the other H. Anhydride formation would be more difficult. The $\alpha$-Br would be near a carboxyl group. The carboxyls and carbons 2,3,4 are



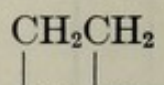

in one plane. No anhydride would be expected. The $\alpha$-H atoms are near each other so that the $\alpha$-Br can react with the other $\alpha$-H to close the third ring. The carboxyls are in one



plane. The degree of strain in this *cage system* of four cyclopropane rings as indicated by models is much less than might be expected.




## *B.* Cyclobutane Derivatives



The preparation of **cyclobutane,** $CH_2CH_2$ / $CH_2CH_2$, b. −15°, involves familiar reactions.

1. Trimethylene bromide, $Br(CH_2)_3Br$, with malonic ester and NaOEt gives cyclobutan-1,1-dicarboxylic ester.
2. Hydrolysis and heat give the monocarboxylic acid.
3. Conversion to the amide and application of the Hofmann reaction give cyclobutyl amine, b. 81°.
4. Exhaustive methylation of the amine gives cyclobutene.
5. Reduction by Ni and $H_2$ at 100° gives cyclobutane.

Cyclobutane is stable to cold HI and to $KMnO_4$. Catalytic hydrogenation at 120° give *n*-butane. Thus the 4-membered ring is more stable than that of cyclopropane.

**Cyclobutene** shows the ordinary olefin reactions. Attempts to make cyclobutadiene give butadiene or acetylene.

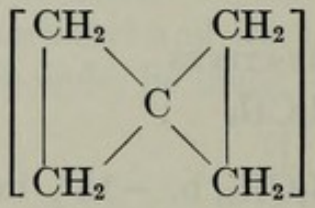
**Cyclobutanol,** $(CH_2)_3CHOH$, b. 123°, along with cyclopropylcarbinol is obtained from the corresponding amine and nitrous acid.

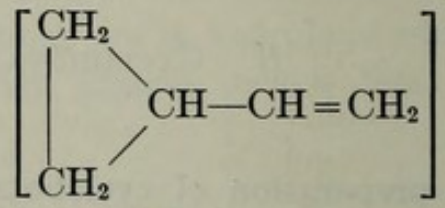
**Cyclobutylcarbinol,** $(CH_2)_3CHCH_2OH$, is obtained by the catalytic reduction of the acid chloride. Its dehydration gives cyclopentene and *methylene cyclobutane,* $(CH_2)_3C=CH_2$, b. 41°. This substance in presence of acids or bases or on heating with alumina gives *methylcyclobutene,* $\begin{matrix} CH=CMe \\ | \quad\quad | \\ CH_2—CH_2 \end{matrix}$, b. 37°. Methylene cyclobutane with nitric acid gives glutaric acid. This is related to the conversion of its chlorohydrin to cyclopentanone by warming with water. Methylene cyclobutane is also obtained by the

action of zinc on pentaerythrityl bromide

$$C(CH_2Br)_4 + 2\,Zn \rightarrow ZnBr_2 + \begin{array}{l} CH_2{-}C{=}CH_2 \\ \quad | \quad\quad | \\ CH_2{-}CH_2 \end{array}$$

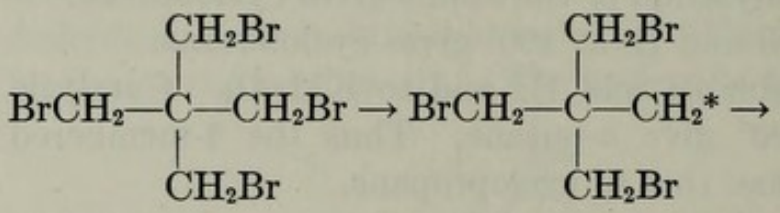
Some Me-cyclobutene is formed at the same time. It was formerly thought that this reaction gave spirobicyclopentane or perhaps vinylcyclopropane.

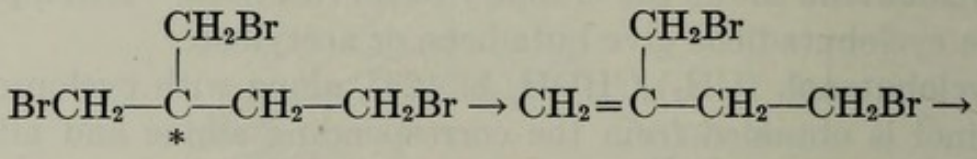


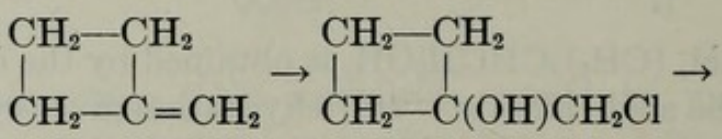


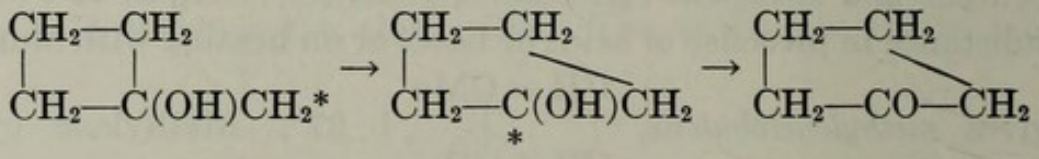
Apparently these substances are *incapable of existence.*

The conversion of the neopentane derivative, pentaerythrityl bromide, through the cyclobutane derivative to cyclopentanone involves rearrangements, ring formation and ring widening which can be shown as follows with the * indicating a carbon with only six electrons (Whitmore 1932).









The initial reaction may be the formation of 1,1-di-bromomethyl-cyclopropane, followed by similar rearrangement with ring widening (Rep. 1923, 116).

**Cyclobutanone,** $(CH_2)_3CO$, b. 100°, is made by the Hofmann reaction on α-bromocyclobutane carboxylic acid amide. Oxidation with nitric acid gives succinic acid. Heating the Ca salt of glutaric acid gives no trace of cyclobutanone. On the other hand Ca ββ-$Me_2$-glutarate apparently gives the ketone which rearranges to mesityl oxide (Rep. 1921, 96).

$$Me_2C(CH_2CO_2)_2Ca \rightarrow Me_2C(CH_2)_2CO \rightarrow Me_2C{=}CHCOCH_3$$

The effect of the gem-$Me_2$ groups in ring closure is notable (Ingold 1921).

Substituted cyclobutandiones, $RCH(CO)_2CHR$, have been prepared and found to be different from the dimers of the ketenes $RCH{=}C{=}O$ (Rep. 1917, 108).

**Cyclobutyl methyl ketone,** $(CH_2)_3CHCOCH_3$, b. 134°, is made from the acid chloride and $Me_2Zn$.

**Cyclobutane carboxylic acids.**

The **monocarboxylic acid,** $(CH_2)_3CHCO_2H$, b. 194°, is stable to HBr. HI at 200° gives *n*-valeric acid. $Br_2$ gives α-substitution. Alkaline $KMnO_4$ forms oxalic acid.

The **1,1-dicarboxylic acid,** m. 155°, loses $CO_2$ above 200°. It is not attacked by cold $Br_2$ or HBr.

The **cis-1,2-dicarboxylic acid,** m. 138°, is made by heating the 1,1,2,2-tetracarboxylic acid in a sealed tube with water at 200°. At 300° it forms an anhydride.

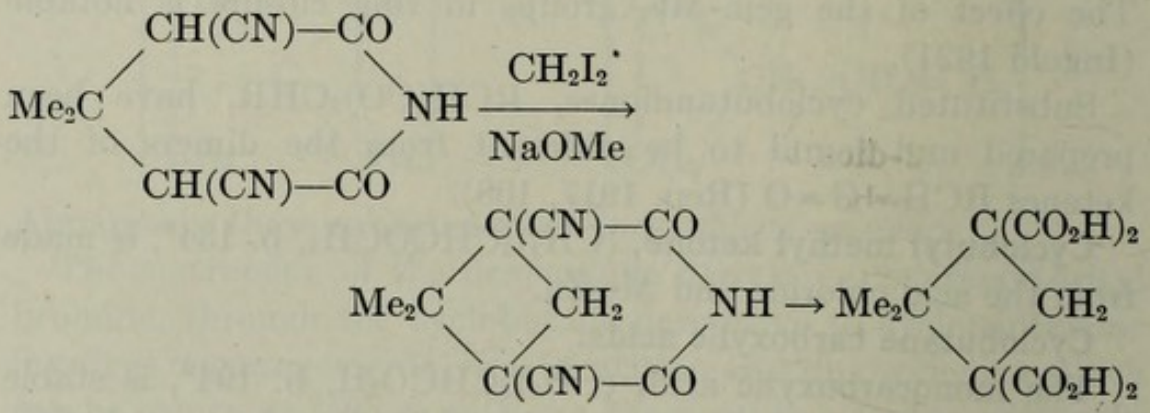
The **trans-1,2-dicarboxylic acid,** m. 131°, is obtained by heating the *cis* acid with hydrochloric acid. It is said to react readily with acetyl chloride to give the anhydride of the *cis* acid, m. 75°. This conversion of a *trans* acid into the *cis*-anhydride is also observed in the truxillic acids (p. 635). The *trans*-acid can be made by hydrolyzing and heating the product of the action of NaCN on αα′-$Br_2$-adipic ester (Fuson).

$$\begin{matrix} CH_2{-}CHBrCO_2R \\ | \\ CH_2{-}CHBrCO_2R \end{matrix} \rightarrow \left[\begin{matrix} CH_2{-}CH(CN)CO_2R \\ | \\ CH_2{-}CHBrCO_2R \end{matrix}\right] \rightarrow \begin{matrix} CH_2{-}C(CN)CO_2R \\ | \quad | \\ CH_2{-}CHCO_2R \end{matrix} \rightarrow \begin{matrix} CH_2{-}CHCO_2H \\ | \quad | \\ CH_2{-}CHCO_2H \end{matrix}$$

The introduction of the CN renders the adjacent α-H reactive enough to close the ring by action with the other Br.

The **cis-1,3-dicarboxylic acid,** m. 136°, is obtained by heating the 1,1,3,3-tetracarboxylic acid.

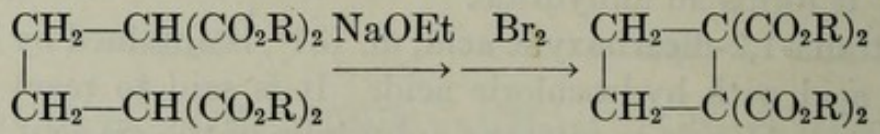
**Norpinic acid,** obtained by oxidizing pinene, is 2,2-$Me_2$-cyclobutan-1,3-dicarboxylic acid. It exists in *cis* and *trans* forms. The synthesis of this acid has offered extreme difficulties. Apparently the gem-$Me_2$ prevents the closing of the 4-ring in most reactions. The difficulty was overcome by using a cyclic imide as starting material for the ring closure (Kerr 1929)



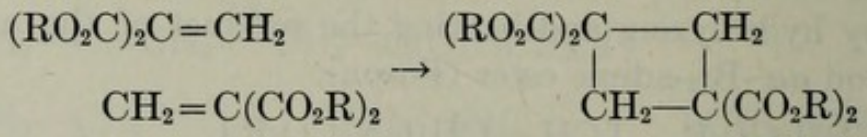

**Caryophyllenic acid,** from the oxidation of caryophyllene is 1,2,2-$Me_3$-cyclobutane-1,3-dicarboxylic acid.

The **trans-1,3-dicarboxylic acid,** m. 171°, is obtained in small yield by the action of NaOEt on $\alpha$-Cl-propionic ester.

The **1,1,2,2-tetracarboxylic acid,** m. 150° dec., is made by the action of $Br_2$ on the disodio derivative of ethylene dimalonic ester.




The **1,1,3,3-tetracarboxylic acid,** is made by the polymerization of methylene malonic ester



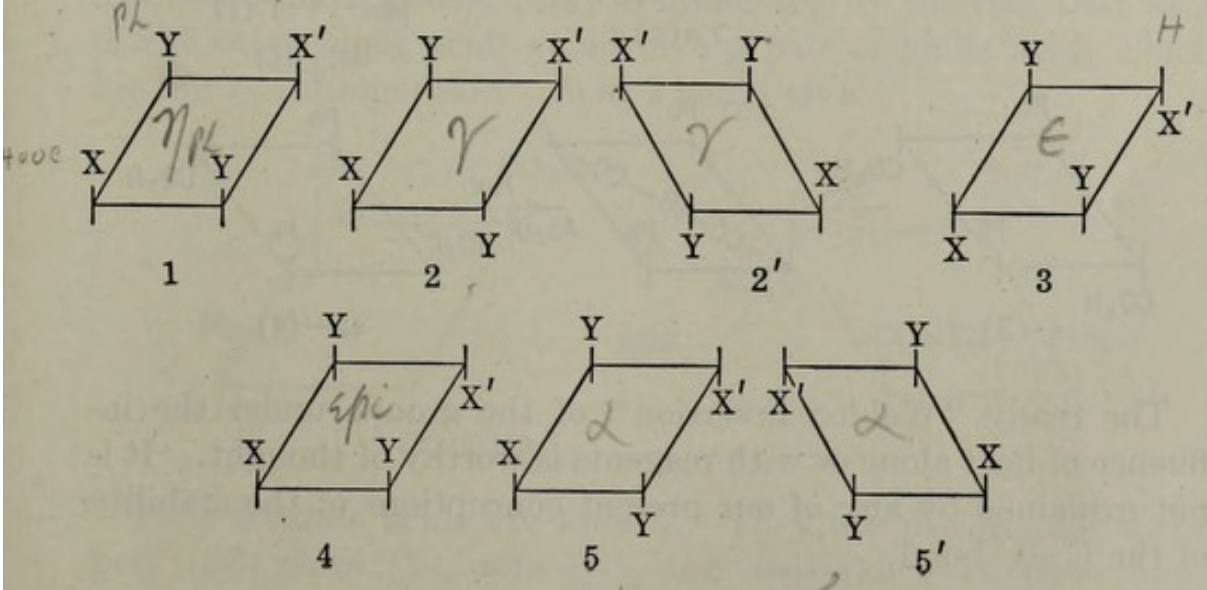

The **truxillic acids** are stereoisomeric 2,4-diphenylcyclobutane-1,3-dicarboxylic acids while the *isotruxillic* or *truxinic* acids are the corresponding 3,4-diphenyl-1,2-dicarboxylic acids. Some of their isomers occur in coca alkaloids. Cinnamic acid polymerizes under the influence of light to give truxillic acids. The formation of benzil, PhCOCOPh, by oxidation of truxinic acids

shows their phenyl groups to be in the 1,2-position. Thus the truxillic acids are formed from cinnamic acid as follows.

$$\begin{matrix} PhCH{=}CHCO_2H \\ HO_2CCH{=}CHPh \end{matrix} \rightarrow \begin{matrix} PhCH{-}CHCO_2H \\ | \quad | \\ HO_2CCH{-}CHPh \end{matrix}$$

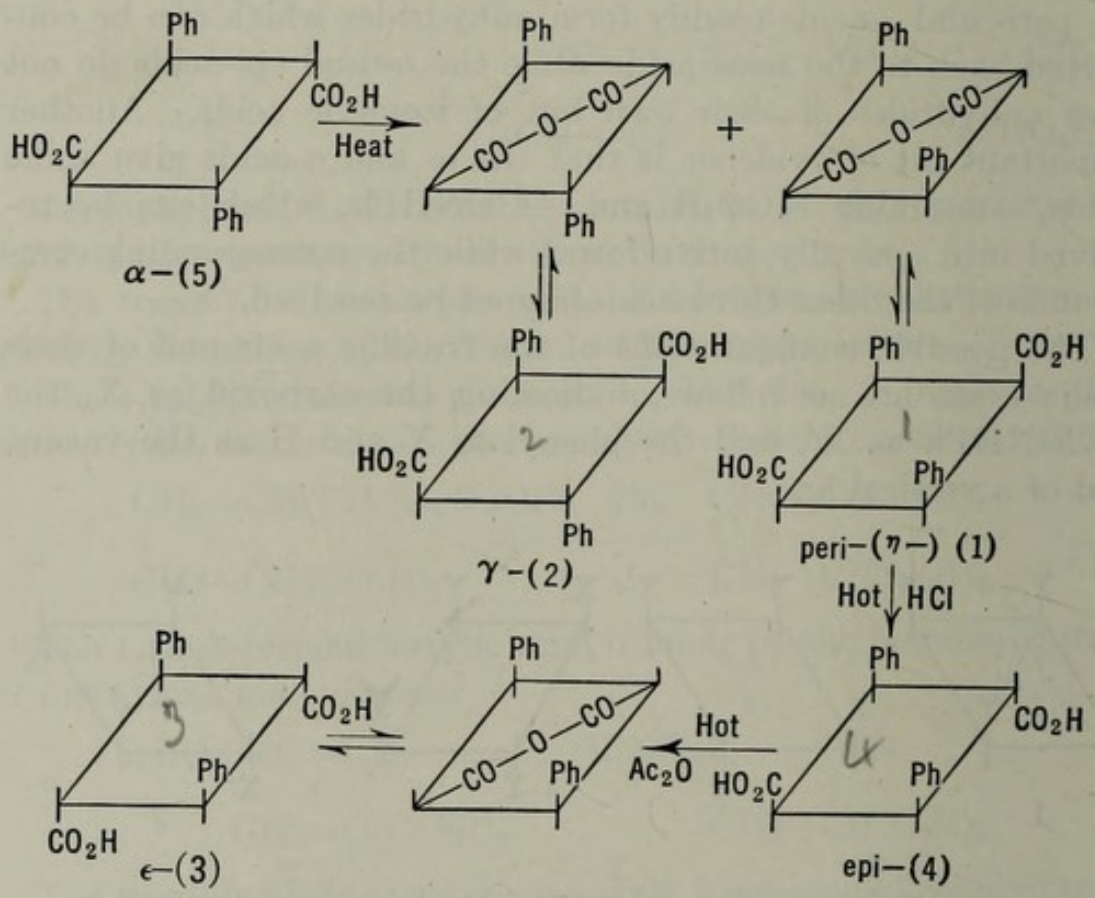
Five stereoisomeric truxillic acids are known (Rep. 1924, 95; 1926, 128). They are designated as alpha ($\alpha$-), gamma ($\gamma$-), peri or eta ($\eta$-), epi, and epsilon ($\epsilon$-). The alpha acid is found in coca leaves and is formed from cinnamic acid. On heating, the alpha acid gives anhydrides which can be converted by water to the gamma- and peri-acids. The peri-acid, with hot HCl, gives the epi-acid which reacts with hot acetic anhydride to give the anhydride of the $\epsilon$-acid. It is to be noted that the $\gamma$-, peri- and $\epsilon$-acids readily form anhydrides which can be converted back to the *same* acids while the $\alpha$- and epi-acids do not give anhydrides of their own but of isomeric acids. Another important bit of evidence is that the $\alpha$- and $\gamma$-acids give anilic acids, containing $-CO_2H$ and $-CONHPh$, which can be resolved into optically active forms while the corresponding compounds of the other three acids cannot be resolved.

The possible configurations of the truxillic acids and of their anilic acids are as follows, indicating the carboxyl as X, the $-CONHPh$ as X′, and the phenyl as Y and H as the vacant end of a vertical line.



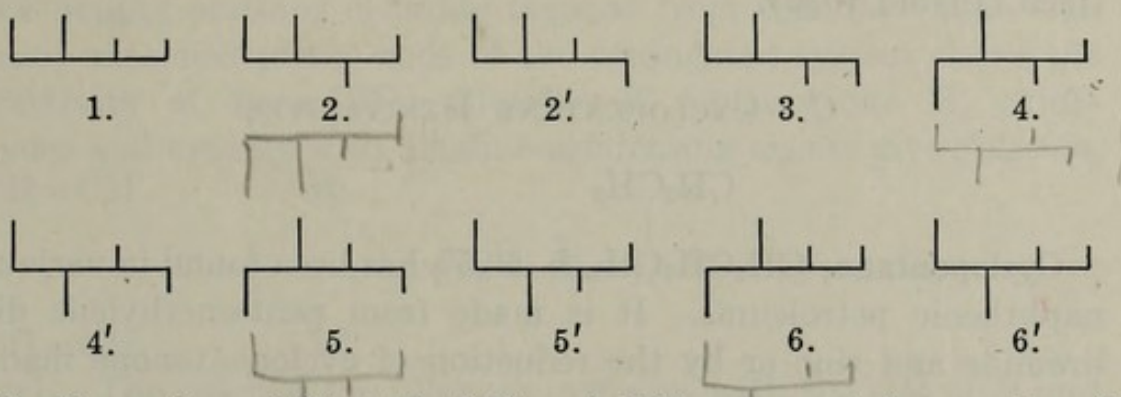
1,3 and 4 are identical with their mirror images and could not exist in optically active forms. 2,2′ and 5,5′ are pairs of enantiomorphs. Thus the $\alpha$- and $\gamma$-acids must correspond to formulas 2 and 5 but, of these, only the $\gamma$-acid forms its own anhydride. Therefore the $\gamma$-acid has configuration 2 which has the carboxyls on the same side of the plane. The $\alpha$-acid corresponds to 5 in which the carboxyls are *trans* to each other as are also the phenyls. The most stable acid which forms its own anhydride is the $\epsilon$-acid which corresponds to 3. The relatively stable acid formed by heating with HCl but not capable of forming its own anhydride is the epi-acid corresponding to 4. This leaves 1 for the peri-acid which forms an anhydride but is unstable to hot HCl.

The changes relating the five acids thus are as follows:

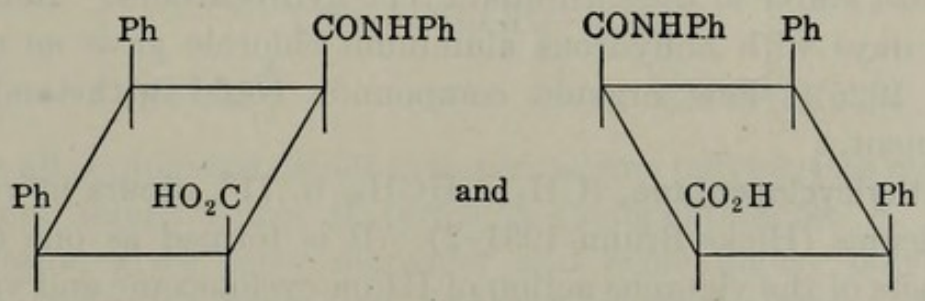



The ready "Walden inversion" of the groups under the influence of heat alone or with reagents is worthy of thought. It is not explained by any of our present conceptions of the stability of the C–C bond.

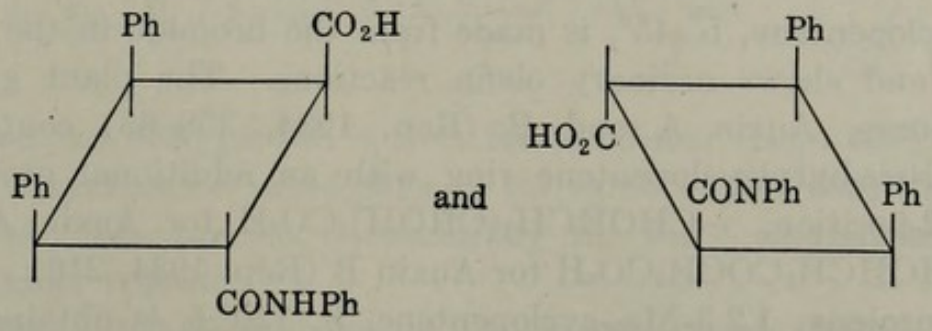
The stereoisomers of the theoretically possible *truxinic acids* may be represented as follows using the heavy line to represent the edge of the cyclobutane plane and long and short lines to represent the phenyl and carboxyl groups respectively.




Configurations 2,2′; 4,4′; 5,5′ and 6,6′ represent four pairs of enantiomorphic dibasic acids whereas 1 and 3 is each identical with its mirror image. Acids 1 and 3 each could give a pair of enantiomorphic anilic acids. Thus 1 could form




The situation is considerably complicated by the fact that *each* of the other eight acids could give a pair of anilic acids which are not enantiomorphic. Acid 2 could give

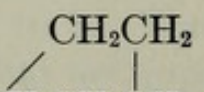



Four truxinic acids are known. They are designated as the beta (β-), delta (δ-), zeta (ζ-), and neo-acids. To these have

been tentatively assigned the configurations 3, 5(5′), 6(6′) and 2(2′) respectively.

Before the truxillic acids were solved the five forms of cyclobutan-1,3-dicarboxylic-2,4-diacetic acids were isolated and identified (Ingold 1922).

### *C.* Cyclopentane Derivatives

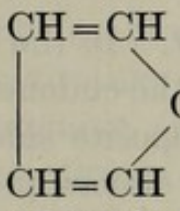
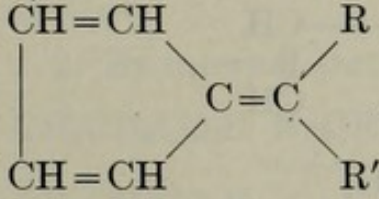


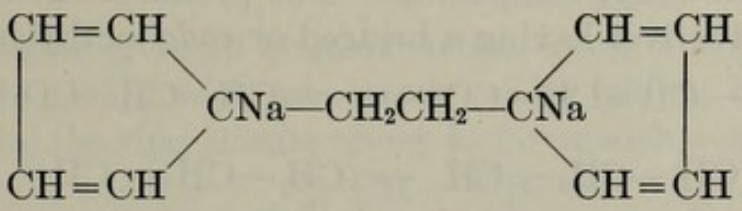
**Cyclopentane,** $CH_2CH_2CH_2CH_2CH_2$, b. 50.5°, has been found in various naphthenic petroleums. It is made from pentamethylene dibromide and zinc or by the reduction of cyclopentanone made from adipic acid. Bromine in sunlight replaces H rather than opening the ring. It is not changed by $H_2$ and catalysts even at 300°. These properties and its occurrence in petroleum indicate its stability as compared with 4- and 3-rings. It is by far the most stable of the saturated cyclic hydrocarbons. Refluxing for 8 days with anhydrous aluminum chloride gave *no change* (Cox 1925). Few organic compounds could withstand this treatment.

**Methylcyclopentane,** $(CH_2)_4CHCH_3$, b. 71°, occurs in various petroleums (Hicks-Bruun 1931–2). It is formed as one of the products of the vigorous action of HI on cyclohexane and various of its derivatives. Hydrogen and Ni at 460° also convert cyclohexane to methylcyclopentane. It is more readily oxidized than cyclopentane, presumably because of the tertiary H. Heating with dil. nitric acid replaces this H by a nitro group.

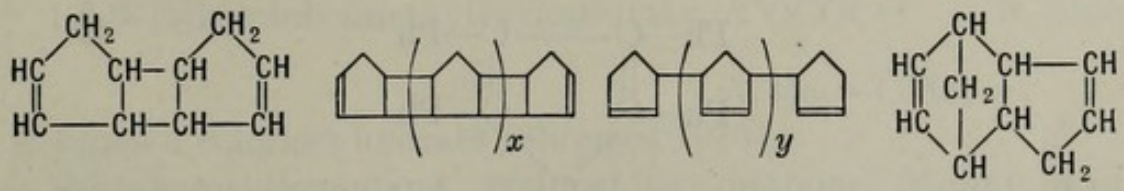
**Cyclopentene,** b. 45°, is made from the bromide in the usual way and shows ordinary olefin reactions. The plant growth hormones, Auxin A and B (Rep. 1934, 358–65) contain a 3,5-di-*sec*-butylcyclopentene ring with an additional group in the 2-position, $-CHOHCH_2(CHOH)_2CO_2H$ for Auxin A and $-CHOHCH_2COCH_2CO_2H$ for Auxin B (Rep. 1934, 216).

**Laurolene,** 1,2,3-$Me_3$-cyclopentene, b. 120°± is obtained by the decarboxylation of laurolenic acid by distillation. It has also been synthesized from $\alpha\alpha'$-$Me_2$-cyclopentanone (Noyes 1910).

**Cyclopentadiene,**  , b. 41°, is obtained from the low boiling portions of crude benzene from coal tar. The $CH_2$ group attached to the ends of the conjugated system shows the reactivity of an $\alpha$-$CH_2$. Metallic K replaces one H. Aldehydes and ketones with alkaline condensing agents give *fulvenes*,  , in which R and R′ may be H, alkyl or aryl. The color of the fulvenes increases with the size of R and R′, becoming red with aromatic substitution. The fulvenes add alkali metals and form dimers.



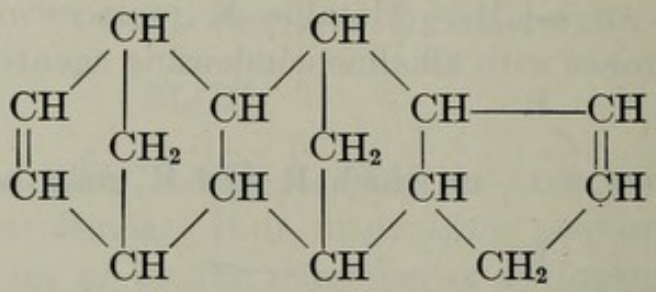
Like all conjugated dienes cyclopentadiene polymerizes readily. At room temperatures it forms di-cyclopentadiene, b. 170°. Distillation gives some monomer and some higher polymers. Various formulas have been assigned to the polymers (Egloff 1931).



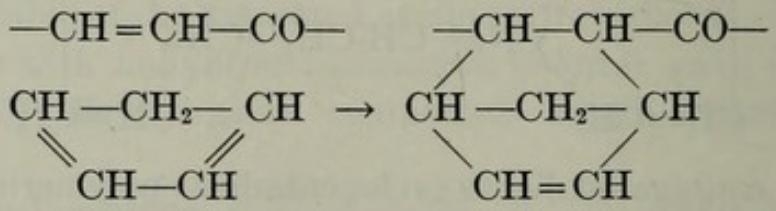
The last has been proved correct for the dimer (Rep. 1931, 87). The polymerization takes place in the same way as does that of isoprene. The process is essentially the same as that of the Diels-Alder reaction.

Di-cyclopentadiene exists in two stereoisomeric forms. Because of the *p*-methylene bridge the cyclohexane ring is necessarily in the *cis* or "boat" form with the 2,3,5,6-carbons in one

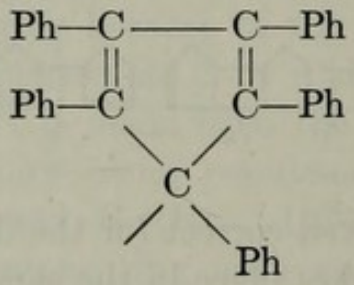
plane and the 1,4-carbons above it. In the *cis* dimer, the 5-ring is on the same side of the plane as the endomethylene group while in the *trans*-dimer it is on the opposite side. Two trimers are known each related to one of the dimers and formed from it by addition of a molecule of cyclopentadiene to the double bond in the 6-ring to give another 6-ring with an endomethylene group.



In much the same way that cyclopentadiene polymerizes, it can act as the diene in the Diels-Alder reaction with $\alpha\beta$-unsaturated carbonyl compounds. The products again are cyclohexane derivatives having a bridged or *endo*-methylene group.



**Pentaphenylcyclopentadienyl** is probably the most stable free radical. It forms violet crystals which show no tendency to associate (Ziegler, Rep. 1928, 156). Its high degree of stability is probably related to its extraordinary possibilities for resonance.



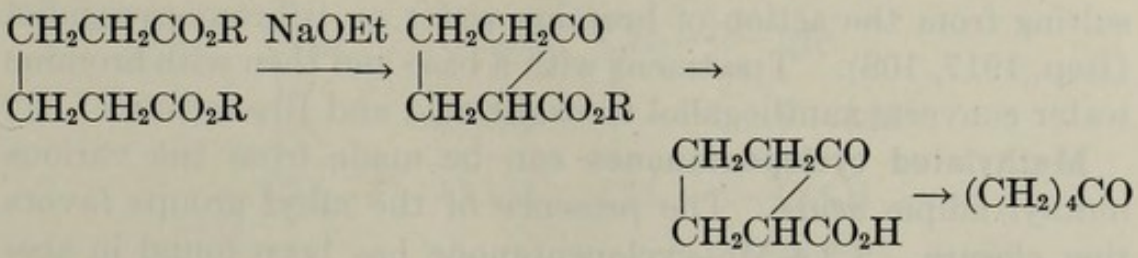
**Cyclopentanol,** cyclopentyl alcohol, $(CH_2)_4CHOH$, b. 140°, is obtained by reducing the ketone. It is an entirely ordinary secondary alcohol. It gives halides which react normally. The unsaturated halide, 3-chlorocyclopentene, acts as a cyclic allyl halide. It has been used to synthesize chaulmoogric acid (Perkins 1927).

**Cyclopentandiol-1,2** is obtained from the olefin, *cis-* m. 47°, *trans-* m. 10°. Dehydration gives the ketone, cyclopentanone.

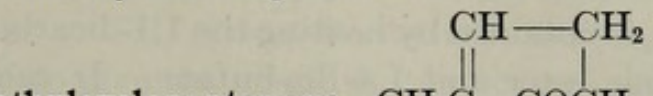
**Cyclopentanone,** adipone, $(CH_2)_4CO$, b. 130°, is made

1. By distilling the calcium salt of adipic acid, obtained by the oxidation of cyclohexanol, prepared in turn by the catalytic hydrogenation of phenol. These steps give a method for going from a 6-carbon aromatic ring to the 5-carbon aliphatic ring. Another method is to heat a mixture of adipic acid and $BaCO_3$ at 300°.

2. By internal acetoacetic ester condensation of adipic ester.

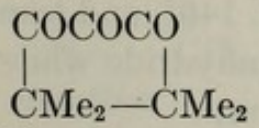


Cyclopentanone gives all ketone reactions both of the CO and of the $\alpha-CH_2$ groups with great ease. The folding back of the $\alpha$-carbons by the ring closure seems to favor such activity.

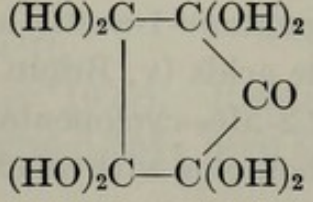


**Methylcyclopentenone,** $CH_3C{=}CHCOCH_2$, b. 157°, is obtained along with the $C_5$ and $C_6$ cyclic ketones in the products of wood distillation.

The active principles of pyrethrum flowers contain the cyclopentane nucleus (Haller, LaForge 1936).

1,2,3-Triketotetramethylcyclopentane,  is blue. It forms a colorless hydrate (Shoppee 1936).

**Pentaketocyclopentane,** cyclopentanpentanone, *leuconic acid,* exists as the tetrahydrate. The water cannot be removed without decomposing the compound. It probably exists with only one free ketone group.



Leuconic acid is made by treating triquinoyl, the hydrate of hexaketocyclohexane, with a base to give a benzilic acid rearrangement, acidifying and heating and oxidizing the *Croconic acid*, the enediol of tetraketo-hydroxy-cyclopentane. Leuconic acid gives a pentoxime and condenses with two mols of an *o*-diamine showing it to have two pairs of adjacent carbonyls as in diacetyl and similar compounds. As would be expected, the accumulated carbonyl groups give instability toward bases. Simply boiling with sodium carbonate solution gives oxalate and mesoxalate.

**Xanthogallol,** is 1,2,3,3-tetrabromo-4,5-diketocyclopentane resulting from the action of bromine water on tribromopyrogallol (Rep. 1917, 108). Treatment with a base and then with bromine water converts xanthogallol to oxalic acid and $Br_5$-acetone.

**Methylated cyclopentanones** can be made from the various methyl adipic acids. The presence of the alkyl groups favors ring closure. 3,3,4-$Me_3$-cyclopentanone has been found in acetone oil (Pringsheim).

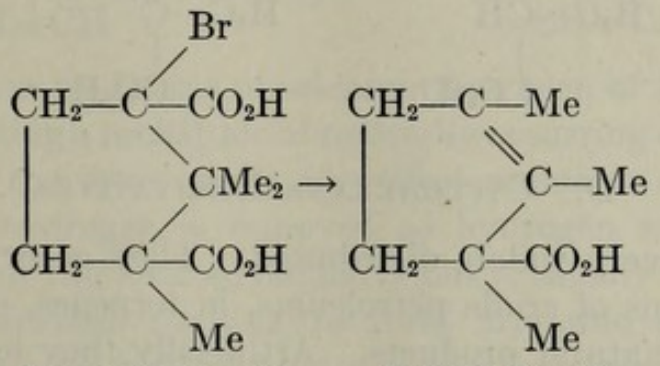
**Cyclopentane carboxylic acids** of greater or less complexity exist in the naphthenic acids of certain petroleums. The *monocarboxylic acid*, b. 215°, is obtained by heating the 1,1-dicarboxylic acid made from malonic ester and 1,4-$Br_2$-butane. It can also be made by $CO_2$ with cyclopentyl Grignard reagent which acts entirely normally. *The 1,2-dicarboxylic acid* is made from the tetracarboxylic ester obtained by the action of bromine on the disodio derivative of 1,3-trimethylene dimalonic ester. It exists as *cis*, m. 140°, and *trans*, m. 160°, acids. Heat converts both to the *cis* anhydride while heating with HCl converts the *cis* to the *trans* form.

Three *1,2,3-tricarboxylic acids* are obtained from $\alpha\alpha'$-$Br_2$-adipic esters, malonic ester and NaOEt. The *cis* form and the *cis trans cis* form are meso while the *cis cis trans* form is racemic and can be resolved by means of the brucine salts. The first and last readily give anhydrides (Rep. 1921, 87; 1922, 77).

3,3,4-Trimethylcyclopentane-1-acetic acid has been identified in petroleum naphthenic acids (v. Braun 1931).

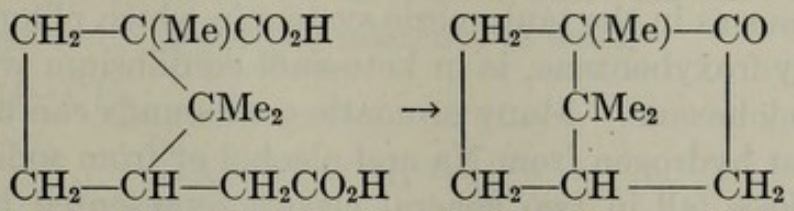
**Apocamphoric acid,** 2,2-$Me_2$-cyclopentane-1,3-dicarboxylic acid and *camphoric acid*, its homolog with an extra methyl group in the

1-position are important oxidation products in the terpene series. Camphoric acid contains two asymmetric carbons and exists in four optically active forms. The specific rotations are all about 48°. The *d*- and *l*-camphoric acids, m. 187°, form anhydrides and are thus *cis* forms while the *d*- and *l*-isocamphoric acids, m. 171°, are *trans* forms. By the action of $Br_2$ and sodium carbonate on camphoric acid, *laurolenic acid*, 2,3,4-$Me_3$-cyclopentene-3-carboxylic acid is obtained.



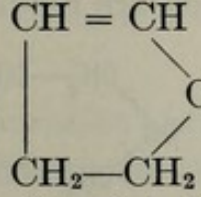

Br-camphoric acid Laurolenic acid

Reduction of camphoric anhydride changes one of the CO groups to $CH_2$ giving the lactone, *campholide*. This reacts with KCN to give the nitrile of homocamphoric acid. Distillation of its Ca salt gives camphor.



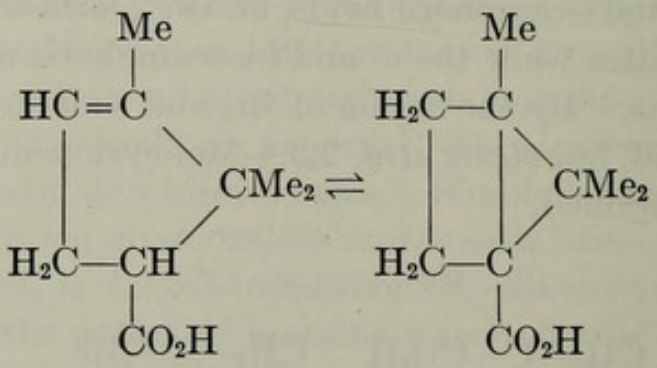

Homocamphoric acid Camphor

**Isocampholic acid** is 2,2,3-$Me_3$-cyclopentane-1-acetic acid.

**Chaulmoogric acid,** m. 68°, and *hydnocarpic acid* are ω-cyclopentenyl acids, 

in which $n$ is 12 and 10 respectively (Stanley 1929). Related acids containing the saturated cyclopentyl group have been made (Yohe 1928).

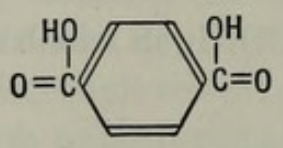
**α-Campholytic acid,** 2,3,3-$Me_3$-cyclopentene-4-carboxylic acid is believed to exist in intra-annular tautomerism with 1,2,2-$Me_3$-3-carboxy-bicyclo(2.1.0)pentane. (Rep. 1922, 114).

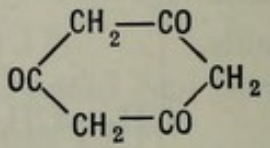



### *D.* Cyclohexane Derivatives

These are very widely distributed. They occur in the naphthenic portions of crude petroleums, in terpenes, camphors and many other natural products. Artificially they have been prepared in great numbers by reactions which take place intramolecularly in the 1,6-position. This includes reactions of two molecules having reactive 1,3-positions. First, two molecules combine and then the 1,6-process closes the ring.

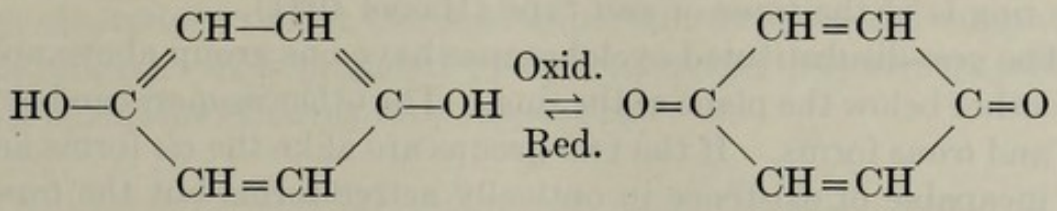
The relation of *true hexamethylene and true benzene derivatives* is very close. Sometimes the transition from one to the other is spontaneous as in the tautomeric system in which phloroglucinol, 1,3,5-trihydroxybenzene, is in keto-enol equilibrium with 1,3,5,-triketocyclohexane. Many aromatic compounds can be reduced by nascent hydrogen from Na and alcohol or from sodium amalgam. These fall in two general classes represented by the dibasic acids and the meta di- and tri-hydroxy compounds. The former contain a grouping like that in the aliphatic αβ-unsaturated ketonic compounds which are similarly reduced and the latter exist in equilibrium with ketones which are readily reduced.



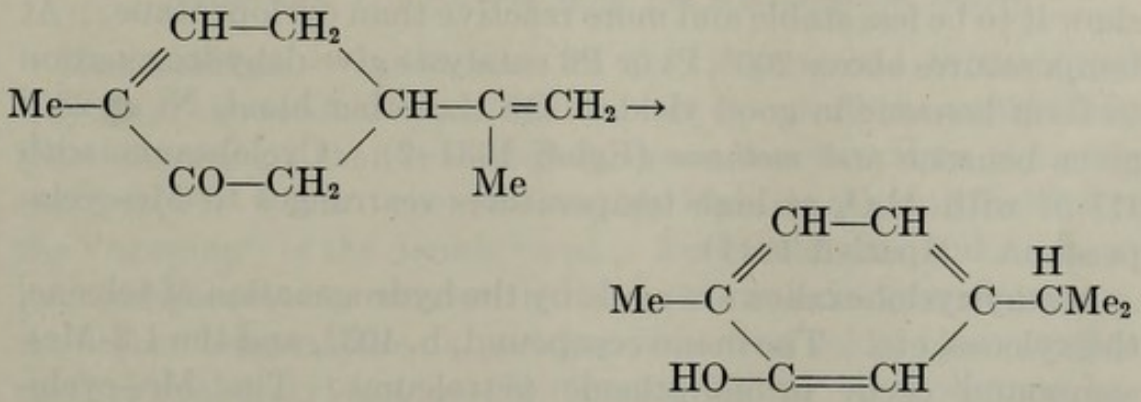

Other aromatic compounds can be converted to the corresponding hydroaromatic or cyclohexane derivatives by catalytic hydro-

genation in presence of Ni, Pt, Pd etc. Conversely, various methods of oxidation and dehydrogenation will change cyclohexane derivatives to aromatic compounds. The interconversion of quinone and hydroquinone is one of the easiest and the best known of these processes.




Dehydrogenation by means of selenium has been of the greatest value in converting a multitude of naturally occurring cyclohexane compounds to the more easily identified aromatic compounds. The "excess" hydrogen is removed as hydrogen selenide. In some cases sulfur can be used similarly but it usually has the disadvantage of further reacting to form aromatic sulfur compounds, whereas the less reactive selenium has less of this tendency. Such methods of conversion to aromatic compounds have been valuable in the study of the constitution of the sterols, the bile acids, the sex hormones, toad and arrow poisons and various alkaloids.

Any series of changes which gives three double bonds in a 6-ring takes place with special ease. Thus carvone changes readily to carvacrol under the influence of acid.




Acid causes the migration of the double bond from the isopropenyl group to the ring where the enolization of the keto group supplies the third double bond to give aromatic character to the ring.

The isomerism of cyclohexane compounds follows the usual principles. The disubstitution products are 1,1-(*gem*); 1,2-

(*ortho*); 1,3-(*meta*); and 1,4-(*para*). The stereochemistry of mononuclear cyclohexane compounds is simplified by the existence of the ring in only one form (p. 621). Existence of *cis* and *trans* rings occurs in compounds containing two or more cyclohexane rings. X-Ray studies of *trans*-1,4-$Br_2$-cyclohexane indicate that the ring is of the *trans* or *seat* type (Hassel 1931).

The *gem*-disubstituted cyclohexanes have one group above and the other below the plane of the ring. The other isomers can have *cis* and *trans* forms. If the two groups are alike the *cis* forms are all incapable of existence in optically active forms but the *trans* forms of the *ortho* and *meta* compounds have no plane of symmetry and can exist in enantiomorphic optical isomers. The *trans para* compounds are symmetrical.

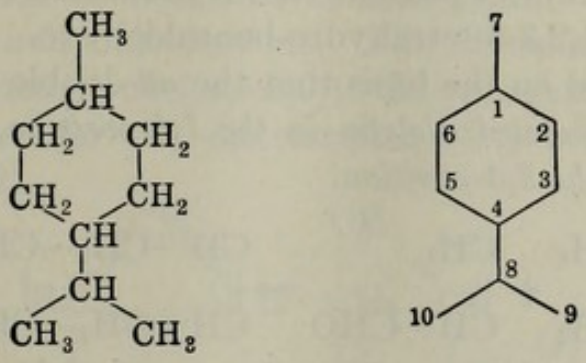
*Saturated Hydrocarbons of the Cyclohexane Series*

**Cyclohexane,** hexamethylene, hexahydrobenzene, $(CH_2)_6$, m. 6.5°, b. 81°, occurs in various petroleums (Bruun 1931–2). It is made from benzene by hydrogenation with Ni at about 200° or with platinum black in glacial acetic acid at 20°. It can also be obtained from many of its derivatives by ordinary reactions. In most of its reactions it resembles the paraffins. Bromine substitutes in the light. Anhydrous aluminum chloride at 150° gives no change. Hot permanganate gives adipic acid. Fuming sulfuric acid converts it to benzene sulfonic acid. These reactions show it to be less stable and more reactive than cyclopentane. At temperatures above 200°, Pt or Pd catalysts give dehydrogenation to form benzene in good yields. On the other hand, Ni at 280° gives benzene and *methane* (Egloff 1931–2). Cyclohexane with HI or with $Al_2O_3$ at high temperatures rearranges to Me-cyclopentane. (Ipatieff 1911).

**Methylcyclohexanes** are made by the hydrogenation of toluene, the xylenes, etc. The mono compound, b. 103°, and the 1,3-$Me_2$-compound occur in nahpthenic petroleums. The $Me_2$-cyclohexanes have been made in all seven theoretically possible forms. They all boil near 120°. The 1,2,4- and 1,3,5-$Me_3$-compounds have been obtained in *cis* and *trans* forms, b. about 140°. The homologs of cyclohexane with longer side chains behave differently with aluminum chloride than do the corresponding benzene

derivatives. Thus Et-cyclohexane gives a mixture of $Me_2$-cyclohexanes while Et-benzene gives mainly $Et_2$-benzene and benzene. Similarly *n*-Pr- and *n*-Bu-cyclohexanes give $Me_3$- and $Me_4$-cyclohexanes respectively (Grignard 1924).

*p*-Methylisopropylcyclohexane, *p-menthane*, b. 170°, is the parent substance to which the most important terpenes and camphors are related. It is prepared by hydrogenating *p*-cymene, (*p*-Me-isoPr-benzene) from spruce turpentine




*p*-Menthane

The meta isomer is related to a few unusual terpenes.

The *aliphatic* hemiterpenes, $C_5H_8$, and monoterpenes, $C_{10}H_{16}$, such as isoprene and myrcene and their derivatives such as geraniol and linalool have already been discussed.

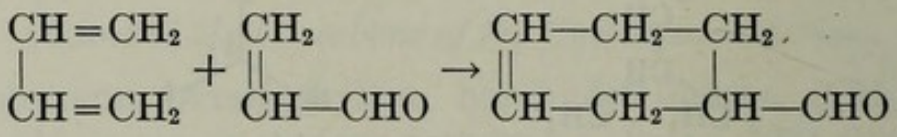
### *Unsaturated Hydrocarbons of the Cyclohexane Series*

**Mono-olefins.** *Cyclohexene*, b. 83°, is prepared in the usual way from the alcohol or the halide. It shows all the usual olefin reactions except that it is slightly more reactive than the open chain $RCH=CHR'$ type, presumably because the ring facilitates the "opening" of the double bond. Acetyl chloride and $AlCl_3$, at low temperatures, convert it to 1-chloro-2-acetylcyclohexane. At higher temperatures a peculiar reduction takes place to give methyl cyclohexyl ketone (Nenitzescu 1936). Cyclohexene has been proposed as a standard to measure the auto-oxidation of cracked gasolines and the efficiency of inhibitors against oxidation (Egloff). The four *mono-olefins of methylcyclohexane* are obtainable from the hexahydrocresols and cyclohexanyl halides, $(CH_2)_5CHCH_2X$. The latter give 1-Me-cyclohexene, b. 111°,

and methylene cyclohexane, b. 103°. The latter has a semicyclic double bond. It readily isomerizes to give the methyl compound.

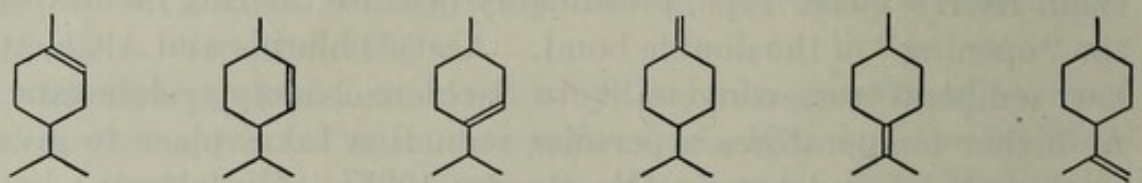
*α*- and *β-cyclogeraniolenes*, 1,1,3-$Me_3$-cyclohexene-3 and -2 are obtained in the ratio 3 : 1 by the action of sulfuric acid with geraniolene, $Me_2C=CHCH_2CH=CMe_2$ and its isomers (S I 92).

A most important process for making complex cyclohexene derivatives in great variety is the Diels-Alder reaction (1928) between a conjugated diene and an *αβ*-unsaturated carbonyl compound. The simplest possible case is between acrolein and butadiene to give 1,2,3,6-tetrahydro-benzaldehyde. The net result can be explained on the basis that the *αβ*-double bond *opens and adds to the conjugated diolefin in the 1,4-position, forming a new double bond in the 2,3-position.*



The conjugated diolefin group can be supplied by ordinary hydrocarbons or by compounds such as furan and N-Me-pyrrole. In the latter cases the resulting cyclohexene ring has an O or N bridge in the 1,4-position. The *αβ*-unsaturation can be supplied by aldehydes, ketones, acids, and even by substances like benzoquinone. The latter can react with one or two molecules of diolefin. The commonest *αβ*-compound used is maleic anhydride. Hydrogenation or dehydrogenation converts the products to derivatives of cyclohexane or of benzene.

The six possible *p-menthenes* are known. They are named as follows:

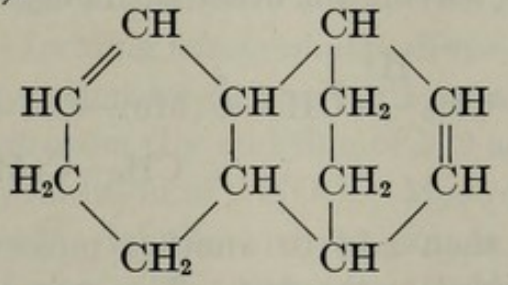


Δ 1- Δ 2- Δ 3- Δ 1(7) Δ 4(8)- Δ 8-

The latter is also designated as Δ8(9)-*p*-menthene. The fourth isomer can be called Δ7- without ambiguity. The use of the Δ has become general but there is no reason why the names *p*-menthene-1, *p*-menthene-1(7), etc., should not be used. Ordi-

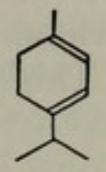
nary *menthene* is the Δ3 isomer, b. 168°, obtained from menthol (3-hydroxy-*p*-menthane) through the xanthate or the chloride. It exists in *d*- *l*- and inactive forms. Oxidation gives β-Me-adipic acid. The menthenes are not found in nature as are the menthadienes, probably because they cannot be built up from isoprene units.

**Diolefins.** Mixtures of cyclohexadiene-1,3 and 1,4 (1,2- and 1,4-dihydrobenzenes) are obtained by elimination reactions from both 1,2- and 1,4-disubstituted cyclohexanes. Oxidation gives oxalic, succinic and malonic acids. The 1,3-isomer gives a stable dimer, 1,4-endoethylene-1,4,5,6,9,10-$H_6$-naphthalene (I) by the ordinary process for the dimerization of a conjugated diene. (Rep. 1932, 112).



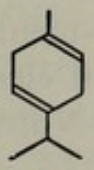

(I)

1,3-Cyclohexadiene can be obtained by heating quinitol and anhydrous $MgSO_4$ (Kasansky 1935). The *p*-menthadienes (*p*-terpadienes) occur widely in plant products. The common forms follow:



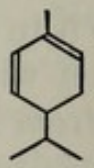
Δ 1, 3–

α-Terpinene
b. 180°



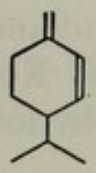
Δ 1, 4–

γ-Terpinene



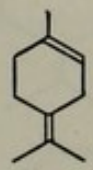
Δ 1, 5–

α-Phellandrene
b. 175°



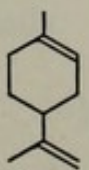
Δ 1, (7), 2–

β-Phellandrene



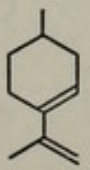
Δ 1, 4 (8)–

Terpinolene
b. 187°



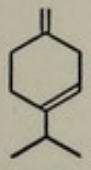
Δ 1, 8 (9)–

Limonene
Dipentene (*dl*)
b. 175°



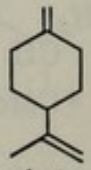
Δ 3, 8 (9)–

β-Terpinene



Δ1, (7), 3–

Pseudolimonene



Δ1, (7), 8 (9)

The addition of two isoprene molecules to give a *p*-menthadiene may be a special case of polymerization under the influence of $H^+$ ions (cf. Whitmore 1934). The addition of the $H^+$ ion to a conjugated diene may be expressed electronically as follows:

$$\overset{\cdot\cdot}{C}::\overset{\cdot\cdot}{C}:\overset{\cdot\cdot}{C}::\overset{\cdot\cdot}{C}\xrightarrow{H^+}H:\overset{\cdot\cdot}{C}:\overset{\cdot\cdot}{C}:\overset{\cdot\cdot}{C}::\overset{\cdot\cdot}{C}\rightarrow H:\overset{\cdot\cdot}{C}:\overset{\cdot\cdot}{C}::\overset{\cdot\cdot}{C}:\overset{\cdot\cdot}{C}$$

$$CH_2=CH-CH=CH_2 + H^+ \rightarrow$$

$$CH_3\underset{*}{C}HCH=CH_2 \rightarrow CH_3-CH=CH-CH_2{}^*$$

in which the * indicates the carbon with only 6 electrons which is in a condition to unite with a negative ion or to add to one carbon of an olefinic linkage, leaving the other with only 6 electrons.

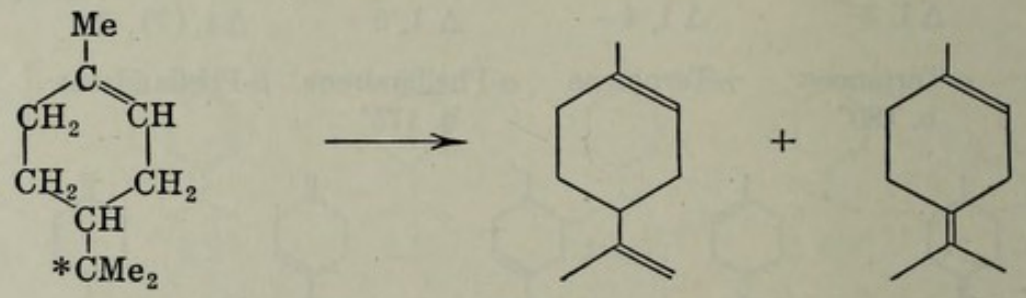
$$CH_2=C(Me)-CH=CH_2 \xrightarrow{H^+} CH_3-\overset{*}{C}(Me)-CH=CH_2 \rightarrow$$

$$CH_3-C(Me)=CH-CH_2{}^*$$

This fragment can then add to another molecule of isoprene *exactly as the $H^+$ added to the first.* The same electronic shift would give

$$CH_3C(Me)=CH-CH_2-CH_2-C(Me)=CH-CH_2{}^*$$

The electronically deficient carbon is now in the 1,6-position to a double bond and adds to it to give a *p*-menthane skeleton with a $\Delta 1$ and the No. 8 carbon with only 6 electrons. This can be stabilized by loss of $H^+$ from No. 9 or No. 4.




Addition and loss of $H^+$ could give all the isomeric dienes. Interesting as this mechanism may be in some respects, it does not in the least explain the ability of individual plants to make

specific menthadienes. Thus citrous fruits produce *d*-limonene while coniferous trees produce the *l*-form. The closely related terpinolene occurs in coriander oil. The close relation of this series to the aromatic series is shown by the conversion of $\alpha$-terpinene to *p*-cymene by heating with $I_2$.

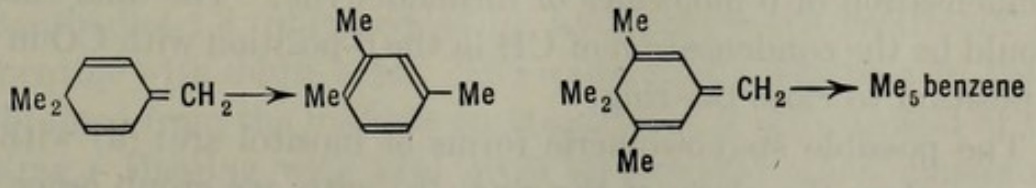
**Moslene** is $\Delta$ 2,4- or $\Delta$ 2,5-menthadiene (Rep. 1921, 89).

**Sylvestrene,** *m*-menthadiene-1,8 or $\Delta$ 1,8(9)-, is found in a few plant products. It has been synthesized. The *carenes*, terpenes containing a cyclopropane ring combined with a cyclohexane ring in the 3,4-position, are widely distributed in nature (Rep. 1925, 131). In many cases the cyclopropane ring is broken giving sylvestrene or related products.

The menthadienes or monocyclic terpenes give the reactions of two double bonds forming *tetrabromides, dihydrochlorides, dihydrobromides*, di-*nitrosochlorides* (with NOCl or with EtONO, acetic acid and HCl), *nitrosites* (by addition of NO and $NO_2$ from $N_2O_3$) and *nitrosates* (by addition of 2 $NO_2$). Most of these are crystalline compounds with definite melting points. The *nitrolamines* (from amines and nitroso chlorides) are also valuable in this way. The nitroso chlorides have the blue color of monomolecular nitroso compounds only when addition takes place in the 4,8-position. Such products are volatile with steam. In other cases the nitroso compound changes to the colorless bimolecular form or to the isonitroso compound, $CH-NO \rightleftharpoons C=NOH$.

**Triolefins.** *p*-menthatriene-1,3,5 is *p*-cymene. 2-Me-*p*-menthatriene-2,6,8 has been obtained from the reaction product of MeMgX with carvone, 2-keto-*p*-menthadiene-6,8.

Various *semi-benzenes*, containing two double bonds in the ring and a third as a semi-cyclic double bond have been obtained (Rep. 1922, 96). In presence of acid these readily rearrange to aromatic compounds.



*Alcohols*

**Cyclohexanol,** hexahydrophenol, hexalin, m. 20°, b. 161°, is made by the catalytic hydrogenation of phenol with Ni at about 170°. It is produced commercially as a solvent. It gives all the usual secondary alcohol reactions. Gentle oxidation gives the ketone while more vigorous action forms adipic acid

$$(CH_2)_4(CO_2H)_2.$$

**Quinitol,** cyclohexandiol-1,4, obtained from hydroquinone exists as *cis*, m. 102°, and *trans*, m. 139°. These taste sweet. Oxidation gives quinone. The *o*- and *m*-isomers are also known. The 1,2,3-triol from pyrogallol exists in three stereo forms, m. 108°, 124° and 148°. The 1,3,5-triol, *phloroglucitol*, m. 184°, is made from phloroglucinol by NaxHg reduction.

**Quercitol,** $CH_2(CHOH)_5$, pentahydroxycyclohexane, m. 234°, $[\alpha]^D = +24°$, occurs in plant products. Reduction with HI gives various products including pyrogallol, phenol and benzene. Oxidation gives malonic acid, mucic acid (configuration $+--+$) and *l*-trihydroxyglutaric acid ($+--$). The possible configurations for quercitol follow:

(*a*) a form with the 5 hydroxyls *above* the plane of the ring. The other possibilities will have 1 or 2 of the hydroxyls *below* this plane. With the $CH_2$ group as No. 6 these possibilities will be (*b,c,d*) with the 1,2, *or* 3-OH below; (*e,f,g,h*) with the 1-OH *and* the 2,3,4 or 5-OH *below;* (*i,j*) with the 2-OH *and* the 3 *or* 4-OH *below*. A study of the models shows that only configuration (*g*) with the 2,3,5-hydroxyls on one side of the plane and the 1,4-hydroxyls on the other can be optically active and contain the configurations in mucic and *l*-$(OH)_3$-glutaric acid.

**Inositol,** hexahydroxycyclohexane, $(CHOH)_6$, occurs widely in nature either free or in combination. It may be formed by the condensation of 6 molecules of formaldehyde. The final change would be the condensation of CH in the 6-position with CO in the 1-position to close the ring.

The possible stereoisomeric forms of inositol are: (a) with all groups *above* the plane of the ring, (b) with *one* group *below* the

plane; (c,d,e) with *two* groups *below* in *ortho*, *meta* or *para* position to each other, and (f,g,h) with *three* groups below in *vicinal*, (1,2,3), *symmetrical* (1,3,5), or *unsymmetrical* (1,2,4), arrangement in respect to each other. Of these all have a plane of symmetry except the last which is the only one capable of optical activity. Thus the naturally occurring optically active inositols have configuration (h) in which the 1,2,4-hydroxyls are on one side of the ring and the 3,5,6- are on the other. It is notable that this corresponds to the configuration of active quercitol.

**Meso-inositol,** m. 225°, occurs free in muscle and in a variety of other animal and plant products. It is widely distributed in plants as *phytin*, an acid hexaphosphoric ester of inositol which occurs as salts of Ca, Mg, K etc. Because of the formation of allomucic acid (++++) by the oxidation of meso-inositol and because its monophosphoric ester cannot be resolved into optically active material the configuration (b) is adopted. Configurations (d to h) could not give the ++++ configuration of allomucic acid. Configuration (c) would give unsymmetrical monophosphoric esters. *d-* and *l-inositols* have been made respectively by the hydrolysis of the monomethyl ethers *pinitol* and *quebrachitol*. Other methyl ethers are *bornesitol* and *dambonitol*.

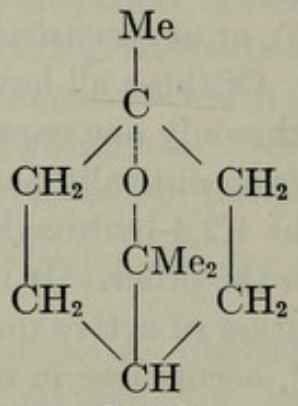
***p*-Menthanols.** The most important, *menthol*, 3-hydroxy-*p*-menthane, m. 43°, b. 216°, $[\alpha]^D = -49.7°$, occurs in peppermint oil. Hydrogenation of thymol, 3-OH-*p*-cymene, gives optically inactive menthol. The three asymmetric carbons in menthol make possible 8 optical isomers of which 4 are known.

***l*-Menthylamine,** 3-amino-*p*-menthane, is obtained along with three optical isomers by the reduction of the oxime of *l*-menthone. It is a strong base and is very useful in resolving *dl*-acids.

**Carvomenthol,** 2-OH-*p*-menthane, is obtained by vigorous reduction of carvone.

***p*-Menthadiols.** The most important of these is 1,8-*terpin*, *p*-menthadiol-1,8, obtained as its hydrate by the treatment of turpentine with dilute acid. The *cis*-form of 1,8-terpin, m. 104°, is obtained from the hydrate on standing over sulfuric acid or on heating. Heating with acid gives an internal ether, *cineole* or

eucalyptole, m. 1°, b. 177°, which is found in many ethereal oils.




Cineole

Cineole forms oxonium salts even with such weakly acid substances as phenol. It contains three 6-membered rings two of which contain an oxygen atom in combination much like that of a pyrone. *Trans* 1,8-terpin is known, m. 157°. It does not form a hydrate.

**Terpin hydrate,** m. 121°, was formerly given the open chain structure $[Me_2C(OH)(CH_2)_3C(OH)(Me)(CH_2)_2OH]$. Such a structure is entirely inconsistent with the melting point of 121° and the loss of water over sulfuric acid at room temperature. The melting point of the hydrate is not surprising. For instance $Me_5$-ethanol, m. 17°, forms a hydrate, m. 83°.

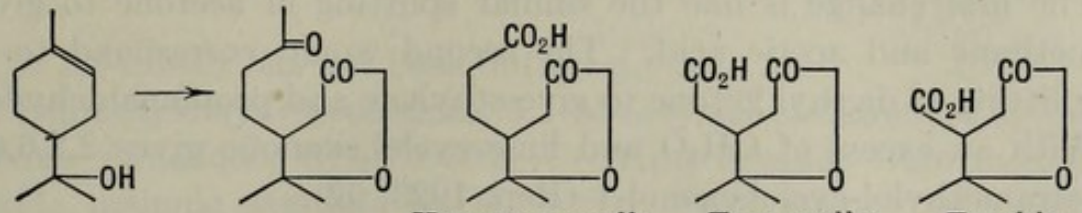
1,8-Terpin hydrate has been made by the action of 3 MeMgX on cyclohexanone-4 carboxylic ester and by ring closure of geraniol or nerol, $Me_2C=CH(CH_2)_2C(Me)=CHCH_2OH$, with acid. Since nerol reacts more rapidly it is assigned the *cis* structure.

| | Position of OH | Δ | m. | b. | $[\alpha]^D$ |
|---|---|---|---|---|---|
| α-Terpineol | 8 | 1 | 40° | 218° | +98.5° |
| β- " | 1 | 8(9) | 33° | 210° | |
| γ- " | 1 | 4(8) | 70° | | |
| 1- " | 1 | 3 | | 210° | |
| 4- " | 4 | 1 | | 212° | +25.4° |
| Piperitol | 3 | 1 | | 103°±(19 mm.) | |
| Dihydrocarveol | 2 | 8(9) | | | |
| Isopulegol | 3 | 8(9) | | | |

1,4-Terpin, *p*-menthadiol-1,4 has been made in *cis* and *trans* form. It gives 1,4-cineole, b. 174°.

***p*-Menthenols.** Many of these occur in nature or have been produced artificially.

*α-Terpineol* occurs widely in etheral oils. Commercial terpineol made by dehydrating terpin hydrate (hydrate of menthandiol-1,8) is a mixture of the first four terpineols listed above. The stepwise oxidation of α-terpineol is as follows:

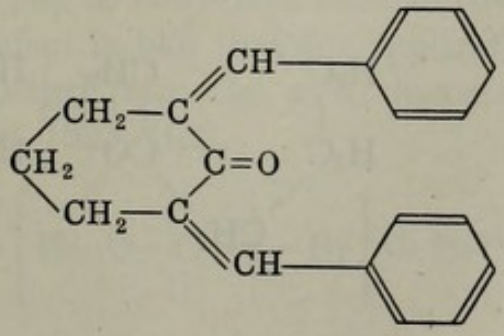



Homoterpenylic Acid — Terpenylic Acid — Terebic Acid

*Terpenylic acid* is the lactone of 2-OH-isobutane-1,1-diacetic acid and *terebic acid* is the γ-lactone of 1-carboxy-2-OH-isobutane-1-acetic acid. An *aldehyde* of this series, found in nature, is *perilla aldehyde* having the aldehyde in place of 7-Me of limonene, Δ 1,8(9)-menthadiene. Its anti-oxime (Peryllartine) is the sweetest substance known being some 2000 times as sweet as sucrose. The taste-principle of saffron, *picrocrocine* is a glucoside of 1-aldehydo-2,6,6-$Me_3$-4-OH-cyclohexene (Rev. Bio. 1934, 460).

### *Saturated Ketones*

Cyclohexanone, b. 156°, is best prepared from the alcohol by catalytic dehydrogenation with Cu at 250°. It gives all the usual ketone reactions. It condenses with 2 PhCHO to give dibenzalcyclohexanone, m. 118°. The yellow color is due to the accumulation of conjugated double bonds (cf. phenyl fulvenes).



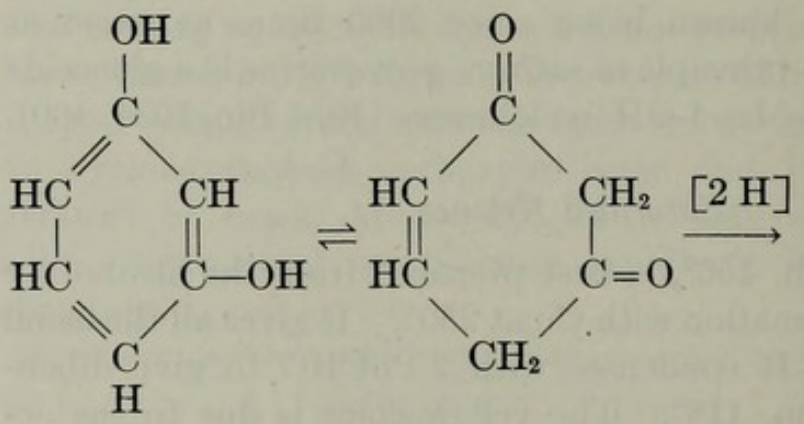
Cyclohexanone contains about 8% of the enol form. It does not give a color with $FeCl_3$, however. Caro's acid opens the ketone ring giving the lactone of ω-hydroxycaproic acid. This reaction is general for cyclic ketones. In sunlight, the aqueous alcoholic solution of cyclohexanone gives caproic acid or

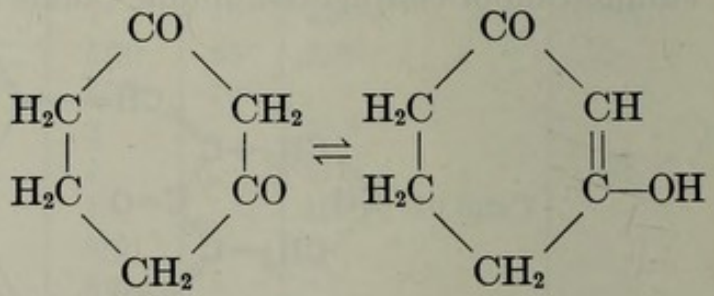
$$CH_2=CH(CH_2)_3CHO.$$

The first change is like the similar splitting of acetone to give methane and acetic acid. The second would correspond to a splitting of diethyl ketone to give ethylene and propionaldehyde. With an excess of $CH_2O$ and lime cyclohexanone gives 2,2,6,6-tetramethylol-cyclohexanol-1 (Rep. 1923, 92).

*Diketones*

The 1,3-isomer, *dihydroresorcinol*, m. 105°, is made by reducing resorcinol with NaxHg in solution kept neutral by $CO_2$. This is the behavior to be expected of an αβ-unsaturated ketone.



The *1,4-isomer*, m. 78°, can be made from its dicarboxylic ester formed from succinylosuccinic ester by acid ring closure.

$$2\,RO_2CCH_2CH_2CO_2R \xrightarrow{NaOEt}$$

$$RO_2CCH_2CH_2COCH(CO_2R)CH_2CO_2R \rightarrow$$

$$RO_2C{-}CHCOCH_2 \rightarrow CH_2COCH_2$$
$$\quad\;|\quad\diagdown \quad\quad\quad\quad\;|\quad\;|$$
$$\quad CH_2COCH{-}CO_2R \quad\quad CH_2COCH_2$$

The 1,2-isomer has not been obtained.

**Dimethyldihydroresorcinol, 5,5-$Me_2$-cyclohexandione-1,3,** methone, dimedone, $CH_2(COCH_2)_2C(CH_3)_2$, is made from mesityl oxide, malonic ester and NaOEt (OS). First, malonic ester adds to the $\alpha\beta$-double bond giving $MeCOCH_2C(Me_2)CH(CO_2R)_2$. The $\alpha$-Me is 1 : 6 to a carboxyl and undergoes an internal acetoacetic ester condensation with it. Treatment of the resulting cyclic carboxylic ester with KOH and HCl gives methone, an important reagent for identifying aldehydes by condensation of the carbonyl of the latter with the methylene groups of two methone molecules to give $RCH[CH(COCH_2)_2CMe_2]_2$. The *2,2-$Br_2$-cpd* is a special brominating agent which gives no HBr. It reacts with dimethylaniline as follows:

$$C_6H_5NMe_2 + Br_2C(COCH_2)_2CMe_2 \rightarrow$$

$$BrC_6H_4NMe_2 + \begin{array}{c} OH \\ | \\ C{-}CH_2 \\ \| \quad\quad \diagdown \\ BrC \quad\quad\quad CMe_2 \\ \diagup \quad\quad \diagup \\ COCH_2 \end{array}$$

The resulting enol can be converted back to the dibromide for reuse. The mechanism is like that for enolization except that a positive Br is expelled from the $\alpha-C$ instead of a positive H (R. Robinson, Rep. 1922, 102).

$$O{=}\underset{|}{\overset{|}{C}}{-}\underset{|}{\overset{|}{C}}{-}Br \xrightarrow{H^+} \left[ H{-}O{-}\overset{*}{\underset{|}{C}}{-}\underset{|}{\overset{|}{C}}{-}Br \right] \rightarrow Br^+ + H{-}O{-}\underset{|}{\overset{\diagdown}{C}}{=}\underset{|}{\overset{\diagup}{C}}$$

Phloroglucinol, in its keto form, is *cyclohexatrione-1,3,5*. *Angustione* is a triketone, 4,4,6-$Me_3$-6-acetyl-cyclohexandione-1,3. It gives the typical reactions of a $\beta$-diketone, ferric chloride reaction, copper compound, loss of acetyl with alkali, etc. (Rep. 1930, 166–7).

Hexaketocyclohexane, cyclohexanhexone, *triquinoyl*, $(CO)_6$, is obtained in hydrated form by oxidizing hexahydroxybenzene. With alkali, it undergoes the benzilic acid rearrangement to give 1-OH-tetraketocyclopentane-1-carboxylic acid.

**Menthone,** b. 207°, and **carvomenthone** are the 3- and 2-keto-*p*-menthanes corresponding to menthol and its isomer.

Menthone chemistry, Read. Rev. *7*, 1–50 (1930).

### *Unsaturated Ketones*

Resorcinol in its ketonic form acts as *cyclohexen-1-dione-3,5*. Ring closure gives 1-acetyl-4-Me-cyclohexene from

$$MeCO(CH_2)_3CH(Me)CH_2CHO,$$

obtained from citronellal and $O_3$. (S I 61). The first step is an internal aldol condensation between the aldehyde group and the alpha H in the 6-position.

**Pulegone,** b. 224, is 3-keto-$\Delta 4(8)$-*p*-menthene. Reduction gives menthol. Heating with water gives acetone and 2-Me-cyclohexanone in the same way that citral gives acetaldehyde and methylheptenone. *Isopulegone* has $\Delta 8(9)$ and is related to isopulegol obtained by ring closure of citronellal,

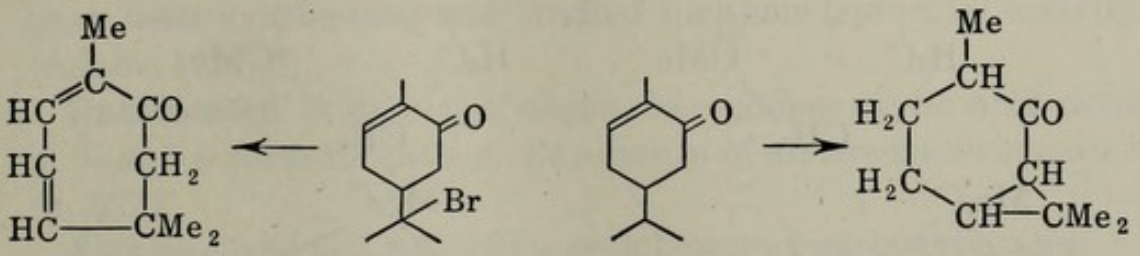
$$CH_2=C(Me)(CH_2)_3CH(Me)CH_2CHO.$$

*Piperitone*, from eucalyptus oil, consists mainly of *p*-menthen-1-one-3, b. 236°. This $\alpha\beta$-unsaturated ketone condenses with benzaldehyde to give a benzal compound involving the Me thus illustrating the activity of H "alpha" to a double bond which is $\alpha\beta$ to a carbonyl group as in $CH-C=C-C=O$ (S I 325, cf. Rep. 1921, 90).

**Carvone,** *p*-menthadien-1,8-one-6 b. 231°, is found widely in plants. On heating with acids, it gives carvacrol, 2-OH-*p*-cymene, thus showing its carbon skeleton and the position of the

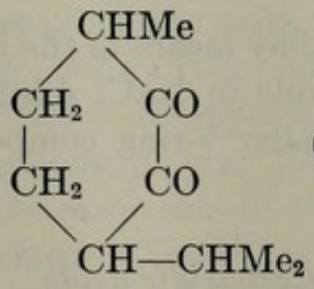
oxygen. The 1-double bond is $\alpha\beta$ to the carbonyl group, and consequently easily reduced. Oxidation of the *dihydrocarvone* thus obtained with $KMnO_4$ gives 4-acetyl-1-methyl-2-ketocyclohexane, thus showing the position of the 8-double bond. In carvone, the latter can be saturated by adding HBr and replacing the Br by H to give *carvotanacetone* which gives pyruvic acid and isopropyl succinic acid on oxidation thus proving the position of the 1-double bond.

If HBr is added to carvone at $\Delta 8$ and then removed by alkali, the product is the 7-ring *eucarvone*, 2,6,6-$Me_3$-cycloheptadien-2,4-one-1. Surprisingly, if the $\Delta 1$ is first reduced and HBr then added at $\Delta 8$, its removal does not widen the 6-ring but closes a 3-ring at the 3-position giving carone.




Eucarvone Carone

A diketone (I) or its mono-enol exists in the *p*-menthane series in *diosphenol* or *Bucco camphor*, m. 83°. The 2,3-position of the oxygen is shown by its preparation by the action of dilute bases on the $\alpha\alpha$-$Br_2$-compounds of both menthone and carvomenthone.

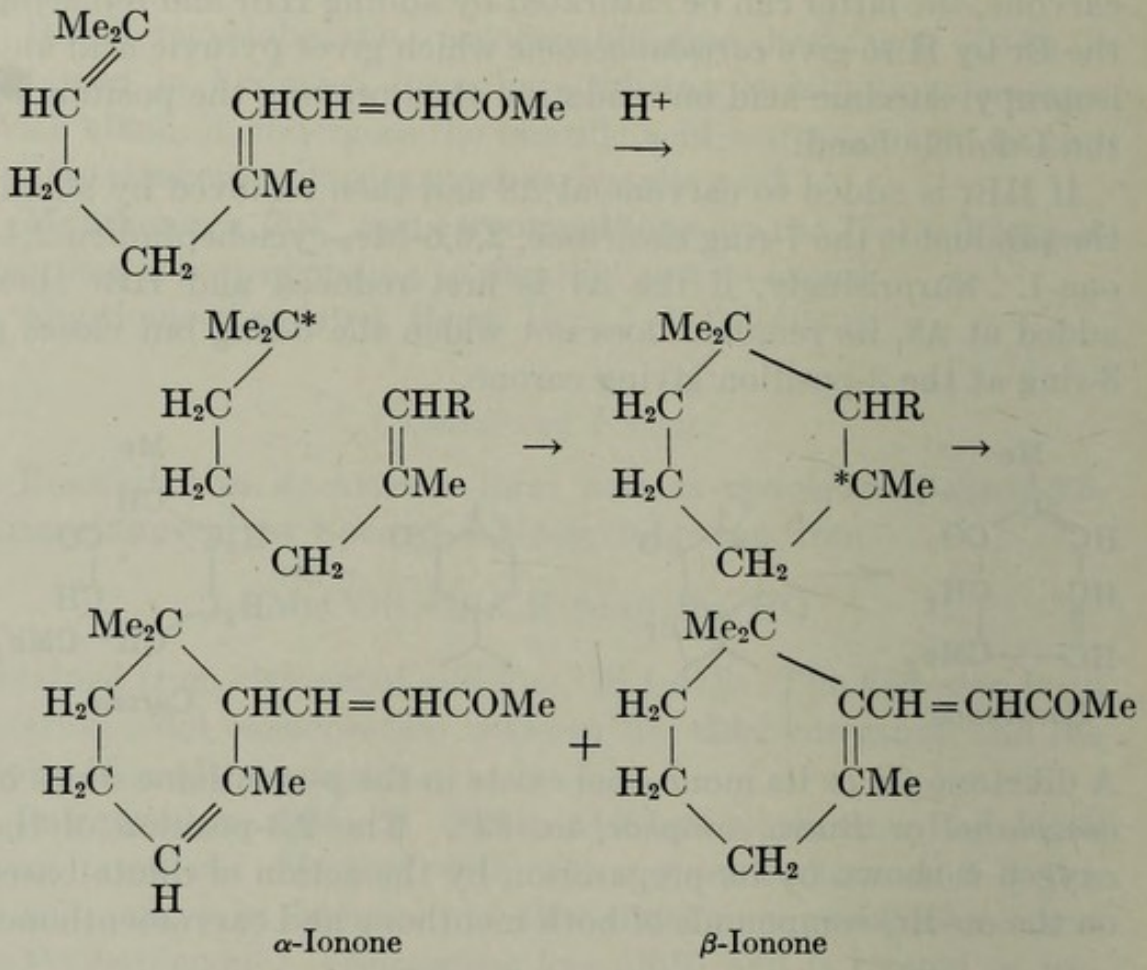



(I)

Such a compound could exist in two mono-enol and a di-enol form. Since it forms only one monoxime, it apparently exists in one mono-enol form or else that one form produces an oxime exclusively.

The artificial violet perfumes, $\alpha$- and $\beta$-*ionones* belong to this series. They are obtained by an ordinary aldol condensation of

citral with acetone to give pseudo-ionone, followed by an acid ring closure. The conversion of the 1,5-diene to a 6-ring by acid is an internal *polymerization* initiated by $H^+$ ion (Whitmore 1934).




α-Ionone β-Ionone

The isomers are separated by means of the $NaHSO_3$ compounds of which the α- is less soluble in NaCl solution. The true violet perfume, β-irone is a similar 7-ring compound, 2-β-acetylvinyl-4,4,5-$Me_3$-cycloheptene.

### *Carboxylic acids*

**Cyclohexane monocarboxylic acid,** hexahydrobenzoic acid, $(CH_2)_5CHCO_2H$, m. 31°, b. 233°, is obtained by reducing benzoic acid by Na and EtOH or catalytically. It is better prepared by the action of NaOBr on methyl cyclohexyl ketone obtained from acetyl chloride, cyclohexene and $AlCl_3$. The dicarboxylic acids have been extensively studied (Baeyer 1873–89) (Rep. 1905, 119).

They are obtainable from the aromatic dibasic acids by reduction with Na or catalytically.

| | Cis. m. | Trans. m. | Trans $[\alpha]^D$ |
|---|---|---|---|
| $H_6$-Phthalic acid | 192° | 215° | 18.5° |
| $H_6$-Isophthalic acid | 163° | 148° | 23.4° |
| $H_6$-Terephthalic acid | 161° | 200° | 0 |

Strangely, both *cis* and *trans* forms of the *o*-acid give anhydrides but the *trans* form changes to *cis* on melting. The *trans*-1,3- and both 1,4-acids fail to give anhydrides. Heating any of the *cis* forms with HCl at 180° gives the *trans* forms. Many complex aliphatic acids having cyclohexyl groups at the ends of the chains have been synthesized and studied for their leprocidal activity. (Adams 1927–8).

**Unsaturated acids.** *p-Methylcyclohexylidene acetic acid* exists in *d*- and *l*- form in spite of the absence of an asymmetric carbon (p. 622).

*Shikimic acid* is 3,4,6-$(OH)_3$-cyclohexene-1-carboxylic acid.

*Sedanolic acid* is 6-carboxy-Δ1-cyclohexenyl-*n*-butylcarbinol. Its lactone is *sedanolide.*

### *Hydroxyacids*

Although aromatic acids can be reduced by Na and EtOH or catalytically and although phenols are easily hydrogenated catalytically, *o*-hydroxybenzoic acid, salicylic acid, with Na and AmOH gives pimelic acid by ring opening.

**Quinic acid,** 1,3,4,5-$(OH)_4$-cyclohexane carboxylic acid is widely distributed among plants. It has the carboxyl and one meta hydroxyl on the same side of the plane of the ring since a stable lactone is formed. The other two hydroxyls are also *cis* to each other since they condense with acetone to give a 5-ring acetal which is not possible with *trans-o*-hydroxyls. Methylation of the acetone compound followed by hydrolysis of the acetal gives a *m*-methoxy-*m'p*-dihydroxy acid which does not form a lactone. Thus the *m'*-OH is trans to the carboxyl and quinic acid has the carboxyl and one meta hydroxyl on one side of the ring while the other three hydroxyls are trans.

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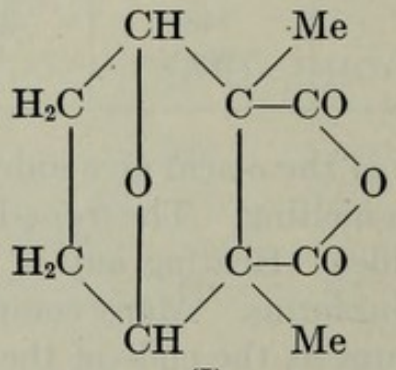
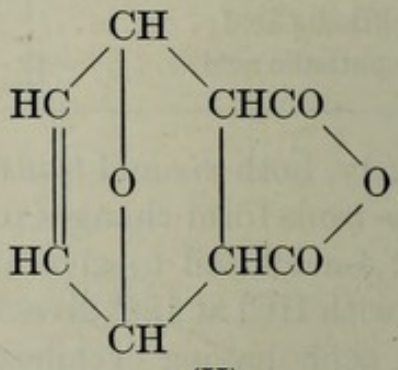
An acid of the cyclohexane series containing a 1,4-ether linkage is *cantharidin*, m. 218°, (I) from Spanish flies, the anhydride of 1,2-$Me_2$-1,2-dicarboxy-3,6-endoxycyclohexane. A related substance (II) can be made by the Diels-Alder reaction between maleic anhydride and furan, the latter supplying the diene system.



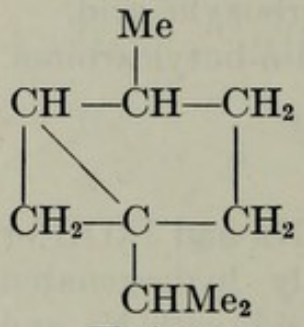

(I)



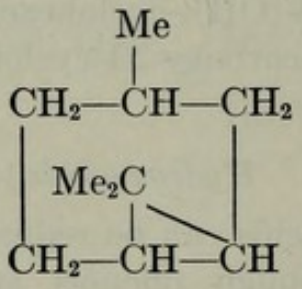

(II)

### *E.* Bi-cyclic Terpenes and Camphors

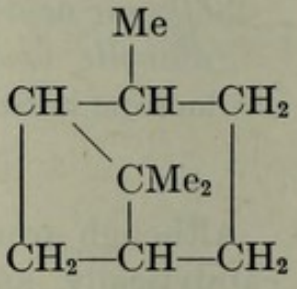
These important natural substances are related to *p*-menthane. The parent hydrocarbons are



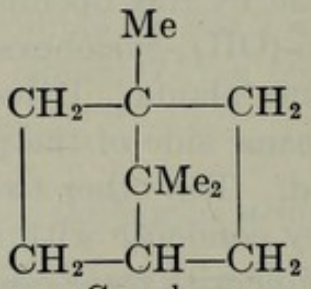

Thujane




Carane




Pinane




Camphane

The systematic names of the four substances are 1-isopropyl-4-Me-bicyclo(3.1.0)hexane; 4,7,7-$Me_3$-bicyclo(4.1.0)heptane; 2,7,7-$Me_3$-bicyclo(3.1.1)heptane, and 1,7,7-$Me_3$-bicyclo(2.2.1)heptane. The numbers in parenthesis indicate how many carbon atoms are

in the three bridges in the bicyclic system. The largest possible ring is used in numbering substituents. In this system *norpinane* is bicyclo(3.1.1)heptane and *norcamphane* is bicyclo(2.2.1)heptane.

The numbering of the positions in the ordinary system is different from that of the related menthanes. The single Me is No. 10 and the *gem*-$Me_2$ system, Nos. 7,8,9. The latter Me groups are also designated as $\pi$. In the carane series the numbering is sometimes such that the cyclopropane ring contains carbons 1 and 6.

### *Thujane Group*

**Thujane,** b. 157°, is obtained by hydrogenating the corresponding olefinic compounds.

**Sabinene,** $\Delta 1(7)$-thujene, b. 164°, occurs widely in essential oils. Oxidation removes the 7-carbon leaving *sabina ketone* which, on further oxidation, gives $\alpha$-tanacetogen dicarboxylic acid, 1-isopropyl-2-carboxy-cyclopropane-1-acetic acid. Sabinene, with acids, undergoes addition to the double bond and opening of the cyclopropane ring, HCl giving 1,4-$Cl_2$-menthane and dil. sulfuric acid giving the corresponding di-tertiary alcohol, 1,4-terpin.

**Sabinol** is 2-OH-sabinene.

$\alpha$- and $\beta$-*Thujene* have $\Delta 1$ and $\Delta 2$. $\alpha$- and $\beta$-Thujone (*tanacetone*) both have a 2-carbonyl group and differ only in the configuration of the 1-carbon. Heat opens the ring between carbons 4 and 6 replacing it by a 6-double bond thus producing *carvotanacetone.* Sulfuric acid opens the ring between carbons 4 and 5 giving *isothujone,* 2,3-$Me_2$-4-isopropyl-cyclopenten-2-one-1. Reduction gives *thujyl alcohol.* Careful oxidation breaks the 6-ring between the CO and the tertiary C to give *$\alpha$-thujaketo acid,* 2-acetyl-1-isopropyl-cyclopropan-1-acetic acid. This acid has been reconverted to thujone (Rev. Bio. 1934, 460).

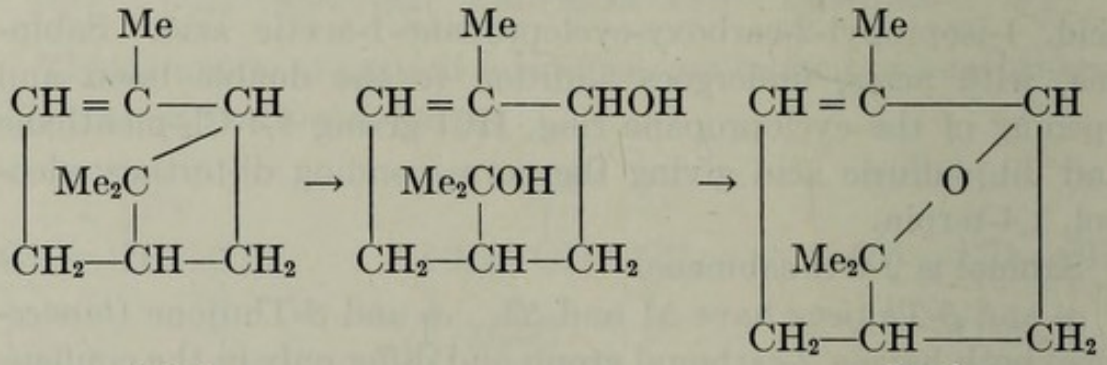
### *Carane Group*

The parent substance is not known. The 2-ketone, *carone,* b. 210° is made by the action of alkali on 8-Br-*p*-menthone-2, an ordinary closing of a 3-ring from a $\gamma$-bromo carbonyl compound. This process is reversed by the action of HBr. Heat replaces the

3-ring of carone by Δ3 giving *carvenone*, *p*-menthen-3-one-2. It is also possible to open the 3-ring between carbons 4 and 8 to give *carvestrene* (*dl*-sylvestrene), *m*-menthadiene-1,8. Carenes are widely distributed in small amounts (Rep. 1925, 131). The commonest has the double bond between carbons 1 and 6 although it is usually described as Δ3.

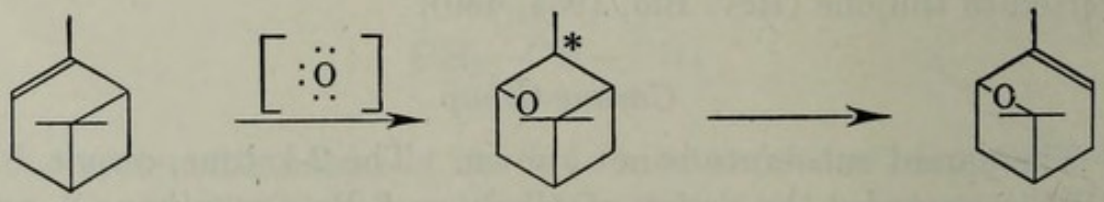
*Pinane Group*

The parent substance is not known. Turpentine oil consists largely of α-pinene, Δ6-, b. 156° and to a less extent of β-pinene, Δ1(7)-, nopinene, b. 163°. α-Pinene is found in various turpentines in *d*-, *l*- and racemic forms. *d*-α-Pinene has $[\alpha]_D^{20} = +53.0$. The pinenes are very reactive. α-Pinene, with air and moisture, gives pinol hydrate (sobrerol) which yields pinol with acids. The accepted explanation is as follows.




α-pinene Pinol

Such a breaking of a 4-ring by oxygen and closing of an ether ring by acid without affecting the double bond seems extraordinary. An alternative explanation is that the oxygen attacks the double bond at the 6-carbon thus leaving the 1-carbon in condition to cause a rearrangement. Under this conception pinol hydrate would simply be the oxonium hydrate of pinol.



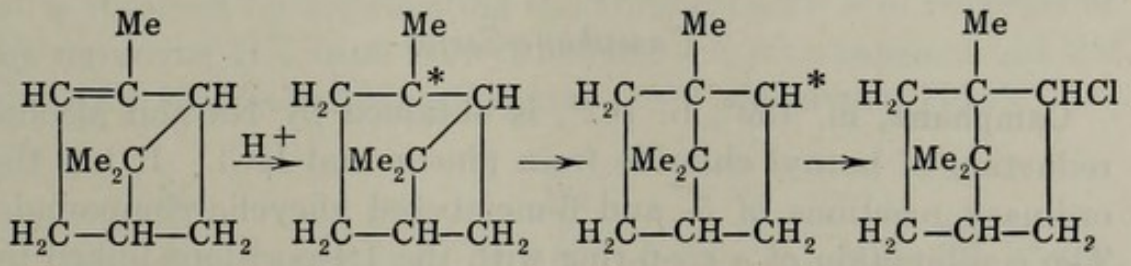

Thus the lack of change in the double bond is apparent rather than real. Pinene, with acids, gives a great variety of products

including esters of borneol, isoborneol, fenchyl alcohol and terpineol as well as limonene, dipentene, camphene, fenchene, $\alpha$-terpinene, etc.

Oxidation of $\alpha$-pinene gives successively $\alpha$-pinonic acid (2,2-$Me_2$-3-acetylcyclobutane-1-acetic acid), pinic acid, (2,2-$Me_2$-3-carboxy-cyclobutane-1-acetic acid), and norpinic acid (2,2-$Me_2$-cyclobutane-1,3-dicarboxylic acid). The addition of dry HCl to $\alpha$-pinene is of great practical importance as the first step in the commercial synthesis of camphor and of great theoretical interest as illustrating a type of rearrangement very common in the bicyclic terpene series. The process is entirely analogous to that by which *t*-butylethylene gives $Me_4$-ethylene hydrobromide $Me_3CCH=CH_2 + HBr \rightarrow Me_2CHCBrMe_2$. The changes may be formulated as follows:

$$Me_3CCH=CH_2 \xrightarrow{H^+} Me_3C\overset{*}{C}H-CH_3 \rightarrow$$

$$Me_2\overset{*}{C}-CHMe_2 \xrightarrow{Br\ominus} Me_2BrC-CHMe_2$$



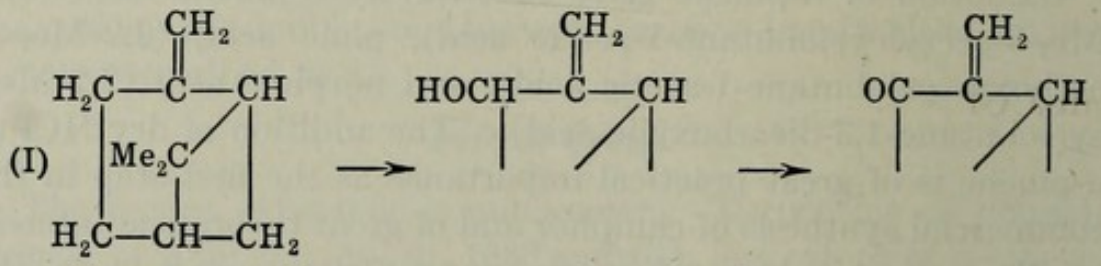

"Pinene hydrochloride"
Bornyl chloride

At $-70°$ pinene gives a true hydrochloride which is stable up to $-10°$ where it rearranges to bornyl chloride. Moist HCl opens the 4-ring of pinene giving 1,8-$Cl_2$-*p*-menthane. The affinity of pinene for HX is so great that it reacts with $NH_4Cl$ on heating to give bornyl chloride and $NH_3$. It thus forms a *neutral reagent which can remove HX* (Rep. 1920, 81).

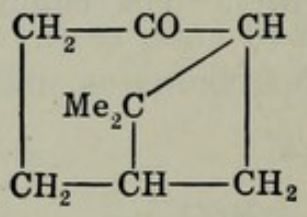
Pinene gives a solid dibromide. When this is heated it gives HBr and *p*-cymene. Pinene on heating at 250° gives dipentene, *dl*-*p*-menthadiene-1,8.

*β-Pinene* (I) is oxidized by air to give pinocarveol and pinocarvone in which the 2-$CH_2$ is changed to CHOH and CO

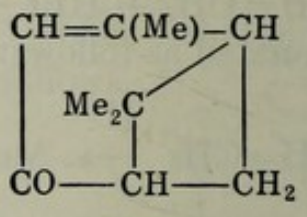
respectively. There is no adequate explanation for this remarkable oxidation of the $CH_2$ group without changing the reactive semicyclic double bond in the $\beta$-pinene.



Oxidation by permanganate replaces the $CH_2=$ by O giving *nopinone* (II). *Verbenone* (III) is 3-keto-pinene.



II

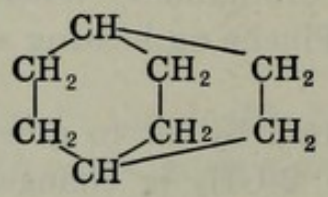


III

*Camphane Series*

**Camphane,** m. 159°, b. 162°, is obtained by Na and alcohol reduction of bornyl chloride from pinene and HCl. It has the ordinary reactions of 5- and 6-membered alicyclic compounds. The combination of a *cis*-6-ring with the 1,4-positions linked by the $Me_2C$ group forming two 5-rings with three atoms in common is entirely free from strain.

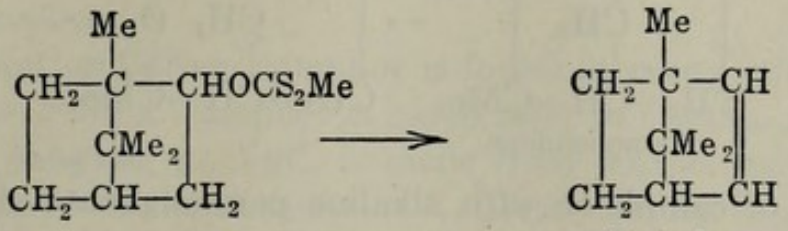
Just as camphane has a carbon bridge between the 1 and 4 carbons, it is possible to have a two carbon bridge between these positions without introducing a strain into the molecule. Bicyclo(2.2.2)octane, m. 170° has been prepared from the corresponding ketone by heating its semicarbazone with NaOEt (Alder 1935, Komppa 1935).



Such an arrangement really consists of three *cis*-cyclohexane rings having the 1 and 4 carbons in common.

*Unsaturated Hydrocarbons*

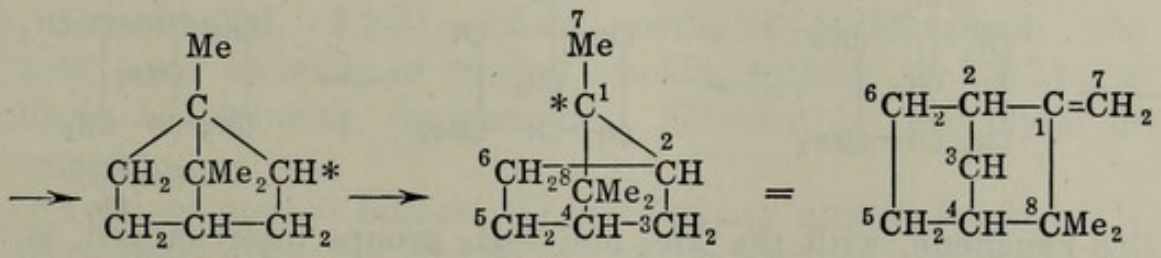
**Bornylene,** m. 114°, b. 150°, cannot be made from borneol by ordinary dehydrating agents as these produce camphene by rearrangement. Conversion of borneol to the Na derivative, treatment with $CS_2$, methylation and finally heating at 200° gives bornylene (Tschugaef)



Bornylene

Bornylene gives ordinary olefin reactions.

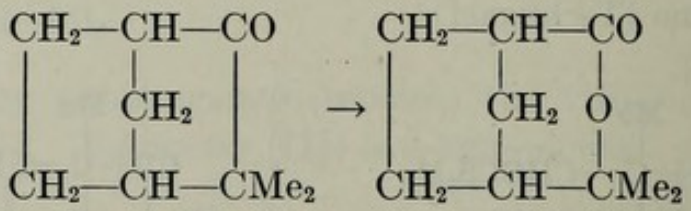
**Camphene,** is reported in various forms, m. 50°±, b. 160°±. It is obtained by dehydrating the borneols with acid reagents or by removing HX from bornyl halides. A rearrangement of the ordinary kind is involved (Wagner, 1897; Meerwein 1914).



Camphene

Camphene adds acids to give bornyl and isobornyl derivatives by a reverse of this rearrangement (Meerwein 1920–27; H II 215–226). Addition of dry HCl at low temperatures gives unstable *camphene hydrochloride* without rearrangement. Dilute alkali gives "*camphene hydrate*" a tertiary alcohol which can be dehydrated to give camphene of the same optical activity as the original. A stereoisomer is made from camphenilone and MeMgX (Rep. 1916, 117–8).

Oxidation of camphene in acid gives camphor. Permanganate oxidation gives a glycol which on treatment with acid gives *camphenilanic aldehyde.* The same aldehyde is obtained from camphene and chromyl chloride. Oxidation gives the corresponding acid and then, by loss of the carboxyl, *camphenilone*, 2,2-$Me_2$-3,6-endomethylene-cyclohexanone. This is also formed by the ozonolysis of camphene although the chief product results from further oxidation to form the lactone of *hydroxycamphenilic acid.*

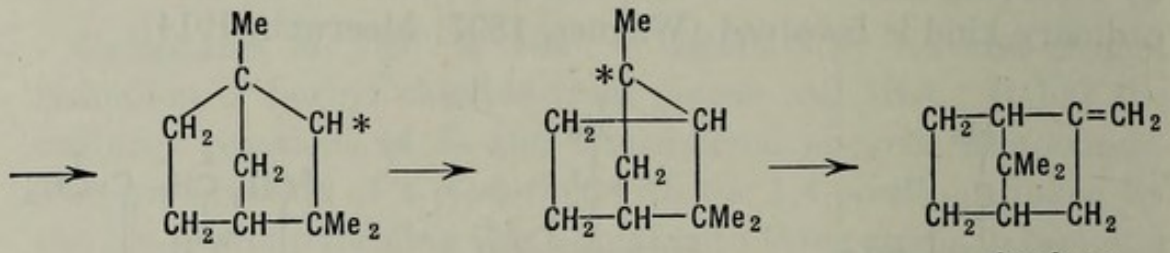


Camphenilone

Oxidation of camphene with alkaline permanganate gives *camphenic acid*, $\alpha$-3-carboxycyclopentyl-isobutyric acid.

**Endocamphene,** 3,3-$Me_2$-4,7-endomethylene-cycloheptene, has been made (Rep. 1927, 120–1).

**$\alpha$-Fenchene** is obtained by dehydrating fenchyl alcohol with rearrangement (Rep. 1917, 110).



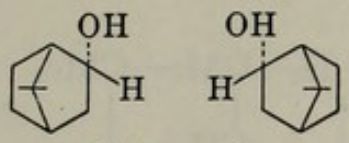
$\alpha$-fenchene

**$\beta$-Fenchene,** with the $Me_2$ and 5-$H_2$ groups interchanged, is obtained from isofenchyl alcohol by a similar rearrangement. This alcohol, by the xanthate method (no rearrangement), gives a *fenchylene*, 3,4,4-$Me_3$-3,6-endomethylene-cyclohexene. *Santene*, 1,2-$Me_2$-3,6-endomethylene-cyclohexene, is the chief dehydration product of *camphenilol.* The lesser product is the unrearranged *camphenilene* with the double bond in the 1,6-position.

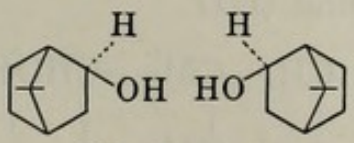
### *Alcohols*

**Borneol,** m. 208°, b. 213°, and isoborneol, m. and b. 216°, each exist in *d*- and *l*-forms. They are stereoisomers, borneol

having its OH on the opposite side of the molecule from the *gem*-$Me_2$ group and isoborneol having its OH near that group.




dl-Borneol




dl-Isoborneol

Mixtures of these substances are obtained by reducing camphor, by hydrating pinene and camphene and from the bornyl and isobornyl halides. Isoborneol is more soluble in most solvents than is borneol.

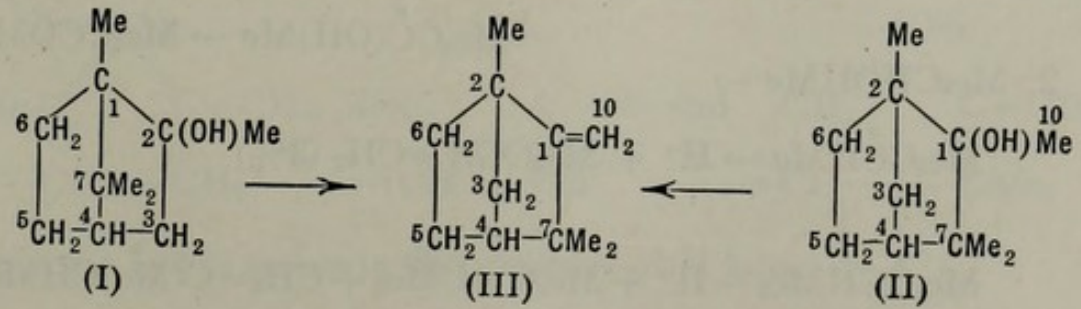
***d*-Borneol** or Borneo camphor is found in many ethereal oils. the *l*-form or Ngai Camphor is much rarer in nature.

**Bornyl chloride,** m. 148°, is made from pinene and HCl. It was the first "artificial camphor." With alkalies it gives camphene which, on oxidation, gives true synthetic camphor. *Bornyl iodide* with alkalies gives bornylene as well as camphene.

**Fenchyl alcohol,** fenchol, is an isomer of borneol with a 3-*gem*-$Me_2$ group and a 1,4-$CH_2$ bridge. It is found among the products of acids with pinene. *Isofenchyl alcohol* differs by having the OH in the 6-position. It is obtained by the reduction of isofenchone.

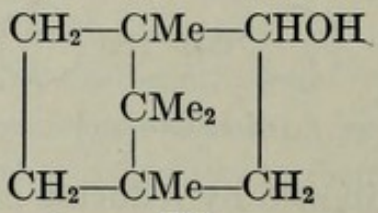
**Camphenilol,** 2,2-$Me_2$-3,6-endomethylene-cyclohexanol, the next lower homolog of fenchyl alcohol, without the 10-Me, is made by reducing camphenilone, obtained by ozonolysis of camphene.

Tertiary methyl borneol (I) and tertiary methyl fenchol (II) have been made by the action of MeMgX on camphor and fenchone respectively. Dehydration of these two alcohols gives the same product, α-Me-camphene (III). Thus the first undergoes rearrangement while the second does not (Rep. 1932, 148).

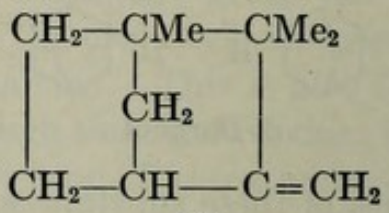



(I) (III) (II)

Hydration of III gives 4-Me-isoborneol (IV) which on dehydration gives mainly $\beta$-Me-camphene (V) and some of the $\alpha$-Me compound (III)

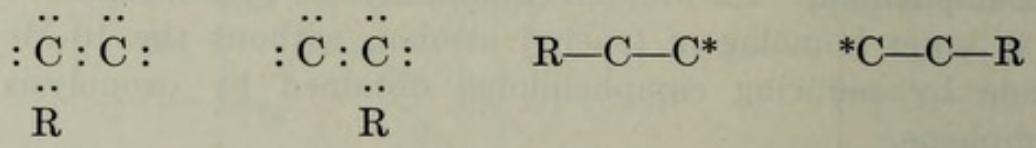


(IV)



(V)

Both III and V, on hydration, give IV. The changes involved include rearrangements which are classified under three names, Wagner (change of ring), Meerwein (shift of methyl) and Nametkin (shift of Me and change of ring). Actually the three changes involve the same fundamental rearrangement as that found in the aliphatic series in the pinacolic and retropinacolic rearrangements and the unnamed rearrangement of a methyl group in certain olefins during hydration. In every case the occasion for the rearrangement is the formation of a carobn with only six electrons which can thus attract a pair of electrons (and their attached group) from an adjacent carbon. As to which of the electron pairs (and attached groups) will be attracted, data are lacking to make prediction possible.



The electronically deficient carbon (indicated by *) may be formed by *removing* a hydroxyl with the complete octet of electrons held by the oxygen.

1. $Me_2C(OH)C(OH)Me_2 \rightarrow Me_2\overset{*}{C}C(OH)Me_2 \rightarrow$

$$Me_3C\overset{*}{C}(OH)Me \rightarrow Me_3CCOMe$$

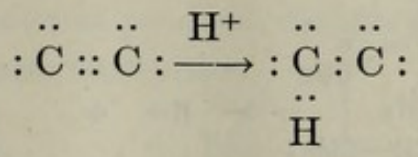
2. $Me_3CHOHMe \rightarrow$

$$Me_3C\overset{*}{C}HMe \rightarrow H^+ + Me_3CCH{=}CH_2 \ (3\%)$$

$$\downarrow$$

$$Me_2\overset{*}{C}CHMe_2 \rightarrow H^+ + Me_2C{=}CMe_2 + CH_2{=}C(Me)CHMe_2$$

The electronically deficient carbon may also be formed by *adding* hydrogen ion to a double bond

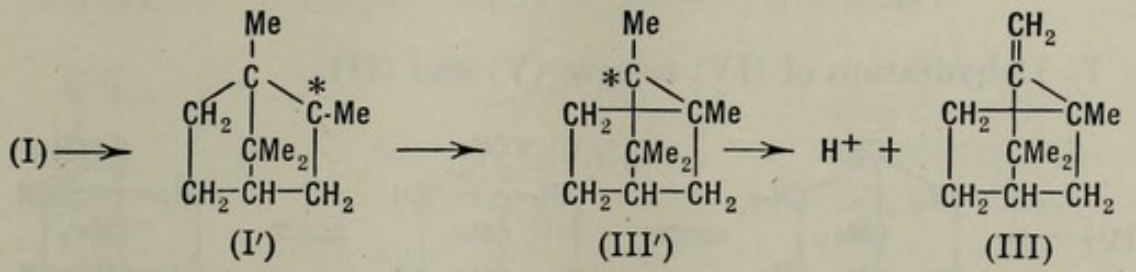


3. $Me_3CCH{=}CH_2 + H^+ \rightarrow Me_3C\overset{*}{C}H{-}CH_3 \rightarrow$

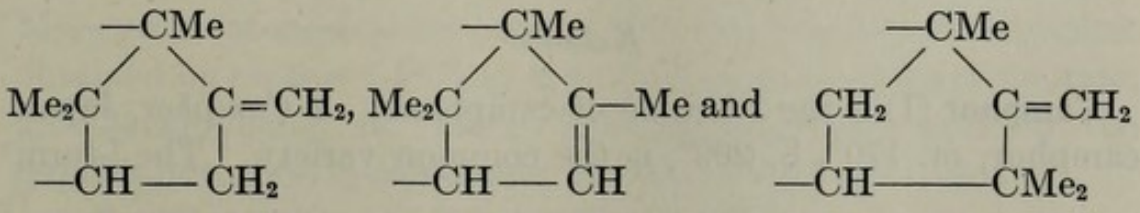
$$Me_2\overset{*}{C}CHMe_2 \xrightarrow{OH^-} Me_2C(OH)CHMe_2$$

In each of these reactions the essential change has been the shift of Me to the electronically deficient carbon.

4. Dehydration of (I) to give (III)

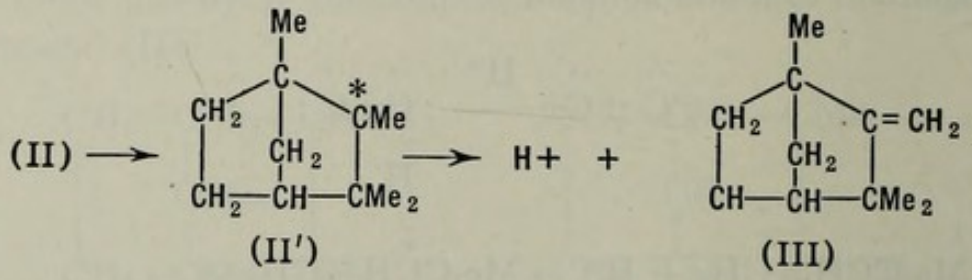


The C* in (I′) attracts the electron pair holding carbons 1 and 6 and this transfers the attachment of carbon 6 to carbon 2 forming a new 5-ring. The C* in (III′) is stabilized by attracting an electron pair from its Me group and expelling the H held by that pair. Evidently this process takes place by preference over the apparently similar one by which the C* in (I′) would have expelled an H from its methyl group or from the neighboring $CH_2$ group without rearrangement. Apparently such a change would have about the same chance as the formation of t-Bu-ethylene from t-BuMe-carbinol. Evidently, of the rings



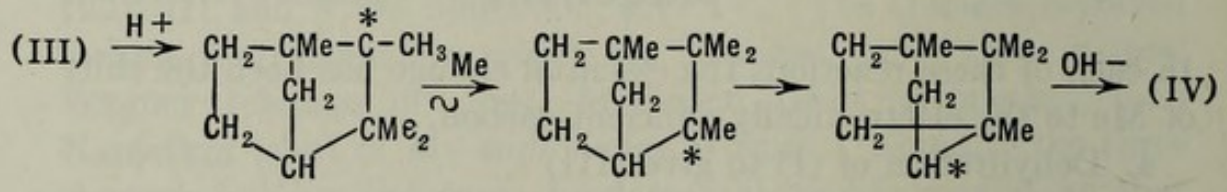
only the last is stable in the presence of H ions.

5. Dehydration of (II) to give (III).



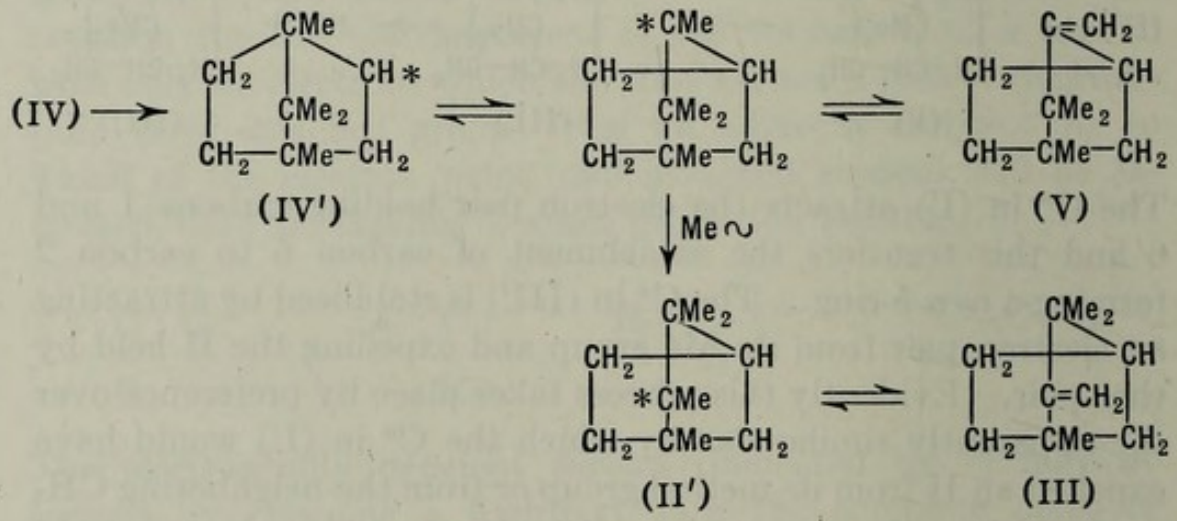

(II′) (III)

6. Hydration of (III) to give (IV).




(II′)

7. Dehydration of (IV) to give (V) and (III).




(IV′) (V) (II′) (III)

8. Hydrations of (III) and (V) to give (IV) take place by the reversal of the steps in 7.

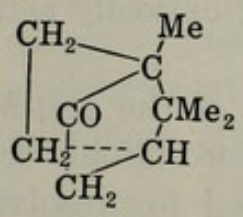
*Ketones*

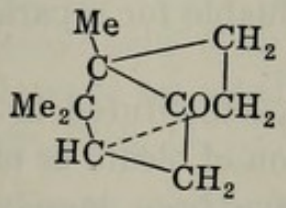
**Camphor** (I) is the 2-ketone of camphane. *d-Camphor*, Japan camphor, m. 179°, b. 209°, is the common variety. The *l*-form

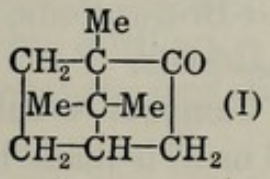
is Matricaria camphor. Large amounts of camphor are used in celluloid, pyralin and similar products from nitrocellulose. In addition to the natural product, camphor is synthesized from pinene obtained from turpentine.

$$\text{Pinene} \xrightarrow{\text{HCl}} \text{bornyl chloride} \xrightarrow{\text{base}} \text{camphene} \xrightarrow[\text{oxid.}]{\text{acid}} \text{camphor.}$$

Camphor, with $P_2O_5$, gives *p*-cymene, and with $I_2$, gives carvacrol (2-OH-cymene). The bridged ring structure of camphor follows from its oxidation to camphoric acid, 1,2,2-$Me_3$-cyclopentane-1,3-dicarboxylic acid; *camphanic acid* (the lactone of the corresponding 3-OH acid), *camphoronic acid* (2,2,3-$Me_3$-3-carboxy-glutaric acid), and finally to $Me_3$-succinic acid.







(I)

*dl*-Camphor

Camphor has been synthesized starting with oxalic and $\beta\beta$-$Me_2$-glutaric esters going through camphoric and homocamphoric acids (Komppa) (Haller). Camphor reacts like ordinary ketones. Reduction gives the stereoisomeric secondary alcohols, borneol and isoborneol. With nitrous acid it gives an isonitroso compound, the C=NOH group being in the 3-position, $\alpha$- to the CO. Hydrolysis gives 3-keto-camphor or *camphorquinone*. The *oxime* of camphor, m. 119°, b. 250° dec., on dehydration forms a cyanide which is hydrolyzed to *campholenic acid*, 2,3,3-$Me_3$-cyclopentene-4-acetic acid. The dichloride of camphor obtained by means of $PCl_5$ at low temperature is the $\alpha$-dichloride, 2,2-$Cl_2$-camphane, m. 148°. This readily rearranges to the $\beta$-dichloride, 2,6-$Cl_2$-camphane, m. 178° (Meerwein 1924).

**α-Bromocamphor,** (3-Br), m. 77°, b. 274°, gives the ordinary reactions of a halogenated ketone but in addition gives a fair

yield of a Grignard reagent with Mg. With $CO_2$, this gives camphor, 3,3′-dicamphor and camphor-3-carboxylic acid. *β-Bromocamphor*, (10-Br, ω-Br), m. 79°, is obtained by heating the corresponding sulfonyl bromide. It reacts normally with hydroxylamine whereas, the α-compound does not. *π-Bromocamphor*, (9-Br), m. 93°, is similarly made from the $-SO_2Br$ compound. The Br is very inactive, not being changed by $AgNO_3$.

*Sulfonic Acids of Camphor*

**Camphor α-sulfonic acid,** substituted in the 3-position, is made from camphor and $ClSO_3Me$. The methyl ester is soluble in bases and is believed to be an enol form.

**Camphor β-sulfonic acid** (Reychler acid), substituted in the 10-Me is formed by sulfuric acid in acetic anhydride. The *d*-α-Br-β-sulfonic acid is valuable for separating optically active materials.

**Camphor π-sulfonic acid,** substituted in one of the *gem*-$Me_2$ (8 or 9) is made by the action of oleum or of chlorosulfonic acid. Both the *d*- and *l*-acid have been largely used for resolving racemic materials. The *α-Br-π-sulfonic acid* is similarly made and used.

Le Camphre et ses Derives, R. Cornubert, 424 pp., Paris 1933.

**Epicamphor** or **β-camphor** in which the CO and α-$CH_2$ groups are interchanged is known (Rep. 1912, 151).

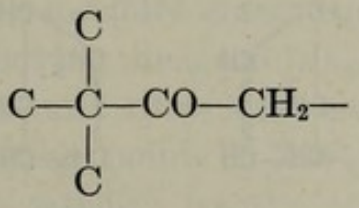
**Isocamphor** is merely an unrelated isomer of camphor, 1-acetyl-3-isopropyl-cyclopentene (Rep. 1912, 151). It is also called *isopinolone.*

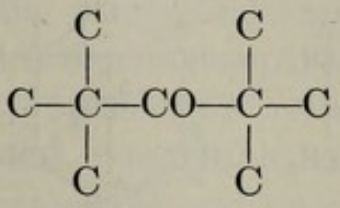
**Apocamphor,** fenchocamphorone, is the lower homolog of camphor without the 7-Me group. Oxidation gives apocamphoric acid, 2,2-$Me_2$-cyclopentane-1,3-dicarboxylic acid.

**Homocamphor,** having an additional $CH_2$ between the CO and $C_4$ has been synthesized (Lipp, Rep. 1920, 91).

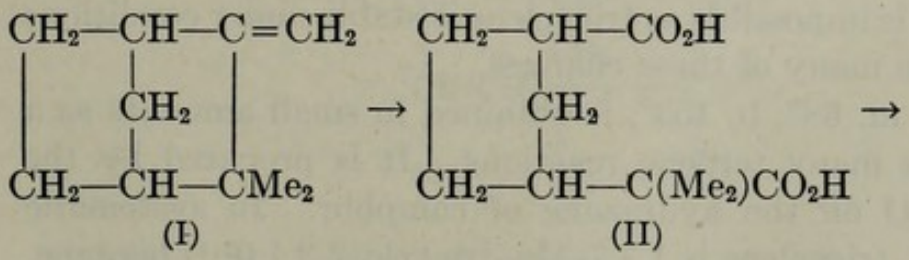
Substituted camphors with alkyl or aryl on $C_4$ are obtained by treating camphor with a Grignard reagent, dehydrating to give an α-substituted camphene, hydrating to a 4-substituted isoborneol and oxidizing to the desired product.

**Fenchone,** m. 6°, b. 193°, is an isomer of camphor with the *gem*-$Me_2$ attached in the 3-position and a 1,4-$CH_2$ bridge. The lower symmetry of the molecule is reflected in its lower melting point. It is found in *d*- and *l*-forms in nature. It is more resistant to oxidation than camphor. This is understandable from a comparison of the environment of the ketone group in the two compounds.

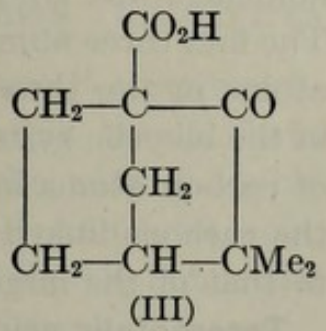




Fenchone has been synthesized using levulinic ester, bromoacetic ester and MeI (Ruzicka Rep. 1917, 109). A substance having the structure of fenchone with the lone methyl changed to carboxyl is *camphenonic* acid (III) obtained by distillation of camphenic acid (II) made by alkaline permanganate oxidation of camphene (I) (Rep. 1916, 117).



(I) (II)



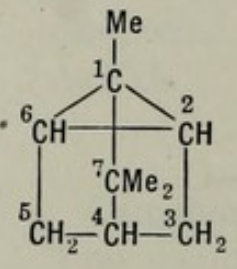
(III)

The first step involves an unusual rearrangement.

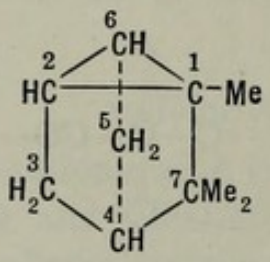
**Isofenchone,** has the *gem*-$Me_2$ attached to the 5-position. Oxidation gives isofenchocamphoric acid, 2,2,4-$Me_3$-cyclopentane-1,4-dicarboxylic acids, its $\alpha$-OH acid and finally $\alpha,\alpha,\alpha',\alpha'$-$Me_4$-glutaric acid.

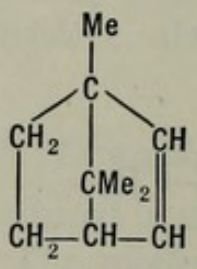
### *F.* Tricyclic Terpene Derivatives

**Cyclene** or **tricyclene,** an isomer of the bicyclic terpenes ($C_{10}H_{16}$) may be regarded as a camphane with the 2,6-positions joined to form a cyclopropane ring with Carbon No. 1. It may be represented in various ways.

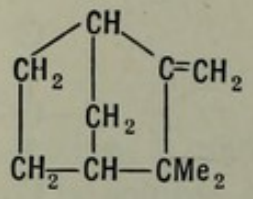



Tricyclene




Bornylene



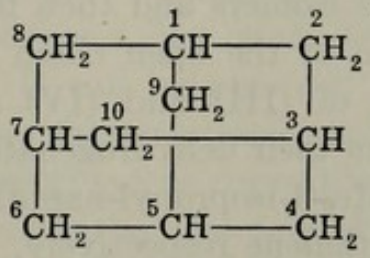

Camphene

Breaking the cyclopropane ring at the 2,6-linkage and at the 1,2-linkage (or 1,6-) would give bornylene and camphene respectively. Before it was obtained as a definite compound, tricyclene was assumed to be the intermediate in the interconversion of the borneols and camphenes and related terpene rearrangements. This function is impossible as tricyclene is stable under conditions which produce many of these changes.

**Tricyclene,** m. 68°, b. 153°, is obtained in small amounts as a by-product in many terpene reactions. It is prepared by the action of HgO on the hydrazone of camphor. In systematic nomenclature, tricyclene is 1,7,7-$Me_3$-tricyclo(2.2.1.$0^{2,6}$) heptane. The first three numbers in parenthesis give the numbers of carbon atoms in the three bridges connecting the two common atoms in the bicyclic system while the fourth number gives the number of carbon atoms in the fourth bridge and its superscripts show the carbons linked by this bridge. The numbering corresponds to that of the largest ring in the tricyclo system.

**Teresantalic acid** from sandalwood oil has a carboxyl in place of one of the *gem*-$Me_2$ in tricyclene. Heat decomposes its Ca salt to give *santene,* 1,2-$Me_2$-3,6-endomethylene-cyclohexene. Its ester can be reduced to *teresantalol* which can be oxidized to the aldehyde and then converted to tricyclene by heating the semicarbazone with NaOEt (Rep. 1927, 121).

**Adamantane,** $C_{10}H_{16}$, m. 268° (sealed tube), obtained from Hodonin crude petroleum from Moravia is one of the most interesting organic compounds found in nature (Landa 1933). It crystallizes in the cubic system, has an odor suggesting camphor and turpentine, and is stable to chromic acid, permanganate and nitric acid. The structure of adamantane follows from its analysis, molecular weight, crystal form and melting point. The latter is especially significant. Of the nearly 200 known substances having the formula $C_{10}H_{16}$ all are liquids except camphene, bornylene and tricyclene with m. 53°, 98° and 68° respectively. The melting point of 268° indicates a remarkable symmetry which is satisfied by the arrangement of the carbon atoms in diamond. This is confirmed by X-ray studies of the hydrocarbon. Thus adamantane is *tricyclo* $(3.3.1.1^{3,7})$ *decane.* Its model shows *four trans cyclohexane rings.* If a unit of 10 carbon atoms could be taken out of diamond and supplied with 16 hydrogen atoms, the result would be a molecule of adamantane.




*G.* Cyclic Sesquiterpenes, $C_{15}H_{24}$, and their Derivavites

These fall in five groups characterized by the following molecular refractions: 1. Open chains with 4 double bonds, 69.6; monocyclic with 3 double bonds, 67.9; bicyclic with 2 double bonds, 66.1; tricyclic with 1 double bond, 64.4; and tetracyclic with no double bond, 62.7. With conjugated double bonds the value is even higher. Thus it is 68.4 for zingiberene.

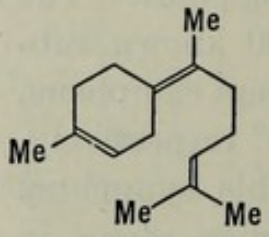
The aliphatic sesquiterpene alcohols, *farnesol* and *nerolidol* have already been considered.

The cyclic sesquiterpenes have 6-membered rings of the terpene type with aliphatic terpene side chains. The structures are those to be expected from the polymerization of three isoprene

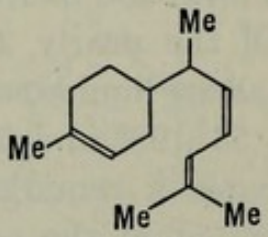
units with one or two ring closures (Wallach, Semmler, Ruzicka). (Bogert, Rev. *10*, 265–94).

The most important monocyclic sesquiterpenes are *bisabolene* (I) and *zingiberene* (II).

**Cadinene** (III), **α-selinene** (IV) and **eudesmol,** the related tertiary alcohol, are bicyclic (Rep. 1929, 146; 1932, 153).



(I)



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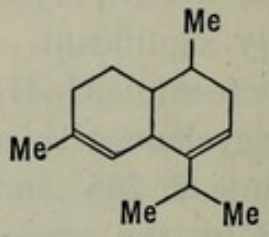
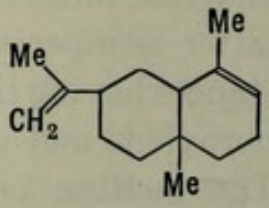


(III)

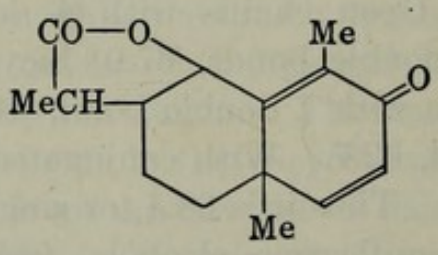


(IV)

*β-Selinene* apparently has a methylene group with semicylic double bond at position 1. (Rep. 1932, 153).

**Machilol, cryptomeradol,** and certain other sesquiterpene alcohols are identical with eudesmol. Acids convert farnesol and nerolidol to (I) and its isomers and then to (III). A different internal polymerization of the open chain sesquiterpenes gives (IV). The structures of (III) and (IV) and related bicyclic compounds follows from their dehydrogenation by S or catalysts to give *cadaline,* 1,6-$Me_2$-4-isopropyl-naphthalene and *eudaline,* 1-Me-7-isopropyl-naphthalene respectively. Substances like selinene and eudesmol lose the *angular methyl group* on dehydrogenation.

**Santonin** is a lactonic ketone related to selinene (IV)




It can be converted to 1-Me-7-Et-naphthalene (Rep. 1931, 169–70; Rev. Bio. 1934, 462). *Artemisin* is 7-OH-santonin, helenin contains *alantolactone* and isomeric substances also related to santonin (Rep. 1932, 156; Rev. Bio. 1934, 462).

**Tricyclic sesquiterpenes** related to (III) and (IV) are known. *Copaene* from copaiba balsam reacts with HCl to give the same di-hydrochloride as does (III). $\alpha$-Santalol (not an alcohol) gives teresantalic acid on oxidation and has structure (V) (p. 680). Less known members of the tricyclic series are *cedrene* and *gurjenene.* Ketones and hydroxy ketones of the sesquiterpenes are known (Rep. 1932, 155). Thus *eremiphilone* is the 3-keto compound of (IV) (Rev. Bio. 1934, 463). Other ketones are *atlantone* and *turmerone* (1933).

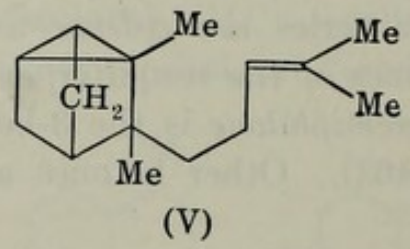
Sesquiterpenreihe. L. Ruzicka. Berlin 1928.

### *Higher Terpenes*

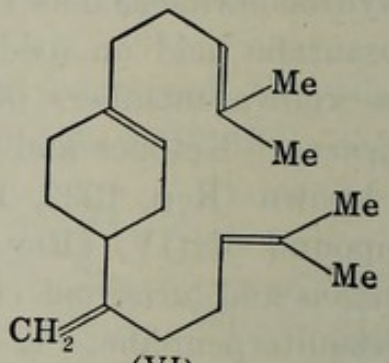
Many *di-* and *tri-terpenes* are known. Just as the terpenes are based on the benzene nucleus and the sesquiterpenes on the naphthalene nucleus, the diterpenes are related to the phenanthrene nucleus (Rep. 1924, 101). The nature of the cyclic nucleus in the tetracyclic triterpenes is not known. *Camphorene,* $C_{20}H_{32}$, has a cyclohexene ring with side chains of aliphatic terpene type (VI). It can be regarded as the product of the polymerization of two myrcene molecules. Further cyclisation by acid gives a hydroanthracene derivative which can be oxidized to benzene-1,2,4,5-tetracarboxylic acid (Rep. 1927, 125). *Vitamin* A, $C_{20}H_{30}O$, (VII), is the primary alcohol of a monocyclic diterpene with one side chain having one extra double bond giving complete conjugation of the 5 double bonds (Karrer) (Rev. Bio. 1934, 464).

**Abietic acid** is a diterpene carboxylic acid, the chief component of rosin (colophony), the residue from the distillation of turpentine. Dehydrogenation with sulfur readily gives retene, 1-Me-7-isopropyl-phenanthrene. The structure of abietic acid is (VIII) or some isomer with shifted double bonds (Rep. 1932, 159–61; Rev. Bio. 1934, 465). The conjugated nature of the double bonds is shown by reaction with maleic anhydride

(Ruzicka 1932). *Pinabietic acid* and *levopimaric acid* are related to abietic acid.




(V)

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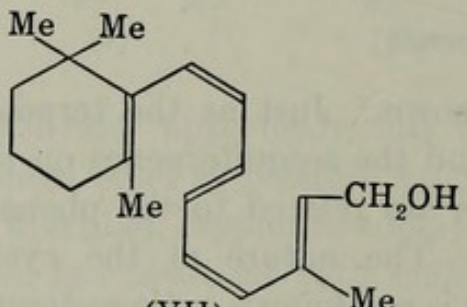
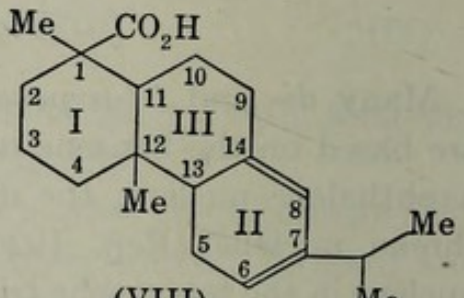



(VII)




(VIII)

**Dextropimaric acid** differs from levopimaric and abietic acids in giving 1,7-$Me_2$-phenanthrene (pimanthrene), in giving formaldehyde on ozonolysis, and in not reacting with maleic anhydride. (Rev. Bio. 1934, 467).

**Agathic acid** is a bicyclic diterpene acid which gives a tricyclic acid, *isoagathic acid* on cyclisation with formic acid. With Se the latter gives 1,7-$Me_2$-phenanthrene (Rep. 1932, 162). A related di-tertiary alcohol is *sclareol* (ibid. 163). *Manool* is a bicyclic diterpene alcohol with two double bonds which gives the same "trihydrochloride" as sclareol (Hosking 1936).

The *sapogenines* (saponines) are related to the *triterpenes*. *Digitonine* has a structure much like that of the sterols (Tschesche 1935). It precipitates sterols having the 3-OH in the *trans* position but not their epimers. Various cyclic triterpenes have been obtained from the open chain compound squalene (Rep. 1927, 127–8). *Elemolic acid*, $C_{30}H_{48}O_{31}$ is a related hydroxy acid. The *amyrenes* and *betuline* are triterpene alcohols. *Ursolic, sumaresinolic, sia-resinolic* and *oleanolic* acids as well as *hederagenine* and *gypsogenine* are triterpene derivatives. Their dehydrogena-

tion with Se has produced such substances as 1,2,3,4-$Me_4$-benzene, 2,7-Me-naphthalene, 1,2,7-$Me_3$-naphthalene (sapotaline), hydroxysapotaline, polymethyl dinaphthyls and $Me_3$-picene (Rev. Bio. 1934, 469–73).

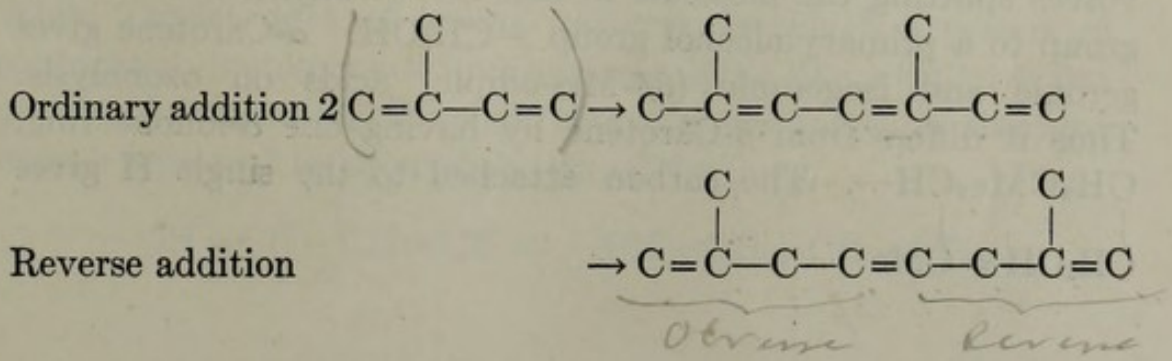
*Carotenoids or Lipochromes*

They are the highly unsaturated fat-soluble coloring matters found in many plant and animal products. The color is due to large numbers of conjugated double bonds. These compounds are *terpenic* in that they can be formulated as constructed from isoprene residues. The two chief hydrocarbons of this series, *lycopene* and *carotene*, have the formula $C_{40}H_{56}$ and so are tetraterpenes containing 8 isoprene units.

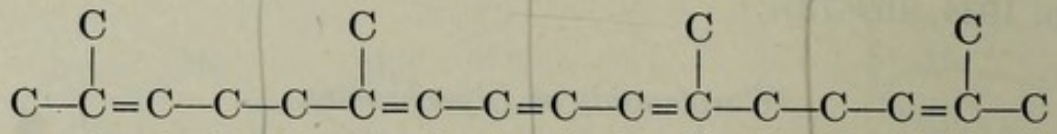
**Lycopene** (lycopin), the red coloring matter of tomatoes, adds 13 $H_2$ on catalytic hydrogenation. In dry oxygen it absorbs 11 atoms of O and becomes colorless. It thus contains no rings. Ozonation and various oxidation procedures give acetone, acetaldehyde, acetic acid, levulic acid, succinic acid, methylheptenone and more complex products. Its formula (Karrer) is

$$Me_2C{=}CHCH_2CH_2C(Me)(=CHCH=CHCMe)_2=CHCH=$$
$$CHCH=(CMeCH=CHCH=)_2C(Me)CH_2CH_2CH=CMe_2$$

The molecule is symmetrical and is made up of two units having the same chain as phytol and farnesol but having alternate double and single bonds starting at the middle and omitting only the double bonds which would be in 4,5-position to each end. Thus, if built up from isoprene or related units, the process could not go from one end of the molecule to the other as in the ordinary linear polymerization of isoprene. It might start at the center from an isomer of myrcene obtained by the "reverse" addition of two molecules of isoprene.



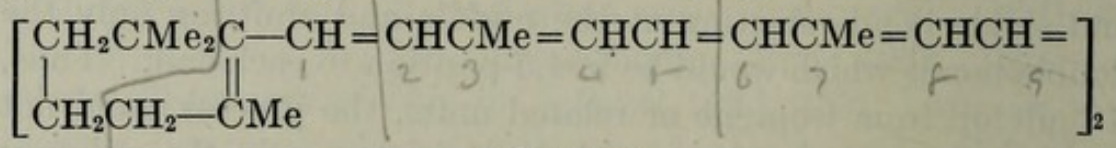
Such a molecule could add an isoprene molecule in the ordinary way at *each* end to give a lower analog of squalene containing a double bond in the central group of four atoms



The addition of one and two more isoprene units at *each* end in the usual way would give the skeletons of squalene (with 2 too few H) and of lycopene (with 8 too many H). The mechanism of the hydrogenation and dehydrogenation of these substances in nature is still a mystery.

Lycopene, in common with the other carotenoids, is readily oxidized by air and gives deep blue colors with conc. sulfuric acid, $SbCl_3$, etc.

The *carotenes*, $C_{40}H_{56}$, isomeric with lycopene, are among the most widely distributed natural coloring matters. *α-Carotene*, m. 174°, is dextrorotatory while its isomer, β-carotene, m. 183° is optically inactive. The structure of β-carotene (Karrer) depends on its absorption of 11 $H_2$ and its oxidation to the αα-$Me_2$-derivatives of adipic, glutaric, succinic and malonic acids, together with large quantities of acetic acid. The formation of the first of these (geronic acid) indicates the presence of β-ionone rings. β-Carotene is thus the product which would be obtained by closing a 6-ring at each end of the lycopene molecule



β-Carotene

β-Carotene is convertible by the animal organism to Vitamin A and is consequently called Provitamin A. The change involves splitting the molecule in half and changing the $-CH=$ group to a primary alcohol group $-CH_2OH$. α-Carotene gives geronic and isogeronic (ββ-$Me_2$-adipic) acids on ozonolysis. Thus it differs from β-Carotene by having one α-ionone ring, $CH_2CMe_2CH-$. The carbon attached to the single H gives
$CH_2CH=CMe$

optical activity. *Zeaxanthin*, $C_{40}H_{56}O_2$, the coloring matter of maize, is a dihydroxyl derivative of β-carotene. Its oxidation gives αα-$Me_2$-succinic acid but no higher acid. Thus the rings at the ends of the molecule are 2,6,6-$Me_3$-4-OH-cyclohexenyl. *Xanthophyll* of green leaves is an isomer of zeaxanthin related to α-carotene. *Crocetin*, $C_{20}H_{24}O_4$, is a dibasic acid with 7 conjugated olefinic linkages and 4 Me groups,

$$(=CHCH=CMeCH=CHCH=CMeCO_2H)_2.$$

Treatment with $TiCl_3$ gives *dihydrocrocetin*, the addition being said to be at the ends of the long conjugated system. The dihydro compound is much more easily oxidized than crocetin. *Bixin* is the monomethyl ester of *norbixin* (I), a $C_{24}$-dibasic acid related to crocetin

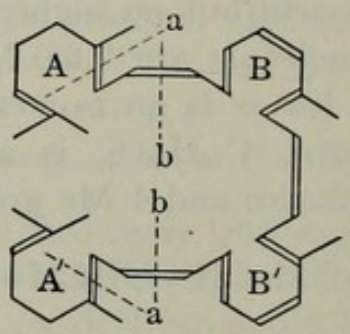
$$(=CHCH=CMeCH=CHCH=CMeCH=CHCO_2H)_2. \quad (I)$$

It thus differs from the latter by having no Me groups on the α-carbons.

**Relation of the carotenoids to each other.** All those of known structure contain the central grouping, $=CH-CH=CH-CH=$, between tertiary carbon atoms. Zeaxanthin and xanthophyll may be regarded as products of mild oxidation of the carotenes which in turn could be formed by cyclisation of each end of the lycopene molecule. Oxidation of lycopene by removing *each end* as far as the second double bond would leave norbixin while oxidation of the carotenes with removal of both 6-rings by breaking the adjacent double bonds would give crocetin. The mechanism for such highly selective oxidations is related to the possibility of the existence of such unusual molecules as those of the polyenes. In many respects conjugated double bonds differ radically from the same number of isolated double bonds. While Thiele's idea of partial valences by which a system of conjugated double bonds involves something like a uniform flux of valence forces along the chain should not be taken too literally, it does represent an approximation of the facts.

$$-CH=CH-CH=CH \rightleftharpoons -CH=CH=CH=CH-$$

Thus lycopin may exist in space in some such arrangement as follows:

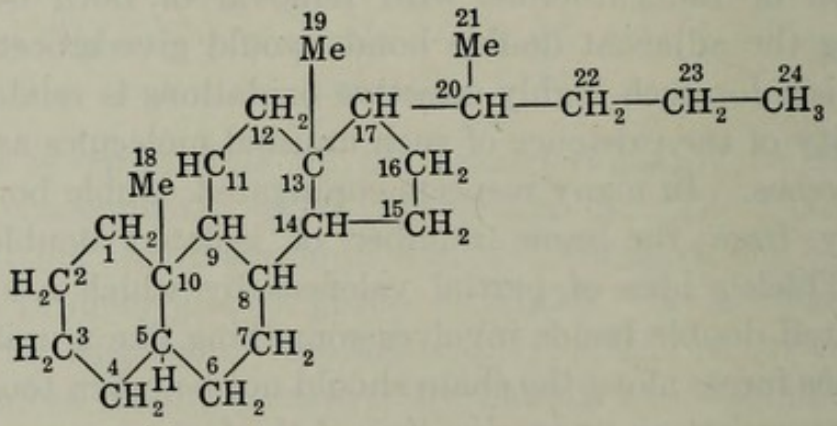



The four rings may be regarded as of chelate nature. When A and A′ change to true rings by elimination of the end double bonds, β-carotene is formed. A different position of one double bond in one ring gives α-carotene. Oxidation at *a* and *b* would give norbixin and crocetin respectively. These might contain the chelate rings B and B′.

Gulland, 1930, Kuhn 1933.

## IV. CHOLANE SERIES

The *cholane* nucleus contains a hydrogenated phenanthrene with a 3-carbon chain attached in the 1,2-position of the phenanthrene to give a 5-ring, two angular methyl groups and a 2-sec-amyl group. It has been prepared from cholesterol and cholanic acid (Rep. 1927, 130). The special system of numbering is used with the large numbers of related natural substances.




This grouping and its modifications occur in the bile acids, the sterols, toad poisons, heart stimulants of the digitalis and arrow

poison type such as strophanthin and ouabain and in the sex hormones.

Fieser, The Chemistry of Natural Products Related to Phenanthrene, A.C.S. Monograph No. 70, 1936.

### *A.* Bile Acids (Gallensäuren)

These are saturated hydroxy acids having the cholane nucleus. They occur in the animal organism combined with acids as in glycocholic and taurocholic acids related to glycine and taurine respectively. They can be reduced to a parent carboxylic acid, *cholaic acid* (*cholanic acid*) having the end (24) Me in the 17-side chain converted to $CO_2H$. Cholanic acid is related to coprostanol (coprosterol) (Rep. 1927, 130). Thus the four rings are united *cis, trans, trans.*

Cholanic acid has been converted to norcholanic, bisnorcholanic, etiocholanic and etiobilianic acids by successive removals of carbon atoms from the side chain and finally by opening Ring IV (Rep. 1927, 130).

The common bile acids are hydroxyl derivatives of cholanic acid: *lichocholic acid*, 3-OH; *deoxycholic*, *hyodeoxycholic* and *chenodeoxycholic acids*, 3,12-; 3,6 and 3,7-$(OH)_2$ respectively; *cholic* and *β-phocaecholic acids*, 3,7,12- and 3,7,23-$(OH)_3$ respectively.

The hydroxyl groups in the bile acids offer points of attack which have finally clarified not only their own structures but that of the sterols and related products. Some of the degradation products of deoxycholic acid are deoxybilianic, choloidanic, pyrocholoidanic, prosolanellic, solanellic, pyrosolanellic and norsolanellic or biloidanic acids (Rev. Bio. 1934, 92).

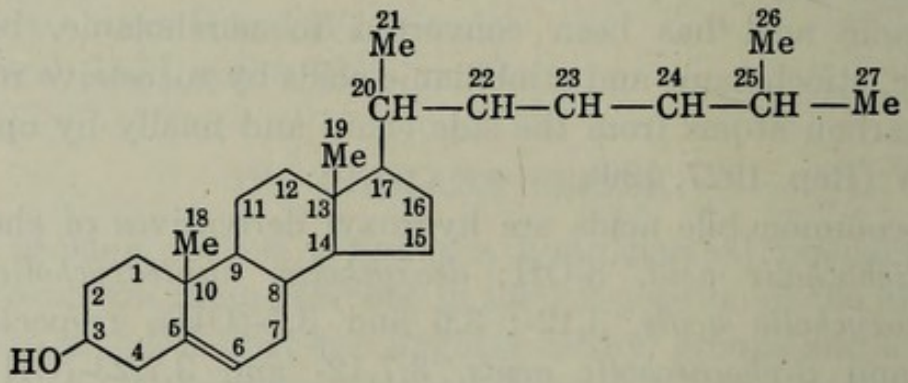
**Choleic acids** are complex coordination compounds of deoxycholic (3,12-dihydroxy cholanic) acid with various other substances such as fatty acids and even aromatic substances such as phenol and naphthalene. The natural choleic acid in bile contains 8 molecules of the bile acid combined with 1 molecule of stearic, oleic, or palmitic acid (Wieland 1916).

## *B.* Sterols

These are widely distributed in plants (phytosterols) and in animals (zoosterols). The sterols are hydroxyl derivatives of omega-isopropyl cholane (p. 684). Thus the 17-side chain is $-CH(Me)(CH_2)_3CHMe_2$. The bile acids probably have their origin in the oxidation of the sterols, one point of oxidation being at the *tert*-H of the isopropyl group thus leading to the elimination of that group.

$$-CH_2CHMe_2 \rightarrow -CH_2C(OH)Me_2 \rightarrow -CO_2H + Me_2CO$$

The most studied example of the zoosterols, *cholesterol*, $C_{27}H_{45}$—OH $[\alpha]^D = -36°$, m. 148°, first found in gall stones, has been assigned the following structure (Rep. 1933, 198; Rev. Bio. 1934, 97).




It is thus 3-OH-Δ5-ω-isopropyl-cholene.

Vigorous dehydrogenation with Se gives chrysene, the process thus eliminating the two angular methyls, opening the 5-ring to give a 6-ring at the expense of the 19-Me and removing the side chain. This result has been disputed (Rep. 1933, 213). *Mild hydrogenation* saturates the 5-double bond giving dihydrocholesterol or *cholestanol* (β-cholestanol). Replacement of its OH by H gives the parent hydrocarbon *cholestane*, $C_{27}H_{48}$. X-ray measurements (Bernal 1932) and surface film studies (Adam 1929) both indicate that the sterols have relatively *flat* molecules. Thus the 9,8-linkage must be *trans*, that is, 7- and 10-carbons must be on opposite sides of the plane of carbons 5,6,8,9,12,13 and hydrogens 8 and 9 are on opposite sides of the molecule. In cholestane, rings I and II are also *trans*, the 5-H and 10-Me being on opposite

sides of the plane of the molecule. Rings III and IV are believed to be *trans* in all the sterols as well as other cholane derivatives. Cholestane can be converted to a stereoisomer of cholanic acid (iso-, allo- or hyo-cholanic acid). *High temperature hydrogenation* or reduction by bacteria, as in the intestines, changes cholesterol to coprostanol, a stereoisomer of cholestanol in which Rings I and II are joined in the *cis* position and the 5-H and 10-Me are on the same side of the molecule. Further reduction gives coprostane (pseudo-cholestane) which can be converted to cholanic acid the parent substance of the bile acids (Rep. 1927, 130). The configurations of the saturated alcohols related to cholesterol are as follows: (Rep. 1934, 208) *cholestanol, trans, trans, trans, trans.* The first *trans* refers to the location of the 3-OH group and the last three to the three ring fusions.

**Epicholestanol,** *cis, trans, trans, trans,* is the *epimer* of cholastanol, differing from it only in the configuration of the single carbon No. 3.

**Coprostanol,** (coprosterol, $\alpha$-cholestanol, pseudo-cholestanol), *cis, cis, trans, trans.*

**Epicoprostanol,** *trans, cis, trans, trans.*

**Allocholesterol,** with the double bond in the 4,5-position, is obtained by treatment with HCl. On hydrogenation it gives coprostanol. Thus the isomerization involves not only the position of the double bond but the configuration of the 3-carbon and the linkage of Rings I and II.

Cholesterol and sterically related substances (with *trans* OH) precipitate saponins such as digitonin.

Coprosterol (coprostanol) is found in feces. It should be noted that it is saturated whereas cholesterol is unsaturated.

The important *phytosterols* include *sitosterol* (isomeric with cholesterol), *stigmasterol, tachysterol, spinasterol* and *ergosterol.* The last is of great importance because ultra violet irradiation converts it to substances related to Vitamin D (*lumisterol, protachysterol, tachysterol, calciferol, toxesterol, suprasterol*-1 and -2). Ergosterol has the same structure as cholesterol with an additional double bond in the 7,8-position and the 17-side chain as

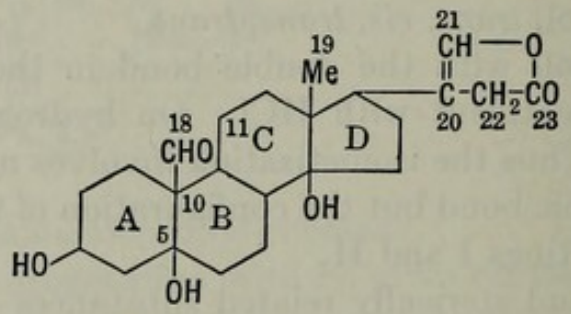
$$-CHMeCH=CHCHMeCHMe_2$$

(Rep. 1933, 210; Rev. Bio. 1934, 101). Ergosterol gives distinct color reactions with trichloroacetic acid (Rosenheim 1929). One of the products of the irradiation of ergosterol is tachysterol believed to be formed by the opening of bond 9,10 with the formation of a double bond at 9,11 (Lettre 1934).

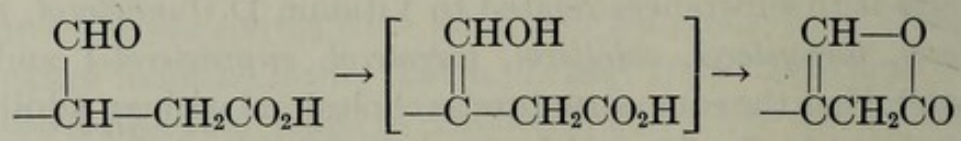
Bile acids and Related Substances. Sobotka, Rev. *15*, 311–75 (1934).

### *C.* Cardiac Aglucones

These are closely related to the bile acids and the sterols but contain angular OH groups and a complex lactone system in the 17-position. They are obtained by hydrolysis of glucosides found in many plants which have been used as sources of heart stimulants and arrow poisons. The best known aglucones contain 23 C atoms. They are *strophanthidin*, *digitoxigenin*, *zitoxigenin*, *digoxigenin*, *periplogenin*, *sarmentogenin*, *uzarigenin*, and *ouabegenin*. *Scillaridin A* has 25 C atoms. (Rep. 1934, 218–38). The most studied of these is *strophanthidin* (Jacobs.) To it is assigned the formula

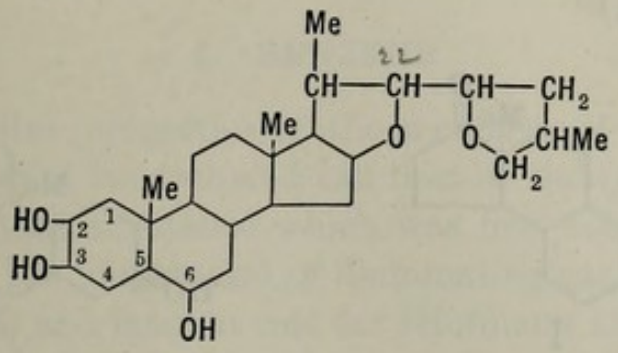



It thus differs from cholesterol in having no cyclic double bond, in having angular OH groups at 5 and 14, in having the 18-Me changed to an aldehyde and in having the 17-group even farther degraded than in the bile acid series to form the lactone of an aldehyde and having the 21-Me as an aldehyde (enol form) and the 23-C as carboxyl




Oxidation opens the lactone ring converting the $-CHO$ to $-CO_2H$ which forms a true lactone with the 14-OH.

The analogs of strophanthidin have only minor modifications from its molecule. Thus *periplogenin* has the 18-Me instead of an aldehyde group. *Digitoxigenin* differs from periplogenin by not having the 5-OH. *Digoxigenin* is like periplogenin but has the OH on $C_{11}$ instead of $C_5$ (Tschesche 1936). Digitogenin has the full cholesterol skeleton with two $H_4$-furan rings involving Ring D and the side chain (Tschesche 1936)

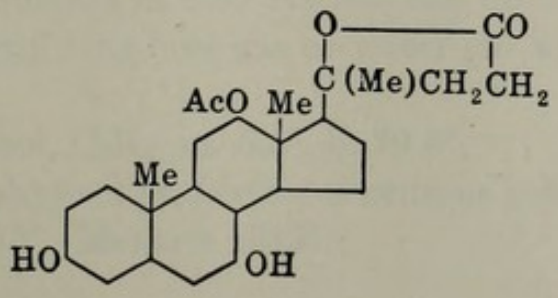



*Gitogenin* has H in place of the 6-OH. *Tigogenin* has H in place of both 6-OH and 2-OH.

### *D.* Toad Poisons

These contain, besides nitrogenous compounds (the bufotenines), cholane derivatives, the *bufagins* and *bufotoxins* (Wieland 1932, Jensen 1934). The bufagins are unsaturated polyhydroxy cholane derivatives related to the cardiac aglucones. Hydrolysis gives formic or acetic acid. This may be due to an ester group or to some splitting of the molecule to give formaldehyde and acetaldehyde (Jensen 1934). Bufotoxins are compounds of the bufagins with suberyl arginine.

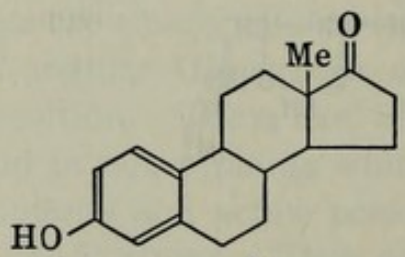
**Bufotalin** may be the monoacetyl derivative of the lactone of γ-hydroxycholic acid.



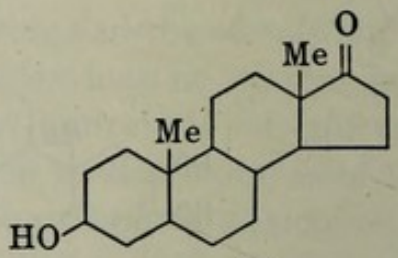
By reduction and hydrolysis it can be converted to cholic acid. Its structure is still not completely settled (Rep. 1934, 238–40).

### *E.* Sex Hormones

These are related to the cholane and sterol series in containing the hydrogenated cyclopentenylphenanthrene nucleus. The chief female and male hormones are *theelin* (oestrone) (I) and *androsterone* (II)




I




II

Theelin is phenolic in properties. This makes its extraction from pregnant urine possible.

*Pregnandiol* differs from androsterone only in having

$$-\mathrm{CHOHMe}$$

in the 17-position in place of the ketonic oxygen. The corpus luteum hormone, *progesterone* has MeCO– at 17- and has the 3-OH oxidized to a ketone with a 4,5-double bond. *Theelol* differs from theelin in having OH groups at 16 and 17. Dehydration and rearrangement of H gives theelin.

This field is at present a very active one.

# PART III

## AROMATIC OR BENZENE SERIES

### I. BENZENE

The distinctive properties of the members of this series are peculiarly those of benzene and can best be shown by a detailed discussion of that substance which was first found in a liquid by-product of the preparation of illuminating gas from whale oil (Faraday 1825) and later in coal tar (Hofmann 1845).

The relation of aliphatic and aromatic compounds. Angeli, Ahr. 1926.

Because of the tremendous amount of work on aromatic compounds and the fact that the latter are obtained from coal tar it might be thought that coal tar and coal are distinctly aromatic in nature. It should be remembered that both coal and coal tar are very complex chemically. In "low temperature" coal tar the amount of aliphatic compounds is considerable (Morgan 1932).

Chemistry of Coal. Tropsch. Rev. *6* (1929).

Hydrogenation of Coal. Bergius 1925.

Coal Tar and Ammonia. Lunge.

The Constituents of Coal Tar. Spielmann, Longmans 1922.

Nitrogen Compounds in Coal. Ahr. 1904, 86 pp.

Benzene and its lower homologs, toluene and the xylenes occur in only small amounts in coal tar but can be obtained in larger quantities by scrubbing coal gas or water gas with suitable high boiling oils.

**Benzene,** benzol, $C_6H_6$, m. 5.5°, b. 79.6°.

Many of the physical properties of benzene indicate a transition point at about 45° (Menzies 1932).

### *A.* Structure of Benzene

A combustion analysis and molecular weight determination prove its empirical formula. Comparison of this formula with that of hexane, $C_6H_{14}$, would indicate benzene to be highly unsaturated. It does not, however, give any reaction with $KMnO_4$ or with bromine water, ordinary reagents for unsaturated compounds. Practically all of its reactions are those of substitution instead of addition. Thus

$$C_6H_6 + HNO_3 \rightarrow \underset{\text{Nitrobenzene}}{C_6H_5NO_2} + H_2O$$

$$C_6H_6 + H_2SO_4 \rightarrow \underset{\text{Benzene sulfonic acid}}{C_6H_5SO_3H} + H_2O$$

$$C_6H_6 + Hg(OCOCH_3)_2 \rightarrow \underset{\text{Acetoxymercuribenzene}}{C_6H_5HgOCOCH_3} + CH_3CO_2H$$

$$C_6H_6 + Cl_2 \rightarrow \underset{\text{Chlorobenzene}}{C_6H_5Cl} + HCl$$

The first three of these reactions take place in the aromatic series with an ease which is unknown with aliphatic and alicylic compounds. Contrary to what might be expected from a $C_6$ compound, only *one* of each of these monosubstitution products has ever been obtained. No isomer of any of them can be obtained from benzene. Thus only one *monochlorobenzene* has ever been made. It is $C_6H_5Cl$, m. $-45°$, b. 132.1°. This means either that the *six H atoms* in benzene are all similarly placed in the molecule so that the same product is obtained no matter which one is replaced or that *one H* atom is so situated that it is more reactive than the others and is always the first to be replaced. A choice between these theoretical possibilities can be reached by a study of the facts regarding further substitution in the benzene molecule. Thus the continued action of chlorine gives the following reaction:

$$C_6H_5Cl + Cl_2 \rightarrow C_6H_4Cl_2 + HCl$$

The resulting product is a *mixture* which can be separated into *three isomeric* dichlorobenzenes with the following properties.

| $C_6H_4Cl_2$ | m. | b. | $d_4^{20}$ | $n_D^{20}$ |
|---|---|---|---|---|
| (A) | 52.9° | 173° | 1.458 | 1.527 |
| (B) | −14.° | 179° | 1.298 | 1.549 |
| (C) | −24.8° | 173° | 1.288 | 1.546 |

Further chlorination is possible.

$$C_6H_4Cl_2 + Cl_2 \rightarrow C_6H_3Cl_3 + HCl$$

In this way (*A*) gives a homogeneous product, a trichlorobenzene which may be called (*D*). When (*B*) is further chlorinated it gives a product which can be separated into *two* trichlorobenzenes, one of which is identical with (*D*), obtained from (*A*) and a different $Cl_3$-benzene which may be called (*E*). When the third $Cl_2$-benzene, (*C*), is chlorinated, it gives a product which is found to be a mixture of *three* trichlorobenzenes, (*D*), (*E*) and a different one which may be called (*F*). The properties of these trichlorobenzenes are as follows:

| $C_6H_3Cl_3$ | m. | b. |
|---|---|---|
| (*D*) | 17° | 213° |
| (*E*) | 50.8° | 219° |
| (*F*) | 63° | 208.5° |

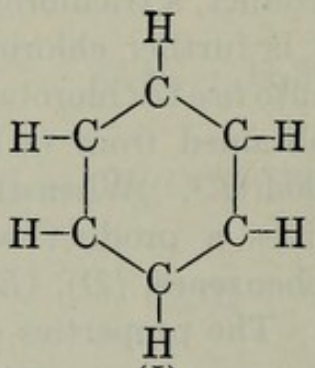
The chlorination of each of these $Cl_3$-benzenes can be continued.

$$C_6H_3Cl_3 + Cl_2 \rightarrow C_6H_2Cl_4 + HCl$$

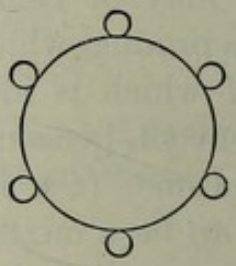
When (*F*), the trichlorobenzene obtainable only from (*C*) and not from (*A*) or (*B*), is chlorinated, the product is a homogeneous tetrachloro-benzene (*G*). Chlorination of (*E*) gives a mixture of (*G*) and another $Cl_4$-benzene (*H*). Similarly (*D*) gives a mixture of three $Cl_4$-benzenes, (*G*), (*H*) and (*I*). The properties of these substances are as follows:

| $C_6H_2Cl_4$ | m. | b. |
|---|---|---|
| (*G*) | 51° | 246° |
| (*H*) | 47° | 254° |
| (*I*) | 137.5° | 246° |

Further chlorination of each of these substances gives only *one* pentachlorobenzene $C_6HCl_5$, m. 86°, b. 277°, and *one* hexachlorobenzene, $C_6Cl_6$, m. 226°, b. 326°. The only explanation of all of the above facts and of countless other facts about benzene and its derivatives, homologs and analogs is that the six carbon and six hydrogen atoms in benzene are arranged in a symmetrical ring (Kekule 1865) (I). This conception of the ring nature of benzene was first expressed by Loschmidt (1861) (cf. Anschütz 1912) (II).



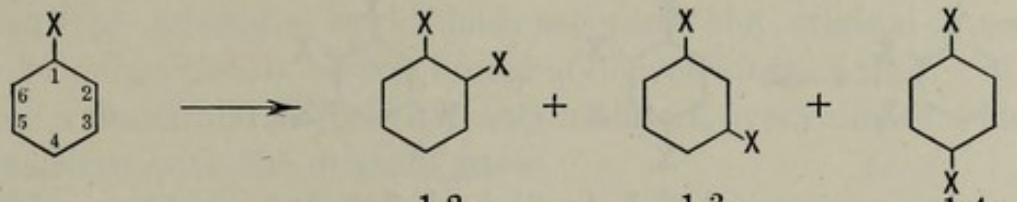

(I)



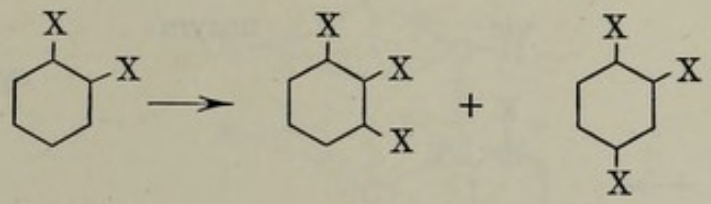
(II)

The fourth valence of each carbon in (I) may be neglected for the time-being. In fact, from a practical viewpoint it is nearly always so neglected because it gives evidence of its existence only under the most unusual circumstances. Thus, if benzene were the only carbon compound known, carbon would be believed to have a valence of *three* except under peculiar conditions. The assumption of the *benzene ring* not only explains the above facts but also makes possible the assignment of a structure formula to each of the chlorinated benzenes described above (p. 696). The number of possible substitutions at the corners of a regular hexagon agrees with the number of isomers actually obtained.

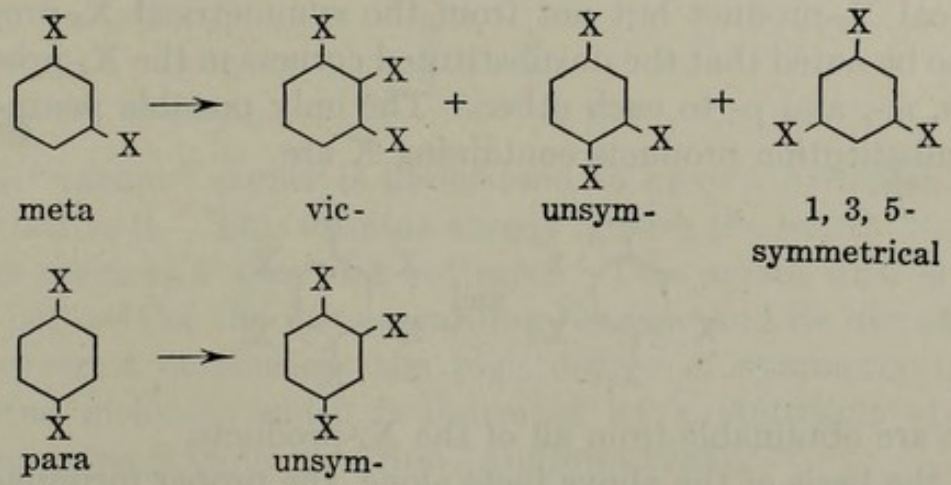
If only one substituent is introduced, only one product can be produced.




Only three disubstitution products are possible since substitution in the 5 and 6 positions gives the same products as in the 2 and 3 positions respectively.

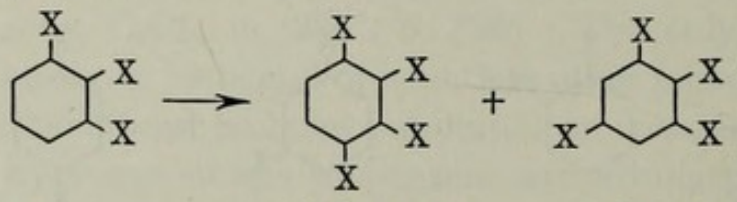



Only *two* trisubstitution products can be derived from the *ortho* compound since the placing of the third group in positions 5 or 6 gives the same *unsym-* and *vic-* products respectively.

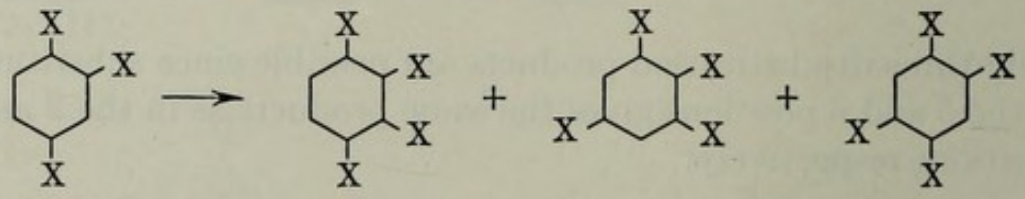



Thus the unsymmetrical trisubstitution product is obtainable from all three disubstitution products while the symmetrical $X_3$-product comes only from the meta compound and the vicinal

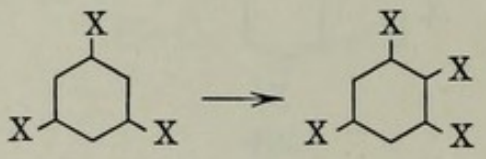
$X_3$-product can be derived from both the ortho and meta compounds.



vic- 1, 2, 3, 4-vic- 1, 2, 3, 5-unsym-

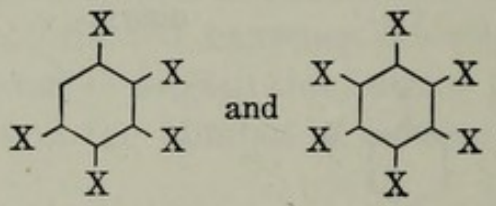


unsym- vic unsym- 1, 2, 4, 5 symmetrical sym



sym- unsym-

The unsymmetrical tetrasubstitution product is obtainable from all three trisubstitution products. The symmetrical $X_4$-product is obtainable only from the unsymmetrical $X_3$-product. The vicinal $X_4$-product is derivable from the vicinal and the unsymmetrical $X_3$-product but not from the symmetrical $X_3$-product. It is to be noted that the unsubstituted corners in the $X_4$-products are *o*-, *m*-, and *p*- to each other. The only possible penta- and hexasubstitution products containing X are



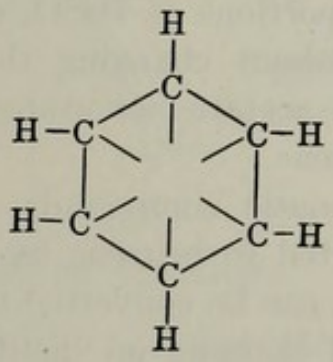
and

These are obtainable from all of the $X_4$-products.

On the basis of the above facts alone, the proper formulas can be assigned to the possible chlorinated benzenes (A) to (I) (p. 693) namely: (A) is 1,4-$Cl_2$-benzene; (B) is 1,2-$Cl_2$; (C) is 1,3-; (D) is 1,2,4-$Cl_3$-; (E) is 1,2,3-$Cl_3$; (F) is 1,3,5-$Cl_3$; (G) is 1,2,3,5-$Cl_4$-; (H) is 1,2,3,4-$Cl_4$; and (I) is 1,2,4,5-$Cl_4$-benzene.

It should be remembered that the details of this elegant demonstration first suggested by Körner were not completed until long after the scientific world had accepted the original guess of Kekule that the six carbon atoms of benzene form a ring. Meantime a multitude of facts has accumulated, every one of which is consistent with the original guess.

The problem of the fourth valence of each carbon in benzene has never been solved. Of the many formulas suggested, the *centric formula* (Armstrong 1887, Baeyer) has survived best probably because it is least definite as to the fourth "bonds."




This formula agrees with the *fact* that the fourth bonds of the carbon atoms in benzene and its derivatives are *different* from ordinary single or double bonds. The formula actually used by organic chemists is the simple hexagon.

Each "vacant" corner is understood to have a hydrogen atom attached to it. This formula simply ignores the fourth bonds or treats them as if they did not exist. This agrees with at least 99.9 per cent of the facts regarding benzene and its derivatives. Moreover it emphasizes the high degree of symmetry of the benzene molecule which is indicated by a multitude of facts including its Raman spectrum (Andrews 1933).

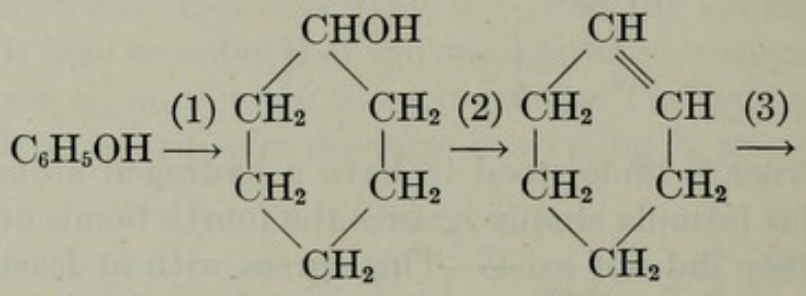
### *B.* Formation of Benzene

1. From coal. The thermal decomposition of the organic compounds in soft coal forms benzene and its homologs (toluene,

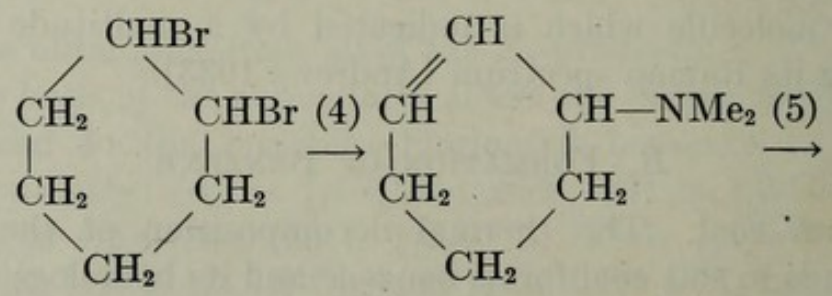
xylenes, etc.) and its analogs (naphthalene, anthracene, etc.). Practically all benzene is obtained by scrubbing the gases from by-product coke plants and illuminating gas plants. Commercial "ninety per cent benzol" is a mixture, 90% of which distills below 100°. "Nitration benzol" boils within one degree of the true boiling point 80.4° (760 mm). Its only impurity is a small amount of thiophene (b.p. 84°). "Molecular weight benzene" is free of thiophene and melts at 5° or higher (true m.p. 5.4°). The small amount of thiophene in commercially pure benzene is removed by taking advantage of its greater reactivity. Thus shaking with several portions of $H_2SO_4$ converts the thiophene to a sulfonic acid without changing the benzene. Similarly, refluxing with mercuric acetate mercurates the thiophene without reacting with the benzene.

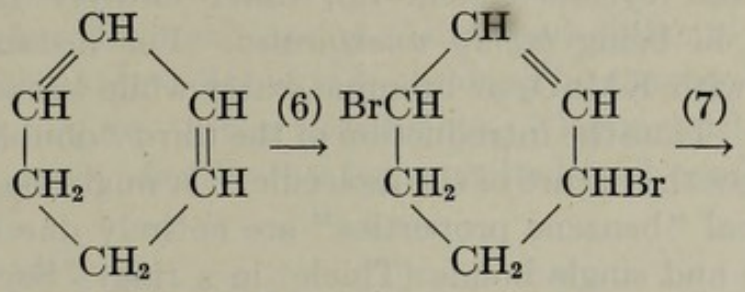
2. From other aromatic compounds. Most aromatic compounds can be converted to benzene by relatively simple reactions. Many of them can be converted to hydroxyl compounds (phenols) which yield benzene on distillation with zinc dust. Homologs and analogs of benzene such as toluene and naphthalene yield carboxylic acids of benzene on vigorous oxidation. These give benzene on heating with soda lime.

3. By synthesis (Willstätter). The steps are as follows:

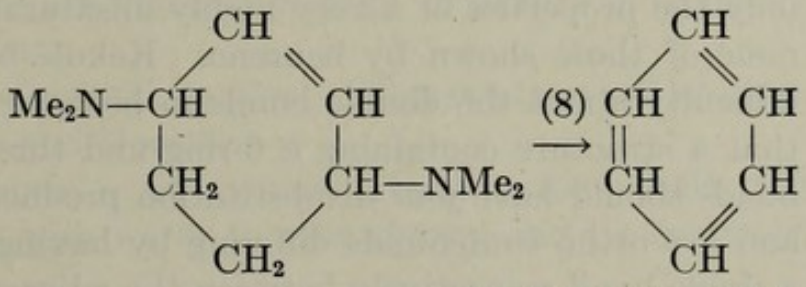



Phenol Cyclohexanol Cyclohexene






Cyclohexadiene-1,3




Cyclohexatriene-1,3,5.

The reactions are carried out as follows:

(1) Hydrogenation with a nickel catalyst.

(2) Dehydration by sulfuric acid.

(3) Addition of bromine.

(4) Treatment of the dibromide with an excess of dimethyl amine. The first step is the removal of one HBr to give an *allyl system* with a very reactive halogen, $-CH=CH-CHBr-$.

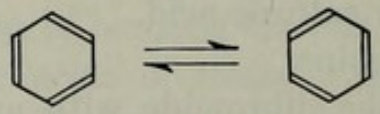
(5) and (8) Exhaustive methylation. Addition of methyl iodide, conversion to the quarternary ammonium hydroxide and destructive distillation to yield trimethylamine, water and olefinic compounds. In the case of (8) the last step takes place even at 0° if the pressure is greatly reduced.

(6) Addition of bromine at the ends of the conjugated system.

(7) An addition reaction of 2 $Me_2NH$ with the bromine atoms which are parts of reactive allyl systems to form $=CHNMe_2.HBr$. An inorganic base or excess $Me_2NH$ removes the HBr.

According to the reactions involved, including the final exhaustive methylation, the product should contain three double bonds arranged in alternate or conjugated form around the 6-carbon ring. The final product is benzene which seldom shows the presence of double bonds. The intermediate compounds,

cyclohexene and cyclohexadiene-1,3, differ entirely from the final product in being *highly unsaturated.* For instance they react readily with $KMnO_4$ or bromine water while benzene does not act at all. Thus the introduction of the third "double bond" entirely changes the nature of the molecule. It might be thought that the typical "benzene properties" are entirely due to alternating double and single bonds (Thiele) in a ring. Such is not the case because cyclooctatetraene-1,3,5,7 (Willstätter) shows only the properties of a very highly unsaturated compound and none of those shown by benzene. Kekulé had recognized this difficulty about the double bonds in benzene and had also seen that a structure containing a 6-ring and three alternate double bonds should have *four* disubstitution products, the para, meta, and *two* ortho compounds differing by having a double bond or a single bond respectively between the adjacent carbons bearing the two substituting groups. In view of the absence of a second ortho compound, Kekule proposed his hypothesis of the oscillation of the double bonds in benzene.



The centric formula then becomes a phase half-way in the oscillation. The results of modern mechanics and X-ray studies have added quantitative confirmation of Kekulé's guess (Pauling 1931, Mack 1932). In modern language, the *oscillation* of the conjugated double bonds becomes *resonance.*

Since the time of Kekulé, evidence for the existence of two forms of certain ortho-disubstituted benzenes has been found (Rep. 1907, 111). Evidence for the oscillation or resonance formula is given by the ozonolysis products of *o*-xylene (p. 712).

Benzene structure. Ahr. 1898, 1928.

### *Reactions of Benzene*

1. Heat links benzene rings together with the elimination of hydrogen.

$$2\,C_6H_6 \rightarrow H_2 + C_6H_5{-}C_6H_5$$

Diphenyl

Smaller amounts of higher products such as *p*-diphenylbenzene, *sym*-triphenylbenzene and 4,4′-diphenyl-diphenyl are obtained. In the laboratory, diphenyl is obtained by passing benzene vapor through hot iron tubes (Berthelot). Commercially the heating is made more effective by using melted lead containing various catalysts.

2. Oxidation.

(*a*) Ordinary oxidizing agents have no effect on benzene unless the conditions used are vigorous enough to oxidize it to oxides of carbon and water.

(*b*) Oxidation by air with catalysts like vanadium oxides gives maleic acid (Weiss and Downs).

(*c*) Ozonation gives a tri-ozonide (Harries, Rep. 1904, 92) which decomposes with water to give glyoxal and its oxidation products.

(*d*) Potassium chlorate and sulfuric acid give "trichlorophenomalic acid," (trichloroacetoacrylic acid) which reacts with alkali to give chloroform and a maleate.

$$Cl_3CCOCH=CHCO_2H \rightarrow CHCl_3 + NaO_2CCH=CHCO_2Na$$

(*e*) The direct oxidation of benzene to phenol or even to benzoquinone has not been achieved although traces of the latter occur during catalytic oxidation. The nearest approach is the production of a mixture of nitrophenols by nitric acid in presence of mercuric salts.

Benzene has valuable anti-knock properties in motor fuels.

3. Reduction.

(*a*) Hydriodic acid converts benzene into a mixture of hexahydrobenzene (cyclohexane) and methylcyclopentane.

(*b*) Catalytic hydrogenation with nickel gives cyclohexane. This reaction takes place less readily than with substituted benzenes.

4. With halogens.

(*a*) Fluorine reacts violently giving hydrogen fluoride and carbon tetrafluoride (Bancroft).

(*b*) In the cold and in darkness, the other halogens merely dissolve in benzene with practically no action. In sunlight, chlorine and bromine *add* to benzene to give compounds, $C_6H_6Cl_6$,

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benzene hexachloride and $C_6H_6Br_6$. They exist in stereomeric forms. These halides are unstable. On heating or in the presence of catalysts like ferric salts, they lose 3 HX readily giving *unsymmetrical* trihalogenated benzenes. Iodine does not react with benzene except in the presence of an oxidizing agent like iodic acid or nitric acid, in which case it gives iodobenzene and *p*-diiodobenzene (*Edinger, Datta*).

$$5\ C_6H_6 + 2\ I_2 + HIO_3 \rightarrow 5\ C_6H_5I + 3\ H_2O$$

The function of the oxidizing agent is to remove the HI which would otherwise reverse the reaction.

(*c*) Chlorine and bromine react with hot benzene in the presence of a great variety of catalysts such as iodine and ferric halides to give *substitution* products of benzene.

$$C_6H_6 + Br_2 \rightarrow C_6H_5Br + HBr$$

Some dihalogen product is always formed.

$$C_6H_5Br + Br_2 \rightarrow C_6H_4Br_2 + HBr$$

This is mainly the para compound with small and approximately equal amounts of the ortho and meta compounds. An analogous *substitution* reaction with an *aliphatic* compound is the action of chlorine on isobutylene to give mainly isocrotyl chloride and no isobutylene dichloride.

$$Me_2C{=}CH_2 + Cl_2 \rightarrow HCl + Me_2C{=}CHCl$$

5. Nitration. Concentrated nitric acid, fuming nitric acid or a mixture of nitric and sulfuric acids converts benzene to nitrobenzene.

$$C_6H_6 + HNO_3 \rightarrow C_6H_5NO_2 + H_2O$$

The reaction is strongly exothermic. In the laboratory this gives no trouble but on a large scale it necessitates effective cooling. The process is not reversible.

Isobutylene gives a similar nitration.

$$Me_2C{=}CH_2 + HNO_3 \rightarrow Me_2C{=}CHNO_2 + H_2O$$

Under ordinary conditions the nitration of benzene gives no dinitrated product. Thus the activity of the benzene ring is

considerably *lessened* by the introduction of a nitro group. Under vigorous nitration conditions (fuming nitric acid and conc. sulfuric acid) a dinitro benzene can be obtained.

$$C_6H_5NO_2 + HNO_3 \rightarrow C_6H_4(NO_2)_2 + H_2O$$

This is almost entirely the meta compound with no more than traces of the ortho and para cpds. Even more vigorous nitration (fuming nitric and fuming sulfuric acids) gives 1,3,5-trinitrobenzene.

The ready formation of nitro compounds in the liquid phase by means of conc. nitric acid is typical of aromatic compounds. Aliphatic hydrocarbons can be nitrated successfully in the vapor phase (Hass 1936).

6. Sulfonation. Concentrated sulfuric acid or, more rapidly, fuming sulfuric acid (oleum) forms benzene sulfonic acid.

$$C_6H_6 + H_2SO_4 \rightarrow C_6H_5SO_3H + H_2O$$

The process can be reversed by using superheated steam or by heating the sulfonic acid with concentrated hydrochloric acid. Under ordinary conditions there is no tendency for the sulfonation of benzene to introduce a second sulfonic acid group. Thus the activity of the benzene ring is also lowered by the presence of a sulfonic acid group. Vigorous sulfonation with oleum introduces a second group.

$$C_6H_5SO_3H + SO_3 \xrightarrow{H_2SO_4} C_6H_4(SO_3H)_2$$

The product is a mixture of *meta* and *para* compounds with the former predominating. Probably the meta compound is formed first and then rearranges to the para compound until an equilibrium is attained. The reversibility of the sulfonation process makes this rearrangement possible.

$$\underset{\text{Meta}}{C_6H_4(SO_3H)_2} + H_2SO_4 \rightleftharpoons H_2S_2O_7 + C_6H_5SO_3H \rightleftharpoons \underset{\text{Para}}{C_6H_4(SO_3H)_2} + H_2SO_4$$

No ortho-benzenedisulfonic acid has ever been detected among the products. Any such product formed is probably rearranged

to the more stable *m*- or *p*-forms. When an anhydrous salt of meta-benzenedisulfonic acid is heated with sulfuric acid, a third sulfonic acid group is introduced.

$$\underset{\text{Meta}}{C_6H_4(SO_3K)_2} + 3\ H_2SO_4 \rightarrow \underset{\text{Sym}}{C_6H_3(SO_3H)_3} + 2\ KHSO_4 + H_2O$$

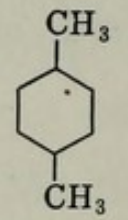
No isomeric benzene trisulfonic acids have been obtained by direct sulfonation.

7. Friedel and Crafts Reaction.

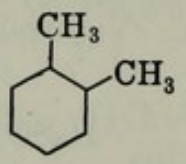
(*a*) Alkyl halides react with benzene in the presence of anhydrous aluminum chloride to give alkyl benzenes. Much less than a molecular amount of aluminum chloride is sufficient to cause this reaction.

$$C_6H_6 + CH_3Cl \xrightarrow{AlCl_3} C_6H_5CH_3 + HCl$$

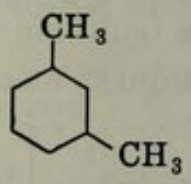
Continued treatment with methyl chloride gives all the possible methylated benzenes ending with hexamethyl benzene. This reaction will not only introduce an alkyl group into the benzene ring, but will cause the transfer of a group from one position to another and even from one molecule to another. Thus the following changes take place in presence of $AlCl_3$.




Para-xylene




Ortho




Meta

$$\underset{\text{toluene}}{2\ C_6H_5CH_3} \rightarrow \underset{\text{xylenes}}{C_6H_4(CH_3)_2} + \underset{\text{benzene}}{C_6H_6}$$

The reaction with ethyl halides is similar to that of the methyl halides. With *n*-propyl halides the chief product is isopropyl benzene with only a small amount of *n*-propylbenzene. At 0° *n*-Bu halides give a mixture of *n*-Bu-benzene and *sec*-Bu-benzene. At higher temperatures the latter is the sole product. Isobutyl halides, in which the tendency to rearrangement is always great, ordinarily give only *t*-Bu-benzene even at −18° although the

use of mere traces of $AlCl_3$ gives small amounts of isobutylbenzene along with the *t*-Bu cpd. Isoamyl halides give isoamylbenzene and *t*-Am-benzene. These rearrangements during the Friedel-Crafts reaction can be explained on the basis of a rearrangement of the halide or of the conversion of the halide to an olefin with the subsequent addition of benzene as H and phenyl according to Markownikoff's Rule. An extreme case of such rearrangement and splitting of the halide has been observed in the furan series (Gilman 1935). Thus a tertiary butyl derivative is obtained from *n*-amyl chloride, *n*-hexyl bromide and even from *n*-octadecyl bromide.

(*b*) Olefins react with benzene and anhydrous aluminum chloride to give the same products as those obtained from the corresponding alkyl halides. Thus ethylene gives all the possible ethylated benzenes including hexaethylbenzene. With higher olefins the addition of benzene under the influence of aluminum chloride follows Markownikoff's Rule. Thus, propylene gives isopropylbenzene, the *n*-butylenes give *sec*-butylbenzene and isobutylene gives *ter*-butylbenzene.

(*c*) Acyl halides and acid anhydrides give carbonyl compounds. In such cases a molecular amount of aluminum chloride must be used since it forms very stable addition products with the carbonyl compounds. Typical reactions of this group follow:

$$COCl_2 \rightarrow C_6H_5C(Cl)=O$$

Phosgene Benzoyl chloride

$$CH_3COCl \rightarrow CH_3COC_6H_5$$

Methyl phenyl ketone, Acetophenone

$$(CH_3CH_2CO)_2O \rightarrow CH_3CH_2COC_6H_5$$

Propionic anhydride Propiophenone

$$C_6H_5COCl \rightarrow C_6H_5COC_6H_5$$

Benzophenone

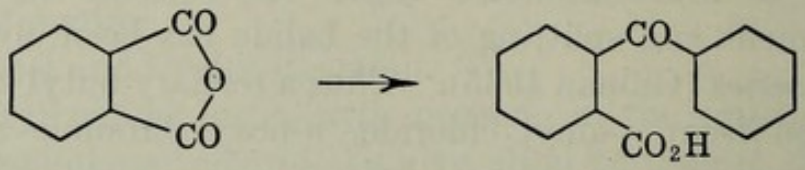
$$HCl + CO \rightarrow C_6H_5C(H)=O$$

Benzaldehyde

Since CO is, in a sense, the anhydride of formic acid it is not

surprising that benzene reacts with Ni carbonyl and $AlCl_3$ in the cold to give benzaldehyde. At high temperatures anthracene is the main product (Rep. 1904, 88).

The most important of the Friedel-Crafts reactions of benzene is that with phthalic anhydride to make *o*-benzoylbenzoic acid which is readily converted to anthraquinone by sulfuric acid.




The action of benzene itself with $AlCl_3$ and HCl gives a mixture boiling up to 360°. One substance formed is 1-Me-3-Ph-cyclopentane.

(*d*) Benzene also reacts in the presence of aluminum chloride with oxygen, sulfur and carbon dioxide.

$$2\,C_6H_6 + O_2 \xrightarrow{AlCl_3} 2\,\underset{\text{Phenol}}{C_6H_5OH}$$

$$C_6H_6 + S \rightarrow \underset{\text{Thiophenol}}{C_6H_5SH}$$

$$C_6H_6 + CO_2 \rightarrow \underset{\text{Benzoic acid}}{C_6H_5CO_2H}$$

Such reactions may be rendered important practically by the cheap anhydrous aluminum chloride made available by its use in the cracking of petroleum (McAfee).

8. With alcohols in the presence of dehydrating agents such as $P_2O_5$ and $H_2SO_4$, secondary and tertiary alkyl benzenes are obtained.

*n*-Butyl alcohol → *sec*-Butylbenzene
*iso*-Butyl alcohol → *ter*-Butylbenzene

9. With aldehydes in the presence of sulfuric acid, diphenylmethane compounds are obtained.

$$R{-}\overset{H}{\underset{|}{C}}{=}O \rightarrow [RCHOHC_6H_5] \rightarrow R{-}CH(C_6H_5)_2$$

The OH in the intermediate compound is very reactive because

of its position alpha to a phenyl group. Formaldehyde gives $Ph_2CH_2$ and higher products including anthracene.

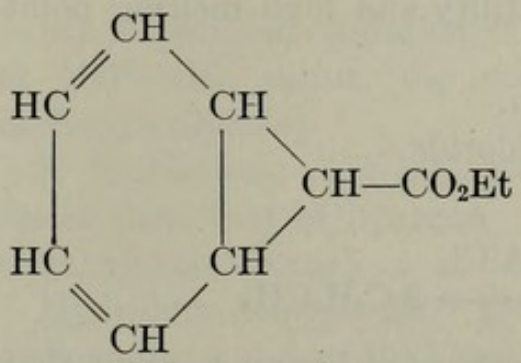
10. Mercuric acetate mercurates benzene when heated under pressure or on refluxing with an alcoholic solution (Maynard). In the latter case the EtOH forms ethyl acetate, thus shifting the equilibrium.

$$C_6H_6 + Hg(OCOCH_3)_2 + C_2H_5OH \rightarrow C_6H_5HgOCOCH_3 + CH_3CO_2C_2H_5$$

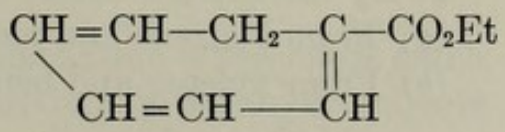
Phenylmercuric acetate
Acetoxymercuribenzene

Mercuration is as characteristic of aromatic compounds as nitration or sulfonation.

11. Ethyl diazoacetate reacts with benzene at 130° to give the bi-cyclic compound norcaradiene carboxylic ester (I) and its rearrangement product cycloheptatriene carboxylic ester (II).




(I)




(II)

12. Metalation (Gilman 1936). Alkali derivatives of benzene can be made by treating it with alkali alkyls.

$$C_6H_6 + EtK \rightarrow C_6H_5K + EtH$$

Some $C_6H_4K_2$ is also formed. Thus the product of the reaction, when treated with $CO_2$, gives a 33% yield of benzoate, a 14% yield of terephthalate, a trace of phthalate but apparently little or no isophthalate.

Benzene vapors are very toxic. Even small amounts of the vapors breathed over a period deplete the blood in both white and red corpuscles and greatly lower the resistance to infection. The only ordinary commercial solvent which is more dangerous than benzene is $Cl_4$-ethane.

## II. HOMOLOGS OF BENZENE

### A. Toluene

*Toluene*, methylbenzene, phenylmethane, toluol, $C_6H_5CH_3$, m. $-92°$, b. 110.8° is obtained after benzene in the distillation of the light oil from scrubbing coal gas.

*Preparation.* 1. By the Wurtz-Fittig reaction from bromobenzene, methyl iodide and metallic sodium. The yield in the reaction between an aromatic and an aliphatic halide is better than would be expected in view of the three possible products. The first step after the formation of the phenyl radical is probably the formation of sodium phenyl, $C_6H_5Na$ (Acree). This reacts readily with the aliphatic halide but not with the aromatic halide. Any ethylene and ethane formed from free methyl radicals escapes during the reaction. Any diphenyl formed from free phenyl radicals is readily separated from the main product because of its lower volatility and high melting point (71°).

2. By the Friedel-Crafts reaction.

(*a*) From benzene and methyl chloride.

(*b*) From xylenes and benzene

$$C_6H_4(CH_3)_2 + C_6H_6 \xrightarrow{AlCl_3} 2\,C_6H_5CH_3$$

The *reactions of toluene* resemble those of benzene except that there is a chance for the reaction to take place either in the side chain or in the ring and that the methyl group exerts a directing or orientating influence on groups entering the ring, directing them mainly to the para and ortho positions with only a small amount entering the meta position.

1. Heat. At dull red heat toluene forms dibenzyl (1,2-diphenylethane).

$$2\,C_6H_5CH_3 \rightarrow C_6H_5CH_2CH_2C_6H_5 + H_2$$

At high temperatures this loses hydrogen to form stilbene (1,2-diphenylethylene). Greater heat gives very complex changes involving such products as benzene, naphthalene, dibenzyl, anthracene, chrysene, benzerythrene, phenanthrene, diphenyl, styrene and traces of methane, acetylene and ditolyl.

2. Oxidation. As with all aromatic hydrocarbons with *side chains*, toluene can be readily oxidized, the side chain alone being changed.

(*a*) Ordinary oxidizing agents such as dilute nitric acid, potassium permanganate and chromic acid mixture (a dichromate and sulfuric acid) convert the methyl to a carboxyl.

$$C_6H_5CH_3 + 3[O] \rightarrow \underset{\text{Benzoic acid}}{C_6H_5CO_2H} + H_2O$$

(*b*) Under special conditions it is possible to oxidize toluene to benzaldehyde, $C_6H_5CHO$. (1) By controlled air oxidation. (2) By oxidation with manganese dioxide and sulfuric acid. (3) By means of chromyl chloride, $CrO_2Cl_2$ (Etard).

(*c*) Oxidation with aqueous potassium persulfate gives dibenzyl (1,2-diphenylethane) together with benzaldehyde and benzoic acid.

(*d*) A peculiar oxidation of toluene occurs when it is heated at 200° with sulfur, the main product being stilbene (*sym*-diphenylethylene).

3. Reduction. The catalytic hydrogenation of toluene is much easier than that of benzene. The product is hexahydrotoluene (methylcyclohexane).

Hydriodic acid at 280° gives methyl cyclohexane, dimethyl cyclopentane and methyl cyclopentane.

4. With halogens there is no tendency to addition as in benzene. Substitution is easier.

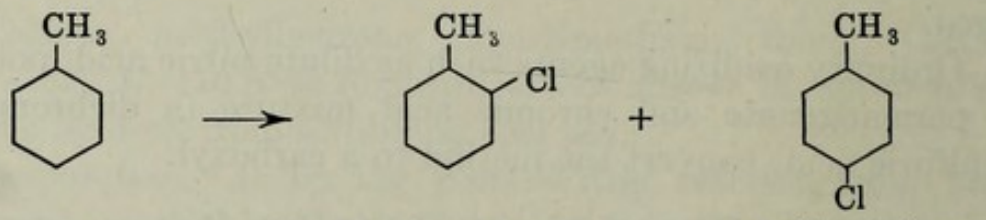
(*a*) Chlorine and bromine react with boiling toluene, especially when exposed to actinic light, to give substitution almost entirely in the methyl group.

$$C_6H_5CH_3 \rightarrow \underset{\text{Benzyl chloride}}{C_6H_5CH_2Cl} \rightarrow \underset{\text{Benzal chloride}}{C_6H_5CHCl_2} \rightarrow \underset{\text{Benzo-trichloride}}{C_6H_5CCl_3}.$$

These substances react like aliphatic halides but are much more active because of the benzene ring in the alpha position. Over a 90% yield of benzyl chloride can be obtained from boiling toluene and dry chlorine in the light.

(*b*) Chlorine and bromine in the presence of halogenation catalysts and in the absence of strong light give mixtures of

ortho and para products with no more than a trace of meta product.




o–chlorotoluene p–chlorotoluene

The nuclear halogens are very unreactive. Further chlorination of the monochloro toluenes gives mainly the *o,p* or 2,4-dichlorotoluene. Over an 80% yield of ring-chlorinated toluenes can be obtained from toluene and wet chlroine in the dark. Chlorination with antimony pentachloride or iodine as catalyst gives ortho and para products in the ratio 55 : 45 (Wertyporoch 1932).

The formation and separation of the monochlorotoluenes is typical of ring-substitution products of toluene in general. The relative proportions of the *o*- and *p*-products can be somewhat modified by the conditions used. They are usually easily separated because the para compounds are mainly solids while the ortho compounds are liquids. There is only a slight difference in boiling point between the isomers. The *p*-compound can be obtained in a high state of purity by freezing it out of the mixture. The mother liquor consists of the *o*-compound and the small amount of *m*-compound formed, the liquid being saturated with the *p*-compound at the temperature of the original freezing. A further separation can be achieved by fractional distillation followed by freezing to remove more of the para compound. *o*-Chlorotoluene is an important dye-intermediate.

5. Nitration of toluene is far easier than with benzene. It gives mainly *o*- and *p*-nitrotoluenes with about 4% of the meta cpd. The large scale on which toluene is nitrated and the refinements of modern commercial distillation make available this small proportion of meta nitrotoluene. Further nitration gives mainly 2,4-dinitrotoluene. This can then be nitrated to 2,4,6-trinitrotoluene (T.N.T.). It is impossible to introduce a fourth nitro group by direct nitration. In the large scale commercial nitration of toluene with nitric acid (d. 1.475) at 30° the following percentages are obtained, para 37, ortho 59, meta 4.

6. Sulfonation of toluene gives a mixture of *o*- and *p*-toluene sulfonic acids. The ortho acid is important in its relation to saccharin.

7. Friedel-Crafts reactions. Toluene, treated with anhydrous aluminum chloride, gives a mixture of xylenes and benzene. When treated with alkyl halides, olefins, etc. and $AlCl_3$, toluene gives para and meta compounds mainly the latter. Thus toluene with $AlCl_3$ and isobutyl chloride gives *m*-*t*-Bu-toluene which can be trinitrated to give a musk substitute (Baur). When anhydrous $FeCl_3$ is used in place of $AlCl_3$ *p*-*t*-Bu-toluene is the chief product.

Toluene with phthalic anhydride and anhydrous aluminum chloride gives *o*-(*p*-toluyl)-benzoic acid which is converted to beta-methylanthraquinone by sulfuric acid.

8. Alcohols and aldehydes condense with toluene in the presence of concentrated sulfuric acid more readily than with benzene. The products contain *para* tolyl groups almost exclusively.

9. Mercuration of toluene in the *p*- and *o*-positions takes place when it is refluxed with mercuric acetate. The chief product is *p*-tolylmercuric acetate (*p*-acetoxymercuritoluene).

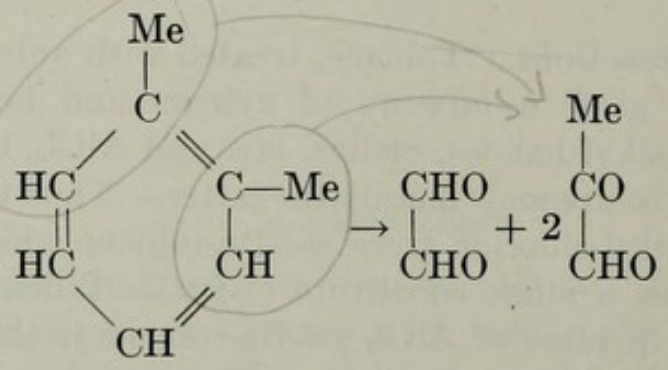
## *B.* Higher Homologs of Benzene

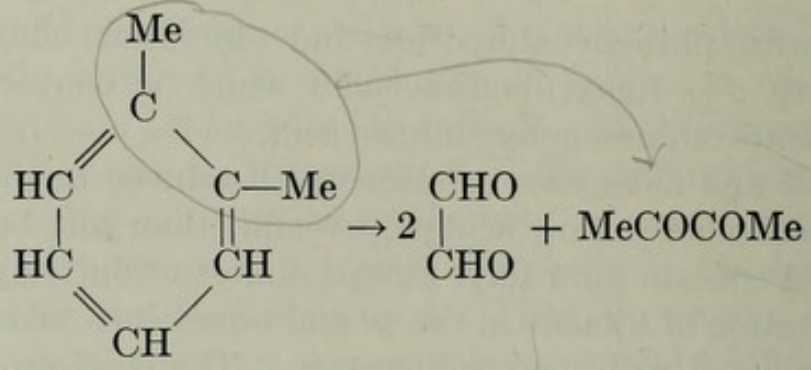
These resemble toluene in properties and reactions.

**Dimethylbenzenes, xylenes,** $C_6H_4(CH_3)_2$, occur in coal tar, the *m*-isomer forming about 70% of the mixture. They cannot be separated by distillation but can by means of $H_2SO_4$. The cold conc. acid leaves the para cpd. unchanged. The solution of the sulfonic acids of the ortho and meta xylenes is treated with $BaCO_3$ and $Na_2CO_3$ in the usual way to eliminate the excess $H_2SO_4$ and to form the Na salts. Evaporation causes the *o*-xylene sulfonate to separate first. After recrystallization, this is hydrolyzed to *o*-xylene by HCl at 190°.

***o*-xylene,** m. −27°, b. 144°, can be synthesized from *o*-Br-toluene, MeI and Na. Oxidation by dil. $HNO_3$ gives *o*-toluic acid. Chromic acid mixture oxidizes it completely to $CO_2$ and $H_2O$. Treatment of *o*-xylene with 15% ozone gives glyoxal and both

methylglyoxal and diacetyl (Levine 1932). This indicates the existence of both Kekulé forms.



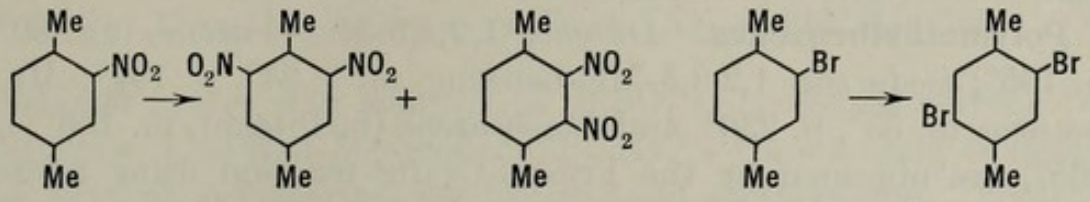




***m*-Xylene,** m. −54°, b. 138.8°, is the most readily available xylene. It can also be prepared from mesitylene by oxidizing one methyl to give mesitylenic acid and eliminating $CO_2$ from the latter. It is not oxidized by boiling 20% nitric acid but is converted to *m*-toluic acid by 30% nitric acid. Chromic acid mixture converts it to isophthalic acid. Chlorination, nitration and sulfonation of *m*-xylene take place readily in the 4-position which is *o*- and *p*- to the methyl groups. Thus in presence of Hg salts, 50% nitric acid converts *m*-xylene to a mixture of 4-$NO_2$-*m*-xylene and 4-$NO_2$-3-Me-benzoic acid, the latter predominating at higher reaction temperatures.

*m*-xylene with isobutyl or *t*-butyl halides or isobutylene in presence of $AlCl_3$ gives 5-*t*-Bu-*m*-xylene in good yield. This, on trinitration, gives an artificial musk. $AlCl_3$ alone converts *m*-xylene to a complex mixture of benzene, toluene, *p*-xylene, mesitylene, pseudocumene, and durene.

***p*-Xylene,** m. 13.2°, b. 138.5°, can be made by the action of Na on MeI and *p*-Br-toluene or *p*-$Br_2$-benzene. It is readily oxidized to *p*-toluic and terephthalic acids. The dinitration of *p*-xylene

gives mainly the 2,6- and 2,3-cpds., with very little of the 2,5-cpd. On the other hand dibromination gives mainly the 2,5-cpd.




*p*-xylene can be sulfonated by fuming sulfuric acid.

The three xylenes have been isolated from an Oklahoma petroleum (White 1932). They constitute about 0.3% of the crude oil.

**Ethylbenzene,** phenylethane, $C_6H_5CH_2CH_3$, m. −92.8°, b. 136.2°, can be made in a variety of ways: (1) from benzene with an ethyl halide or ethylene in presence of $AlCl_3$, (2) from bromobenzene, an ethyl halide and Na and (3) by reduction of styrene, $PhCH=CH_2$. Halogenation attacks mainly the $\alpha$−C. Oxidation gives benzoic acid. Many derivatives of ethylbenzene have been made (Cline 1927).

**Trimethylbenzenes,** $C_6H_3(CH_3)_3$, are contained in small amount in coal tar. *Hemimellitene*, 1,2,3-$Me_3$-benzene, b. 176°, *Pseudocumene*, 1,2,4-$Me_3$-benzene, m. −57.4°, b. 169.3°, is separated from mesitylene by means of its sparingly soluble sulfonic acid. Its structure is proved by its synthesis from MeI and bromo-*p*-xylene. *Mesitylene*, 1,3,5-$Me_3$-benzene, m. −53°, b. 164.8°, can be made from acetone or methylacetylene by the action of sulfuric acid.

**Propylbenzenes,** $C_6H_5C_3H_7$, are synthesized by the usual reactions. *n-Propylbenzene*, $C_6H_5CH_2CH_2CH_3$, m. −101.6°, b. 158°, is made by the Wurtz-Fittig reaction but not by the Friedel-Crafts reaction. *Isopropylbenzene*, $C_6H_5CH(CH_3)_2$, b. 154°, is made from benzene and either propyl chloride in presence of $AlCl_3$.

**Cymene,** *p*-methylisopropylbenzene, *p*-cymene,

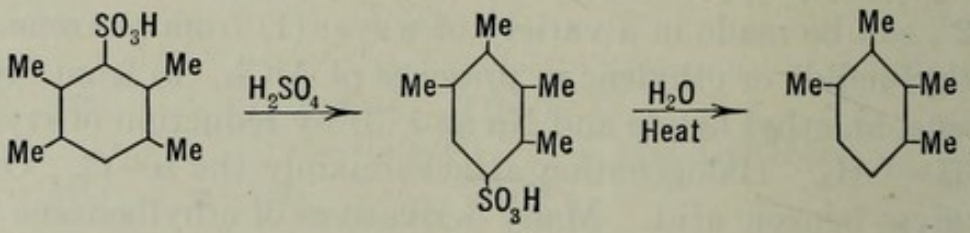
$$CH_3C_6H_4CH(CH_3)_2,$$

m. −73.5°, b. 177°, is found in many essential oils, notably in spruce turpentine from which it can be obtained cheaply. It is

also formed by heating camphor with $P_2O_5$. Oxidation gives *p*-toluic acid, *p*-methylacetophenone, *p*-isopropylbenzoic acid (*cumic acid*) or terephthalic acid (Senseman 1932).

**Polymethylbenzenes.** *Durene*, 1,2,4,5-$Me_4$-benzene, m. 80°, b. 195°; *isodurene*, 1,2,3,5-$Me_4$-benzene, m. −24°, b. 197°; *$Me_5$-benzene*, m. 53°, b. 230°, and *$Me_6$-benzene* (mellitene), m. 166°, b. 265°, are obtained by the Friedel-Crafts reaction using mixed xylenes and MeCl(OS) (Smith 1932).

**Prehnitene,** 1,2,3,4-$Me_4$-benzene, m. −4°, b. 204°, cannot be made by the Friedel-Crafts reaction but is obtained by the *Jacobsen reaction* of cold concentrated sulfuric acid with durene sulfonic acid.




Isodurene undergoes a similar change. Pentamethylbenzene similarly gives hexamethylbenzene and prehnitene sulfonic acid (Smith 1929–1933).

A good example of steric hindrance to addition reactions is the failure of trihaloacetyl derivatives of durene and isodurene to give the haloform reaction even on boiling with concentrated alkali (Fuson 1931).

All except two of the possible *ethylated* benzenes are known. Their boiling points are as follows: ethylbenzene, 136.1°; diethylbenzenes, *o*- 184.5°, *m*- 181.5°, *p*- 183°; triethylbenzenes, *unsym*- 218°, *sym*- 218°; tetraethylbenzenes, *vic*- 254°, *sym*- 250° (m. 13°); $Et_5$-benzene, 277°; $Et_6$-benzene, 298° (m. 129°).

## III. UNSATURATED BENZENE HYDROCARBONS

*Styrene*, "styrol," cinnamene, phenylethylene, vinylbenzene, $C_6H_5CH=CH_2$, b. 146°, is readily obtained by heating cinnamic acid (OS) or by the usual methods for introducing a double bond as by elimination of water or HBr from phenylmethylcarbinol, β-phenylethyl alcohol or their bromides. Another method is to

add HBr to cinnamic acid and then boil the water solution of the sodium salt of the β-bromohydrocinnamic acid.

$$PhCHBrCH_2CO_2Na \rightarrow NaBr + CO_2 + PhCH=CH_2$$

A glacial acetic acid solution of $H_2SO_4$ polymerizes styrene to distyrene, 1,3-$Ph_2$-3-Me-propene, b. 311°. On standing or heating, styrene polymerizes readily to solid metastyrene. Hydroquinone inhibits this polymerization (OS). Styrene adds HBr to give $C_6H_5CH_2CH_2Br$. Nitric acid gives ω-nitrostyrene, $PhCH=CHNO_2$. This reaction is like that of nitric acid with isobutylene.

The activating effect of the phenyl group on the double bond is shown not only by the ready polymerization of styrene but by the fact that the treatment of a solution of ethylene in styrene with bromine results in almost exclusive addition to the latter substance (Ingold). With formaldehyde, styrene gives the following products (Rep. 1920, 79):

$$PhCH(CH_2OH)_2,\ PhCH(CH_2O)_2CH_2.$$

For diphenylethylenes, etc., see p. 837.

**Allylbenzene,** $C_6H_5CH_2CH=CH_2$, b. 157°, is made from allyl bromide and a phenyl Grignard reagent in the usual way for 1-olefins. On heating with alcoholic KOH it gives *propenylbenzene,* $C_6H_5CH=CHCH_3$, b. 177° which has been synthesized in many ways including the conversion of ethylphenylcarbinol to its chloride and removal of HCl by alcoholic KOH. The shift of a double bond from the 2-position in relation to a phenyl group to the 1-position is readily achieved in much the same way that a double bond shifts to the αβ-position in relation to a carboxyl group.

**1-Phenylbutadiene,** $C_6H_5CH=CHCH=CH_2$, has been studied extensively (Muskat 1929–34). It adds exclusively in the 3,4- rather than the 1,4-positions. HOCl and HOBr give

$$PhCH=CHCHOHCH_2X.$$

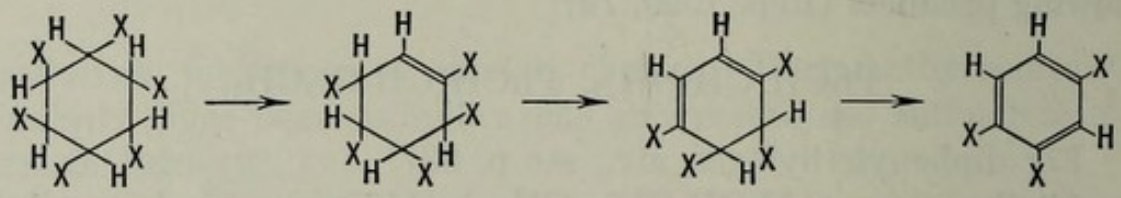
The presence of Br or $NH_2$ in the 4-position does not change the mode of addition.

**Phenylacetylene,** $C_6H_5C{\equiv}CH$, b. 142°, can be made in a variety of ways, probably best by dropping ω-bromostyrene into fused KOH (OS). It gives the usual acetylene reactions including the formation of metal derivatives and hydration with sulfuric acid to give acetophenone.

## IV. AROMATIC HALOGEN COMPOUNDS

### *A.* Addition Compounds

The long exposure of benzene in sunlight to chlorine or to bromine vapor gives the products $C_6H_6X_6$. Stereoisomeric forms of *benzene hexachloride,* one melting at 157° and the other subliming at 310° are known. *Benzene hexabromide,* m. 212° (Matthews 1901). The hexahalides lose 3 HX giving *unsym*-trihalogenbenzenes on treatment with bases. The steps involved may be the following:



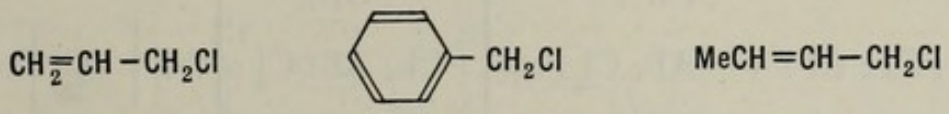
In the first step, no choice is possible because of the symmetry of the molecule. The second step takes place as indicated because of the greater reactivity of the allylic halogen of the system $XC{=}C{-}CX$ as compared with that of the system $C{=}CX{-}CX$. Whichever X is removed in the last step, the product is the unsymmetrical trihalide.

### *B.* Substitution Compounds

These are known in great numbers. They fall in two classes depending on whether the halogen is in the side chain or in the ring.

1. **Halogen in side chain.** These compounds are really aryl-substituted alkyl halides and follow the same regularities as do the parent halides (p. 71) except that a halogen alpha to an aromatic ring, as in benzyl halides, is even more reactive than in the corresponding alkyl halides. A consideration of the formula

of benzyl chloride (II) shows it to have an allyl chloride grouping (I).

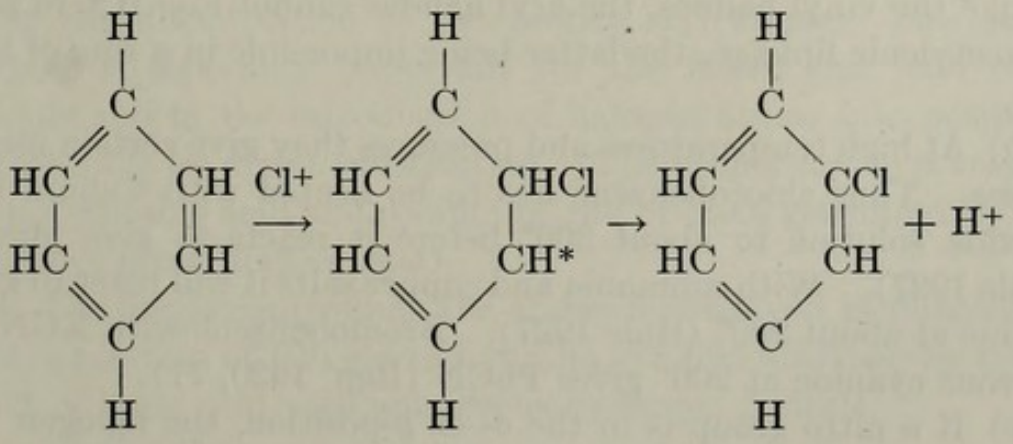



(I) (II) (III)

The analogy is strengthened by the fact that the Grignard reagent of (II) gives rearrangements much as does that of crotyl chloride (III) the entering group going in the *o*- and 3-positions respectively (Gilman).

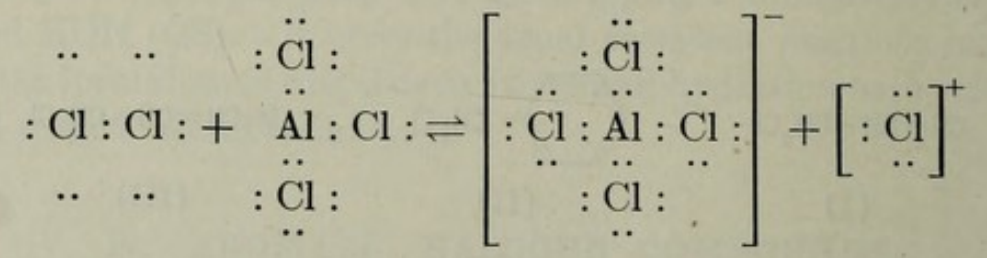
*o*- and *p*-Hydroxybenzyl halides are peculiar in not being soluble in alkali. Instead they are converted to methylene quinones (p. 807).

2. **Halogen in ring.** In presence of catalysts or halogen carriers such as iodine or various metal halides including those of iron and aluminum, chlorine and bromine replace H atoms of the benzene ring readily. This replacement probably resembles that which takes place in the action of chlorine on isobutylene to give an unsaturated chloride instead of the expected isobutylene dichloride (p. 41). In each case, after the first Cl has added, it is easier for a proton to be expelled than for the second Cl to add. In the case of benzene this is probably due to the strong tendency to revert to a completely conjugated system.




The function of the halogen carrier may be to favor the addition of a halogen with 6 electrons to the extra electron pair of one of

the benzene double bonds. Thus

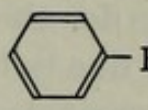


Iodine does not replace aromatic H because the reverse substitution by HI takes place more readily

$$C_6H_6 + I_2 \rightleftharpoons C_6H_5I + HI$$

This tendency can be overcome by using an oxidizing agent such as nitric acid which will destroy the HI (Datta 1916). The true aryl halides are peculiarly inactive with the following exceptions:

(*a*) They react with metals such as Mg, Na and Cu (Ullmann, Rep. 1904, 87) to form Grignard reagents and to give coupling reactions, Na being most useful in causing the reaction of an aryl halide with an alkyl halide and Cu to cause the union of two aryl residues. The inactivity of the true aryl halides resembles that of the vinyl halides.

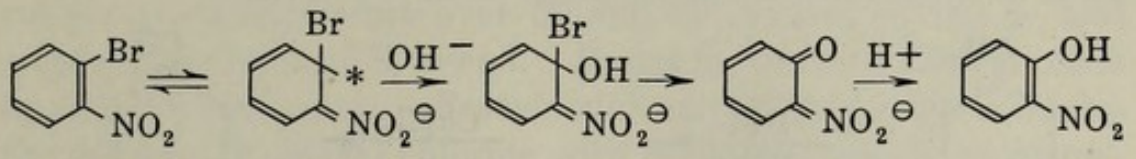
 $CH_2=CHBr$

Unlike the vinyl halides, the aryl halides cannot lose HX to give an acetylenic linkage, the latter being impossible in a ring of this size.

(*b*) At high temperatures and pressures they give certain metatheses. Thus chlorobenzene has to be heated with sodium hydroxide solution to about 300° before it reacts to give phenol (Hale 1927). With ammonia and copper salts it will react to give aniline at about 200° (Hale 1927). Bromobenzene with KCN or cuprous cyanide at 200° gives PhCN (Rep. 1920, 77).

(*c*) If a nitro group is in the *o*- or *p*-position, the halogen becomes readily reactive with basic reagents such as NaOH and $NH_4OH$ to give nitrophenols and nitroanilines. The point of attack is undoubtedly the nitro group and the reactions proceed

by addition rather than by true metathesis. The steps may be as follows:



In the action with ammonia, the groups $-NH_2$ and $=NH$ play the same part as $-OH$ and $=O$.

*Preparation.* The only compounds of wide importance are the halides of benzene and toluene which will be considered separately (pp. 720, 724).

*A.* Homologs and substitution products of benzyl halides, $ArCH_2X$. In some cases these can be made directly as in the case of the benzyl halides themselves but usually they are made from the corresponding arylcarbinols which are prepared by the usual reactions.

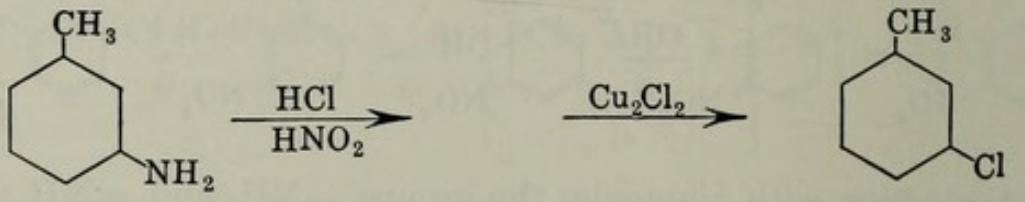
*B.* True aromatic halides can be made by direct halogenation but the position taken by the halogen is not subject to control. The action of reagents like $PCl_5$ does not usually replace phenolic OH by Cl but gives stable and unreactive phosphates. An exception is the case of the nitrophenols in which the OH is readily replaced by Cl.

The best method for the controlled introduction of a halogen is by the diazotization of the proper aryl amine. This preparation is especially important for the fluoro and iodo compounds and in the introduction of halogen atoms into positions not possible by direct substitution. The proper amine is treated with a suitable acid and sodium nitrite or $N_2O_3$ generated by the action of nitric acid on $As_2O_3$.

1. For fluoro compounds the amine is dissolved in fluoroboric acid, a solution of $BF_3$ gas in hydrofluoric acid obtained by treatment of boric acid with anhydrous hydrogen fluoride.

$$ArNH_2 + HBF_4 + HNO_2 \rightarrow 2\,H_2O + ArN_2BF_4 \xrightarrow{\text{heat}} ArF + N_2 + BF_3$$

2. Chloro and bromo compounds are made by treating the diazonium halide with the proper cuprous halide and warming. Thus *m*-chlorotoluene can be made from *m*-toluidine.

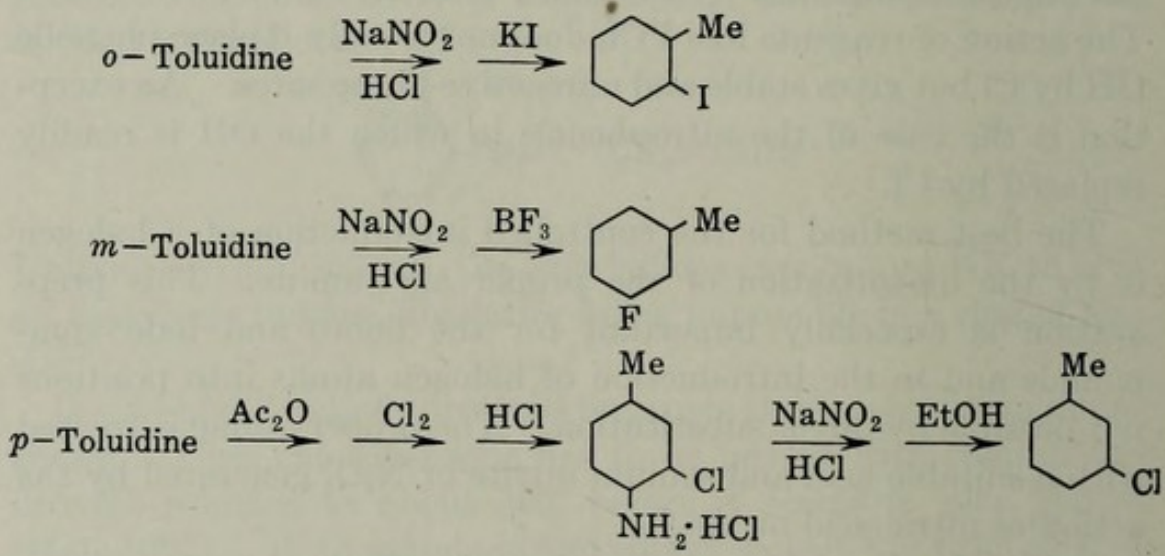



An indirect method of achieving the same result is to chlorinate *p*-acetoluidide, remove the acetyl group, diazotize and remove the diazonium group by reduction with alcohol.

3. Iodo compounds are obtained by simply warming the aryl diazonium chloride with an inorganic iodide.

All of these preparations give tarry by-products and usually some phenols. The halides can be obtained by steam distillation from alkaline solution, the tars and alkali phenolates being non-volatile with steam.

A few examples of the use of diazotization to prepare aryl halides follow:




*Individual Halides of Benzene and its Homologs*

Because of the aliphatic nature of their reactions, attention will be turned first to those with halogen in the aliphatic side chain.

**Benzyl chloride,** $C_6H_5CH_2Cl$, b. 175°, is made by chlorinating boiling toluene in the light. The Cl is very reactive.

Thus KCN readily gives phenylacetonitrile, $PhCH_2CN$. The reactivity of substituted benzyl halides has been extensively studied (Rep. 1929, 137–40). Nitration of benzyl chloride readily gives somewhat over 50 and 30 percent of the *p*- and *o*-cpds. and about 15% *m*-cpd. *Benzyl bromide*, b. 198°, is made by direct bromination. *Benzyl iodide*, m. 24°, is readily made by the reaction of benzyl chloride with KI in acetone or methanol. All the benzyl halides, especially the iodide, are lachrymators.

Benzyl chloride is used to make benzaldehyde and to introduce the benzyl group on the nitrogen atom in certain dyes.

The preparation of benzylmagnesium chloride takes place readily to about 95% at the same time a small amount of di-*p*-tolyl, m. 120°, is formed. This indicates the formation of free radicals (Gilman 1929). Benzyl-magnesium halides give some normal reactions to form benzyl derivatives while in other cases they also give *o*-tolyl derivatives (Gilman 1927, Johnson 1932).

Certain compounds in which the benzyl group is "negative" are obtained as follows:

$$PhCH_2MgCl \xrightarrow{HgCl_2} (PhCH_2)_2Hg \xrightarrow{Na} PhCH_2Na \xrightarrow{Me_4NCl} PhCH_2NMe_4$$

The last two compounds are ionized in non-aqueous solvents. Water hydrolyzes them to give toluene (Rep. 1917, 117).

Further chlorination of benzyl chloride gives benzylidene or *benzal chloride*, $C_6H_5CHCl_2$, b. 203°, and *benzotrichloride*, $C_6H_5CCl_3$, b. 213°. As usual with polyhalides, they are less reactive than the monohalide. They can be converted to benzaldehyde and benzoic acid by vigorous hydrolysis.

Benzotrichloride, with suitable reagents such as AgF or HF gives *benzotrifluoride*. The oxidation of this substance destroys the benzene ring with formation of $F_3CCO_2H$ thus illustrating the great stability of the C—F linkage. Nitration of benzotrichloride gives mainly the *meta* nitro cpd. (65%).

### *Orientation in Benzene Compounds*

The different *orientating effects of different groups* in the benzene ring were early observed. At first it was thought that a com-

pound like toluene gave only *ortho* and *para* products when a second group was introduced and that a compound like nitrobenzene gave only *meta* products. The fact is that all possible products are formed in all cases but groups can be divided into two classes, (1) those which direct an entering group mainly to the *ortho* or *para* position and (2) those which direct mainly to the *meta* position. Another way to regard the difference in these two classes of groups is that the first *facilitate* substitution in the *ortho* and *para* positions while the second *hinders* substitution in these positions thus allowing the *meta* position to react (Reid). This viewpoint agrees with the fact that the *o,p*-directing groups speed up substitution while the *m*-directing groups make it slower. Much work has been done and a tremendous amount has been written on orientation in benzene compounds.

The original rule on orientation was that of Crum Brown and Gibson (1892). They stated that the group X will be meta-orientating if the compound HX can be oxidized readily to HOX. Since the following take place readily:

$$H(NO_2) \rightarrow HONO_2 \qquad H(SO_3H) \rightarrow HOSO_3H$$
$$H(CHO) \rightarrow HOCHO \qquad H(CO_2H) \rightarrow HOCO_2H$$

the groups $NO_2$, $SO_3H$, CHO and $CO_2H$ should be meta-directing. This agrees with facts such as the formation of 90% *m*-, 8% *o*- and 1% *p*-dinitrobenzene from the nitration of nitrobenzene at 30°. Since the following changes *do not* take place readily:

$$H(Cl) \not\rightarrow HOCl \qquad H(OH) \not\rightarrow HO{-}OH$$
$$H(NH_2) \not\rightarrow HONH_2 \qquad H(CH_3) \not\rightarrow HOCH_3$$

The groups Cl, OH, $NH_2$ and $CH_3$ should be ortho-para-directing. This agrees with facts such as the formation of over 90% *o*- and *p*-nitrotoluenes in the nitration of toluene.

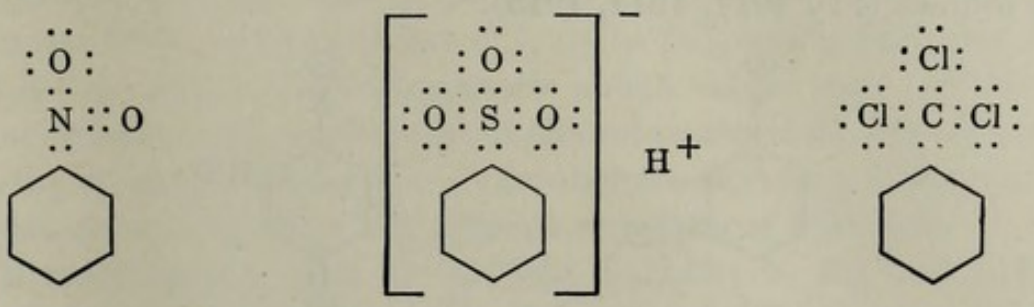
There are glaring exceptions to any rule on orientation. For instance the mercuration of nitrobenzene gives over 50% *o*- and about 40% and 10% *m*- and *p*-products (Coffey 1925).

The meta-directing power of groups has come to be associated with their multiple linkages. Almost the only exception to this relation is the meta-directing effect of the $-CCl_3$ group. This

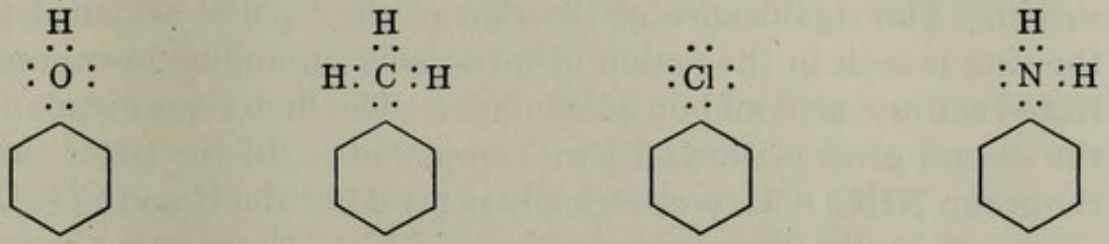
follows the Crum Brown-Gibson Rule, however, inasmuch as

$$H(CCl_3) \rightarrow HOCCl_3 \rightarrow COCl_2$$

takes place readily. Another similarity between benzotrichloride and other meta orienting compounds is in the *cloud of exposed electrons.*



By contrast the *o,p*-orienting groups are poor in electrons



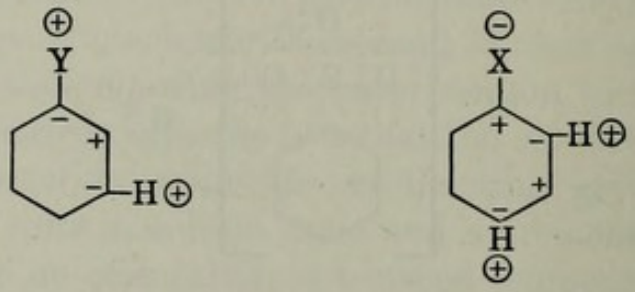
The meta directing power of the $CCl_3$ group is approached by the $CHCl_2$ group. Thus benzal chloride, on nitration gives *o*-, *m*-, and *p*-cpds. in 23, 39 and 43% yields. The nitration of benzyl chloride gives only about 4% *m*-cpd. which is the same amount as with toluene.

The relative proportions of *ortho* and *para* products are influenced by conditions and by the nature of the entering group. Thus bromobenzene on chlorination gives nearly as much *ortho* as *para* cpd. but on sulfonation gives essentially the pure *para* product. A fairly complete list of the orientating effects of groups has been worked out (Vorländer 1919).

1. *Meta*-directing: $SO_3H$, $NO_2$, CHO, $CO_2H$, $CO_2R$, $CONH_2$, COR, $COCO_2H$, CN, $CCl_3$, $NH_3X$, $NR_3X$.

2. *Ortho-para*-directing: OH, OR, OAc, $NH_2$, NHR, $NR_2$, NHAc, N=N, $CH_3$, $CH_2Cl$, $CH_2ONO_2$, $CH_2SO_3H$, $CH_2NH_2$, $CH_2CN$, $CH_2CO_2H$, $CH_2CH_2CO_2H$, $CH=CHCO_2H$, $CH=CHNO_2$, $C\equiv CCO_2H$, $C_6H_5$, Na, K (Gilman 1936).

The polar nature of the atom attached to the benzene ring is probably the deciding factor in orientation (Ingold). A positive "pole" directs to the meta position. This effect also slows down the velocity of substitution as compared with that in compounds containing *o*-*p*-directing groups. The effect of "positive" and "negative" groups on benzene substitution has been expressed as follows (Fry 1911, 1914, 1915).




The H atoms marked + are the ones removed on further substitution. The significance of the sign of the "pole" attached to the ring is seen in the action of nitric acid on aniline in concentrated sulfuric acid and on acetanilide. The first gives meta and the second gives ortho and para compounds. In the latter case the group $NHCOCH_3$ is electrically neutral but the H and $COCH_3$ are "positive." Therefore the N attached to the ring is a negative pole. Consequently *o*- and *p*-substitution follows. On the other hand the aniline sulfate solution contains the strongly positive group $-NH_3^{\oplus}$ and consequently gives *m*-substitution. The "metalation" of benzene apparently offers an exception to this generalization. Thus phenylpotassium reacts with EtK to give mainly the *p*-$K_2$-compound (Gilman 1936).

$$C_6H_5K + EtK \rightarrow p\text{-}C_6H_4K_2$$

The relation of electrical properties of groups in relation to their orientating power has been extensively studied (Rep. 1926, 129–144; 1927, 148–158; 1928, 137–150; 1930, 130–142).

### *D.* Individual Aromatic Halides

**Fluorobenzene,** $C_6H_5F$, b. 85°, is made from aniline by diazotization. It is completely inert. The nearness of its boiling point to that of the corresponding hydrogen compound, benzene (80°) is characteristic of fluorine compounds.

**Chlorobenzene,** phenyl chloride, $C_6H_5Cl$, b. 132°, is obtained by the chlorination of benzene using various catalysts such as $FeCl_3$, $I_2$ etc. (EP 755). Since it is an important intermediate for phenol, aniline and the nitrated chlorobenzenes, it is made in large amounts. The yield of chlorobenzene and its by-products varies with the conditions (Bourion 1920). If 65% of the benzene is chlorinated, the yield of products is about as follows: chlorobenzene 58%, *p*-$Cl_2$-benzenes 6%, *o*-$Cl_2$- 2%, *m*-$Cl_2$- less than 1%, 1,2,3-$Cl_3$- and 1,2,4-$Cl_3$-benzenes about 0.5% each (Britton). The nitration and sulfonation of chlorobenzene take place mainly in the *o*- and *p*-positions. Chlorobenzene gives a Grignard reagent on heating with Mg without any solvent (Gilman).

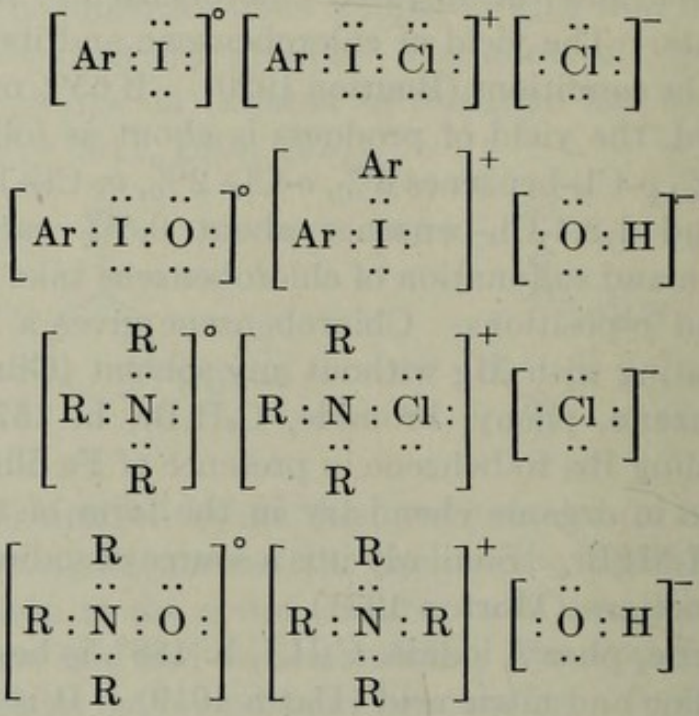
**Bromobenzene,** phenyl bromide, $C_6H_5Br$, b. 157°, is readily made by adding $Br_2$ to benzene in presence of Fe filings. It is of special value in organic chemistry in the form of the Grignard reagent, $C_6H_5MgBr$. Similarly it is a source of sodium phenyl for synthetic reactions (Morton 1931).

**Iodobenzene,** phenyl iodide, $C_6H_5I$, b. 188°, is best made from benzene, iodine and nitric acid (Datta 1919). It is chiefly interesting because of the polyvalency of its iodine atom. With dry $Cl_2$ in anhydrous inert solvents, it gives a yellow crystalline compound, $C_6H_5ICl_2$, *phenyl iodide chloride.* Bases change this to *iodosobenzene,* $C_6H_5IO$, a yellow substance which explodes at 210° and can form salts with acids. HCl gives the dichloride while HOAc gives a diacetate. On standing or warming, it undergoes disproportionation to give phenyl iodide and *iodoxybenzene,* $C_6H_5IO_2$. This is a crystalline, neutral compound which explodes at 230°. Iodosobenzene can be made directly from iodobenzene by oxidation with ozone or peracetic acid. Iodoxybenzene can be made from iodosobenzene and Caro's acid, $H_2SO_5$, or from iodobenzene and perbenzoic acid. Treatment of iodosobenzene with phenylmagnesium bromide gives *diphenyliodonium hydroxide,* a strong base.

$$ArIO + ArMgX \rightarrow Ar_2I-OMgX \rightarrow Ar_2I-OH$$

This can also be obtained by treating a mixture of iodoso- and iodoxy-benzene with AgOH. Diphenyliodonium iodide, $Ph_2I.I$, m. 176°, is a salt like $Me_4NI$. Heat decomposes it to 2 PhI.

The nature of these polyvalent compounds of iodine is better expressed electronically than by ordinary bonds. Analogous nitrogen compounds are given for comparison



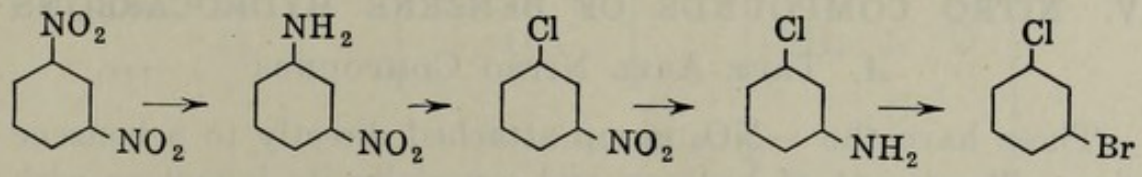
*Halides of Benzene Homologs*

These resemble phenyl or benzyl halides depending on the position of the halogen in the ring or the side chain. Certain exceptional reactions occur. Thus the fusion of ortho and para chlorotoluenes with NaOH and Cu powder at 315° gives about 25 and 35 per cent *meta* cresol respectively (Meharg 1932). Similar results were obtained with *o*-Cl-ethylbenzene. Yields as high as 70% *m*-cresol have been obtained from *o*-Cl-toluene. The normal hydrolysis products are obtained if a copper reactor is used instead of one of iron (Britton).

*Aromatic Polyhalides*

These are obtained by direct halogenation or by diazotization of suitable amines. Further substitution in a phenyl halide takes place almost exclusively in the *ortho* and *para* positions. The *meta*-disubstituted product is formed in very small amounts. Thus chlorination or nitration of chlorobenzene gives mainly *o*-

and *p*-dichlorobenzene and *o*- and *p*-nitrochlorobenzene. Further action gives mainly the unsymmetrical or 1,2,4-trichloro- and chlorodinitrobenzenes. In chlorination, all three possible tetrachlorobenzenes are formed while in nitration the final product is 1,2,4,6-chlorotrinitrobenzene because of the *meta*-orienting effect of the nitro groups. *m*-Dihalogenated benzenes are best obtained by alternate reduction and diazotization of *m*-dinitrobenzene. For instance




*p-Dichlorobenzene* (Para, Paradow), m. 56°, b. 173°, is obtained as a by-product in the chlorination of benzene. It is extensively used as a moth and caterpillar repellant. It is also an intermediate for making *p*-chlorophenol and hydroquinone. *o-Dichlorobenzene*, m. −17.6°, b. 179°, is a cheap by-product of the para compound because it has to be removed in order to raise the m.p. and prevent the latter from caking. It is used as a high-boiling solvent, for an insecticide and in making *o*-chlorophenol and pyrocatechol. A curious preparation of *o*-$Cl_2$-benzene is by heating *o*-Br-nitrobenzene with $NH_4Cl$ at 320° (Rep. 1904, 94).

The *trichlorobenzenes* are the *sym-*, m. 63°, b. 208°, the *vic-* m. 53°, b. 219°, and the *unsym-* m. 17°, b. 213°. These properties illustrate the effect of symmetry in raising the solidification point and the vapor pressure. The 1,2,4-cpd. is obtained exclusively by the action of bases with benzene hexachloride. It is also the chief product of the trichlorination of benzene. *Hexachlorobenzene*, m. 227°, b. 326°, is readily obtained by exhaustive chlorination.

***p*-Dibromobenzene,** m. 87°, b. 219°, is a by-product of the bromination of benzene. It readily gives a Grignard reagent and less readily gives a di-Grignard reagent.

Hexaiodobenzene, $C_6I_6$, m. 350°, is obtained from benzene heated at 180° with $I_2$ and 60% oleum (Durand 1935).

**Arylsubstituted unsaturated halides** are known in great numbers. *β- or ω-Bromostyrene*, $C_6H_5CH=CHBr$, is readily obtained by boiling cinnamic acid dibromide with sodium carbonate.

$$PhCHBrCHBrCO_2Na \rightarrow NaBr + CO_2 + PhCH=CHBr$$

With fused KOH it gives phenyl acetylene. With alcoholic KOH the chief product is $PhCH=CHOEt$.

## V. NITRO COMPOUNDS OF BENZENE HYDROCARBONS

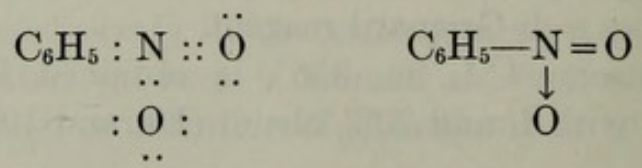
### *A.* True Aryl Nitro Compounds

These have the $-NO_2$ group attached directly to a benzene ring. Treatment of benzene and especially its homologs with concentrated nitric acid readily gives mononitro derivatives

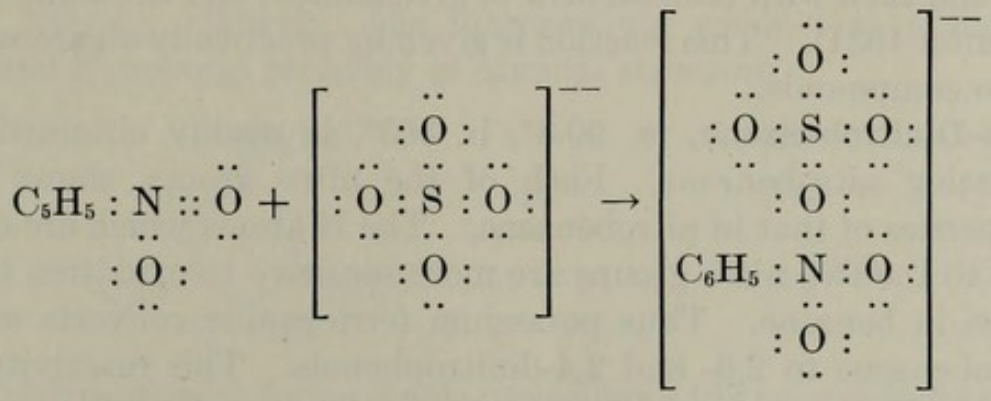
$$C_6H_6 + HONO_2 \rightarrow H_2O + C_6H_5NO_2$$

The use of mixtures of nitric acid with sulfuric acid, of fuming nitric acid (d. > 1.4) and of mixtures with fuming sulfuric acid increases the intensity of the nitration process. Thus, whereas, concentrated nitric acid will give only the mononitro compound, a mixture with concentrated sulfuric acid will form *m*-dinitrobenzene (with traces of the *o*- and *p*-isomers). Mixtures of the two fuming acids give finally 1,3,5-trinitrobenzene which is resistant to further nitration.

**Nitrobenzene,** Oil of Mirbane, Essence of Mirbane, $C_6H_5NO_2$, m. 5°, b. 208°, is a very pale yellow liquid of the odor of bitter almonds. It is made by the nitration of benzene with nitrating acid, mixed acid, a mixture of concentrated nitric and sulfuric acid. On a large scale, very careful cooling is necessary because of the exothermic reaction. On the laboratory scale the relation of surface to volume of the small flasks used readily gives the necessary cooling. The value of the parachor for nitro benzene indicates that the nitro group contains only one true double linkage and a coordinate linkage.



Nitrobenzene forms a crystalline "sulfate," $PhNO_2.H_2SO_4$, m. 11°, which can be crystallized from ether (Rep. 1923, 94). The formation of such a product may be pictured electronically

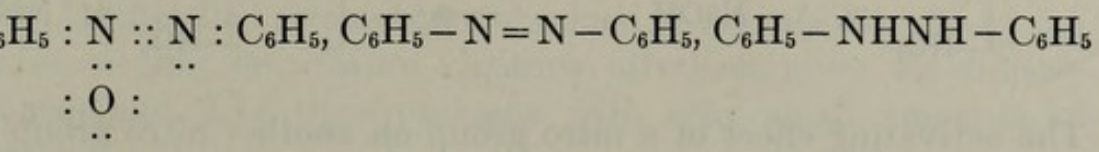


It would thus be analogous to the nitric acid compound of a sulfoxide. The C—N linkage in nitrobenzene is very stable. No reaction is known by which it can be split without complete decomposition of the molecule.

Reduction of nitrobenzene gives a variety of products. With acids and active metals, the oxygen atoms are removed and replaced by 2 H to give aniline

$$C_6H_5NO_2 + 6\,[H] \rightarrow 2\,H_2O + C_6H_5{-}NH_2$$

Under other conditions only one O is removed and replaced by 2 H to give phenylhydroxylamine, $C_6H_5NHOH$, which readily undergoes rearrangement to *p*-aminophenol, $HOC_6H_4NH_2$. Various alkaline reductions give bimolecular reduction products.



| Azoxybenzene | Azobenzene | Hydrazobenzene |
|---|---|---|
| m. 36° | m. 67°, b. 297° | m. 131° |

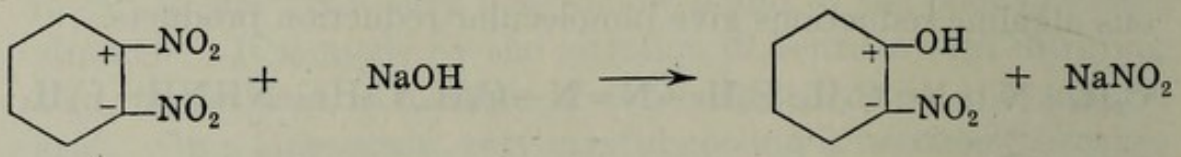
The older formulas for azoxybenzene, containing the O attached to both N atoms or the O attached by a double bond to one N, are less accurate than the unsymmetrical formula with coordinately linked oxygen. According to this formulation, azoxybenzene is related to the amine oxides.

All three bimolecular reduction products of nitrobenzene give aniline on vigorous acid reduction.

Nitrobenzene gives the *Piria Reaction* when heated with a sulfite and then with mineral acid to give aniline, and sulfanilic acid (Hunter 1931). This reaction is given by practically all aromatic nitro compounds.

***m*-Dinitrobenzene,** m. 90.8°, b. 303°, is readily obtained by nitrating nitrobenzene. Each of the nitro groups shows the properties of that in nitrobenzene, The H atoms which are *o*- or *o,p*- to the two nitro groups are more sensitive to oxidation than those in benzene. Thus potassium ferricyanide converts *m*-dinitrobenzene to 2,6- and 2,4-dinitrophenols. This reactivity of the *o,p*-H atoms does not extend to ordinary substitution reactions which take place with difficulty and then mainly in the *m*-position.

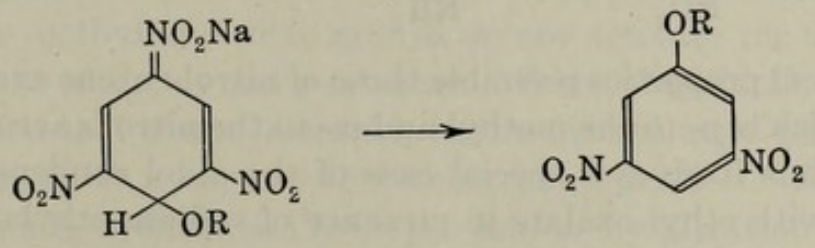
***o*-Dinitrobenzene,** m. 118°, b. 319°, and *p-dinitrobenzene,* m. 172°, b. 299°, are formed in only minute amounts by direct nitration. They are prepared from the corresponding nitroanilines by replacing the $NH_2$ by $NO_2$ on diazotization and treatment with excess nitrous acid and $Cu_2O$. A nitro group in the *o*- or *p*-position to another nitro group does not exhibit the stable C—N linkage found in nitro- and *m*-dinitro benzenes. Treatment with alkali or ammonia replaces one of the $NO_2$ groups by OH or $NH_2$ respectively. This behaviour has been regarded as indicating an alternating polarity in the benzene carbon atoms (Fry 1915).




The activating effect of a nitro group on another nitro group in the *o*- and *p*-position but not on one in the *m*-position is similar to the effect on H and halogen atoms in these positions.

**1,3,5-Trinitrobenzene,** *sym*-trinitrobenzene, m. 122°, can be made directly by vigorous nitration of the *m*-dinitro compound with a mixture of fuming nitric and sulfuric acids but is more conveniently prepared from trinitrotoluene (OS). It resembles the dinitro compound, including the ease of oxidation of the H atoms each of which is *o,o,p*- to nitro groups. Substitution

reactions are unknown, however. While one nitro group does not activate another one in the *m*-position, two such groups have an activating effect on a third, as is shown by the action of *sym*-trinitrobenzene with sodium alcoholates to give replacement of one $NO_2$ by alkoxyl. The intermediate product is a highly colored compound probably of quinoid structure.



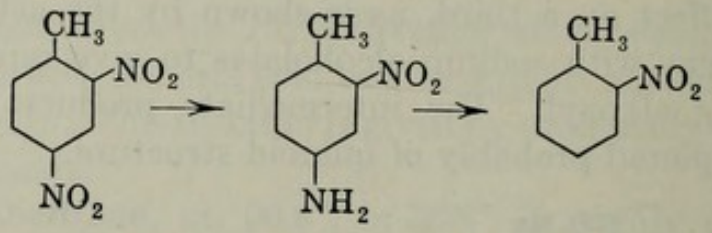

Trinitrobenzene forms stable molecular addition products with various aromatic and unsaturated hydrocarbons. These compounds often have melting points higher than either component. Thus the compounds with naphthalene (m. 80°) and with acenaphthene (m. 97°) melt at 152° and 168° respectively. The cpd. with 2 $C_6H_6$ melts at 71°.

1,2,4-Trinitrobenzene, *asym*-trinitrobenzene, m. 57°, is made from dinitroaniline. The 1-$NO_2$ is readily replaced by OH or $NH_2$ because of the activating influence of the *o*- and *p*-$NO_2$ groups.

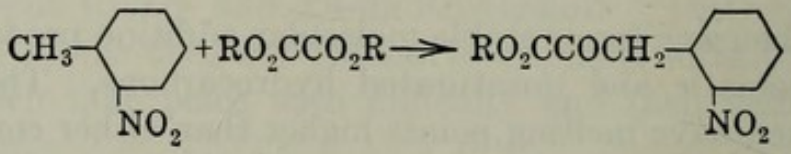
**Nitrotoluenes** are obtained by nitrating toluene. As is usual, the *o*- and *p*-H atoms in toluene are more easily replaced than the H atoms in benzene. Nitration of toluene under mild conditions gives mainly *o*- and *p*-$NO_2$-toluenes with less than 5% *m*-. The relative proportions of *o*- and *p*- depend somewhat on conditions although the *o*-compound usually predominates. On a large scale, the finished products are obtained in the ratio 61 : 35.5 : 3.5 for *o*-, *p*- and *m*-. More vigorous nitration gives 2,4-dinitrotoluene and 2,4,6-trinitrotoluene with only small amounts of isomers.

***o*-Nitrotoluene,** $CH_3C_6H_4NO_2$, m. −10°, b. 218°, is separated from its isomers by means of alternate freezing and distillation, thus taking advantage of its lower freezing and boiling points. It can be freed from traces of the *p*-compound by long boiling with alcoholic NaOH which reduces the latter. On acidification and steam distillation, the pure *o*-compound distills. The pure *o*-compound can also be made from 2,4-dinitrotoluene by partial

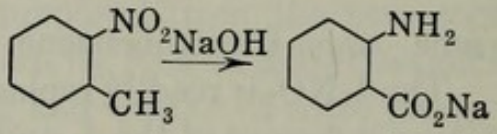
reduction to convert the *p*-$NO_2$ group to amino which can be replaced by H by diazotization in presence of alcohol.



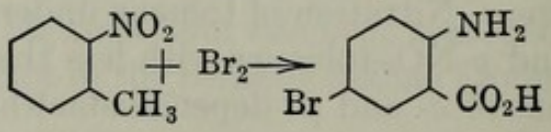
Its chemical properties resemble those of nitrobenzene except that the H which is *p*- to the methyl and *m*- to the nitro is activated by both. Thus it gives a special case of the aldol condensation in reacting with ethyl oxalate in presence of sodium ethylate.



On treatment with alkali, *o*-nitrotoluene undergoes internal oxidation and reduction to give *o*-aminobenzoic acid.

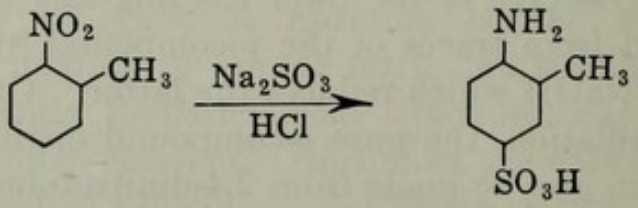


A similar process takes place when bromine is dropped into *o*-nitrotoluene heated to 170°.

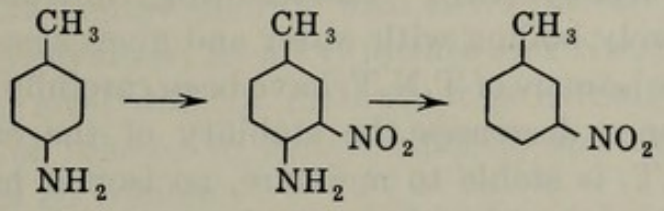


In spite of these internal oxidations of the methyl group it is not as easily converted to carboxyl by ordinary oxidizing agents as in the *m*- and *p*-isomers. Thus dilute nitric acid and chromic acid mixture do not give *o*-nitrobenzoic acid but permanganate does.

*o*-Nitrotoluene gives a 34% yield of 2-toluidine-5-sulfonic acid by the Piria reaction.

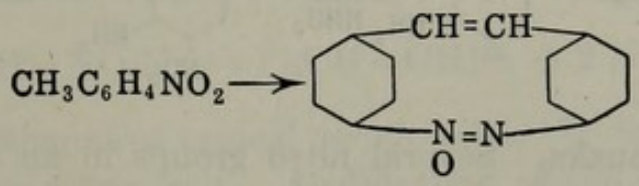


***m*-Nitrotoluene,** m. 16°, b. 230°, is formed in very small amounts in the commercial nitration of toluene (4%). In order to improve the quality of the *o*- and *p*-compounds it is separated and is available in about 90% purity. It is possible to remove the impurities of *o*- and *p*-compounds by means of their reaction with ethyl oxalate and NaOEt. The *m*-compound does not react, since the methyl and nitro groups do not activate the same H as in the case of the *o*- and *p*-isomers. When the reaction mixture is acidified and steam distilled, the *m*-nitrotoluene passes over, the substituted pyruvic esters being non-volatile. The *m*-compound can be synthesized from *p*-toluidine by nitration and elimination of the $NH_2$ group. The nitro group enters almost entirely *o*- to the $NH_2$ group because of its greater orienting influence.




***p*-Nitrotoluene,** m. 51°, b. 234°, is readily separated from the nitration mixture obtained from toluene. Its reactions are like those of the *o*-isomer. The H atoms *o*- to the methyl are *m*- to the nitro group and are consequently more active than the H atoms in nitrobenzene or in *m*-nitrotoluene. Boiling with dilute nitric acid oxidizes the methyl group to form *p*-nitrobenzoic acid. A similar reaction takes place with the *m*-compound but not with the *o*-compound.

Hot aqueous KOH produces an oxidation-reduction process with *p*-nitrotoluene which involves two molecules with the formation of a 12-member ring (Rep. 1917, 117)




**2,4-Dinitrotoluene,** m. 70°, is readily obtained by nitrating toluene or the *o*- or *p*-mononitro derivatives. It gives the ex-

pected reactions and, in addition, reacts readily with aldehydes, the methyl H atoms behaving as $\alpha-H$ (Rep. 1904, 98).

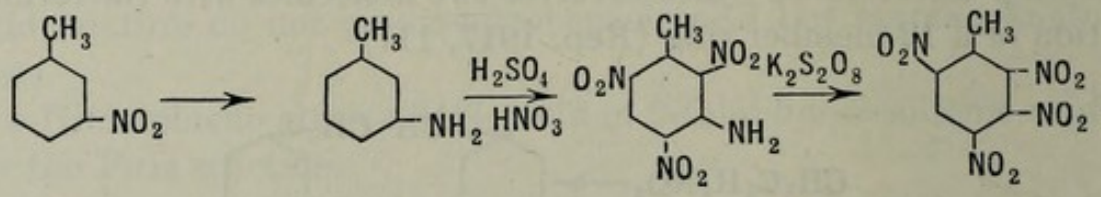
$$CH_3C_6H_3(NO_2)_2 + RCHO \rightarrow H_2O + RCH=CHC_6H_3(NO_2)_2$$

The reactivity of the methyl group is like that found in crotonic aldehyde (p. 270).

**2,4,6-Trinitrotoluene,** T.N.T., Trotyl, Tolite, m. 81.5°, obtained by exhaustive nitration of toluene is an important high explosive. It is relatively safe because of its difficulty of detonation. In fact it will burn without exploding. Attempts to further nitrate trinitrotoluene give oxidation of the methyl to carboxyl and splitting to give tetranitromethane (Rep. 1914, 99). Oxidation of T.N.T. with chromic acid mixture converts the methyl to carboxyl (OS). The resulting trinitrobenzoic acid loses $CO_2$ on merely boiling with water and gives *sym*-trinitrobenzene (OS). The isomers of T.N.T. have been carefully studied because their presence decreases the stability of the explosive. Thus while T.N.T. is stable to moisture, an isomer having two nitro groups ortho to each other would react with moisture to give nitrous acid and a nitrated cresol. The absence of such isomers is assured by careful insistence on the correct melting point for T.N.T.

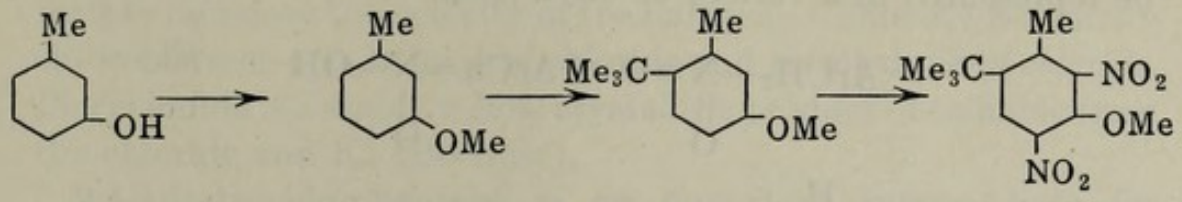
All six possible trinitrotoluenes have been made (Rep. 1915, 88).

**2,3,4,6-Tetranitrotoluene** has been made as an explosive but has the disadvantage of lower stability both to shock and to the action of water. The fourth nitro group cannot be introduced by nitration but is obtained by oxidizing an amino group with a persulfate. The steps for its preparation follow.




**Artificial musks.** Several nitro groups in an aromatic compound containing a tertiary butyl group give an odor resembling natural musk. Toluene or xylene treated with an isobutyl or tertiary butyl halide and aluminum chloride give considerable

amounts of *m-tert*-butyl compounds. Three nitro groups can be introduced into these to give *toluene musk* and *xylene musk*. Musk Ambrette is made from *m*-cresol.




### *B.* Aryl Substituted Aliphatic Nitro Compounds

**Phenynitromethane,** ω-nitrotoluene, $C_6H_5CH_2NO_2$, b. 226°, $C_6H_5CH=NO_2H$, m. 84°, can be made from toluene in several ways.

1. Heating with dilute nitric acid in a sealed tube.
2. Treatment of benzyl chloride with silver nitrite.
3. From benzyl cyanide, an alkyl nitrate and NaOEt. While this appears the most difficult method, it is actually the best. The conversion of toluene to benzyl chloride and the latter to the cyanide gives no trouble

$$C_6H_5CH_2CN + EtONO_2 + EtONa \rightarrow C_6H_5C(CN)=NO_2Na$$

Hydrolysis of the nitrile group and elimination of the resulting carboxyl proceed smoothly.

$$C_6H_5C(CN)=NO_2Na \xrightarrow{NaOH} C_6H_5C(CO_2Na)=NO_2Na \xrightarrow{acid} CO_2 + C_6H_5CH_2NO_2$$

The structure is proved by reduction to benzyl amine,

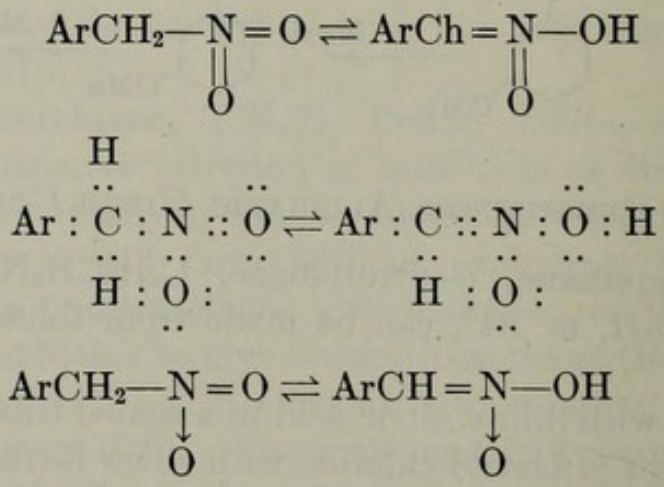
$$C_6H_5CH_2NH_2.$$

The Na cpd. on heating gives stilbene (Rep. 1905, 103).

$$2\ PhCH=NO_2Na \rightarrow PhCH=CHPh + 2\ NaNO_2$$

Phenylnitromethane is a typical pseudo acid. It dissolves slowly in alkali to give a true salt. Acidification of the salt gives the solid *acinitro* form which is rapidly soluble in bases and gives a conducting solution in water, whereas the liquid form does not.

On standing, the solid acinitro form changes to the liquid true nitro compound. The former gives a color with ferric chloride while the latter does not. The structures of the two forms may be represented in a variety of ways (Rep. 1927, 107–8).



Aromatic nitro compounds with unsaturated side chains may be illustrated by the nitrostyrenes.

**ω-Nitrostyrene,** $C_6H_5CH=CHNO_2$, is obtained by the direct action of styrene with nitric acid by a process resembling the action of chlorine with isobutylene (p. 42). *o-Nitrostyrene*, $O_2NC_6H_4CH=CH_2$, and its isomers are obtained from the corresponding nitrocinnamic acids by adding HBr and hydrolyzing with elimination of carboxyl. *o-Nitrophenylacetylene*, $O_2NC_6H_4C\equiv CH$, and its isomers are similarly obtained by adding $Br_2$ to the cinnamic acid, removing 2 HBr and decarboxylating.

### *C.* Nitro Compounds of the Aromatic Halides

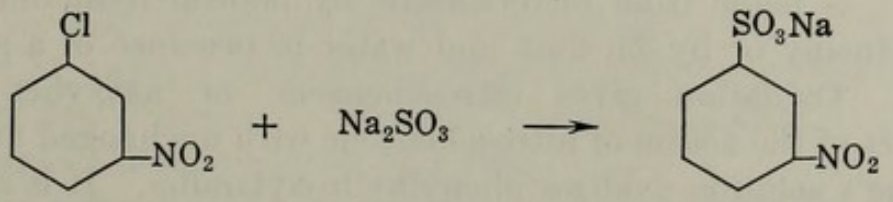
*o*- and *p*-Nitro-halogen-benzenes, in a ratio of about 3 : 7, are obtained by nitrating the phenyl halides. The isomers are readily separated because of the higher melting points and lower solubilities of the *p*-isomers. The *o*-isomer is obtained in a eutectic mixture with the *p*-compound. The mixture can be separated by alternate distillation and freezing or recrystallization. Further nitration gives 2,4- and 2,4,6-polynitro compounds. The halogen atoms which are ortho or para to a nitro group readily give metathetical reactions with reagents like bases, ammonia and alkali sulfides to give nitrophenols, nitroanilines and nitrophenyl sulfides

and disulfides (Rep. 1921, 132–7). This reactivity is in sharp contrast to the usual inactivity of aromatic halides (p. 718). The presence of two or three nitro groups in *o*- and *p*-positions further increases the activity of the halogen. Thus 2,4,6-trinitrochlorobenzene acts as an acid chloride and is called *picryl chloride*. Picryl iodide is a stable yellow crystalline product obtainable from the chloride and KI (Boehner).

2,4-Dinitrochlorobenzene is an important intermediate for various *sulfur dyes*. It is also used in making picric acid, first being hydrolyzed to dinitrophenol which can be easily converted to the trinitro compound.

A single nitro group will not render an aromatic halogen atom active enough to react with sodium malonic ester. If the positions *o*- and *p*- to the halogen contain *also* a MeCO or CN grouping, then reaction is possible.

*m*-Nitro-halogen-benzenes may be obtained by the vigorous chlorination or bromination of nitrobenzene. A more convenient method, suitable also for the iodo compound is the replacement of the amino group in *m*-nitroaniline which is easily made by the partial reduction of *m*-dinitrobenzene or by the nitration of aniline in conc. sulfuric acid. The halogen meta to the nitro group is not activated as is that ortho or para to such a group. An exception is found in the action with alkali sulfite solutions which takes place with the *m*- as well as with the *o*- and *p*-compounds (Sprung 1930).




### *D.* Nitroso and Hydroxylamino Derivatives of Aromatic Hydrocarbons

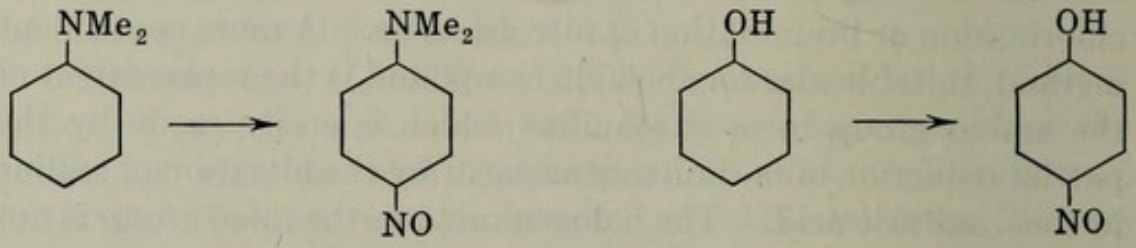
**Nitrosobenzene,** $C_6H_5NO$, m. 68°, is a colorless crystalline substance which gives green solutions. The solid is a dimer while the colored solutions contain the monomer. Nitrosobenzene is most readily obtained by the oxidation of phenylhydroxyl amine, $C_6H_5NHOH$, by ferric chloride or chromic acid solution. It can

also be made by the action of nitrosyl chloride, NOCl, on diphenylmercury. Its structure is indicated by its reduction to aniline and its oxidation to nitrobenzene. It condenses with amines much as carbonyl compounds do but the intermediate addition compound of the aldol type loses water spontaneously to give an azo compound.

$$C_6H_5N{=}O + H_2NC_6H_5 \rightarrow [C_6H_5N(OH)NHC_6H_5] \rightarrow C_6H_5N{=}NC_6H_5$$

In $CS_2$ solution it is bimolecular. In such a solution $Br_2$ or $HNO_3$ gives *para* substitution (Ingold 1925.) *p*-Bromonitrosobenzene has a more reactive halogen than the Cl in picryl chloride.

**Nitroso compounds** of aromatic substances containing activating groups like dialkylamino and hydroxyl can be made directly by treatment with nitrous acid.




**β-Phenylhydroxylamine,** or simply phenylhydroxylamine,

$$C_6H_5NHOH,$$

m. 81°, is made from nitrobenzene by neutral reduction either catalytically or by Zn dust and water in presence of a salt like $CaCl_2$. Oxidation gives nitrosobenzene or azoxybenzene, a product of the action of nitrosobenzene with unchanged material. Fehling's solution oxidizes phenylhydroxylamine. It is a strong base in contrast to aniline. Conc. $H_2SO_4$ converts it to the sulfate of *p*-aminophenol, the parent substance of the photographic developer Metol. Air and mild oxidizing agents like Fehling's solution convert it to azoxybenzene while chromic acid mixture gives nitrosobenzene.

A test for an aromatic nitro cpd. is treatment with Zn dust and water to give a phenylhydroxylamine which is capable of reducing Fehling's solution.

## VI. ARYLAMINES

### *A.* Phenyl Amine and its Homologs

These are known in great numbers and variety and are of the greatest practical and theoretical importance. Those with the $NH_2$ in the side chain are made by the ordinary aliphatic reactions. The true aromatic amines with the $NH_2$ attached directly to an aromatic nucleus are made in various ways.

1. By reduction of the corresponding nitro compound. A great variety of reducing agents may be used including active metals and acids, stannous chloride, ammonium sulfide and ferrous hydroxide.

2. By reaction of a chloro compound with $NH_3$ either alone or with catalysts such as copper salts. Chloro derivatives of aromatic hydrocarbons require temperatures around 200° but the presence of nitro and similar groups lowers the reaction temperature to around 100°.

3. By the reaction of phenols with $NH_3$ and zinc chloride at about 300°.

4. By Hofmann's amide reaction with a hypohalite or a halogen and a base.

The aromatic primary amines are extraordinarily weak bases. Thus the basic dissociation constants for $C_6H_5NH_2$, $CH_3NH_2$ and $NH_3$ in water solution are about $3 \times 10^{-10}$, $5 \times 10^{-4}$ and $2 \times 10^{-5}$ respectively.

*Aniline*, aminobenzene, phenyl amine, $C_6H_5NH_2$, colorless, m. 6°, b. 182°, is typical of the aromatic amines. It was discovered by various workers and appears in the early literature as "Krystallin," "cyanol" ("Kyanol"), and "benzidam." Aniline is prepared commercially in two ways:

1. By reduction of nitrobenzene with iron and water and a small amount of acid. The cycle of changes is probably

$$2\,HCl + Fe \rightarrow 2\,[H] + FeCl_2$$

$$6\,[H] + C_6H_5NO_2 \rightarrow C_6H_5NH_2 + 2\,H_2O$$

$$6\,FeCl_2 + 16\,H_2O + C_6H_5NO_2 \rightarrow C_6H_5NH_2 + 6\,Fe(OH)_3 + 12\,HCl$$

The net result is expressed as follows, the HCl behaving in a sense as a catalyst.

$$2\,Fe + 4\,H_2O + C_6H_5NO_2 \rightarrow C_6H_5NH_2 + 2\,Fe(OH)_3$$

2. By heating ammonia and chlorobenzene at about 200° with a mixture of cuprous oxide and chloride. The latter is the catalyst and the former prevents the formation of $NH_4Cl$ which tends to reverse the reaction (Hale 1927). The net reaction is as follows:

$$2\,C_6H_5Cl + 2\,NH_3 + Cu_2O \rightarrow C_6H_5NH_2 + Cu_2Cl_2 + H_2O$$

Without the $Cu_2O$ the reaction would be

$$C_6H_5Cl + 2\,NH_3 \leftrightarrows C_6H_5NH_2 + NH_4Cl$$

The cuprous chloride is treated with enough alkali to change most of it to the oxide and the mixture is used for the next charge. Thus the overall change is

$$C_6H_5Cl + NH_3 + NaOH \rightarrow C_6H_5NH_2 + NaCl + H_2O$$

*Properties.* The properties of aniline are characteristic of aromatic amines in general. It is a weaker base than ammonia. Its salts readily hydrolyze. The temperatures at which it is completely miscible with various hydrocarbons are characteristic of the latter. Thus the C.T.S. (critical solution temperatures) for aniline of the heptanes vary from 66.3° for triethylmethane to 78.8° for diisopropylmethane (Edgar 1929). The C.T.S. for cycloparaffins are lower than for the open chain compounds, the values for cyclohexane being 31°, for Me-cyclohexane 41° and for decahydronaphthalene 34°, The values for olefins are lower than for saturated compounds, 26° for octene-1, 68° for cetene and −20° for cyclohexene, The values for aromatic compounds are too low to be useful.

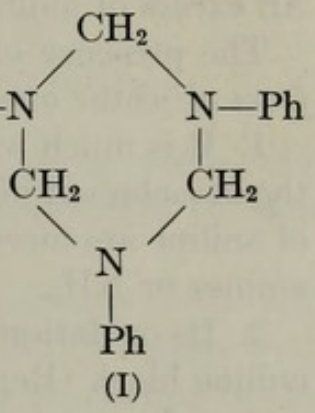
*Reactions.* Aniline *resembles the aliphatic primary amines* in many ways. It forms crystalline salts with strong acids, substituted ammonium salts of chloroauric and chloroplatinic acids, and double salts with $ZnCl_2$, $HgCl_2$ etc. The H atoms of the $NH_2$ are replaceable by alkali metals. They are also replaceable by halogens on treatment with hypohalous acids. It adds alkyl halides and can finally be converted to a quarternary ammonium

compound. It reacts with aldehydes. With formaldehyde it gives crystalline anhydroformaldehyde-aniline, m. 40° (I). This action is another example of a process which continues until a stable 6-ring can be formed.

$$PhNH_2 + CH_2O \rightarrow PhNHCH_2OH \rightarrow PhNHCH_2NHPh \rightarrow$$

$$PhNHCH_2N(Ph)CH_2OH \rightarrow PhNHCH_2N(Ph)CH_2NHPh \rightarrow$$

$$PhNHCH_2N(Ph)CH_2N(Ph)CH_2OH \rightarrow$$



(I)

With chloroform and alcoholic KOH aniline gives the carbylamine test forming phenyl isocyanide, $C_6H_5NC$, of characteristic odor. With $CS_2$ it forms a thiourea, *thiocarbanilide* which reacts with acids to give *phenyl mustard oil.* These properties are illustrated by the following formulas and equations:

| | | | |
|---|---|---|---|
| $ArNH_3Cl$. | $(ArNH_3)_2SO_4$. | $(ArNH_3)AuCl_4$. | $(ArNH_3)_2PtCl_4$. |
| $(ArNH_2)_2.HgCl_2$. | $ArNHNa$. | $ArNHBr$. | |
| $ArMeNH_2I$. | $ArMe_2NHI$. | $ArMe_3NI$. | |
| $(ArNH)_2CHR$. | $ArN=CHAr$ (Schiff's bases). | | |

The latter occur as amorphous polymers.

$$ArNH_2 + CHCl_3 + 3\,KOH \rightarrow ArNC + 3\,KCl + 3\,H_2O$$

$$2\,ArNH_2 + CS_2 \rightarrow (ArNH)_2CS + H_2S$$

$$(ArNH)_2CS + HCl \rightarrow ArNCS + ArNH_3Cl$$

Aniline reacts with an excess of phosgene to give *phenylisocyanate,* $C_6H_5NCO$.

$$PhNH_2 + COCl_2 \rightarrow PhNCO + 2\,HCl$$

Phenylisocyanate is valuable for the identification of alcohols

and primary and secondary amines by converting them to phenyl urethanes and substituted ureas of definite melting points.

$$PhNCO + ROH \rightarrow PhNHCO_2R$$
$$PhNCO + RNH_2 \rightarrow PhNHCONHR$$
$$PhNCO + R_2NH \rightarrow PhNHCONR_2$$

Naphthylisocyanate, made from naphthylamine is similarly used. An excess of aniline with phosgene gives *sym*-diphenylurea.

The presence of an aromatic ring in aniline causes it to *differ from aliphatic amines:*

1. It is much weaker as a base. This is presumably related to the attachment of the $NH_2$ to an unsaturated system. The salts of aniline are more readily hydrolyzed than those of the aliphatic amines or $NH_3$.

2. Its oxidation is much more complex, resulting in azobenzene, aniline black (Rep. 1909, 99), *p*-aminophenol, phenols, quinones, and various resinous products. The practically important products are quinone, $O=C_6H_4=O$, formed by vigorous oxidation and aniline black, $C_6H_5N=(C_6H_4=N-C_6H_4-N)_3=C_6H_4=NH$, formed under milder conditions (Green 1913). Aniline ordinarily darkens rapidly on standing, due to oxidation. This can be retarded if the aniline is entirely free from nitrobenzene and is stored in aluminum containers.

3. Substitution readily takes place in the *o*- and *p*-positions. This may take place by an initial attack on the nitrogen atom. Thus bromination probably involves the steps

$$C_6H_5NH_2 \rightarrow C_6H_5NHBr \rightarrow BrC_6H_4NH_2$$

The migration from N to the ring always takes place in the *p*- or *o*-position. No *m*-compound is formed. The migration may be intra- or intermolecular. The ready substitutions include nitration, sulfonation, halogenation and mercuration.

A peculiar type of substitution is involved in the rearrangement of an alkyl group from N to the *p*- or *o*-position on heating the hydrochlorides of N-alkyl anilines.

An exception to the usual *o*- and *p*-substitution of aniline is its nitration in conc. sulfuric acid solution to give a considerable amount of *meta*-nitroaniline (Rep. 1915, 89).

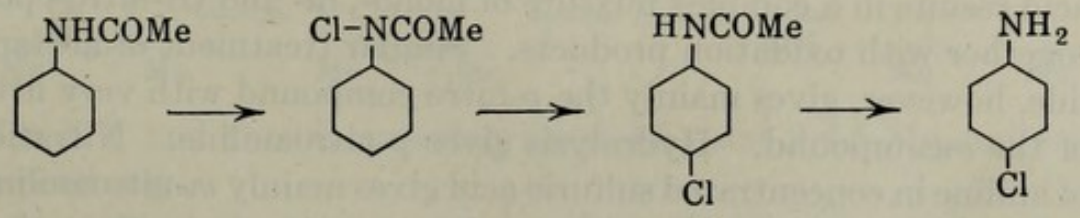
4. The most important difference is in its action with nitrous acid. Whereas aliphatic primary amines react with nitrous acid and HCl to give nitrogen and alcohols, chlorides and olefins both without and with rearrangement, the aromatic primary amines give *diazonium salts* which are moderately stable and can be used in a great variety of reactions. This process of *diazotization* is of great practical and theoretical importance.

$$ArNH_2 + HCl + HNO_2 \rightarrow ArN_2Cl + 2\,H_2O$$

The solution of benzene diazonium chloride is stable while cold.

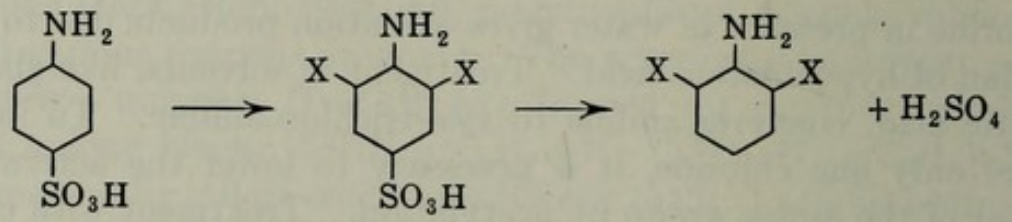
5. Aniline readily undergoes catalytic hydrogenation to form cyclohexylamine (Rep. 1920, 87).

**Halogenated anilines.** The amino group activates the *o*- and and *p*-H atoms to a high degree. The treatment of aniline with chlorine in presence of water gives oxidation products due to the action of hypochlorous acid. Treatment in solvents, like glacial acetic acid, converts aniline to *sym*-trichloroaniline. To introduce only one chlorine, it is necessary to lower the activating effect of the amino group by acetylation. Treatment with chlorine then gives *p*-chloroacetanilide with very little of the ortho isomer. The first step is probably the formation of N-chloroacetanilide which rearranges in presence of acid to the *p*-compound. Vigorous hydrolysis of the anilide gives *p*-chloroaniline, m. 71°, b. 231°.




It is also readily obtained by the acid reduction of *p*-nitrochlorobenzene. Its *o*- and *m*-isomers are similarly prepared from the nitro compounds. The presence of the halogen decreases the basic properties of the amine. The bromoanilines are obtained similarly. *Sym-Tribromoaniline*, m. 119°, is readily obtained by passing air through bromine and into an aqueous solution of aniline hydrochloride. It can also be made by simply mixing solu-

tions of bromine and aniline hydrochloride. Its great insolubility was utilized in the first method for extracting bromine from sea water for use in Ethyl fluid in gasoline (p. 86). The sea water was treated with amounts of aniline and chlorine corresponding to the bromine content. Insoluble $Br_3$-aniline was precipitated, one pound being obtained from about 2500 gallons of sea water. Now the liberated bromine is simply blown out by means of air and absorbed in a carbonate solution. Monobromoaniline is obtained like the monochloro cpd. *Triiodoaniline*, m. 185°, is made by using iodine monochloride ICl, much as bromine is used. 2,4-Dihalogenated anilines are made by the halogenation of acetanilide. 2,6-Dihalogenated anilines are made by the careful halogenation of sulfanilic acid followed by the removal of the sulfonic acid group by steam at about 200°.




If excess of halogen is used, the sulfonic acid group is replaced by halogen.

It should be remembered that halogenated anilines are even more dangerously toxic than aniline itself.

**Nitroanilines.** The direct treatment of aniline with nitric acid results in a complex mixture of mono-, di- and tri-nitro-cpds. together with oxidation products. Similar treatment of acetanilide, however, gives mainly the *p*-nitro compound with very little of the *o*-compound. Hydrolysis gives *p*-nitroaniline. Nitration of aniline in concentrated sulfuric acid gives mainly *m*-nitroaniline.

Nitroanilines are better prepared from nitro derivatives than from aniline, the *o*- and *p*-compounds by treating *o*- and *p*-nitrochlorobenzenes with $NH_3$ and the *m*-compound by partial reduction of *m*-dinitrobenzene.

In the nitroanilines, the amino group has practically completely lost its basic nature. The nitro group has the same effect on the *o*- and *p*-positions as in the chloro compounds. Thus *o*- and *p*-nitroanilines can readily be hydrolyzed to the nitrophenols by

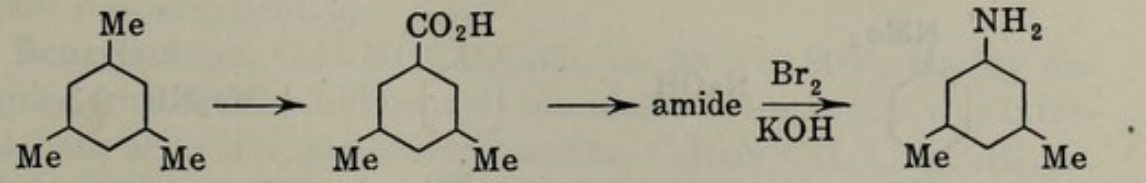
bases. *sym-Trinitroaniline, picramide,* $C_6H_2(NH_2)(NO_2)_3$, m. 188°, is readily obtained from the chloro compound and $NH_3$. Hydrolysis gives picric acid, trinitrophenol. 2,3,4,6-Tetranitroaniline, the explosive T.N.A., is made from *m*-nitroaniline with mixed sulfuric and nitric acids.

***o*-, *m*-, and *p*-Toluidines,** aminotoluenes, $CH_3C_6H_4NH_2$, b. 199.8°, 202.9°, and 200.3° respectively (Berliner 1927), are obtained by reducing the nitrotoluenes. *p*-Toluidine melts at 43°, and the three acetyl derivatives, the *acetotoluidides* melt at 110°, 65° and 153° respectively. The basic properties of the $NH_2$ group are not greatly changed by the methyl group in the ring. The acetotoluidides can be oxidized to acetaminobenzoic acids.

All six possible *xylidines,* aminoxylenes or C-dimethylanilines, $(CH_3)_2C_6H_3NH_2$, are known. They are obtained from the corresponding nitro cpds. Names, melting points and boiling points are as follows:

(1) 1,2,3-xylidine, *v-o*-xylidine, liq., 223°;

(2) 1,2,4-xylidine, *u-o*-xylidine, 49°, 226°; (3) 1,3,2-xylidine, *v-m*-xylidine, liq., 216°; (4) 1,3,4-xylidine, *u-m*-xylidine, liq., 212°; (5) 1,3,5-xylidine, *s-m*-xylidine, liq., 220°; 1,4,2-xylidine, *p*-xylidine, 15°, 213°. The 1,3,4-cpd. is also made by rearranging N-$Me_2$-aniline by heat. Commercial xylidine contains all the isomers except the 1,3,5-compound. This can be obtained by the Hofmann reaction on the amide of mesitylenic acid.



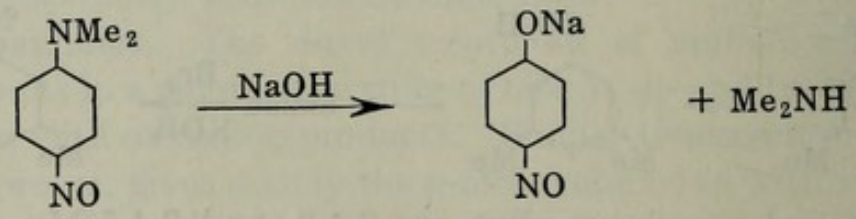

Mesidine and pseudocumidine are 2,4,6- and 2,4,5-$Me_3$-anilines respectively.

Aromatic primary amines can be identified by means of a great variety of derivatives including the acetyl cpds. and the *p*-toluene sulfonates (Noller 1932).

### *B.* N-Alkylanilines

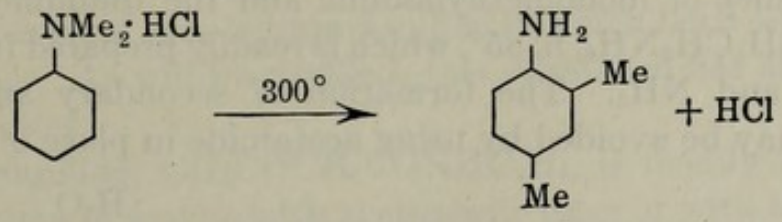
These are obtained by treating aniline with alkylating agents. Monomethylaniline and dimethylaniline are made by heating

aniline, MeOH and HCl or $H_2SO_4$ under pressure. They cannot be separated by distillation because they both boil at 192°. The addition of a methyl would be expected to raise the boiling point by increasing the molecular weight but it also lowers the boiling point by increasing the symmetry of the molecule. They can be separated by acetylation of the monomethylaniline, the acetyl derivative being insoluble in acid while the unreacted dimethylaniline readily dissolves. The introduction of methyl groups decreases the basicity of the nitrogen, the basic ionization constants $\times 10^{-10}$ of $PhNH_2$, PhNHMe and $PhNMe_2$ being about 3.5, 2.6 and 2.4. The reactions of mono- and di-methylanilines are those typical of secondary and tertiary amines except that the benzene ring gives the possibility of substitution reactions. As with aniline, substitution by halogen, nitro, sulfonic and similar groups takes place readily in the *o*- and *p*-positions. Moreover a nitroso group is readily introduced. Monomethylaniline with nitrous acid gives the expected nitrosamine, PhN(NO)Me. Under the influence of alcoholic HCl, the nitroso group rearranges to the *p*-position to give $ON-C_6H_4-NHMe$. When dimethylaniline is treated with nitrous acid, *p*-nitrosodimethylaniline, m. 85°, results. The NO group can be oxidized to $NO_2$ or reduced to $NH_2$. Moreover the NO group in the *p*-position activates the dimethylamino group so that boiling with bases gives *p*-nitrosophenol and dimethylamine.

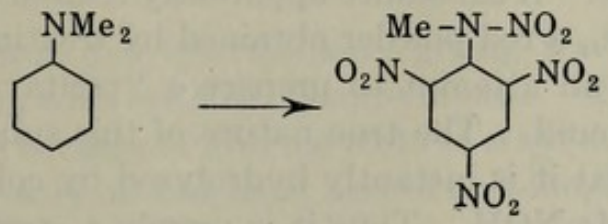



This reaction is useful in making pure higher secondary amines such as di-*n*-butyl amine from N-di-*n*-butylaniline. The activity of the *p*-H in dimethylaniline is also shown by its easy condensation with phosgene to give Michler's ketone, $(Me_2NC_6H_4)_2CO$, an important dye intermediate, and with aromatic aldehydes to give triphenylmethane dyes such as Malachite Green. Further evidence of the activity of the ring is shown in the action of heat on the hydrochlorides of the methylanilines, methyl groups migrat-

ing to *p*- and *o*-positions. This process is used commercially to make 2,4-xylidine.




Vigorous nitration of dimethylaniline in presence of $H_2SO_4$ gives N-Me-2,4,6,N-tetranitroaniline, the explosive *Tetryl*.




**Diethylaniline,** $C_6H_5N(C_2H_5)_2$, b. 216°, prepared from aniline and EtBr, is used for certain rhodamine dyes.

Higher N-alkylanilines are obtained by means of alcohols or alkyl halides. The possibility of rearrangement of the reagents should be kept in mind. The migration of a higher alkyl group to the *p*-position may involve rearrangement within the group. Thus N-isoamylaniline on heating with HCl gives *p-ter*-amylaniline hydrochloride, whereas heating with $CdSO_4$ as a catalyst gives *p*-isoamylaniline.

**Benzylaniline,** $C_6H_5NHCH_2C_6H_5$, m. 38°, b. 306°, readily obtained from aniline and benzyl chloride, is an important dye intermediate as is also *methylbenzylaniline*, $C_6H_5N(CH_3)CH_2C_6H_5$, m. 9°, b. 306°.

**Quaternary ammonium compounds** of the type $(ArNR_3)X$ are obtainable if the alkyl groups are not too complex and if the aryl group is not substituted in both ortho positions. Examples of these limitations are the inactivity of sym-$Br_3$-aniline with MeI and the fact that PhNMeEt reacts readily with MeI but $PhNMe_2$ reacts very incompletely with EtI. Correspondingly greater difficulties are obtained with larger and with branched groups.

**Phenyltrimethylammonium hydroxide,** $(C_6H_5NMe_3)OH$ is a colorless soluble strong base which can be made from its chloride

by alcoholic NaOH with the precipitation of NaCl. Heat decomposes it to MeOH and $PhNMe_2$.

An isomer of monomethylaniline and the toluidines is *benzyl amine*, $C_6H_5CH_2NH_2$, b. 85°, which is readily prepared from benzyl chloride and $NH_3$. The formation of secondary and tertiary amines may be avoided by using acetamide in place of ammonia.

$$PhCH_2Cl + NH_2COMe \rightarrow PhCH_2NHCOMe \xrightarrow{H_2O} PhCH_2NH_2$$

It is more basic than its isomers. The N-alkyl derivatives are still more basic. A substance apparently related to benzyl amine is $PhCH_2NMe_4$, a red powder obtained by treating $Me_4NCl$ with $PhCH_2Na$, in an attempt to prepare a "pentavalent" nitrogen organic compound. The true nature of this substance is shown by the fact that it is instantly hydrolyzed by cold water to give toluene and $Me_4NOH$. Thus it is merely a special quarternary ammonium salt in which the benzyl group serves as the negative ion, $(Me_4N)^+(CH_2Ph)^-$ (Schlenk 1917).

Benzyl dialkyl amines, $PhCH_2NR_2$, with acetic anhydride give benzyl acetate and $R_2NCOMe$.

Benzyltrimethylammonium hydroxide, $(PhCH_2NMe_3)OH$, as would be expected, is a strong base.

The next homolog, *phenylethylamine*, $C_6H_5CH_2CH_2NH_2$, is formed from *phenylalanine* during the decay of certain proteins. It is also related to physiologically active substances like adrenalin, ephedrin and tyramine.

### *C.* Acyl Arylamines

Just as ammonium acetate on heating gives acetamide, so the salts of organic acids and aryl amines readily give acyl derivatives of the amines. The resulting compounds are *anilides*, *toluidides*, *xylidides*, etc. The acetyl derivatives of most arylamines are crystalline solids of definite melting points.

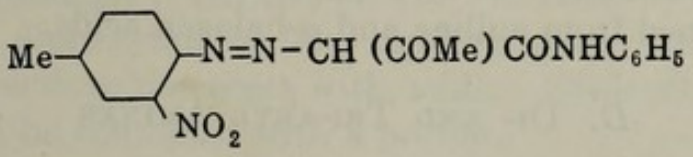
**Acetanilide,** $C_6H_5NHCOCH_3$, m. 115°, b. 304°, is readily formed by refluxing aniline and acetic acid. In glacial acetic acid, it shows slight basic properties forming a salt with HCl. Acetanilide was formerly used in medicine as "antifebrine." Treatment with $P_2S_5$ gives thioacetanilide, PhNHCSMe. *Diacetanilide*,

$PhN(COMe)_2$, m. 37°, is formed by vigorous treatment of acetanilide with acetyl chloride or acetic anhydride. Strange to say, *o*-substituted anilines give diacetyl derivatives with great ease. This is true even of *sym*-tribromoaniline in which both *o*-positions are occupied. As will be recalled, this substance has almost no basic properties.

**Acetoacetanilide,** $CH_3COCH_2CONHC_6H_5$, is readily available from the action of aniline with acetoacetic ester or with the dimer of ketene (acetylketene).

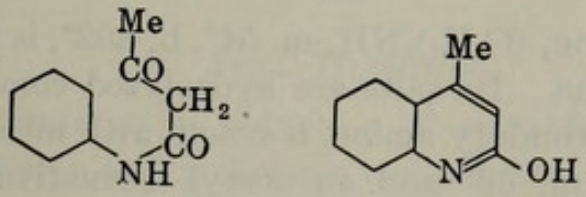
$$MeCOCH=C=O + PhNH_2 \rightarrow PhNHCOCH_2COMe$$

It is an important dye intermediate, giving the stable Hansa Yellows by action with suitable diazonium salts. These are more readily available because of lowered costs of ethyl acetate, sodium and acetoacetic ester on one hand and of acetone, ketene and its dimer on the other.

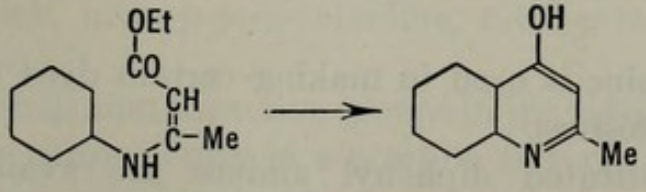



Hansa Yellow G,

Dehydration of acetoacetanilide gives ring-closure to form γ-Me-α-OH-quinoline.




At lower temperatures aniline gives a derivative of the enol form of acetoacetic ester, $PhNHC(Me)=CHCO_2Et$, β-phenylamino-crotonic ester. This, on heating gives γ-OH-α-Me-quinoline.



Dibasic acids react in all possible ways. Thus oxalic acid gives *oxanilic acid*, $PhNHCOCO_2H$, m. 150° and oxanilide, $(PhNHCO)_2$, m. 252°. Carbonic acid is related to carbanilide, diphenyl urea, $(PhNH)_2CO$, m. 235°, b. 260°, and *phenyl isocyanate*, phenyl carbimide, $C_6H_5NCO$. The former is obtained by passing phosgene, $COCl_2$, into excess aniline while the latter is formed by heating aniline hydrochloride and passing in an excess of phosgene. Phenyl isocyanate is valuable for the identification of primary and secondary alcohols with which it forms crystalline *phenyl urethanes*, $PhNHCO_2CH_2R$ and $PhNHCO_2CHRR'$. It dehydrates tertiary alcohols with the formation of diphenylurea. *Thiocarbanilide*, diphenylthiourea, $(PhNH)_2CS$, m. 154°, a derivative of thiocarbonic acid, is readily made by boiling aniline with $CS_2$. With HCl it gives *phenyl mustard oil*, phenyl isothiocyanate, PhNCS, b. 222°. This gives crystalline mixed thioureas with primary and secondary amines, PhNHCSNHR, PhNHCSNRR'.

**Phenylglycine,** $C_6H_5NHCH_2CO_2H$, and related compounds are readily obtained from aniline and $\alpha$-halogen acids.

### *D.* Di- and Tri-aryl Amines

**Diarylamines** are obtained by heating an arylamine with its hydrochloride or that of another amine.

$$ArNH_2 + ArNH_3Cl \rightarrow Ar_2NH + NH_4Cl$$

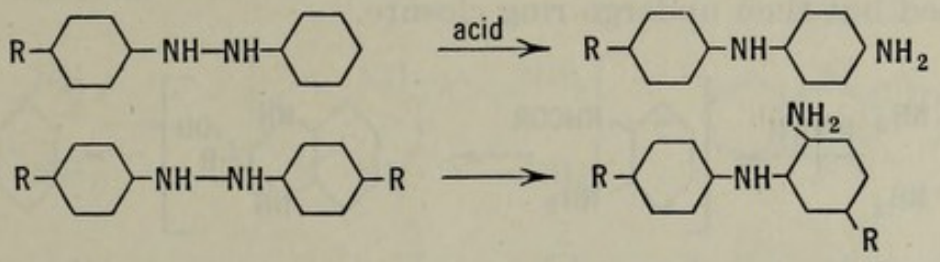
**Diphenylamine,** $(C_6H_5)_2NH$, m. 54°, b. 302°, is an even weaker base than aniline. Its salts are hydrolyzed completely by cold water. As a secondary amine, it reacts with nitrous acid to give a nitrosamine, m. 66° and an acetyl derivative, m. 103°. In sulfuric acid it gives a blue color with a trace of nitrous acid. Its nitrosamine undergoes rearrangement with alcoholic HCl to form *p*-nitrosodiphenylamine $ON-C_6H_4NHC_6H_5$ (Fischer-Hepp Rearrangement).

Diphenylamine gives N-metal cpds. more readily than aniline or ammonia.

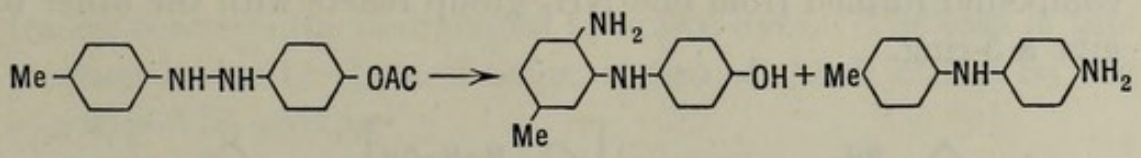
Diphenylamine is used in making certain dyes and as a stabilizer for explosives.

Many substituted diphenyl amines are available by the

*semidine rearrangement.* This is of two types, the para and the ortho which can be illustrated as follows (Rep. 1922, 97).

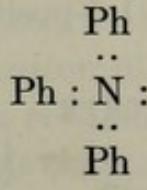



A more complex example involving both types follows




The elimination of the OH group in the latter product is unusual (ibid).

**Triphenylamine,** $(C_6H_5)_3N$, m. 127°, is made by dissolving Na in boiling diphenylamine and adding phenyl bromide. Triphenylamine does not react with acids. Evidently the electron pair cannot be combined with a proton.



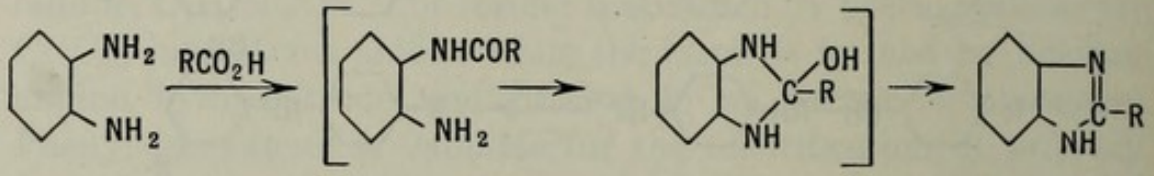

### *E.* Aryl Diamines

These are obtained by reduction of suitable dinitro, amino nitro, amino nitroso and amino azo compounds. The *o*-, *m*-, and *p*-compounds can be considered separately.

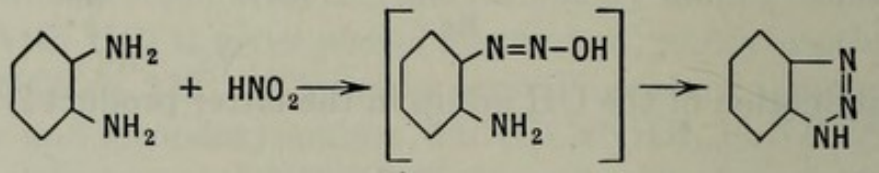
**Ortho diamines** are best prepared by reducing *o*-nitroanilines. Thus *o*-phenylene diamine involves the steps chlorobenzene, *o*-nitrochlorobenzene, *o*-nitroaniline and *o*-phenylene diamine. Similarly a toluylene-*o*-diamine can be made; *p*-toluidine, *p*-acet-toluidine, nitro-*p*-acet-toluidine, nitro-*p*-toluidine, toluylene-*o*-diamine.

The *o*-diamines contain active groups in the 1,4-position to each other and are consequently in a position to form 5- and 6-membered rings with suitable reagents.

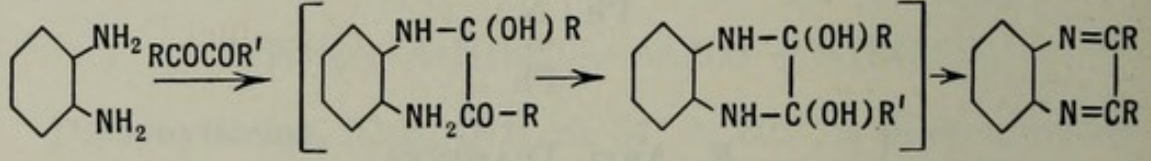
1. With organic acids they give benzimidazoles instead of giving ordinary acyl derivatives. The latter are probably first formed but then undergo ring closure.



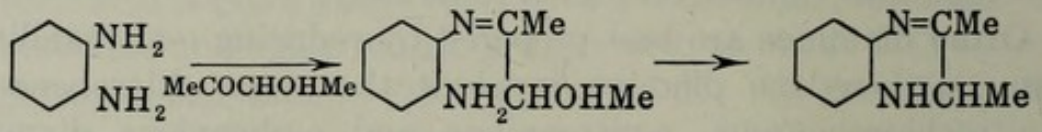

2. Nitrous acid gives azoimino compounds. The diazonium compound formed from one $NH_2$ group reacts with the other to give a 5-ring.



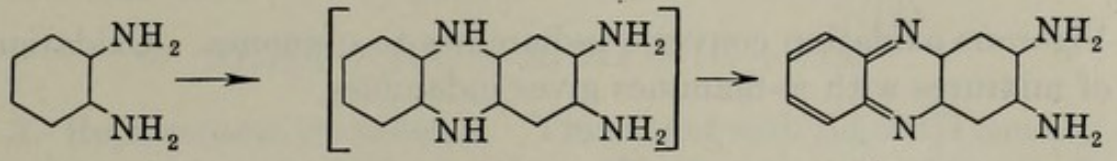

3. With $\alpha$-diketones and $\alpha$-ketoalcohols they give *quinoxalines* and dihydroquinoxalines respectively. Again the reaction is undoubtedly initiated at one amino group to produce a product containing active groups in the 1,6-position to each other.



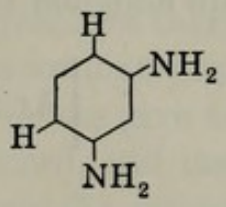

Thus glyoxal and *o*-phenylene diamine give *quinoxaline* itself. Acetoin gives dimethyl-dihydroquinoxaline.



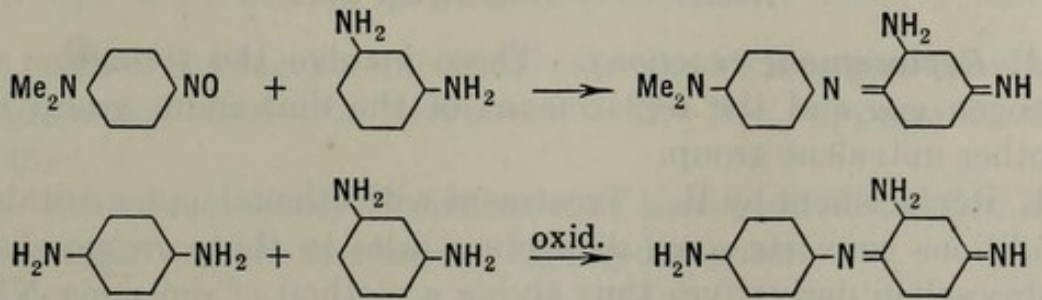
4. Careful oxidation, as with $FeCl_3$, gives diaminophenazines. The *p*-position to each $NH_2$ group reacts with an $NH_2$ from another molecule.



**Meta diamines** are best prepared by reduction of *m*-dinitro compounds formed by direct nitration. Nitrous acid, even in traces, converts the *m*-diamines to brown dyes. The ease of this reaction is due to the activation of two of the H atoms by the *o*- and *p*-$NH_2$ groups.



One of these reacts with a molecule of diazotized amine. Thus, with excess of amine, the product is 3′,2,4-triaminoazobenzene. Other examples of the activation of these H atoms is the ready formation of indamines from *m*-diamines with *p*-nitrosodimethylaniline or with *p*-diamines on oxidation.



Indamines

**Para diamines** are made by reduction of a variety of compounds

1. *p*-Nitroanilines obtained either by nitration of acetanilides or from *p*-nitrochloro derivatives.

2. *p*-Nitroso derivatives.
3. Amino azo compounds.

$$C_6H_5N{=}NC_6H_4NH_2 \rightarrow C_6H_5NH_2 + H_2NC_6H_4NH_2$$

Vigorous oxidation converts *p*-diamines to quinones. Oxidation of mixtures with *m*-diamines gives indamines.

## VII. DIAZONIUM SALTS AND RELATED COMPOUNDS

### *A.* Diazonium Salts

As has been seen, primary aromatic amines can be diazotized with nitrous acid to give moderately stable solutions which lose $N_2$ only on standing or heating. These solutions contain *diazonium salts* to which are assigned the structures

$$Ar{-}\underset{\displaystyle Cl}{\underset{|}{N}}{\equiv}N \qquad \left[Ar : \ddot{N} : N :\right]^{+} Cl^{-}$$

Insoluble amines can be diazotized by first converting them to soluble sulfamic acids by treatment with chlorosulfonic acid.

$$ArNH_2 \xrightarrow{ClSO_3H} ArNHSO_3H \xrightarrow[HCl]{HNO_2} ArN_2Cl + H_2SO_4$$

#### *Reactions of Diazonium Salts*

*A.* ***Replacement reactions.*** These involve the formation of nitrogen gas and the replacement of the diazonium group by another univalent group.

1. Replacement by H. Treatment with ethanol under suitable conditions converts some diazonium salts to the corresponding hydrocarbon derivatives thus giving a method of replacing $NH_2$ by H. Thus an alcohol-benzene solution of *sym*-$Br_3$-aniline treated with concentrated sulfuric acid and sodium nitrite gives *sym*-$Br_3$-benzene (OS).

$$Br_3C_6H_2NH_2 + H_2SO_4 + NaNO_2 + C_2H_5OH \rightarrow C_6H_3Br_3 + N_2 + CH_3CHO + NaHSO_4 + 2\,H_2O$$

In other cases the diazonium group is replaced by $OC_2H_5$ instead of by H.

2. Replacement by OH. This is the common decomposition of diazonium salts, especially on warming with sulfuric acid.

$$ArN_2X + H_2O \rightarrow ArOH + N_2 + HX$$

3. Replacement by halogen. Treatment with KI or HI usually gives an iodo compound smoothly. Replacement by Cl or Br is usually best achieved in presence of the proper acid and copper powder (Gattermann) or the proper cuprous halide dissolved in the corresponding acid (Sandmeyer). Heating the diazonium fluoroborate gives replacement by F.

4. Replacement by CN. This is a special case of the Sandmeyer-Gattermann reaction taking place with $KCu(CN)_2$.

5. Replacement by aryl residues takes place when a dry diazonium salt is heated with an aromatic hydrocarbon and $AlCl_3$.

6. Miscellaneous replacements give aryl thiocyanates, sulfides, sulfonic acids and nitro, fluoro, and mercury compounds.

*B. **Reactions which retain the nitrogen atoms.***

1. Reduction gives aryl hydrazines. In this way phenyl hydrazine is prepared (OS).

$$PhN_2Cl + 2\,Na_2SO_3 + 2\,H_2O \rightarrow PhNHNH_2.HCl + 2\,Na_2SO_4$$

2. Alkaline oxidation gives nitramines among other products.

$$ArN_2Cl + 2\,NaOH + [O] \rightarrow ArN{=}NO_2Na + NaCl + H_2O$$

3. Active hydrogen compounds of various kinds give coupling reactions in which the *azo group*, $-N{=}N-$, appears in the product.

*a.* Active methylene compounds like acetoacetic ester give azo compounds and the tautomeric aryl hydrazones.

$$MeCOCH_2CO_2R + ArN_2Cl \rightarrow \begin{matrix} MeCOCH(CO_2R){-}N{=}N{-}Ar \\ \downarrow\uparrow \\ MeCOC(CO_2R){=}N{-}NH{-}Ar \end{matrix}$$

*b.* Aryl amines give *diazo-amino compounds.*

$$ArN_2Cl + ArNH_2 \rightarrow ArN{=}N{-}NHAr$$

*c.* Aromatic compounds with highly activated ring H atoms such as phenols, naphthols and N-dialkyl-anilines couple in the active position

$$ArN_2Cl + C_6H_5NMe_2 \rightarrow ArN{=}N{-}C_6H_4NMe_2$$
$$C_6H_5OH \rightarrow ArN{=}N{-}C_6H_4OH$$

These compounds are typical azo dyes.

While simple diazonium salts have to be prepared in solution as used, some of the more complex ones can be prepared as *solid stabilized diazonium compounds* usually as double salts with zinc chloride mixed with drying agents such as aluminum sulfate and with certain stabilizing agents such as di- and trisulfonic acids of naphthalene.

Benzenediazonium perbromide, $C_6H_5N_2BrBr_2$, is a crystalline solid obtained by adding $Br_2$ and HBr to a diazonium salt. It liberates $I_2$ from KI. Its constitution may be as follows:

$$\left[Ph : \ddot{N} : \ddot{N} : \ddot{Br} :\right]^{++} 2\,Br^-$$

With $NH_3$ it gives benzene diazoimide, the phenyl ester of hydrazoic acid

$$PhN_2Br_3 + 4\,NH_3 \rightarrow PhN_3 + 3\,NH_4Br$$

The structure of phenyl azoimide is written variously.

$$Ph{-}N{=}N{\equiv}N \qquad Ph{-}N\begin{matrix}\diagup N \\ \| \\ \diagdown N\end{matrix} \qquad Ph : \ddot{N} : \ddot{N} : \ddot{N} :$$

X-Ray measurements indicate a linear structure.

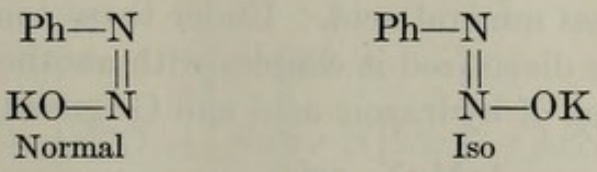
### *B.* Diazo Compounds

Benzene diazonium salts with KOH give a precipitate of *potassium benzene normal diazotate* which can also be prepared from nitrosobenzene and hydroxylamine.

$$PhNO + H_2NOH + KOH \rightarrow PhN{=}NOK + 2\,H_2O$$

It gives the following reactions.

1. HCl gives benzene diazonium chloride.
2. With alkaline solutions of phenols, it gives azo dyes.
3. Alkaline reduction gives phenyl hydrazine.
4. Oxidation gives potassium benzene diazoate, $PhN=NO_2K$.
5. With benzoyl chloride and alkali it gives a benzoyl derivative, $PhN=NOCOPh$.
6. Heating with KOH at 130° gives an isomeric isodiazotate which shows reactions 1 to 5 and thus is a stereoisomer rather than a structural isomer (Hantzsch). The isomerism is like that of the oximes. The *syn* form has been assigned to the normal diazotates which lose $N_2$ more readily than do the isodiazotates which are given the *anti* structure.

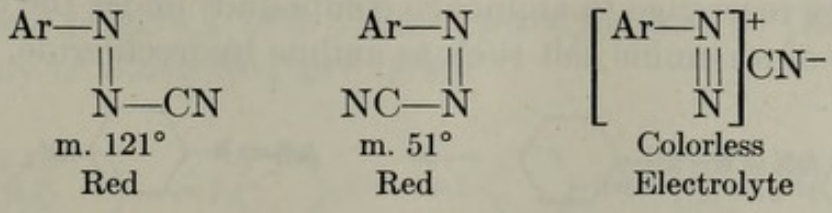



The free acids corresponding to these salts are very unstable, either losing N to give phenol or isomerizing to a nitrosamine

$$PhOH + N_2 \leftarrow PhN=N-OH \rightarrow PhNH-N=O$$

Diazotized *p*-nitroaniline with NaOH gives a stable isodiazotate, $O_2NC_6H_4N_2ONa$, which is used in making Para Red by acidifying with HCl and coupling with β-naphthol.

Diazo sulfonates and cyanides are also known. The latter may occur in three forms one of which is an electrolyte. The forms from diazotized *p*-anisidine are assigned the structures




### *C.* Diazoamino Compounds

The following types are possible.

1. $ArN=N-NHAr$ 2. $ArN=N-NHAr'$ 3. $ArN=N-NRAr$
4. $ArN=N-NHR$ 5. $RN=N-NHR$ 6. $RN=N-NHR'$

The unsymmetrical types 2,4, and 6 exist in equilibrium with their tautomers having H at the other end of the nitrogen chain.

They are pale yellow crystalline neutral compounds of fair stability. Thus *diazoaminobenzene*, PhN=N−NHPh, m. 98°, crystallizes in bright yellow plates or prisms and is moderately stable.

*Preparation.* 1. From a diazonium salt and an amine. The tautomeric nature of the product from a primary amine is shown by the production of the same product from benzene diazonium chloride and *p*-toluidine and from *p*-toluene diazonium chloride and aniline. This character is further shown by the reaction of the product with hot sulfuric acid to give phenol, *p*-cresol, aniline and toluidine.

2. From a primary aryl amine and insufficient nitrous acid in absence of excess mineral acid. Under these conditions as soon as a molecule is diazotized it couples with another molecule.

3. From esters of hydrazoic acid and Grignard reagents

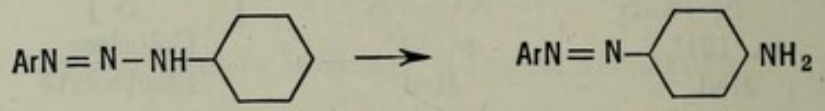
$$ArN_3 \xrightarrow{ArMgX} \xrightarrow{acid} ArN=N—NHAr$$

Alkyl groups can also be used.

*Reactions.* 1. The imino nitrogen does not form salts with acids. The H is replaceable by metals and by acetyls however.

2. They behave like their components. Thus boiling diazoaminobenzene with sulfuric acid gives $N_2$, phenol and aniline while with HBr it gives bromobenzene and aniline. Nitrous acid and HCl convert a diazoamino compound to two molecules of a diazonium chloride.

3. They rearrange to aminoazo compounds under the catalytic influence of an amine salt such as aniline hydrochloride.




If the *p*-position is occupied and the *o*-position is open the rearrangement takes place more slowly to that position.

### *D.* Azo, Hydrazo and Azoxy Compounds

It has been seen that the alkaline reduction of nitrobenzene to aniline can be made to go through the steps of azoxybenzene, azobenzene and hydrazobenzene.

**Azo compounds,** $ArN=NAr$, $ArN=NAr'$, and $ArN=NR$ are neutral substances which are insoluble in water but soluble in organic solvents. The wholly aromatic compounds are red solids while the mixed aromatic aliphatic type forms yellow liquids.

*Preparation.* 1. By controlled reduction of nitro or azoxy compounds with alkaline reducing agents such as NaOH and Zn dust, sodium amalgam or sodium stannite solution.

2. By distilling azoxybenzene with Fe.

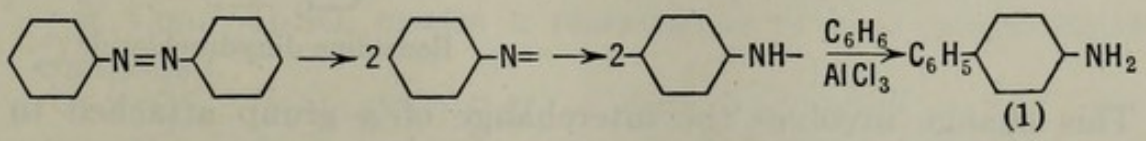
3. By oxidation of hydrazobenzene or of amino compounds by $KMnO_4$. The reaction is likely to go partly to the azoxy stage.

4. By condensation of an aromatic nitroso compound with an amine.

$$ArNH_2 + ArNO \rightarrow \left[\begin{array}{c} OH \\ | \\ ArN—NHAr \end{array}\right] \rightarrow ArN=NAr$$

5. Substituted azo compounds containing activating groups such as OH and $NH_2$, either free or alkylated, are obtained by coupling aromatic amines or phenols with diazonium salts. These products form the important class of azo dyes.

*Reactions.* Oxidation gives azoxy compounds while reduction gives hydrazo and amino compounds. A very striking reaction is that of aromatic azo compounds with aromatic hydrocarbons and $AlCl_3$. The azo compound, under the influence of the $AlCl_3$ apparently splits into free radicals. The action of benzene and azobenzene to give a 70% yield of *p*-xenylamine (I) (Pummerer 1926) may be illustrated as follows:

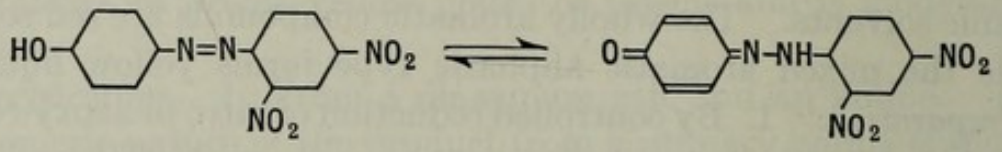



(1)

Azobenzene and biphenyl in this reaction give a fair yield of $C_6H_5C_6H_4C_6H_4NH_2$.

**Azobenzene,** $C_6H_5N=NC_6H_5$, m. 68°, b. 293°, crystallizes in red plates. It is readily obtained by adding the calculated amount of Zn dust to an alcoholic NaOH solution of nitrobenzene.

Certain hydroxyazobenzenes act as quinone monohydrazones while others do not (Lauer 1935).



The quinone structure is evidenced by the addition of cyclopentadiene according to the Diels-Alder reaction.

**Hydrazo compounds,** ArNHNHAr, etc. are colorless crystalline compounds which do not form salts with acids. They are readily *produced* by reduction of azo compounds with excess zinc dust and alkali, with ammonium sulfide or with sodium hydrosulfite.

*Reactions.* 1. While acids do not form salts the imino-H atoms are replaceable by alkali metals and by acetyl and nitroso groups.

2. Vigorous reduction, as with NaxHg, gives the amine.

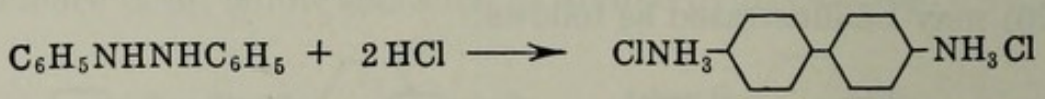
3. Mild oxidizing agents like air or ferric chloride give azo compounds.

4. Heat, or even long standing, results in disproportionation to an azo compound and an amine.

$$2\ ArNHNHAr \rightarrow ArN{=}NAr + 2\ ArNH_2$$

As a matter of fact this is a monomolecular reaction and probably involves a primary disproportionation into aniline and ArN= a nitrogen radical which dimerizes to azobenzene (Stieglitz 1913).

5. Mineral acids cause the benzidine rearrangement which gives diaminodiphenyls.



Benzidine dihydrochloride

This change involves the interchange of a group attached to nitrogen and a *p*-hydrogen analogous to the rearrangement of a nitroso group from N to the *p*-C. In this case the change occurs twice. If the *p*-position in one ring is blocked, only one change is possible and the *semidine rearrangement* takes place to give amino diphenylamines.

$$p\text{-}MeC_6H_4NHNHC_6H_5 \rightarrow p\text{-}MeC_6H_4NHC_6H_4NH_2\text{-}p.$$

**Hydrazobenzene,** $C_6H_5NHNHC_6H_5$, m. 131°, camphor odor.

**Azoxy compounds,** $ArN=N(O)Ar$, $ArN=N(O)Ar'$ and

$$Ar'N=N(O)Ar,$$

are yellow or red crystalline compounds.

*Preparation.* 1. The symmetrical compounds are best made by reduction of nitro compounds with alcoholic KOH.

2. By careful oxidation of simple or mixed azo compounds.

3. By condensation of a nitroso compound and an aryl hydroxylamine. This reaction was the basis of the older erroneous symmetrical formulation of the azoxy grouping.

$$ArN=O + Ar'NHOH \rightarrow \left[\begin{array}{c} ArN-NAr' \\ | \quad | \\ HO \quad OH \end{array}\right] \rightarrow$$

$$H_2O + \left[\begin{array}{c} ArN\text{——}NAr' \\ \diagdown \quad \diagup \\ O \end{array}\right]$$

Incorrect

The unsymmetrical character of the azoxy group is shown by the formation of two isomeric azoxy compounds by the oxidation of an unsymmetrical azo compound (Angeli). The formula usually assigned to the azoxy compounds having a "pentavalent" N is probably less accurate than the electronic formula.

$$Ar-N=N-Ar \qquad Ar:\underset{\cdot\cdot}{N}::\underset{\cdot\cdot}{N}:Ar \qquad Ar-N=N-Ar$$
$$\quad\;\; \| \qquad\qquad\qquad\quad :\underset{\cdot\cdot}{O}: \qquad\qquad\quad \downarrow$$
$$\quad\;\; O \qquad\qquad\qquad\quad\;\; O$$

*Reactions.* 1. Reduction gives azo compounds.

2. Conc. $H_2SO_4$ causes a rearrangement to a *p*-hydroxyazo compound.

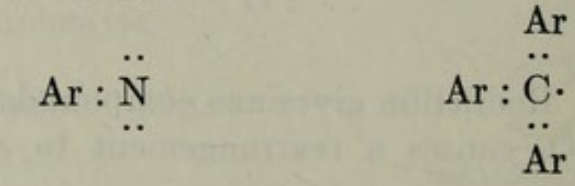
$$ArN=N(O)C_6H_5 \rightarrow ArN=NC_6H_4OH\text{-}p$$

**Azoxybenzene,** $C_6H_5N=N(O)C_6H_5$, m. 36°, pale-yellow crystals, insoluble in organic solvents, is prepared from nitrobenzene and sodium arsenite (OS).

**Hydrazines,** derivatives of $H_2NNH_2$, of all possible types are known. The most important is *phenyl hydrazine,* $C_6H_5NHNH_2$, m. 23°, prepared by reduction of benzene diazonium chloride with

$Na_2SO_3$ (OS). It is strongly basic and is a powerful reducing agent. Its sulfate, on treatment with HgO, gives benzene diazonium sulfate. Vigorous reduction converts it to aniline and ammonia. Alkylation of the base or its metal derivatives takes place on the N next to the phenyl giving unsymmetrical derivatives such as *methyl phenyl hydrazine*, $PhMeNNH_2$ which is an important reagent for sugars. The most important reaction of phenylhydrazine is that with ketones and aldehydes and with simple sugars. The crystalline character, ease of purification and definite melting points make the resulting *phenylhydrazones* and *osazones* valuable for purposes of isolation and identification. The discovery of phenyl hydrazine by Emil Fischer gave him the key with which he later unlocked the problems of the monosaccharides. With carbonyl compounds which do not give crystalline phenylhydrazones, the *p*-substituted phenylhydrazines are valuable. The most important of these are the *p*-bromo-, *p*-nitro-, and *p*-phenyl-compounds. *Unsym*-Diphenylhydrazine, $(C_6H_5)_2NNH_2$, m. 34°, is obtained by reducing the nitroso compound of diphenyl amine with Zn and acid. It reacts with carbonyl compounds like phenylhydrazine.

**Completely substituted hydrazines,** $Ar_2NNAr_2$, are obtained by oxidizing $Ar_2NH$ with $PbO_2$. On standing, these change to $Ar_3N$ and $ArN=NAr$. In benzene they give colored solutions presumably containing free ArN radicals (Wieland). Such a bivalent free radical has six electrons in contrast to the seven of a hydrocarbon free radical.



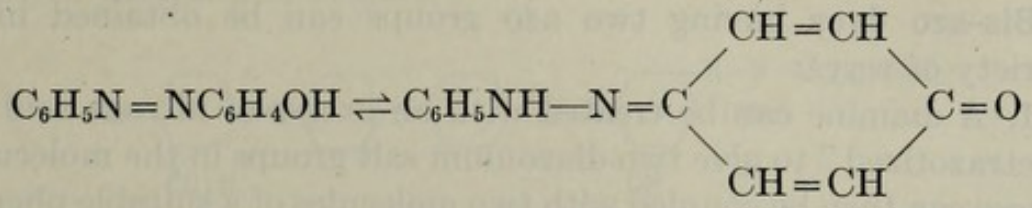
## *E.* Azo Dyes

These contain in addition to the *chromophore* group, $-N=N-$, an *auxochrome* group which is either basic like $NH_2$ or $NMe_2$ or acidic like OH. These active groups either hold the dye to the fiber in the *direct dyeing* of silk or wool or to the *mordant* such as the hydroxides of various heavy metals to give the colored *lakes* formed in the *indirect dyeing* of cotton. The structure of an azo

dye is readily found by vigorous reduction with Sn and HCl to give two amines which can then be identified.

$$ArN{=}NArX + 4\,[H] \rightarrow ArNH_2 + XArNH_2$$

Hydroxyazo compounds are probably tautomeric.



The *chrysoidines* are a group of yellow to brown dyes including *p*-aminoazobenzene, Aniline Yellow, and its derivatives. They are obtained by coupling a suitable diazonium salt with a suitable aryl amine. If a primary amine is used, the first product is a diazoamino compound which can be rearranged to the desired product by warming with an amine hydrochloride as a catalyst.

$$ArN_2Cl + ArNH_2 \rightarrow ArN_2NHAr \rightarrow ArN_2ArNH_2$$

The aryldiazo group always shifts to the *p*-position if possible. If that is occupied, it shifts more slowly to the *o*-position. *Chrysoidine* itself, the hydrochloride of 2,4-diaminoazobenzene, is obtained from benzenediazonium chloride and *m*-phenylene diamine. Both $NH_2$ groups in the latter activate the same H. *Bismarck Brown* is the hydrochloride of 2,4,3′-triaminoazobenzene obtained by the treatment of 2 mols of *m*-phenylene diamine in acid with 1 mol of nitrous acid. Thus, as soon as an amino group reacts, the resulting diazonium salt couples with another molecule of diamine. *Methyl Orange* is the Na salt of helianthine, 4-dimethylamino-azobenzene-4′-sulfonic acid, obtained by diazotizing sulfanilic acid and coupling with dimethylaniline. *Methyl Red*, is the Na salt of 4-$Me_2N$-azobenzene-2′-carboxylic acid, similarly prepared from anthranilic acid and dimethyl aniline (OS).

The *Tropaeolines* are dyes including *p*-hydroxyazobenzene and its derivatives. *Tropaeolin O* or *Resorcinol Yellow*, 2,4-dihydroxyazobenzene-4′-sulfonic acid, is prepared from diazotized sulfanilic acid and resorcinol. *Para Red* is the product of diazotized *p*-nitroaniline and an alkaline solution of beta-naphthol, the coupling taking place in the 1-position. This is used as a dry color for

paints, etc., and is produced in the fiber by soaking the cloth in a solution of Na betanaphtholate, drying, and then passing it through a solution of the diazonium salt. This solution is usually made from a stabilized solid *p*-nitrobenzene diazonium salt ("nitrosamine red").

**Bis-azo dyes** having two azo groups can be obtained in a variety of ways:

1. A diamine can be treated with an excess of nitrous acid or "tetrazotized" to give two diazonium salt groups in the molecule. These can then be coupled with two molecules of a suitable phenyl or aryl amine. A modification of *Bismarck Brown* is obtained by coupling tetrazotized *m*-phenylene diamine with 2 mols of the diamine.

2. An amino derivative of an azo compound can be diazotized and coupled. *Sudan III* is thus obtained from aminoazobenzene and β-naphthol.

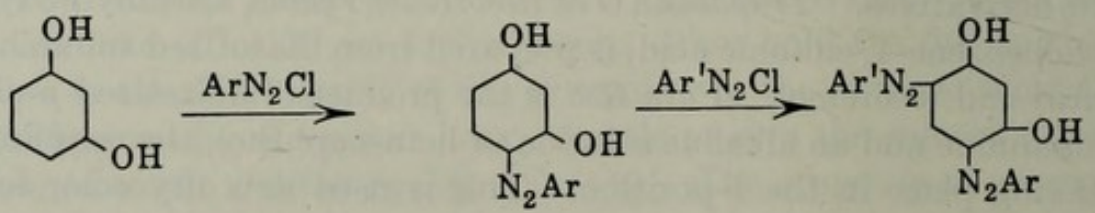
3. The $NH_2$ in a nitroamine may be protected by conversion to the sulfamic acid, the $NO_2$ can be reduced, diazotized with 1 mol of $HNO_2$, and coupled with a suitable phenol or amine. Then the sulfamino group can be diazotized with excess $HNO_2$ and coupled.

$$O_2NArNH_2 \xrightarrow{ClSO_3H} O_2NArNHSO_3H \rightarrow H_2NArNHSO_3H \rightarrow$$

$$ClN_2ArNHSO_3H \xrightarrow{Ar'X} XAr'—N_2ArNHSO_3H \xrightarrow{HNO_2}$$

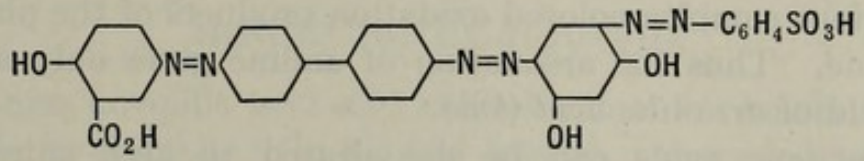
$$XAr'—N_2—ArN_2Cl \xrightarrow{Ar''Y} XAr'N_2ArN_2Ar''Y$$

4. A diamine or a dihydric phenol can be coupled with 2 mols of a diazonium salt or successively with one mol of each of two different diazonium salts. This procedure is possible because after one such coupling has taken place a second coupling takes place much more slowly.



If Ar is the radical of *m*-xylidine and Ar′ that of sulfanilic acid the product is *Resorcinol Brown.*

**Tris-azo and tetrakis-azo dyes** are obtained by applications of the same principles. *Congo Brown G* is the product of coupling diazotized sulfanilic acid with the bis-azo dye from benzidine, salicylic acid and resorcinol.




*Hessian Brown BB* is obtained by coupling 2 mols of diazotized sulfanilic acid with the bis-azo dye from the coupling of tetrazotized benzidine with 2 mols of resorcinol.

## VIII. AROMATIC COMPOUNDS OF MEMBERS OF THE PHOSPHORUS FAMILY

Many such compounds are known. In formulas they resemble the compounds of nitrogen. In general they can be made by treating the inorganic halides with aromatic Grignard reagents or aromatic mercury compounds (Michaelis). Thus

$$PCl_3 + Ph_2Hg \rightarrow PhPCl_2 + PhHgCl$$

Because of their use in the treatment of protozoal diseases such as syphilis and African sleeping sickness, the aromatic compounds of arsenic have been studied most extensively.

The most important aromatic compounds of arsenic are the arsonic acids (arsinic acids), $ArAsO_3H_2$. These are most generally prepared from a diazotized amine and sodium arsenite.

$$ArN_2Cl + Na_2HAsO_3 \rightarrow ArAsO_3HNa + NaCl + N_2$$

The process is entirely analogous to the preparation of a sulfonic acid from sodium sulfite (p. 166). Another preparation is by the combined oxidation and hydrolysis of an aryl dichloroarsine by chlorine water

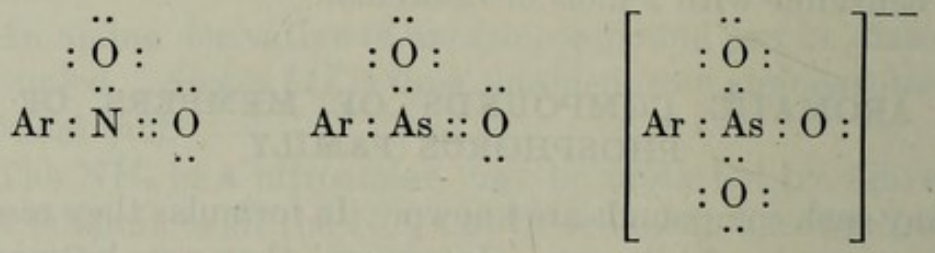
$$ArAsCl_2 + Cl_2 + 3\ H_2O \rightarrow ArAsO_3H_2 + 4\ HCl$$

If an activating group such as OH or $NH_2$ is present, direct arsonation with sirupy arsenic acid is possible.

$$HOC_6H_5 + H_3AsO_4 \rightarrow H_2O + HOC_6H_4AsO_3H_2$$

The reaction requires a higher temperature than does nitration. This causes a greater amount of oxidation by the arsenic acid to give various complex colored oxidation products of the phenol or the amine. Thus the arsonation of aniline gives only about a 15% yield of *arsanilic acid* (OS).

The arsonic acids can be dehydrated to give anhydrides, $ArAsO_2$, analogous to the nitro compounds. The relation may be shown electronically:



The inability of the nitrogen to assume a hydrated form corresponding to the arsonic acids is probably due to the smallness of its kernel as compared with that of arsenic and corresponds to the non-existence of orthonitric acid, $H_3NO_4$.

The aryl arsonic acids are crystalline solids.

The arsonic acid group is attached firmly to the aromatic nucleus and can be removed only by heating with HI.

The aryl arsonic acids give soluble alkali and insoluble heavy metal salts.

Reduction converts the arsonic acids to *arsenoxides*, ArAsO, corresponding to nitroso compounds, to arseno compounds, $ArAs=AsAr$, analogous to azo compounds, and to primary arsines, $ArAsH_2$, related to aniline as $AsH_3$ is to $NH_3$.

**Arsanilic acid,** *p*-aminophenyl arsonic acid, $H_2NC_6H_4AsO_3H_2$, readily obtained by the direct arsonation of aniline (OS) shows all the properties of an aromatic amine and an arsonic acid. Its sodium salt is *Atoxyl* formerly used in protozoal diseases but abandoned because of its high toxicity.

**Phenol arsonic acid,** *p*-hydroxyphenyl arsonic acid,

$$HOC_6H_4AsO_3H_2,$$

from the direct arsonation of phenol (Conant 1919), is the main intermediate for Salvarsan.

**Tryparsamide,** N-phenylglycineamide-4-arsonic acid,

$$H_2NCOCH_2NHC_6H_4AsO_3H_2,$$

made from arsanilic acid and chloroacetamide (Jacobs 1919) is valuable in sleeping sickness and has been proposed for use in paresis.

**Arsenobenzene,** $C_6H_5As=AsC_6H_5$, m. 196°, pale yellow crystals can be made from phenyl arsine and phenyl arsenoxide or by the reduction of phenyl arsonic acid.

The *arseno group* is much less stable than the azo group. Thus heat converts arsenobenzene to *triphenylarsine*, $(C_6H_5)_3As$, and arsenic. Chlorine, oxygen and sulfur break the As—As bond to give $ArAsCl_2$, ArAsO and ArAsS.

Substituted arsenobenzenes containing hydroxyl or amino groups or combinations of them are less toxic than the arsonic acids and have replaced them in therapy.

When an arsonic acid containing a nitro group is reduced, either or both groups may be attacked depending on the reducing agent used.

1. Both groups can be reduced completely by an active metal and a strong acid to give aminoaryl arsines such as $H_2NC_6H_4AsH_2$.

2. The nitro group can be reduced to amino and the arsonic acid group to arsenoxide by sulfurous acid with catalysts like HI, $SOCl_2$ etc. to give amino arsenoxides, $H_2NC_6H_4AsO$.

3. The nitro group can be reduced by ferrous hydroxide without changing the arsonic acid group to give $H_2NC_6H_4AsO_3H_2$.

4. The arsonic acid group can be reduced to give an arseno compound without changing the nitro group by means of phosphorous acid, $H_3PO_3$, or hypophosphorous acid, $H_3PO_2$.

5. The most important reduction gives the aminoarseno compounds. This is best given by sodium hydrosulfite, $Na_2S_2O_4$.

**Salvarsan, Arsphenamine,** "606," Kharsivan, Arsenobillon, 3,3′-diamino-4,4′-dihydroxyarsenobenzene hydrochloride (Ehr-

lich), was the first important arsenical drug and is still made and used in large amounts. Several preparations are known. *p*-Hydroxyphenyl arsonic acid, obtained by direct arsonation of phenol or by diazotization of arsanilic acid, is nitrated ortho to the hydroxyl group. Reduction of this product with sodium hydrosulfite gives the base of salvarsan. Salvarsan is kept free from air because of its ready conversion to the more toxic arsenoxide. It is probable that the latter is the actual therapeutic agent in the body since salvarsan does not kill protozoa *in vitro* whereas the arsenoxide does. The latter has been introduced into therapy as Mapharsen, 3-amino-4-hydroxyphenylarsenoxide.

*Neosalvarsan,* neoarsphenamine, "914," is the sodium salt of the formaldehyde sulfoxylate of salvarsan base. The grouping $-NHCH_2OSONa$ renders it soluble in water to give a neutral solution whereas salvarsan gives a strongly acid solution which has to be exactly neutralized just before its use. Many modifications of the salvaran structure have been prepared and tested.

Compounds have been prepared containing arsenic as a member of a heterocyclic ring. The best known of these is 10-chloro-5,10-dihydrophenarsazine, Adamsite, "DM," obtained from diphenylamine and $AsCl_3$. It was prepared during the World War as a toxic sternutatory.

"Organic Arsenical Compounds." Raiziss and Gavron. A.C.S. Monograph No. 15.

**Organic compounds of antimony** have been prepared in great numbers by reactions much like those used for arsenicals.

"Organic Derivatives of Antimony." Christiansen, A.C.S. Monograph No. 24.

## IX. AROMATIC COMPOUNDS OF MERCURY AND OTHER METALS

These have been studied in great variety. Mercury derivatives especially are known for every type of aromatic hydrocarbon and their derivatives.

**Mercury diphenyl, diphenylmercury,** $(C_6H_5)_2Hg$, m. 121°, is typical of the aromatic *mercuri-bis* compounds in which both valences of mercury are attached to carbon.

*Preparation.* 1. From bromobenzene and dilute sodium amalgam in presence of catalysts such as ethyl acetate.

2. From mercuric chloride or phenylmercuric chloride and excess phenyl magnesium bromide.

3. From phenylmercuric halides and various reagents which remove mercuric ions from solution more completely than does a base. The reaction

$$2\ ArHgX \rightleftharpoons Ar_2Hg + HgX_2$$

usually goes to the left. Removal of Hg ions causes it to go to the right. Alkali sulfides give insoluble HgS and leave diphenylmercury. Iodides, thiosulfates and similar compounds give stable complex ions of mercury. Alkaline reducing agents such as sodium stannite, copper and pyridine, and hydrazine (Gilman 1936) give metallic mercury and the diarylmercury.

4. From the double salt of benzene diazonium chloride and $HgCl_2$ heated with copper (Nesmejanov 1929).

$$2\ PhN_2Cl.HgCl_2 + 6\ Cu \rightarrow Ph_2Hg + Hg + 2\ N_2 + 6\ CuCl$$

This is the most general preparation of aromatic mercuri-bis compounds and gives substances otherwise not readily available. Thus di-β-naphthylmercury is easily made from β-naphthylamine (OS).

*Reactions.* 1. Diphenylmercury is *stable* to water, alcohols, ammonia, hydrogen sulfide and other active hydrogen compounds which decompose C—Mg linkages.

2. With strong acids, the C—Hg linkages are split stepwise, the first one being much more easily split than the second.

$$Ph_2Hg \xrightarrow{HX} C_6H_6 + PhHgX \xrightarrow{HX} HgX_2 + C_6H_6$$

3. Halogens also break the C—Hg linkages stepwise

$$Ph_2Hg \xrightarrow{X_2} PhX + PhHgX \xrightarrow{X_2} HgX_2 + PhX$$

In this respect thiocyanogen, $(SCN)_2$ acts like a halogen (Söderbäck 1919).

4. Active metals replace the mercury. In this way phenyl compounds of Na, Mg, Zn, Cd, Al and Bi have been obtained.

5. Halides of non-metals such as boron, silicon, phosphorus, arsenic and antimony react with mercury diphenyl to give phenyl compounds of the non-metal. One or more of the halogen atoms are replaced by phenyl, depending on conditions.

6. Mercuric salts give a reaction characteristic of mercuri-bis compounds to form the half organic mercury derivatives

$$Ar_2Hg + HgX_2 \rightarrow 2\ ArHgX$$

7. Reactions which might be expected but which fail are ones analogous to certain Grignard reactions. Thus there is no action with carbonyl compounds and no metathesis with alkyl halides. In the latter case the organic mercury compound acts at high temperature as a *hydrocarbo base* (L. W. Jones 1918)

$$Me_2CHCH_2Br + Ph_2Hg \rightarrow PhHgBr + C_6H_6 + Me_2C{=}CH_2$$

**Phenylmercuric salts** are obtainable in a variety of ways:

1. By direct mercuration of benzene by mercuric acetate in alcohol solution (Maynard 1924)

$$C_6H_6 + Hg(OAc)_2 \rightarrow C_6H_5HgOAc + HOAc$$

Mercuration is a general process and follows the same course as bromination but is less vigorous than the latter process. Treatment of the phenylmercuric acetate with halide solutions gives phenylmercuric halides.

2. From benzene sulfinic acid and mercuric chloride.

$$PhSO_2H + HgCl_2 \rightarrow PhHgCl + SO_2 + HCl$$

This gives a very general process for introducing mercury into a specific position in an aromatic nucleus. The process can start with a known amine and go to the sulfinic acid by diazotization or can start with a known sulfonic acid and go through the sulfonyl chloride to the sulfinic acid. The most readily available aromatic mercurial is *p*-tolylmercuric chloride made in this way from the by-product, *p*-toluene sulfonyl chloride, of saccharin manufacture (OS).

3. By diazotization of aniline through the double salt with mercuric chloride (Nesmejanov).

4. By the action of mercuric salts on various substances such as phenyl magnesium bromide, phenyl boric acid, $PhB(OH)_2$, or phenyl arsenoxide, PhAsO.

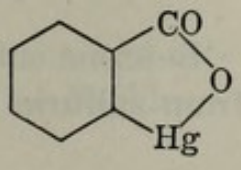
The *reactions* of the phenylmercuric salts resemble those of diphenylmercury.

Mercury derivatives of aromatic compounds containing activating groups such as hydroxyl and amino are readily available by direct mercuration in positions para and ortho to these groups. Just as the $NH_2$ and OH groups render the *o*- and *p*-H atoms more readily replaceable they weaken a C—Hg bond in the *o*- or *p*-position. Such compounds react more readily with acids than do phenylmercuric derivatives.

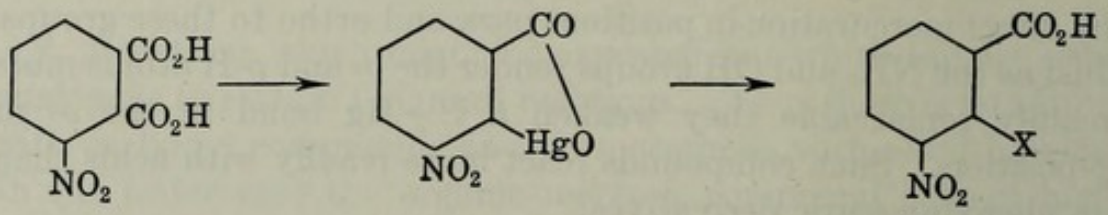
The ease of mercuration of such compounds can be illustrated by phenol. Thus if dry mercuric acetate is added to an excess of hot phenol the chief products are *o*- and *p*-acetoxymercuriphenol and 2,4-di-acetoxymercuri-phenol. When the mixture is poured into hot water, the first two and the excess of phenol dissolve. Thus the more highly mercurated products can be removed by filtration while hot. Treatment of the filtrate with hot NaCl solution precipitates *p*-chloromercuriphenol. Another filtration while hot gives a filtrate which deposits *o*-chloromercuriphenol in a high state of purity on cooling (OS). The careful treatment of this compound with 1 mol of halogen or thiocyanogen gives the corresponding *o*-substituted phenol very satisfactorily (OS).

Mercury derivatives of aromatic compounds containing *meta*-directing substituents can also be obtained by direct mercuration. Usually a mixture of all possible compounds is obtained with the *ortho* predominating. Consequently an indirect method of preparation is usually employed to obtain a pure product. Thus the three mercuri-benzoic acids are best obtained respectively by oxidation of *p*-chloromercuritoluene (OS), from diazotized *m*-aminobenzoic acid and from phthalic anhydride by heating with mercuric acetate to give anhydro-*o*-hydroxymercuribenzoic acid (OS).

$$C_6H_4(CO)_2O \rightarrow C_6H_4(CO_2Na)_2 \rightarrow C_6H_4(CO_2)_2Hg \longrightarrow CO_2 +$$



This reaction is general for aromatic dibasic acids which form internal anhydrides. In the case of 3-nitrophthalic acid, the 2-carboxyl is eliminated exclusively (OS). This gives a method of making such substances as 2-bromo-3-nitrobenzoic acid which would not otherwise be available (OS). The corresponding iodo compound has been invaluable in preparing ortho substituted diphenyls by the action of Cu (Adams).




Organic Compounds of Mercury. Whitmore, A.C.S. Monograph No. 3, 1921.

## X. AROMATIC SULFONIC ACIDS

One of the most notable characteristics of aromatic hydrocarbons and their derivatives is the ease with which they can be sulfonated by treatment with concentrated or fuming sulfuric acid or chlorosulfonic acid, $ClSO_3H$.

Benzene sulfonic acid, $C_6H_5SO_3H$, is readily obtained from benzene and sulfuric acid on heating.

$$C_6H_6 + H_2SO_4 \rightarrow H_2O + C_6H_5SO_3H$$

The C—S linkage is very stable. It can be broken by heating at about 150° with hydrochloric acid or superheated steam or by fusion with strong alkalies.

$$PhSO_3H + H_2O \rightarrow C_6H_6 + H_2SO_4$$
$$PhSO_3Na + 2\,NaOH \rightarrow PhONa + Na_2SO_3 + H_2O$$

In one of these processes the phenyl appears to be "negative" and in the other "positive." Another important replacement of the sulfonic acid group gives benzonitrile on fusion with alkali cyanide.

$$PhSO_3Na + NaCN \rightarrow Na_2SO_3 + PhCN$$

Benzene sulfonic acid as a strong acid, forms salts. It differs from sulfuric acid in giving soluble Ba and Ca salts. It forms

esters with primary alcohols. These, on heating alone, give olefins while heating with excess alcohol gives ethers. Thus aromatic sulfonic acids are useful catalysts for the preparation of olefins and ethers. They have the advantage of not causing charring as does sulfuric acid. Sulfonic esters react fairly smoothly with Grignard reagents to form hydrocarbons (Gilman).

$$ArSO_3R + R'MgX \rightarrow R{-}R' + ArSO_3MgX$$

If the ester of a halogenated alcohol is so used, this method can be employed to make higher alkyl halides. Thus the carbon chain of an alkyl halide can be increased by three carbons by converting it to the Grignard reagent and heating with a sulfonic ester of 3-chloropropyl alcohol (Rossander 1928)

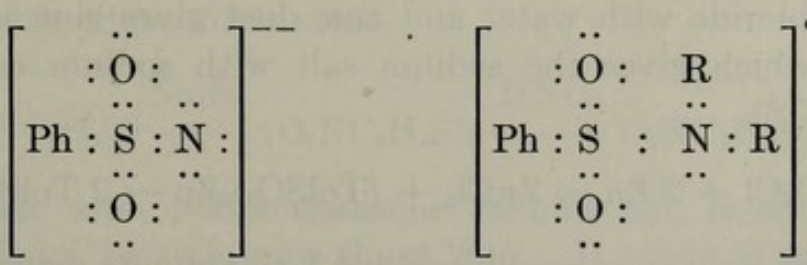
$$RMgX + ArSO_3(CH_2)_3Cl \rightarrow R(CH_2)_3Cl$$

Inorganic acid chlorides such as $PCl_5$ replace the hydroxyl with chlorine forming *benzene sulfonyl chloride*, $PhSO_2Cl$.

$$PhSO_3H + PCl_5 \rightarrow PhSO_2Cl + POCl_3 + HCl$$

This behaves as an acid chloride. It is only slightly reactive with cold water but reacts in the usual way with hot water, bases and ammonia. The product of the last reaction, *benzene sulfonamide*, m. 150°, is representative of the aromatic sulfonamides which are useful in identifying sulfonic acids because they are easily purified crystalline substances of definite melting points.

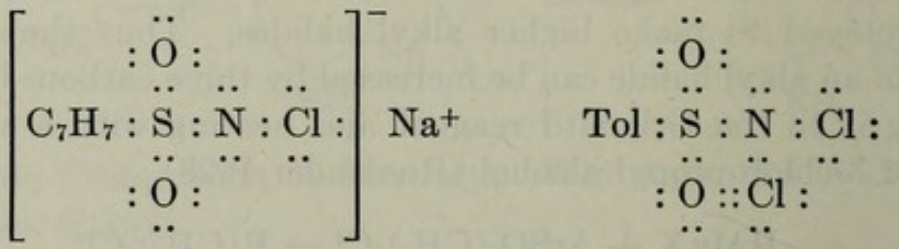
The sulfonamides differ from the amides of carboxylic acids in being soluble in alkalies. This solubility is due to the H attached to nitrogen since $PhSO_2NH_2$ and $PhSO_2NHR$ are soluble in alkali while $PhSO_2NR_2$ is not.



The Hinsberg method of separating primary, secondary and tertiary amines is based on this property (p. 189). The N-chloro-

derivatives of the sulfonamides obtained by the action of HOCl have antiseptic properties.

**Chloramine T** (Tolamine) is the sodium salt of N-chloro-*p*-toluene sulfonamide obtained from the amide and NaOCl solution (I). *Dichloroamine-T* is the N-dichloro compound (II). *Halozone* is the corresponding carboxylic acid obtained by oxidizing *p*-toluene sulfonamide with chromic acid mixture and treating the product with alkali and chlorine.



I II

The ortho sulfonic acid of toluene is important as related to saccharin. Toluene on treatment with excess of chlorosulfonic acid gives a considerable amount of *o*-toluene sulfonyl chloride with the *p*- and *m*-compounds as by-products. In this process the chlorosulfonic acid acts both as a sulfonating agent and an acid chloride

$$C_7H_8 \rightarrow C_7H_7SO_3H \rightarrow C_7H_7SO_2Cl$$

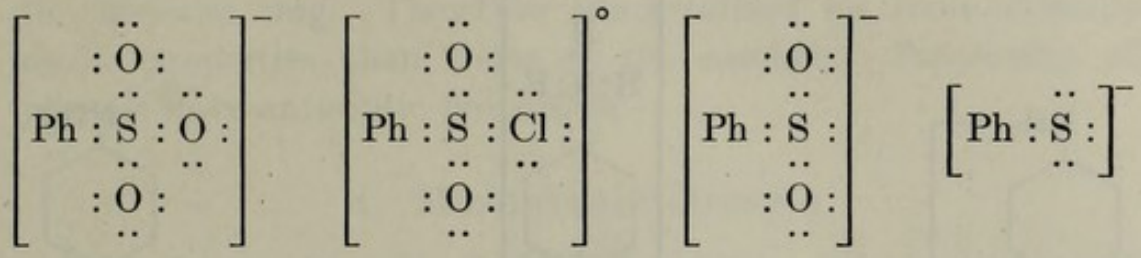
The *p*-toluene sulfonyl chloride is an important by-product.

**Aryl sulfonyl chlorides** on vigorous acid reduction, as with Zn dust and acid, give thiophenols. The acids themselves cannot be thus reduced. The chlorides with neutral or basic reducing agents give sulfinic acids, $ArSO_2H$, or their salts. Thus *p*-toluene sulfonyl chloride with water and zinc dust gives zinc *p*-toluene sulfinate which gives the sodium salt with sodium carbonate solution (OS).

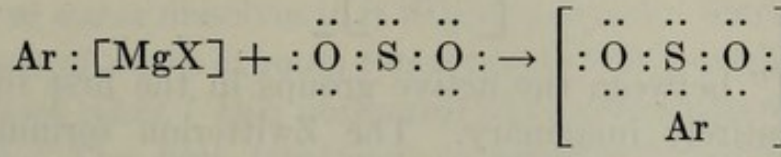
$$2\ TolSO_2Cl + 2\ Zn \rightarrow ZnCl_2 + (TolSO_2)_2Zn \rightarrow 2\ TolSO_2Na$$

The sulfinic acids are readily oxidized to sulfonic acids. They differ from the latter in being reducible to thiophenols by acid

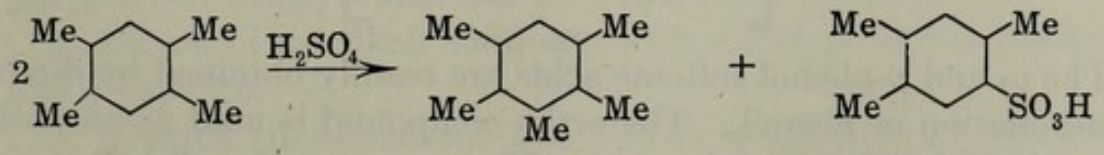
and metals. The sulfinic acid group is replaced by the HgCl group on boiling with $HgCl_2$ solution.



Sulfinic acids can also be prepared from Girgnard reagents and $SO_2$.



**Sulfonic acids of the homologs of benzene** are known in great numbers. Those containing at least four substituent groups have been extensively studied because of the *Jacobsen reaction*, a peculiar process in which groups like alkyl, halogen or sulfonic acid shift intermolecularly under the influence of concentrated sulfuric acid (L. I. Smith 1936). The peculiar action of sulfuric acid on durene is an example.

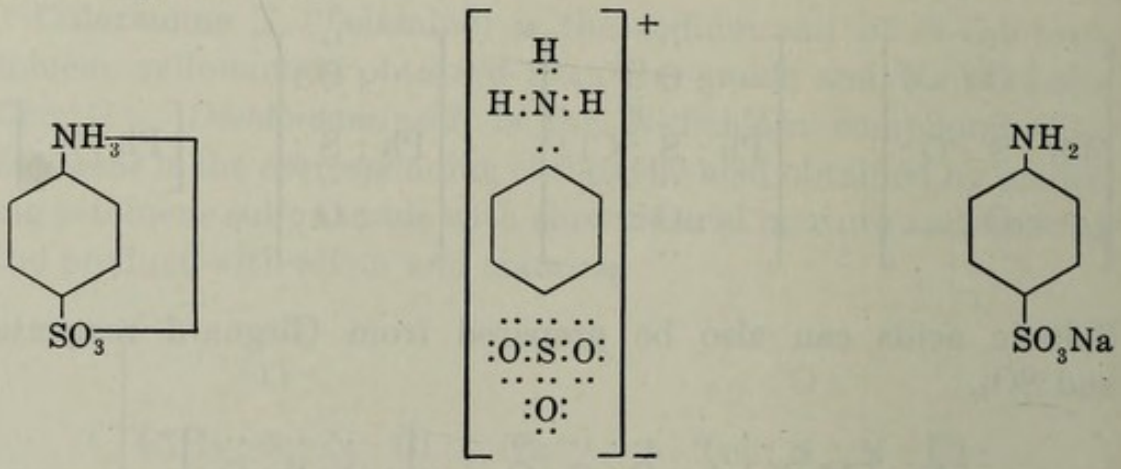


Nitration, sulfonation, and halogenation of benzene sulfonic acid give mainly the meta compounds. The *o*- and *p*-nitrobenzene sulfonic acids are made by oxidizing the corresponding disulfides with dilute nitric acid.

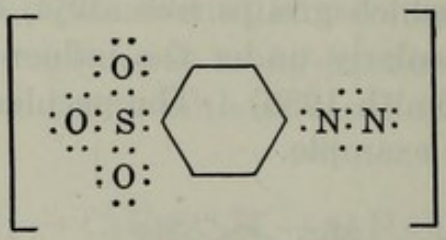
$$O_2NC_6H_4Cl \xrightarrow{Na_2S_2} (O_2NC_6H_4S)_2 \xrightarrow{HNO_3} O_2NC_6H_4SO_3H$$

**Sulfanilic acid,** *p*-aminobenzene sulfonic aid, is obtained by "baking" aniline sulfate to about 200°. It exists as an internal salt or "Zwitterion." With strong bases it gives salts but does not do so with acids. This is because of the strongly acid nature

of the sulfonic acid group. These relations are shown in the following formulas:




The "bond" between the active groups in the first formula is probably entirely imaginary. The Zwitterion formula better represents the facts. The *m*-isomer, *metanilic acid*, is obtained by reducing the *m*-nitrobenzene sulfonic acid obtained by sulfonating nitrobenzene. Diazobenzene sulfonic acid is a relatively stable diazonium salt.




The *o*- and *p*-phenol sulfonic acids are readily obtained by direct sulfonation of phenol. The ortho compound is used as an antiseptic, Aseptol or Sozolic acid. The corresponding di-iodo compound is Sozoiodol, a substitute for iodoform.

Sulfanilamide and some of its derivatives have a specific action on streptococci (*Prontylin, Prontosil*).

Just as the $NH_2$ and OH groups activate the *o*- and *p*-H atoms, so do they loosen the sulfonic acid groups in these positions. Thus the sulfonic acids of aniline and phenol are much more readily hydrolyzed than those of benzene. An example of this is the conversion of *o*-phenol sulfonic acid to the *p*-compound by boiling water. This represents the results of two equilibrium reactions rather than a true rearrangement.

$$o\text{-acid} + H_2O \rightleftharpoons \text{phenol} + H_2SO_4 \rightleftharpoons p\text{-acid} + H_2O$$

The *p*-acid is less readily hydrolyzed and is formed predominantly during sulfonation.

## XI. PHENOLS

**Phenols** have at least one hydroxyl group attached directly to the benzene ring. They are characterized by more strongly acidic properties than those of the alcohols. Practically all phenols have antiseptic properties.

### *A.* Monohydric Phenols

**Phenol,** carbolic acid, $C_6H_5OH$, m. 42°, b. 181°, occurs in coal tar along with many homologs (*tar acids*). The pure white crystalline substance turns red due to partial oxidation. A small amount of water dissolves in it to give a liquid. Phenol is soluble in 15 parts of water at room temperature and is readily soluble in alcohol and ether. It is poisonous and gives dangerous burns on the skin. The best treatment is immediate application of a dilute solution of bromine in glycerol which converts the phenol to the very insoluble tribromophenol. Treatment with alcohol is also effective.

*Preparation.* The methods used to obtain phenol apply to its homologs in general.

1. From coal tar. Extraction by a base followed by acidification, usually by $CO_2$ in the form of flue gases, gives a mixture of phenols (tar acids) which can be fractionally distilled.
2. Fusion of an alkali sulfonate with alkali gives the phenate and a bisulfite.
3. Heating chlorobenzene and NaOH in presence of diphenyl oxide under pressure gives sodium phenate (Hale 1927).
4. A diazonium sulfate solution on heating gives a phenol.
5. The direct oxidation of benzene to phenol has not yet been achieved.

*Reactions.* A consideration of the formula of phenol shows several relations of its hydroxyl to the rest of the molecule. It can be regarded as a tertiary alcohol but the acidic properties do not correspond to such a classification since tertiary alcohols are less acidic than primary and secondary alcohols. Moreover tertiary alcohols are hard to oxidize whereas phenols are very sensitive to oxidation. Phenol may also be regarded as a vinyl

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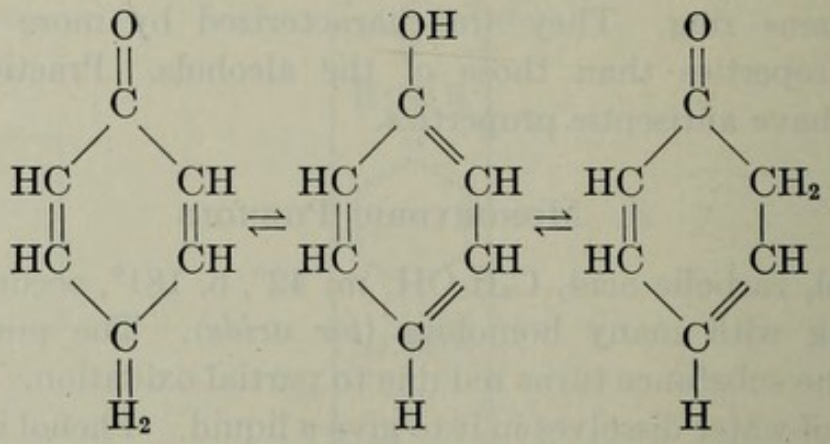
alcohol and an allyl alcohol. Moreover there is evidence that a tendency to tautomerism also exists in the phenols.



This process probably involves the addition of $H^+$ ion at the 2,4, or 6 position followed by the expulsion of $H^+$ ion from the hydroxyl and a corresponding shift of bonds. The tautomerism of phenol probably accounts for its easy oxidation. It undoubtedly accounts for its easy hydrogenation to hexahydrophenol (cyclohexanol, hexalin).

The reactions of phenol are typical of this class of compounds. They may be divided into three groups: those involving (*A*) the H of the hydroxyl group, (*B*) the hydroxyl group itself and (*C*) the *o*- and *p*-H atoms of the ring.

*A. Reactions involving the replacement of the hydroxyl hydrogen.*

1. The hydrogen is replaceable by means of strong bases to give phenolates, phenates or phenoxides, ArONa, etc. These are readily hydrolyzed but not to the same extent as the alcoholates. Since phenol is a very weak acid, it is liberated from its salts by $CO_2$.

$$C_6H_5ONa + CO_2 + H_2O \rightarrow C_6H_5OH + NaHCO_3$$

2. Replacement of the H of the hydroxyl group by acid groups gives esters. This process takes place less readily than with primary and secondary alcohols. *Phenyl acetate*, $C_6H_5OCOCH_3$, b. 193°, obtained by heating phenol, acetic anhydride and anhydrous sodium acetate is much more readily hydrolyzed than ordinary acetates. Salts of phenyl hydrogen sulfate such as $C_6H_5OSO_3K$ occur normally in the urine of the herbivora and in that of other animals after ingestion of phenol.

3. Ethers of phenol are readily obtained by treating a phenolate or a phenol in alkaline solution with an alkylating agent such as MeI or $Me_2SO_4$. *Anisole*, $C_6H_5OCH_3$, b. 154° and *phenetole*, $C_6H_5OC_2H_5$, b. 170°, are the best known phenyl ethers. *Diphenyl ether*, diphenyl oxide, $(C_6H_5)_2O$, m. 28°, b. 259°, is obtained by heating chlorobenzene and NaOH under high pressure (Dow). It is valuable as a high temperature heat transfer medium (Dowtherm). *Phenolates*, phenates PhONa, give metathetical reactions with alkyl halides with unusual smoothness apparently because of the great activity of the phenolate ion, $PhO^-$.

4. Phenol gives a violet color with ferric chloride. Many phenols give characteristic colors with this reagent.

*B. Replacement of the hydroxyl group.*

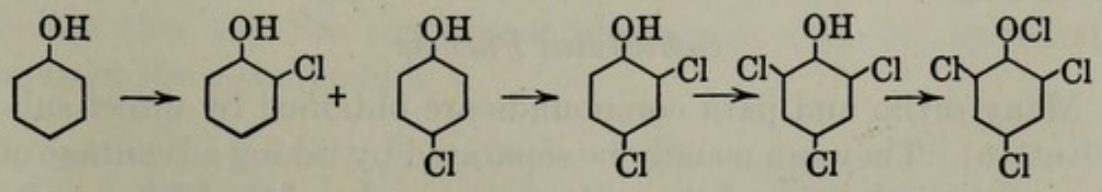
1. Reduction or replacement by H is achieved by distillation with zinc dust. This process is valuable in studying the structure of complex phenols.

2. The replacement of the OH by halogen on treatment with halides of phosphorus, etc. takes place only to a limited extent, the chief products being esters of phosphorus acids, etc.

3. Replacement of the OH by $NH_2$ is obtained by heating with the addition compound of $NH_3$ and zinc chloride or calcium chloride.

*C. Reactions of the o- and p-H atoms of the ring.*

1. Ordinary substitutions by halogenation, nitration and sulfonation are very easy. The ease of oxidation is so great, however, that care has to be used to avoid complex oxidation products. Careful chlorination gives trichlorophenol and finally trichlorophenyl hypochlorite.



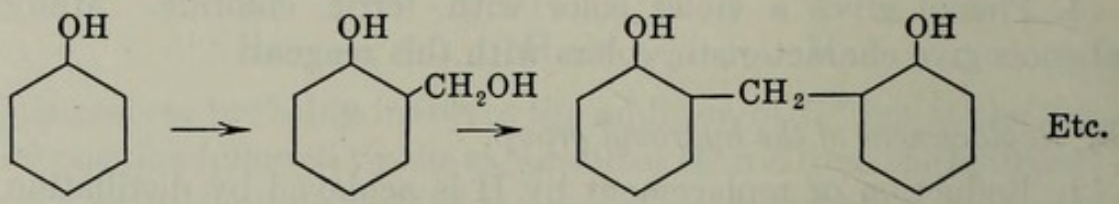

Phenol can be nitrated by dilute nitric acid in the cold. More vigorous treatment gives tarry oxidation products. Nitrated phenols are better prepared by hydrolysis of the nitrated chlorobenzenes.

2. Coupling with diazonium salts takes place readily, mainly in the para position.

3. A replacement of ring H takes place in the Kolbe synthesis of phenolic acids from phenates and $CO_2$.

4. Similarly the Reimer-Tiemann synthesis of phenolic aldehydes from phenates and chloroform involves an *o*- or *p*-H.

5. The most important use of phenol is based on the reactions of its *o*- and *p*-H atoms with formaldehyde to give resins of the bakelite type (redmanol, condensite etc). Steps such as the following are involved.




Such reactions can take place at three places in each phenol molecule. The resulting large molecules are too complex to crystallize and consequently form resins (Wanscheidt 1936).

6. Various complex reactions, such as oxidation, involve the ring hydrogen atoms. Liebermann's reaction consists of mixing the phenol with concentrated sulfuric acid and adding a little nitrite or a nitrosamine to produce a colored solution which turns blue or green on addition of alkali.

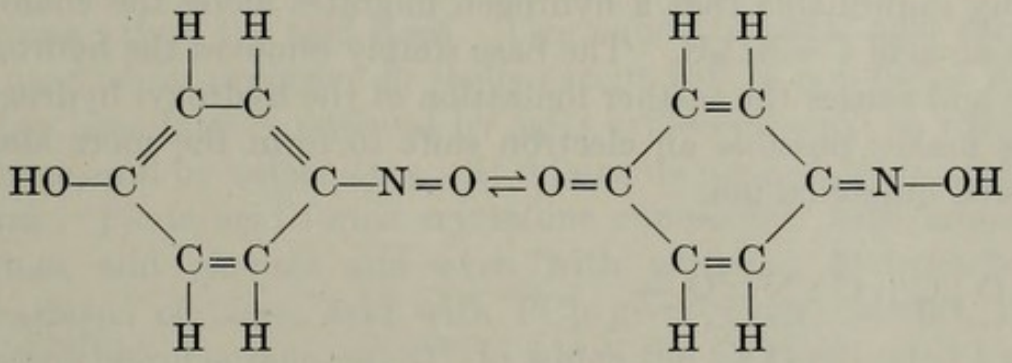
**Thiophenol,** mercaptobenzene, phenyl mercaptan, phenyl hydrosulfide, $C_6H_5SH$, b. 172°, is made by acid reduction of benzene sulfonyl chloride or by treating phenol with phosphorus pentasulfide. It has a vile odor. It gives ordinary mercaptan reactions such as the formation of $(PhS)_2Hg$ and PhSHgCl and ready oxidation to $(PhS)_2$. With benzene diazonium salts it gives $Ph_2S$.

### *Substituted Phenols*

Many ortho and para compounds are obtained by direct substitution. They can usually be separated by taking advantage of the greater volalitity of the ortho compound and the higher melting point of the para compound. The meta compounds are usually made from the corresponding nitro compound by reduction to the amine and diazotization of the latter.

*p*-Bromophenol is readily obtained by brominating phenol in a solvent such as $CS_2$ (OS). *p*-chlorophenol is obtained by the action of *p*-dichlorobenzene with NaOH under pressure. The *o*-compound is prepared similarly. *o*-Bromo- and *o*-iodo-phenol can be obtained by diazotizing the *o*-halogenated aniline or from *o*-chloromercuriphenol. Phenol can be directly iodinated by treatment with iodine and HgO in water suspension. Excess halogen converts phenol to the 2,4,6-trihalogenated products. Aqueous phenol with bromine water gives a precipitate of *sym*-tribromophenol, m. 92°.

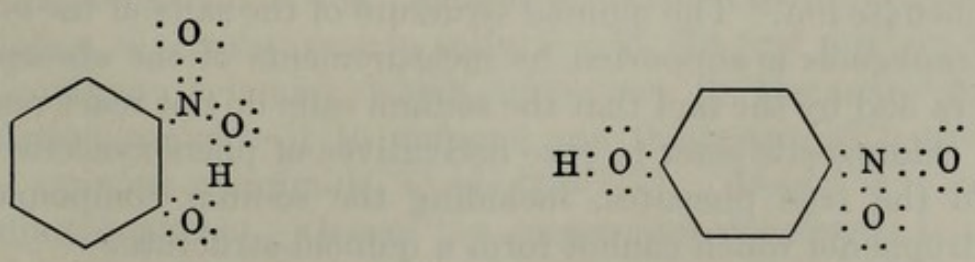
***p*-Nitrosophenol,** $HOC_6H_4NO$, is readily obtained from phenol and nitrous acid, from any *p*-nitroso-N-dialkylaniline and aqueous alkali, or from the controlled action of hydroxylamine with *p*-benzoquinone. It is identical with the monoxime of quinone.



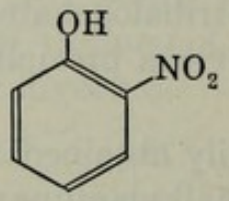
It forms colorless needles or greenish plates. It detonates on heating.

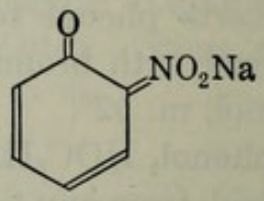
*Nitrophenols*

Treatment of phenol with cold dilute nitric acid gives a mixture of the *o*- and *p*-nitrophenols which can be separated by steam distillation, the ortho compound being volatile. This marked difference in volatility is believed to indicate the existence of a chelate ring and the consequent absence of a simple hydroxyl group in the *o*-compound.

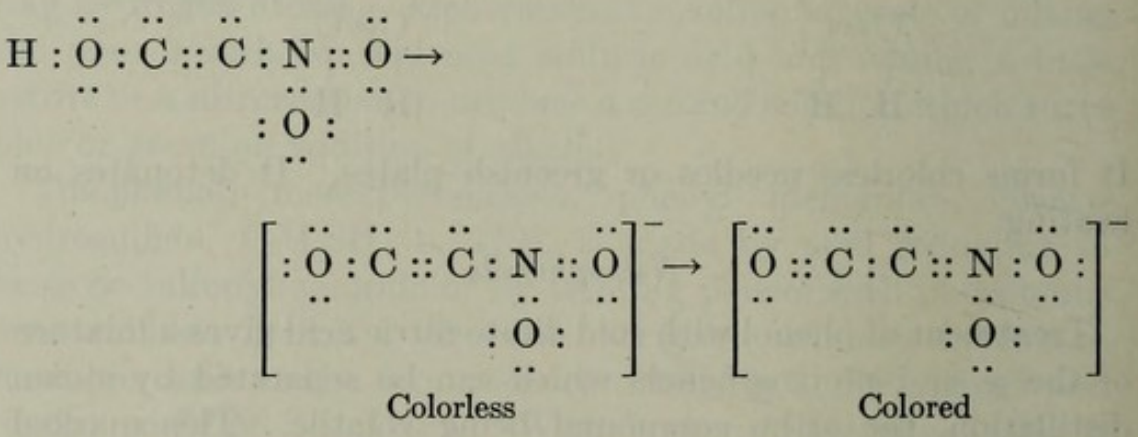


A better method for preparing these substances is by the action of bases on the readily available *o*- and *p*-nitro-chlorobenzenes (p. 736). The nitro group activates the chlorine in *o*- or *p*-position so that high temperatures and pressures are not necessary. The *o*- and *p*-nitrophenols form highly colored salts with bases or even alkali carbonates. These salts probably have quinoidal structures.



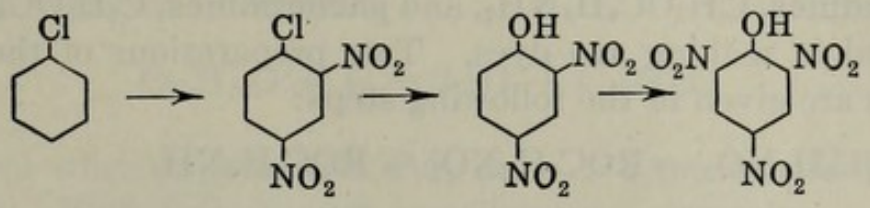

The systems $HO-C=C-NO_2$ and $HOC=C-C=C-NO_2$ found in *o*- and *p*-nitro phenols are not greatly ionized. Moreover, it is highly improbable that a hydrogen migrates along the chain to give an acid $C=NO_2H$. The base simply removes the hydrogen ions and causes the further ionization of the hydroxyl hydrogen. This makes possible an electron shift to form the more stable colored quinoidal ion.



Colorless Colored

Acidification supplies $H^+$ ions to the carbonyl oxygen and reverses the process. In a phenol not containing a nitro group in the *o*- or *p*-position, the removal of $H^+$ ion by the base leaves merely the phenate ion. The quinoid structure of the salts of the *o*- and *p*-nitrophenols is supported by measurements of the absorption spectra and by the fact that the sodium salts do not react readily with chloroacetic ester to give derivatives of phenoxyacetic acid as do the true phenates, including the sodium compound of *m*-nitrophenol which cannot form a quinoid structure.

The 2,4- and, less readily, the 2,6-dinitrophenols are obtained by further nitration. In presence of sulfuric acid, the nitration can be carried to the final step of *sym*-trinitrophenol or *picric acid*, m. 122°. This substance is a fairly strong acid. When the hydroxyl hydrogen is removed there are three different possible shifts to give a stable quinoidal ion. While it can be made from phenol it is better prepared in the following steps:




Picric acid is an explosive and a dye for silk and wool. The salts of picric acid, even those with the alkali metals, are much more explosive than the acid itself. Consequently picric acid cannot be used as an explosive in shells except with a non-metal liner. It has been largely replaced by safer explosives such as trinitrotoluene, and by better dyes. It retains its use as a treatment for burns. Picric acid forms crystalline compounds with aromatic amines and phenols and even with aromatic hydrocarbons. Treatment of picric acid with $PCl_5$ gives *picryl chloride*, *sym*-trinitrochlorobenzene, m. 81°, in which the Cl is activated by all three nitro groups.

### *Amino Phenols*

They are made by reduction of nitrophenols. The *o*- and *p*-compounds can also be made from the nitrochlorobenzenes and ammonia. They do not form phenates but give salts with strong acids. The free *o*- and *p*-bases are readily oxidized while the *m*- is not. Thus the first two and their derivatives are used as photographic developers.

***p*-Aminophenol,** m. 184°, rodinol, is obtained by the electrolytic reduction of nitrobenzene in sulfuric acid, the first product being β-phenylhydroxylamine which rearranges to the aminophenol. Oxidation converts it to quinone and treatment with chlorine gives quinone chlorimide, $O=C_6H_4=NCl$. *Amidol* is a salt of 2,4-diaminophenol. One of the commonest developers is *metol*,

pictol, N-methyl-*p*-aminophenol which can be made from hydroquinone and monomethylamine or by heating *p*-hydroxyphenylglycine in solution in a phenol.

$$HOC_6H_4NHCH_2CO_2H \rightarrow CO_2 + HOC_6H_4NHCH_3$$

***m*-Aminophenol** is best made by the alkali fusion of *m*-aminobenzene sulfonic acid.

**Anisidines,** $CH_3OC_6H_4NH_2$, and **phenetidines,** $C_2H_5OC_6H_4NH_2$, are used in making azo dyes. Two preparations of these substances are given in the following steps:

1. $ClC_6H_4NO_2 \rightarrow ROC_6H_4NO_2 \rightarrow ROC_6H_4NH_2$

2. $ROC_6H_4NH_2 \rightarrow ROC_6H_4N_2Cl \xrightarrow{\text{Phenol}}$

$$ROC_6H_4N{=}NC_6H_4OH \rightarrow ROC_6H_4N{=}NC_6H_4OR \rightarrow 2\,ROC_6H_4NH_2$$

The second preparation is valuable only when phenol is cheap.

**Aceto-*p*-phenetidine, phenacetine,** $EtOC_6H_4NHCOMe$, is an antipyretic.

*Homologs of Phenol*

Many of these are found in tar from coal and from wood and in certain essential oils. Commercial *cresylic acid* contains a small amount of phenol, the three cresols and considerable amounts of higher phenols including various xylenols. Various higher *tar acid* fractions are also available. The interest in these mixtures of phenol homologs is largely because of their increasing use to make resins with formaldehyde. For this purpose fractions of fairly definite composition are in increasing demand.

The three *cresols*, m. 31°, 12° and 36°, can be obtained pure by diazotization of the three toluidines. It is possible to fractionate the cresol mixture from coal tar into *o*-cresol, b. 191° and a mixture of *m*- and *p*-cresols, b. 202° and 202.5°. A mixture of cresols with various soaps gives a soluble disinfectant, *lysol*, *cresoline*, etc. The *o*- and *m*-cresol can be obtained by heating phosphorus pentoxide with carvacrol and thymol respectively. The six *xylenols* have the following melting and boiling points: *ortho*-xylenols, 1,2,3-, 73°, 213°; 1,2,4-, 65°, 222°; *meta*-xylenols,

1,2,3-, 74.5°, 212°; 1,3,4-, 25°, 209°; 1,3,5, *sym*-, 64°, 220°; *para*-xylenol, 1,3,4, 75°, 209°. Mixed xylenols are available commercially. *Symmetrical xylenol* is readily separated (Kester 1932).

**Carvacrol** is 2-hydroxy-4-isopropyltoluene. It occurs in certain essential oils but is best prepared by heating camphor with iodine. This remarkable change in structure involves the elimination of only two H atoms.

$$C_{10}H_{16}O + I_2 \rightarrow 2\,HI + C_{10}H_{14}O$$

Carvacrol when heated with $P_2S_5$ gives *p*-cymene (*p*-isopropyltoluene). With $P_2O_5$ it gives propylene and *o*-cresol.

**Thymol** is an isomer of carvacrol having the OH in the 3-position. It is readily available from oil of thyme. Its reactions are like those of its isomers except that $P_2O_5$ gives *m*-cresol.

### *B.* Dihydric Phenols

These resemble the monohydric phenols in most chemical properties. Those with the hydroxyls in the ortho or para position are especially sensitive to oxidation and are valuable reducing agents and serve as developers in photography.

*Catechol*, pyrocatechin, pyrocatechol, Brenzcatechin, *o*-dihydroxybenzene, *o*-$C_6H_4(OH)_2$, m. 105°, b. 240°, can be made by alkaline fusion of *o*-phenol sulfonic acid or *o*-dichlorobenzene. It has also been prepared by the action of HI on its monomethyl ether, *guaiacol*, found in beechwood tar. It is a powerful reducing agent, precipitating silver even from cold silver nitrate. Cautious oxidation with silver oxide gives orthobenzoquinone. (Willstaetter).

Its alkaline solution absorbs oxygen readily. Ferric chloride gives a green color. Bromination readily introduces 4 Br atoms. The product is oxidized by nitric acid to give dark red tetrabromo-*o*-benzoquinone.

**Veratrole,** m. 22°, b. 207°, is the dimethyl ether of pyrocatechol.

**Creosol,** b. 222°, 2-methoxy-4-methylphenol, a homolog of guaiacol, is also found in beechwood tar.

**Resorcinol,** resorcin, *m*-dihydroxybenzene, m. 110°, b. 276°, is prepared by the potash fusion of both *m*- and *p*-disulfonic acids of benzene. It is also obtained by similar fusion of all three of the bromobenzenesulfonic acids and of *m*-phenol sulfonic acid. It gives a dark violet color with $FeCl_3$. Although a less vigorous reducer than its *o*- and *p*-isomers it reduces silver nitrate solution on warming and an ammoniacal silver solution even in the cold. Its chief uses are in the preparation of fluorescein by action with phthalic anhydride and of hexylresorcinol. Because of the positions rendered very active by the *op*-hydroxyl groups it is a valuable coupling component of azo dyes. Nitration gives *styphnic acid*, *sym*-trinitroresorcinol which gives *styphnates* which are used for identification purposes much like picrates.

**Orcinol,** *sym*-dihydroxytoluene, (1,3,5), m. 108°, b. 290°, is found in various lichens. With phthalic anhydride it gives no compound analogous to fluorescein.

**Hydroquinone, quinol,** *p*-dihydroxybenzene, m. 170°, b. 286°, is prepared by the reduction of quinone, usually with sulfurous acid. Most oxidizing agents first change it to quinhydrone and then to quinone. Its strong reducing properties make it the most valuable photographic developer. Fusion with KOH in presence of air gives 1,2,4-trihydroxybenzene.

### *C.* Trihydric Phenols

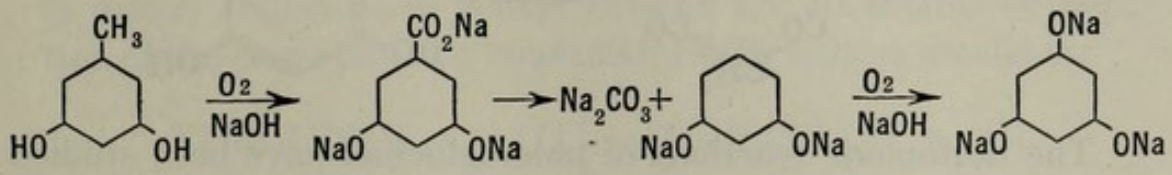
**Pyrogallol,** pyrogallic acid, 1,2,3-trihydroxybenzene, m. 134°, b. 309°, is made by thermal decarboxylation of gallic acid. It is a powerful reducing agent especially in alkaline solution as in its common use for absorbing oxygen in gas analysis. It differs from its symmetrical isomer in not reacting as a ketone with hydroxylamine.

**Phloroglucinol,** *sym*-trihydroxybenzene, m. 219°, occurs in various natural resins and in the glucoside *phloridzin*. The preparations of phloroglucinol involve a variety of principles.

1. By fusion of benzene-1,3,5-trisulfonic acid with alkali.

2. By similar fusion of resorcinol in presence of air. Thus benzene-*m*-disulfonic acid can be converted to phloroglucinol in much the way that anthraquinone *mono*sulfonic acid is converted to the *dihydroxyl* compound, alizarin.

3. A related although apparently remarkable preparation is by the fusion of *orcinol*, 3,5-$(OH)_2$-toluene with NaOH in presence of air. The following changes probably occur

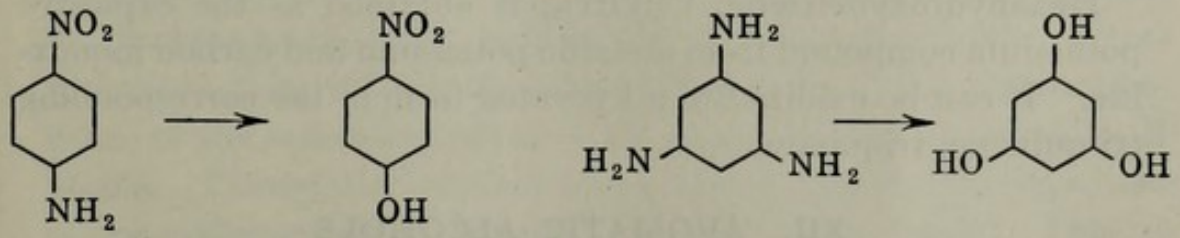



4. *sym*-Triaminobenzene is hydrolyzed to the trihydroxy cpd. by merely boiling its hydrochloride with water. The same product is obtained from the corresponding benzoic acid. The steps involved in the preparation of phloroglucinol from commercial trinitrotoluene would be as follows:

$$\text{T.N.T.} \xrightarrow[(OS)]{[O]} C_6H_2(NO_2)_3CO_2H \xrightarrow{[H]} C_6H_2(NH_2)_3CO_2H \xrightarrow[H_2O]{HCl}$$

$$CO_2 + 3\,NH_3 + C_6H_3(OH)_3$$

This ready hydrolysis of *negative* groups in the *meta* position to each other is interesting in view of the ready hydrolysis of such groups when *ortho* or *para* to *positive* groups like the nitro group. Thus the following changes take place readily.



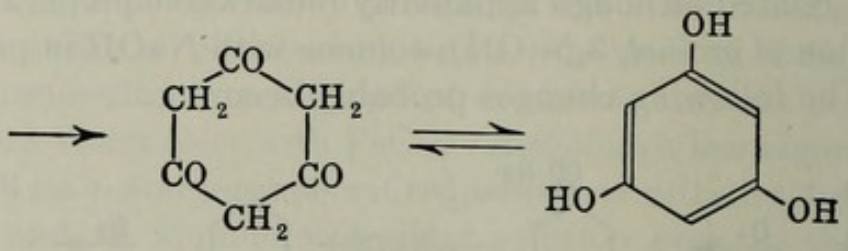

On the other hand the hydrolysis of *m*-nitroaniline and of *p*-phenylene diamine is not easy.

5. Acetone and malonyl chloride in presence of $CaCO_3$ form phloroglucinol (Komninos 1918). In this reaction the carbonyl groups of the acid chloride give an aldol condensation with the

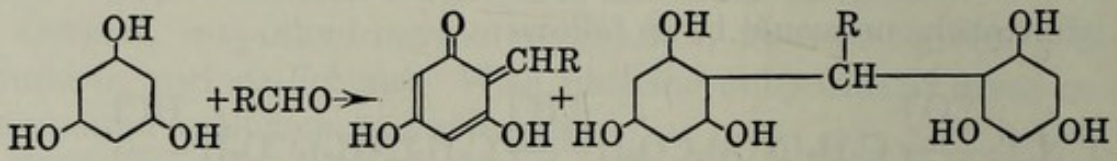
$\alpha$-H atoms of the acetone

$ClCOCH_2COCl + CH_3COCH_3 \rightarrow$

$ClCOCH_2C(OH)(Cl)CH_2COCH_3 \rightarrow ClCOCH_2COCH_2COCH_3 \rightarrow$



The tautomeric reactions of phloroglucinol have been studied extensively. It gives ordinary phenolic reactions but also acts as triketocyclohexane. The *trioxime*, $C_6H_6(=NOH)_3$, decomposes at 140°. The condensation with aldehydes (Rep. 1914, 129) involves both forms.



A similar process is responsible for its use in determining pentosans. The latter are converted by HCl to furfural which forms an insoluble cpd. with phloroglucinol.

**Hydroxyquinol,** hydroxyhydroquinone, 1,2,4-$(OH)_3$-benzene, can be made by alkaline fusion of hydroquinone in presence of air. Its triacetate is formed by the action of glacial acetic acid with quinone. It does not react with hydroxylamine.

**Hexahydroxybenzene,** $C_6(OH)_6$, is obtained as the explosive potassium compound from metallic potassium and carbon monoxide. It can be oxidized to a hydrated form of the corresponding tri-quinone, triquinoyl.

## XII. AROMATIC ALCOHOLS

These compounds have hydroxyl attached to a side chain or aliphatic portion of a mixed aliphatic aromatic compound such as toluene or diphenylmethane. They may be regarded and are often named as aryl derivatives of carbinol. Their reactions are analogous to those of the corresponding classes of aliphatic alco-

hols. The activity of OH on a carbon attached directly to an aryl group is increased. Similarly, the activity of H in a like position is increased toward oxidation and removal in dehydration. In other words, *H and OH when alpha to a benzene ring are unusually active.*

**Benzyl alcohol,** phenylcarbinol, $C_6H_5CH_2OH$, b. 205°, is readily made from benzyl chloride and a base. It is only slightly soluble in water. Substituted benzyl alcohols are obtainable by reduction of the corresponding benzamides with sodium amalgam.

$$XC_6H_4CONH_2 + 4\,[H] \rightarrow XC_6H_4CH_2OH + NH_3$$

**Benzhydrol,** diphenylcarbinol, $(C_6H_5)_2CHOH$, m. 69°, b. 299°, is a typical secondary alcohol both in its preparations and its reactions. The presence of the two phenyl groups attached to a single carbon excludes the possibility of rearrangements.

**Triphenylcarbinol,** $(C_6H_5)_3COH$, m. 159°, can be made from diphenylketone and PhMgBr and by the hydrolysis of the corresponding halides. The effect of the three phenyl groups is shown by its preparation by the oxidation of triphenylmethane and by its ready reduction to triphenylmethane by zinc and acetic acid. Some reducing agents like titanous chloride convert the carbinol to triphenylmethyl.

**Phenylethyl alcohol,** $\beta$-phenylethyl alcohol, benzylcarbinol, $C_6H_5CH_2CH_2OH$, b. 221°, occurs in rose oil and is much used in perfumes. It is best prepared by the reduction of ethyl phenylacetate, $PhCH_2CO_2Et$. This process is best carried out by means of absolute alcohol and sodium (Bouveault and Blanc). Catalytic reduction is likely to cause dehydration of the carbinol because of the activating effect of the phenyl group on the alpha H atoms. Phenylethyl alcohol has also been prepared by the action of phenylmagnesium chloride with ethylene oxide. This is probably the only commercial use of the Grignard reagent.

**Phenylmethylcarbinol,** $\alpha$-phenylethyl alcohol, $C_6H_5CHOHCH_3$, b. 203°, is best prepared from acetaldehyde and PhMgBr. Since it is readily dehydrated, all traces of acid must be eliminated before its distillation.

**ω-Phenylpropyl alcohol,** $C_6H_5(CH_2)_3OH$, b. 235° is obtained by reducing *cinnamyl alcohol*, styryl carbinol, "styrone,"

$$C_6H_5CH=CHCH_2OH,$$

m. 33°, b. 258°, which occurs as a cinnamic ester (styracin) in storax. Cinnamyl alcohol gives typical allylic rearrangements. Thus treatment with $PBr_3$ gives both $PhCH=CHCH_2Br$ and $PhCHBrCH=CH_2$.

## XIII. AROMATIC ALDEHYDES

The direct attachment of the aldehyde group to an aromatic ring gives substances resembling trimethylacetaldehyde in having no alpha hydrogen and thus giving neither aldol condensations nor polymerizations. On the other hand the carbonyl group is very reactive.

**Benzaldehyde,** oil of bitter almonds, $C_6H_5CHO$, b. 179°, is typical of aromatic aldehydes. It occurs as the glucoside, *amygdalin.*

*Preparation.* 1. It is made starting from toluene by a variety of processes.

*a.* Benzyl chloride, $C_6H_5CH_2Cl$, is hydrolyzed and oxidized by heating with water and a mild oxidizing agent such as a nitrate of lead or copper. Benzyl chloride can also be converted to benzaldehyde by heating with alkali and the calculated amount of chromate, the aldehyde being distilled out as fast as formed.

*b.* Benzal chloride, $C_6H_5CHCl_2$, can be hydrolyzed either with acid or lime to give benzaldehyde.

*c.* Benzoic acid can be converted to benzoyl chloride which can be converted to benzaldehyde by hydrogen in presence of a palladium catalyst. (Rosenmund 1922).

$$PhCOCl + H_2 \rightarrow HCl + PhCHO$$

Benzoyl chloride can be converted to its cyanide and then to phenyl glyoxylic acid which loses $CO_2$ on distillation.

$$PhCOCl \rightarrow PhCOCN \rightarrow PhCOCO_2H \rightarrow CO_2 + PhCHO$$

These last two methods are specially applicable to complex alde-

hydes and give a method for going from an aromatic amine through the nitrile and acid to the aldehyde.

*d.* Etard's reagent, $CrO_2Cl_2$, converts an aromatic methyl group to an aldehyde group. The mechanism of this process involves the formation of intermediate compounds such as

$$C_6H_5CH_3.2\ CrO_2Cl_2$$

2. Benzaldehyde can be made from benzene.

*a.* By the action of carbon monoxide at high pressure.

*b.* By the treatment of benzene with CO in presence of HCl and anhydrous aluminum chloride. In this process it may be assumed that formyl chloride, HCOCl, is the active agent.

*c.* The Grignard reagent from chloro- or bromo-benzene reacts with an excess of an alkyl formate at low temperature to give benzaldehyde.

$$PhMgBr + HCO_2R \rightarrow PhCH(OR)OMgBr \rightarrow ROMgBr + PhCHO$$

An alkyl orthoformate similarly gives the acetal of benzaldehyde which can readily be hydrolyzed by dilute acid.

$$PhMgBr + CH(OR)_3 \rightarrow ROMgBr + PhCH(OR)_2$$

The *reactions* of benzaldehydes may be divided into those of (I) the aldehyde hydrogen, (II) the carbonyl group and (III) the benzene nucleus.

I. The H of the aldehyde group has the usual reactivity, being readily oxidized to OH. Thus benzaldehyde which has been exposed to air always contains benzoic acid. The absence of alpha H atoms makes possible reactions not observed in their presence.

*a.* Chlorine replaces the H to give benzoyl chloride whereas in ordinary aldehydes it gives an alpha chloro aldehyde.

*b.* Alkalies bring about an oxidation and reduction, the Cannizzaro reaction.

$$2\ PhCHO + KOH \rightarrow PhCO_2K + PhCH_2OH$$

If the aldehyde is entirely peroxide-free, the reaction does not take place (Kharasch 1935).

*c.* Alkali cyanides give the *benzoin condensation* in which the H plays the part of the active H in the aldol condensation.

$$2\ PhCHO \rightarrow PhCHOHCOPh$$

II. *A.* The carbonyl group gives the usual *addition* reactions.

*a.* Reducing agents and catalytic hydrogenation give benzyl alcohol.

*b.* Hydrocyanic acid gives mandelonitrile, PhCHOHCN.

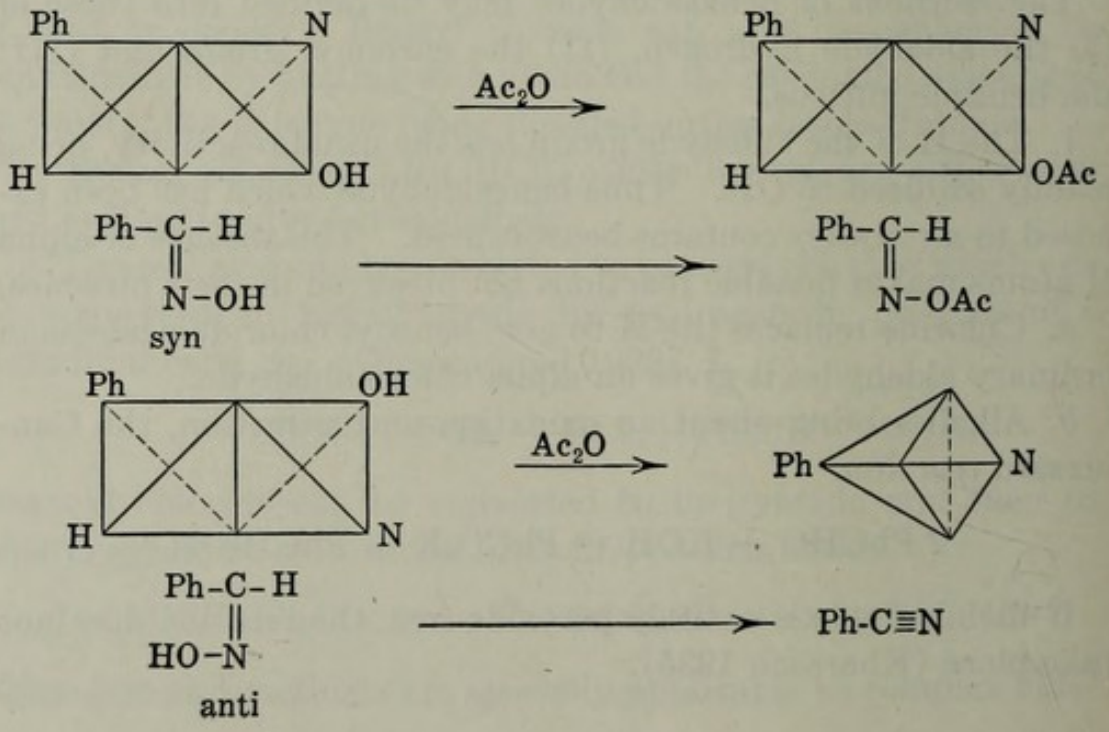
*c.* Sodium bisulfite gives a crystalline addition compound which has been shown to be a hydroxy sulfonate, $PhCHOHSO_3Na$.

*B.* The condensation reactions of the carbonyl group probably take place by way of initial addition.

*a.* Primary amines first give addition products and then benzal (benzylidene) amines or *Schiff's bases.*

$$PhCHO + PhNH_2 \rightarrow [PhCHOHNHPh] \rightarrow PhCH{=}NPh$$

*b.* Hydroxylamine gives *syn* or *alpha* benzaldoxime, m. 35°. Acids convert this to the *anti* or *beta* benzaldoxime, m. 125°. The latter reacts with acetic anhydride to give benzonitrile. This reaction was formerly thought to indicate the *syn* form. The stereochemistry of the oximes has been studied in great detail by means of substituted benzaldehydes (Meisenheimer 1921, Brady 1923–33, Rep. 1925, 105–11; 1926, 126–8).



Obviously the models used are inadequate to show the mechanism by which *trans* elimination takes place.

*c.* Hydrazine gives benzalazine, $PhCH=N-N=CHPh$, m. 93°. High temperatures convert it to $N_2$ and stilbene.

*d.* Phenyl hydrazine gives benzaldehyde phenyl hydrazone, $PhCH=NNHPh$, m. 152°.

*e.* It gives the aldol condensation with the alpha H of suitable aldehydes and ketones. The influence of the phenyl group on an $\alpha-OH$ causes the spontaneous dehydration of the aldol first formed. Thus benzaldehyde and acetaldehyde in presence of dilute base or a trace of HCl give cinnamic aldehyde readily.

$$PhCHO + CH_3CHO \rightarrow [PhCHOHCH_2CHO] \rightarrow PhCH=CHCHO$$

Acetone gives benzal acetone, $PhCH=CHCOMe$, m. 42°, and dibenzalacetone, $(PhCH=CH)_2CO$, m. 112°. The latter is valuable as an identifying derivative of both acetone and benzaldehyde.

*f.* A reaction related to the aldol condensation is the *Perkin synthesis* of unsaturated acids from aromatic aldehydes, sodium salts of aliphatic acids and their anhydrides. Thus cinnamic acid is prepared by heating benzaldehyde, anhydrous sodium acetate and acetic anhydride.

$$PhCHO + CH_3CO_2Na + Ac_2O \rightarrow [PhCHOHCH_2CO_2Na] \rightarrow PhCH=CHCO_2Na + 2\,AcOH$$

*Hydrogen which is alpha to a carboxyl group or to a conjugated system containing a carboxyl takes part in this reaction.* Thus sodium propionate gives $\alpha$-methylcinnamic acid while sodium crotonate gives $PhCH=CHCH=CHCO_2H$.

*g.* Aromatic compounds containing active ring H such as dimethylaniline condense with benzaldehyde in presence of zinc chloride. This is an important preparation for triphenylmethane dyes.

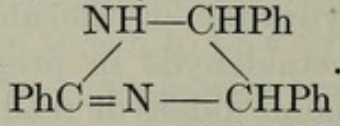
$$PhCHO \rightarrow [PhCHOHC_6H_4NMe_2] \rightarrow PhCH(C_6H_4NMe_2)_2$$

The failure to obtain the intermediate product is another example of the activity of OH alpha to phenyl.

*h.* The reaction of benzaldehyde with $NH_3$ illustrates again the activating effect of an aryl group on an alpha OH. The steps may include the following:

$$PhCHO \rightarrow PhCH(OH)NH_2 \rightarrow PhCH{=}NH \rightarrow PhCH(NH_2)_2 \rightarrow$$
$$PhCH(NHCHOHPh)_2 \rightarrow \underset{\text{Hydrobenzamide}}{PhCH(N{=}CHPh)_2}$$

Acids convert hydrobenzamide to a dihydroglyoxaline derivative, *amarin*,



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*C.* Treatment with $PCl_5$ gives benzal chloride, $PhCHCl_2$. Once again the absence of alpha H precludes side reactions.

III. Sulfonation and nitration give ring substitution mainly in the meta position.

**m-Nitrobenzaldehyde,** m. 58°, is obtained with about 20% of the *o*-compound by direct nitration of benzaldehyde. Reduction of its bisulfite compound gives a solution of *m-aminobenzaldehyde* useful in making triphenylmethane dyes.

**o-Nitrobenzaldehyde,** m. 40°, and its *p*-isomer, m. 106°, are prepared by the controlled oxidation of *o*- and *p*-nitrocinnamic acids obtained by direct nitration. *o*-Nitrobenzaldehyde in sunlight or in presence of alkali undergoes intramolecular oxidation and reduction to give *o*-nitrosobenzoic acid.

**Phenyl acetaldehyde,** $\alpha$-tolualdehyde, $C_6H_5CH_2CHO$, b. 194°, is best prepared from cinnamic acid by first adding HOCl and then rearranging and decarboxylating the product.

$$PhCH{=}CHCO_2H \rightarrow PhCHOHCHClCO_2H \rightarrow$$
$$[PhCH_2C(OH)ClCO_2H] \rightarrow [PhCH_2COCO_2H] \rightarrow PhCH_2CHO$$

**Cinnamic aldehyde,** $C_6H_5CH{=}CHCHO$, b. 246°, is readily obtained from cinnamon oil through the bisulfite compound. It is a typical alpha beta unsaturated carbonyl compound. Reducing agents readily saturate the double bond, presumably by a process of 1,4-addition. Complete reduction gives $Ph(CH_2)_3OH$. Treatment with aluminum alkoxides gives cinnamyl alcohol.

$$3\ PhCH{=}CHCHO + Al(OCHMe_2)_3 \rightarrow$$
$$(PhCH{=}CHCH_2O)_3Al + 3\ Me_2CO$$

The action of cinnamic aldehyde with bisulfites is characteristic of alpha beta unsaturated aldehydes. Three types of compounds are possible:

(I) $PhCH=CHCH(OH)SO_3Na$,
(II) $PhCH(SO_3Na)CH_2CH(OH)SO_3Na$,
and (III) $PhCH(SO_3Na)CH_2CHO$.

(I) is obtained by the action of cold bisulfite solution on the aldehyde. Boiling with water converts (I) to (II) and free aldehyde. (II) can also be made from the aldehyde and an excess of hot conc. bisulfite solution. Boiling (II) with dilute sulfuric acid gives (III). Dry distillation or treatment with hot dilute NaOH solution converts all three to the free aldehyde.

The use of cinnamic aldehyde in aldol condensations gives substances with complex conjugated systems of double bonds. Thus, with acetaldehyde it gives $PhCH=CHCH=CHCH=O$.

## XIV. AROMATIC KETONES

These show typical ketone reactions except to the extent that an aryl group attached directly to a carbonyl group provides no alpha H and offers a greater amount of steric hindrance to certain addition reactions than do simple aliphatic groups.

**Acetophenone,** methyl phenyl ketone, acetylbenzene, Hypnone, $C_6H_5COCH_3$, m. 20°, b. 202°, is best *prepared* by the Friedel-Crafts reaction from benzene, acetyl chloride and aluminum chloride. Molecular amounts of the latter must be used because it forms a stable addition compound with the product of the reaction. This is generally true of carbonyl compounds.

*Reactions.* Acetophenone gives typical ketone reactions. It forms an oxime, m. 59° and a phenylhydrazone, m. 105°. These are not known in stereoisomeric forms. This may be due to the much greater stability of one form because of the wide difference in the phenyl and methyl groups or, more probably, to the possibility of tautomeric change.

$$\begin{array}{ccccc} Ph{-}C{-}CH_3 & & Ph{-}C{=}CH_2 & & Ph{-}C{-}CH_3 \\ \| & \rightleftharpoons & | & \rightleftharpoons & \| \\ N{-}OH & & NHOH & & HO{-}N \end{array}$$

Acetophenone is readily reduced and adds HCN in the usual way. The effect of the phenyl group is shown by the failure to form compounds with bisulfites. Halogenation readily gives *phenacyl halides*, $PhCOCH_2X$. *Phenacyl chloride*, ω-chloroacetophenone, is a widely used relatively harmless lachrymator ("CN") used for controlling mobs and the like. It is best made from chloroacetyl chloride, benzene and aluminum chloride. Vigorous oxidation converts acetophenone to benzoic acid. Controlled oxidation with cold alkaline $KMnO_4$ attacks only the methyl group giving $PhCOCO_2H$, phenylglyoxylic acid (benzoylformic acid).

Treatment of acetophenone with cold fuming nitric acid gives mainly the *m*-nitro compound with a smaller amount of the *o*-compound. Warming with conc. nitric acid gives

$$PhCOC(NO):C(NO)COPh.$$

The alpha H atoms of acetophenone readily take part in aldol condensations. Thus benzaldehyde and a trace of dilute base give $PhCH=CHCOPh$, *benzalacetophenone, chalcone*, m. 58°. Mild treatment of acetophenone with HCl gives *dypnone*, $MePhC=CHCOPh$. Longer treatment continues the condensation process to give *sym*-triphenylbenzene. Polyhydroxychalcones are used in the synthesis of flavones.

**Substituted acetophenones** have been made in great variety. Direct nitration of acetophenone gives mainly *m*-nitroacetophenone, m. 81°. The chief by-product is the oily *o*-compound but the latter is best prepared by the action of 30% sulfuric acid on the product of *o*-nitrobenzoyl chloride and sodioacetoacetic ester. Both carboxyl and acetyl are removed.

$$O_2NC_6H_4COCH(CO_2R)COCH_3 \rightarrow O_2NC_6H_4COCH_3$$

*p*-Nitroacetopheneone, m. 81°, can be prepared similarly from *p*-nitrobenzoyl chloride but a better method starts with the nitration of cinnamic acid which readily gives the *p*-compound

$$O_2NC_6H_4CH=CHCO_2H \xrightarrow{Br_2} \xrightarrow{HOK}$$

$$O_2NC_6H_4C\equiv CCO_2K \xrightarrow[H_2SO_4]{70\%} CO_2 + O_2NC_6H_4COCH_3$$

The last step involves the hydration of the triple bond and the splitting of the resulting keto acid. It is a general process for producing the acetyl group.

$$RC{\equiv}CCO_2H \rightarrow RCOCH_2CO_2H \rightarrow RCOCH_3$$

Reduction of the nitroacetophenones with Sn and HCl gives the three *aminoacetophenones*, *o*-, oil, *m*-, m. 93°, *p*-, m. 106°, b. 294°. The *p*-compound can also be made by heating aniline or acetanilide with an excess of acetic anhydride and zinc chloride. The aminoacetophenones can be diazotized in the usual way.

In some cases, substituted acetophenones are made by the Friedel-Crafts reaction of acetyl chloride with a substituted aromatic compound such as chlorobenzene or the phenyl ethers like anisole. This is not possible with compounds containing groups like carboxyl, hydroxyl and nitro which react with aluminum chloride.

**Benzophenone,** diphenyl ketone, $(C_6H_5)_2CO$, m. $\alpha$-49°, $\beta$-26°, b. 306°, is best prepared by the Friedel-Crafts reaction on benzoyl chloride and benzene. It can also be made by oxidizing diphenylmethane. It forms an oxime, m. 140°, and a phenylhydrazone, m. 105°. Reduction gives benzhydrol (I) and benzpinacol (II) m. 186° dec.

$$\underset{}{Ph_2CO} \rightarrow \underset{\text{I}}{Ph_2CHOH} + \underset{\text{II}}{Ph_2C(OH)C(OH)Ph_2}$$

The formation of the latter, and especially its ready rearrangement on dehydration to give benzpinacolone, $Ph_3CCOPh$, m. 182°, show the danger of considering too literally the term steric hindrance.

Vinyl phenyl ketone, $CH_2{=}CHCOPh$, adds PhMgBr entirely 1,4- to give only $PhCH_2CH_2COPh$ (Kohler). A similar result is obtained with propenyl phenyl ketone, $MeCH{=}CHCOPh$. By contrast the isomeric methyl cinnamyl ketone, $MeCOCH{=}CHPh$ adds mainly to the carbonyl group giving only about 10% 1,4-addition.

## XV. PHENOLIC ALCOHOLS, ALDEHYDES AND KETONES

Many of these either occur in nature or are readily prepared from natural products. *Saligenin* and *anisyl alcohol* are *o*-hydroxy- and *p*-methoxy-benzyl alcohols. *Coniferyl alcohol*, obtained from the glucoside *coniferin*, is

$$3\text{-MeO-4-HO-C}_6\text{H}_3\text{CH}=\text{CHCH}_2\text{OH}.$$

The *o*- and *p*-hydroxybenzyl alcohols are very sensitive to acid, readily undergoing complex condensation reactions. This peculiarity is the basis of resin formation from phenols and formaldehyde (Bakelite). The first step is an aldol-type condensation involving the carbonyl of the formaldehyde and an H which is *o*- or *p*- to the hydroxyl to form a hydroxybenzyl alcohol. *o*- and *p*-Aminobenzyl alcohols are even more sensitive to acid. Thus *p*-$NH_2$-benzyl alcohol with acid gives $(C_7H_7N)_x$. This product presumably is a long chain polymer

$$\text{HOCH}_2\text{C}_6\text{H}_4\text{NH}(\text{CH}_2\text{C}_6\text{H}_4\text{NH})_y\text{CH}_2\text{C}_6\text{H}_4\text{NH}_2.$$

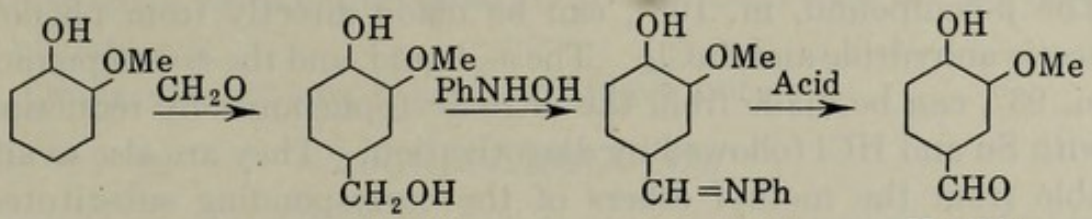
A similar product is obtained when attempts are made to prepare *p*-aminobenzyl halides from the corresponding nitro compounds.

**Salicylaldehyde** and **anisaldehyde** are *o*-OH and *p*-OMe-benzaldehydes. 3,4-Dihydroxybenzaldehyde is *protocatechuic aldehyde* while the 3-methyl ether of the latter is *vanillin* and the 3,4-methylene ether is *piperonal*.

Salicylaldehyde is obtained by the Reimer-Tiemann reaction (see below) using carefully controlled conditions. The other aldehydes of this group are made from naturally occurring allyl or propenyl phenol ethers. The former are rearranged to the latter by means of alkali and the $\alpha\beta$-double bond is broken by oxidation to give an aldehyde group. *Anethole*, *p*-$\text{MeOC}_6\text{H}_4\text{CH}=\text{CHMe}$ gives anisaldehyde.

**Eugenol**, 4-OH-3-OMe-$\text{C}_6\text{H}_3\text{CH}_2\text{CH}=\text{CH}_2$ gives *isoeugenol* and then vanillin. The common preparation of vanillin is from

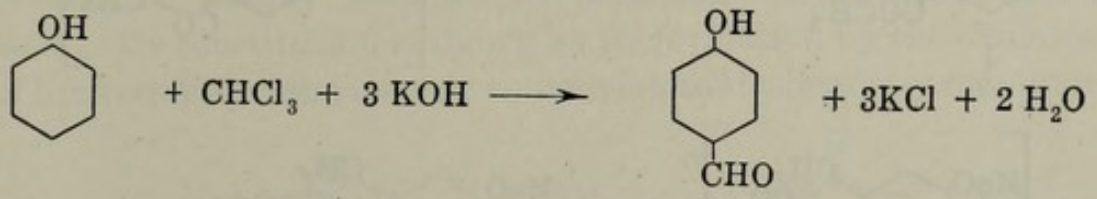
guaiacol in the following steps:




Vanillin

**Safrole,** 3,4-$CH_2O_2C_6H_3CH_2CH=CH_2$, through *isosafrole* gives piperonal. The splitting of the methylene group to give protocatechuic aldehyde is not easy. It can be achieved by treatment with cold $PCl_5$ to change the $=CH_2$ to $=CCl_2$. Hydrolysis gives $=C=O$ forming a carbonate which on further hydrolysis gives the free dihydroxy cpd.

Phenols treated with alkali and chloroform (*Reimer-Tiemann*) are converted to the corresponding *o*- and *p*-hydroxyaldehydes.




Similarly phenols react with HCN and HCl in presence of zinc chloride to give formimides which can be hydrolyzed to hydroxy aldehydes (Gattermann). If RCN is used in place of HCN the final product is a ketone. For the HCN process, a convenient method is to treat a suspension of $Zn(CN)_2$ in dry ether with dry HCl and then add the phenolic compound (Adams).

$$Zn(CN)_2 + 2\,HCl \rightarrow ZnCl_2 + 2\,HCN$$

$$C_6H_5OH + HCN + HCl \rightarrow HOC_6H_4CH{=}NH.HCl \xrightarrow{H_2O} HOC_6H_4CHO + NH_4Cl$$

The most important member of this group is vanillin, the active flavoring material of the vanilla bean. It can be made by oxidizing acetyl isoeugenol obtained by isomerizing eugenol with a base and acetylating with acetic anhydride.

$$3\text{-MeO-4-OH-}C_6H_3CH_2CH{=}CH_2 \xrightarrow{KOH} ArCH{=}CH{-}CH_3 \xrightarrow{Ac_2O} \xrightarrow{[O]} \text{Vanillin.}$$

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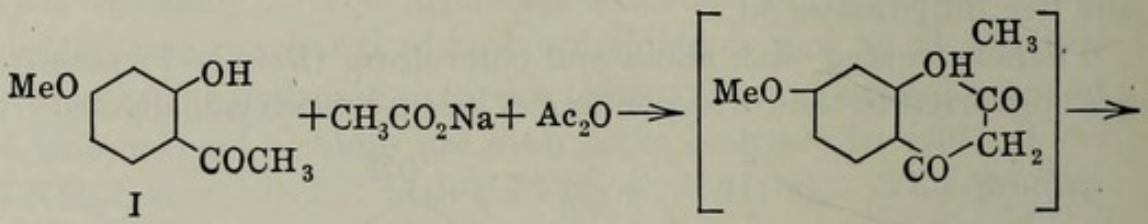
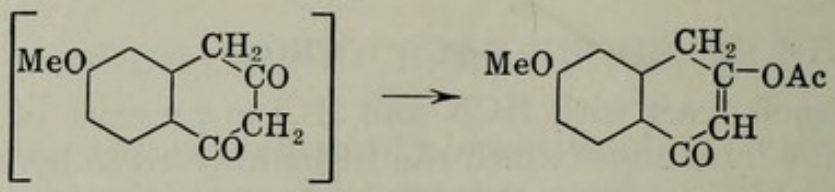
The three *hydroxyacetophenones* or *acetyl phenols* are known. The *p*-compound, m. 108°, can be made directly from phenol, acetic anhydride and $ZnCl_2$. The *o*-, liquid, and the *m*-compound, m. 93°, can be made from the nitro acetophenones by reduction with Sn and HCl followed by diazotization. They are also available from the methyl ethers of the corresponding substituted benzoylacetic esters and phenylpropiolic acids.

**Resacetophenone,** acetoresorcinol, $2,4\text{-}(OH)_2\text{-}C_6H_3COCH_3$, m. 142°, is readily obtained by heating resorcin with acetic acid and zinc chloride. Its monomethyl ether is *peonol*, m. 50°. Peonol (I) gives an interesting modification of the Perkin synthesis to give dehydrodiacetylpeonol (III).



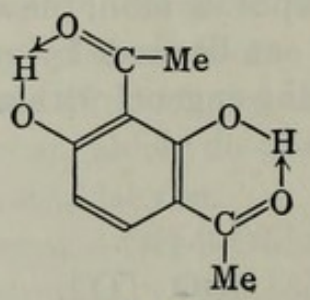

I



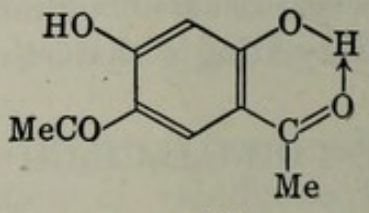

II III

Treatment of III with a carbonate gives II, which is tautomeric with the 6-Me ether of $1,3,6\text{-}(OH)_3$-naphthalene.

The *2,4-* and *4,6-diacetylresorcinols* differ widely in properties. The first m. 91° and is volatile with steam while the second m. 182° and is non-volatile with steam (Baker 1934). These differences are explained on the basis of chelate rings.




2,4-




4,6-

Apparently alternating unsaturation is necessary for a stable 6-chelate ring.

**Quinacetophenone,** C-acetylhydroquinone,

$$2,5\text{-}(OH)_2C_6H_3COCH_3,$$

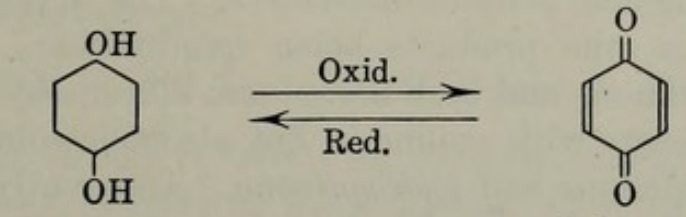
m. 202°, is made from hydroquinone, acetic acid and zinc chloride. Similarly prepared, is *4-acetylpyrocatechol*, m. 116°.

## XVI. QUINONES AND RELATED COMPOUNDS

### *A.* Benzoquinones

The simple quinones are conjugated diketocyclohexadienes closely related to ortho and para dihydroxy benzene derivatives.

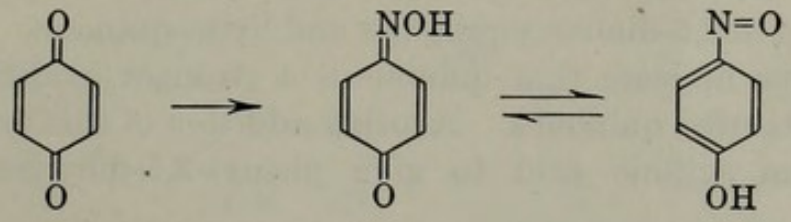
**Benzoquinone, quinone,** $C_6H_4O_2$, m. 116°, yellow pungent crystals, is readily obtained by oxidizing aniline with chromic acid. Its constitution is shown by its formation by the oxidation of hydroquinone and its easy conversion to the latter by reduction.




Hydroquinone Quinone

**Quinhydrone** is a crystalline green compound of these two substances in equimolecular proportions. It is the first product of the oxidation and reduction of the two substances.

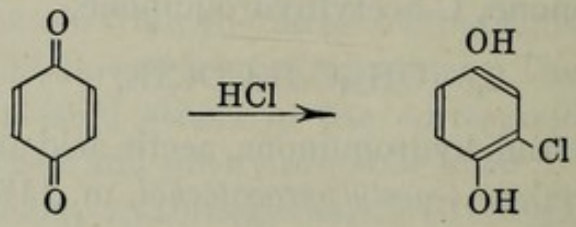
Quinone reacts with 1 mol of hydroxylamine hydrochloride to give a monoxime which is identical with *p*-nitrosophenol.



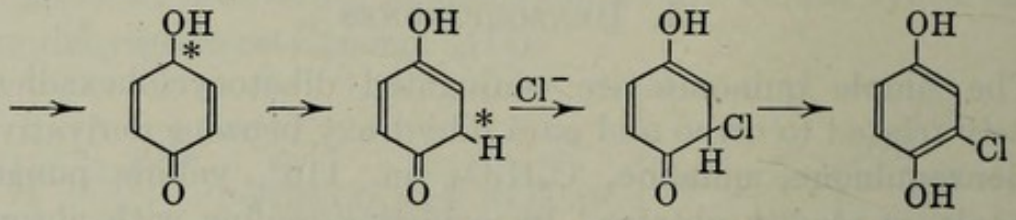

The change to the latter may be regarded as involving the addition of a hydrogen ion to the carbonyl oxygen with the expulsion of one from the NOH gp.

Quinone can give either addition or substitution reactions with

halogens depending on conditions. It adds halogen acids in a peculiar way to give mono-halogen hydroquinones.




This process probably involves two 1 : 3 shifts as follows (the * indicating a C with only 6 electrons):

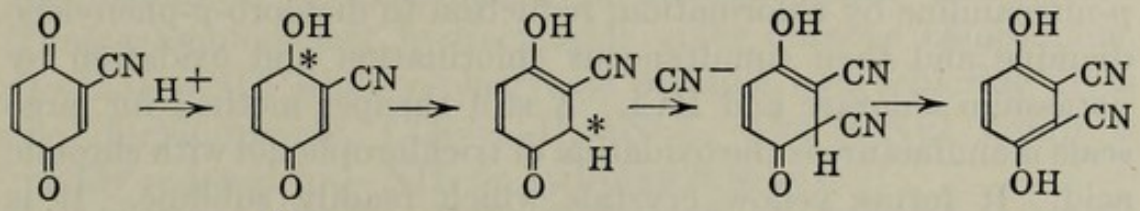



The first of these corresponds to the older conception of 1,4-addition and the second to enolization. The last step gives the completely conjugated benzene derivative. The action of HBr is more complex, the products being quinhydrone, a reduction product of quinone and both mono- and dibromohydroquinones.

Quinone reacts with aniline in hot alcoholic solution to give *2,5-dianilinoquinone and hydroquinone.* Apparently a molecule of aniline adds to give 2-anilinohydroquinone much as HCl adds to quinone. This is then oxidized by a molecule of quinone which is thus reduced to hydroquinone. The resulting 2-anilinoquinone can then add another molecule of aniline to give *2,5-dianilinohydroquinone* which is oxidized to the final product. There is no evidence of any addition to give a 2,3- or a 2,6-product. Primary alcohols react with quinone in presence of $ZnCl_2$ to give 2,5-dialkoxyquinones and hydroquinone. Changes of this type indicate that quinone is a stronger oxidizing agent than substituted quinones. Another addition of this type is that of benzene sulfinic acid to give phenyl-2,5-dihydroxyphenyl sulfone.

The one reaction in which two molecules add *unsymmetrically* to quinone is the action of a cyanide and a mineral acid in which the products are 2,3-dicyanohydroquinone and hydroquinone. The first part of the process may be the formation of cyanohydro-

quinone in the same way that HCl adds to quinone. Oxidation of this by quinone would give hydroquinone and cyanoquinone. The latter might be expected to add HCN to form the 2,5-dicyano derivative. Apparently the course of the reaction is as follows (* indicating a carbon with only 6 electrons)



I.

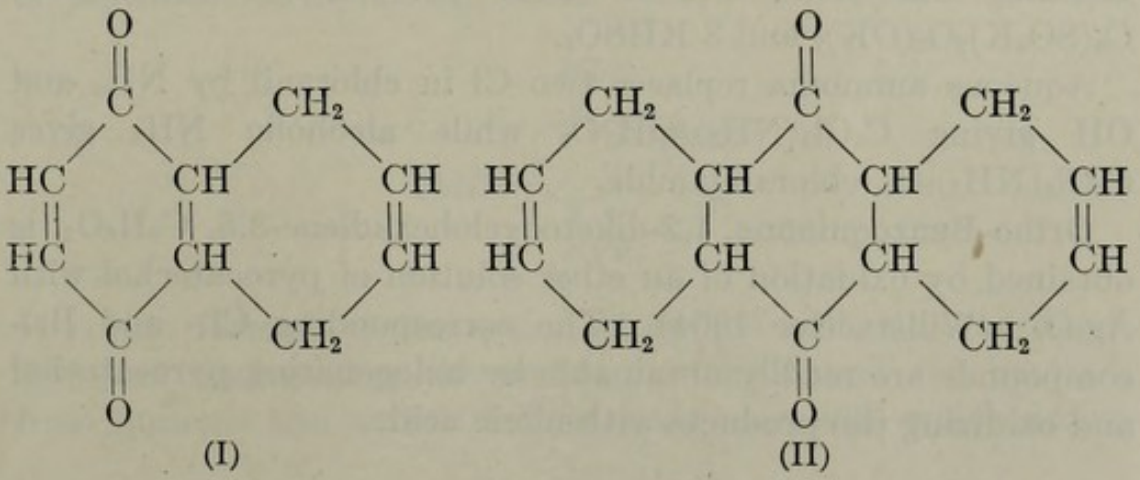
By analogy to other addition reactions of quinone the intermediate (I) might have been expected to undergo the allylic shift with carbons 5 and 6 with the entry of the second CN at 5. This apparently is prevented by the strong tendency to form a *double bond alpha beta to the CN group* in (I).

Quinone undergoes internal oxidation and reduction when treated with acetic anhydride and sulfuric acid, giving the acetate of hydroxyhydroquinone.

$$C_6H_4O_2 + 2\ Ac_2O \rightarrow C_6H_3(OAc)_3 + AcOH$$

This peculiar change is merely an addition analogous to that of HCl to quinone, followed by the formation of the stable triacetate.

The formula of benzoquinone indicates it to be an alpha beta unsaturated ketone. This is confirmed by its participation in the Diels-Alder reaction with conjugated dienes. Thus it reacts with butadiene to give 5,8,8,10-$H_4$-1,4-naphthoquinone (I) and 1,4,5,8,11,12,13,14-$H_8$-anthraquinone (II).



(I) (II)

With cyclopentadiene, quinone gives similar products having *endomethylene* groups, $-CH_2-$ connecting the 5,8-positions in (I) and the 1,4- and 5,8-positions in (II).

**Chloranil,** tetrachloroquinone, $C_6Cl_4O_2$, m. 290° (sealed tube), is formed by chlorinating quinone but is better prepared from *p*-nitroaniline by chlorination, reduction to dichloro-*p*-phenylene diamine and then simultaneous chlorination and oxidation by potassium chlorate and HCl. A still cheaper method for large scale manufacture is the oxidation of trichlorophenol with chromic acid. It forms yellow crystals which readily sublime. It is used commercially as an oxidizing agent in the preparation of dyes such as methyl violet. It oxidizes halogen acids to the halogens with the formation of $Cl_4$-hydroquinone. It is stable to strong oxidizing agents such as aqua regia, nitric acid and concentrated sulfuric acid. In contrast to its stability to acid reagents, is its ready reactivity with various alkaline reagents. The usual result is the replacement of the 2- and 5-Cl atoms. The ease of replacement of the Cl atoms recalls the reactivity of acid chlorides. Dilute KOH gives *potassium chloranilate,* $C_6Cl_2O_2(OK)_2.H_2O$, dark red needles. An even more surprising change is the action of $NaNO_2$ solution to give sodium nitranilate, $C_6(NO_2)_2O_2(ONa)_2$. The corresponding potassium salt is only sparingly soluble. Aniline and sodium phenolate react with chloranil with the replacement of two Cl atoms by PhNH and PhO groups respectively. Dilute $KHSO_3$ replaces two Cl by 2 $SO_3K$ groups and reduces the quinone to a hydroquinone. Conc. $K_2SO_3$ gives insoluble *potassium thiochronate,* $C_6(OH)(OSO_3K)(SO_3K)_4.4\,H_2O$. Heating this with 2 KOH gives *potassium euthiochronate,* $C_6(SO_3K)_2O_2(OK)_2$ and 3 $KHSO_3$.

Aqueous ammonia replaces two Cl in chloranil by $NH_2$ and OH giving $C_6Cl_2(NH_2)(OH)O_2$ while alcoholic $NH_3$ gives $C_6Cl_2(NH_2)_2O_2$, chloranilamide.

**Ortho-Benzoquinone,** 1,2-diketocyclohexadiene-3,5, $C_6H_4O_2$, is obtained by oxidation of an ether solution of pyrocatechol with $Ag_2O$. (Willstaetter 1904). The corresponding $Cl_4$- and $Br_4$-compounds are readily obtainable by halogenating pyrocatechol and oxidizing the products with nitric acid.

### *B.* N-Analogs of Quinones

Compounds in which $=N-$ takes the place of one or both $=O$ groups are known in great variety. These include:

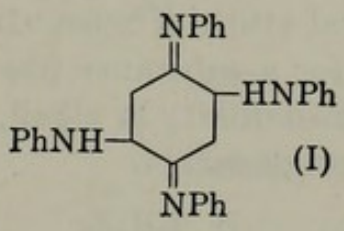
1. **Chloroimides** containing the $=NCl$ group and formed by the oxidation by hypochlorite of suitable amino compounds. Thus *p*-aminophenol hydrochloride gives quinone chloroimide, $O=C_6H_4=NCl$ while *p*-phenylene diamine hydrochloride gives the di-chloroimide, $ClN=C_6H_4=NCl$. The $=NCl$ group is readily reduced to $-NH_2$ or hydrolyzed to $=O$.

2. **Quinone diimide,** $HN=C_6H_4=NH$, is obtained as bright yellow crystals which explode on heating and can be reduced to *p*-phenylene diamine or hydrolyzed to quinone.

3. **Quinone monoxime,** $O=C_6H_4=NOH$, has already been mentioned as the stable tautomeric form of *p*-nitrosophenol just as $MeCOCH=NOH$ is related to $MeCOCH_2NO$. In both cases the $-N=O$ group tends to take a hydrogen ion and become $=NOH$, thus causing the expulsion of $H^+$ from another part of the molecule. *Quinone dioxime,* $HON=C_6H_4=NOH$, dec. 240°, is best made from "*p*-nitrosophenol" and hydroxylamine hydrochloride. It gives a *syn-* and an *anti*-diacetate, m. 147° and 190° dec.

4. **Quinone monoanile,** $O=C_6H_4=NC_6H_5$, m. 97°, red crystals and *quinone dianil,* $C_6H_5N=C_6H_4=NC_6H_5$, m. 180°, are obtained by oxidizing *p*-OH-diphenylamine and diphenyl-*p*-phenylene diamine, $C_6H_4(NHC_6H_5)_2$.

**Azophenin** (I), the dianil of 2,5-dianilinoquinone, is obtained by a variety of processes including the action of heat on a mixture of *p*-nitrosodiphenylamine, aniline and aniline hydrochloride.

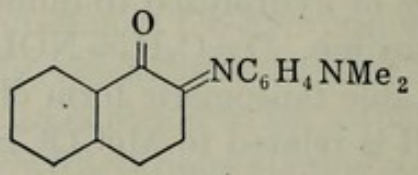



(I)

It is also formed by the action of aniline with quinone dianil. The fact that neither the mono- nor the di-anil can be made from quinone and aniline indicates the ease with which aniline

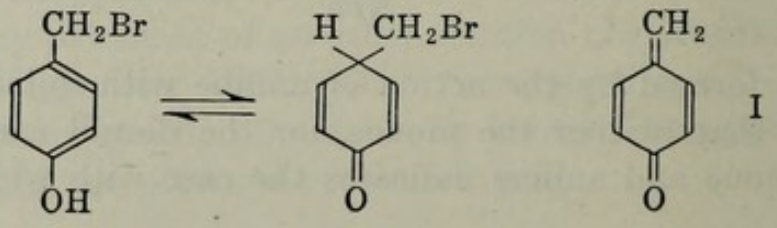
adds 1 : 4 to the system O=C−C=C rather than 1 : 2 to the carbonyl group.

**Indamines** and **indophenols** are dyes related to the quinone anils. *Phenylene Blue* is made by oxidizing a mixture of aniline and *p*-phenylene diamine. The dye is the hydrochloride of $NH_2C_6H_4N=C_6H_4=NH$. Other indamine dyes are *Bindschedler's Green* and *Toluylene Blue*. *p*-Nitrosodimethylaniline can be substituted for the *p*-diamine in the preparation of indamines. *Indophenols* are similarly made by oxidizing a mixture of a phenol or a naphthol with a *p*-diamine or *p*-nitrosodimethylaniline. *Indophenol Blue* is made from the latter and α-naphthol. It has the structure



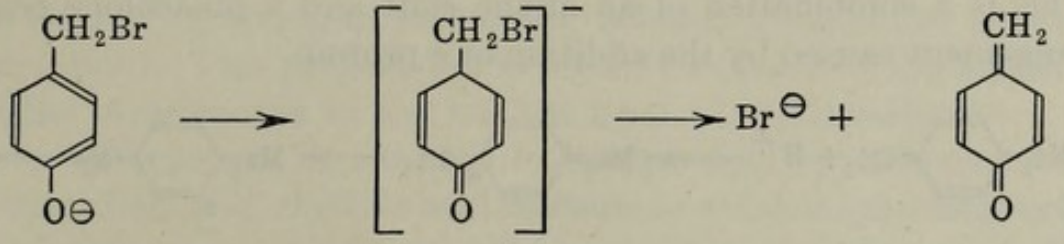

### C. Pseudophenols, Methylene Quinones and Semibenzenes

A phenol having an *o*- or *p*-side chain with a halogen alpha to the ring behaves abnormally with bases. Instead of dissolving to give a phenolate the halogen is removed and a methylene quinone is obtained. Many such *pseudo phenols* have been studied (Zincke, Auwers 1898–1907). Most of these have been very complex but the principles involved may be illustrated by the unknown *p*-hydroxybenzyl bromide. They show well the difference between the older conservative conception that a structure formula was purely a "reaction" formula and did not necessarily indicate the actual structure of the molecule and the more modern conviction of the literal truth of most structural formulas. As the ordinary formula for a substance like *p*-OH-benzyl bromide would not explain its insolubility in alkali, a quinoidal or pseudophenol structure was proposed.

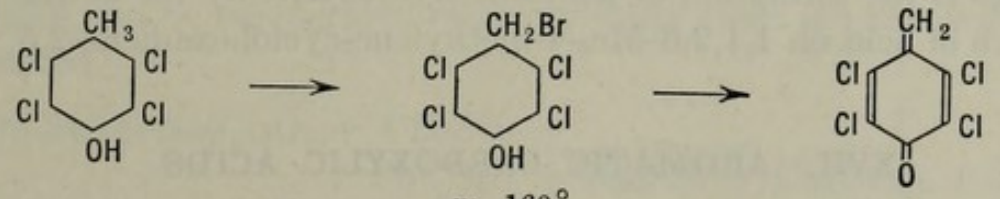



I

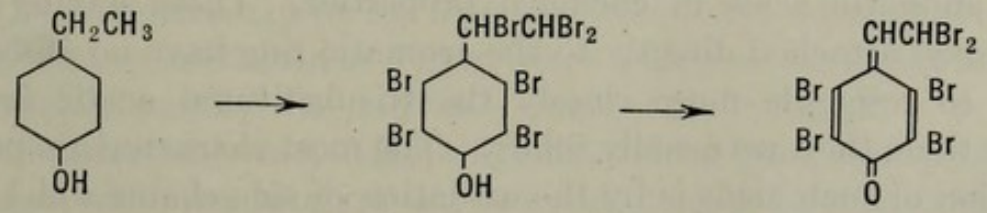
The first formula corresponds to the formation of an acetate in the ordinary way while the second gives a ready interpretation of the formation of the methylene quinone (I) by the action of alkali. It is more probable that the substance has the true phenol formula and that the presence of the halogen alpha to the ring makes possible the formation of the methylene quinone from the phenolate ion formed by the action of the base.

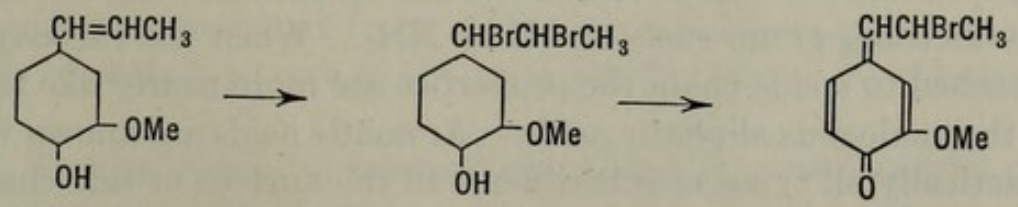



The net result is that a normal reaction, started in one part of the molecule, causes a change in another reactive part of the molecule before the first change has reached its ordinary conclusion. Some of the "pseudophenols" and related methylene quinones which have been prepared follow:



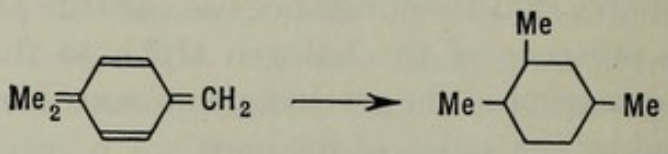

m. 160°



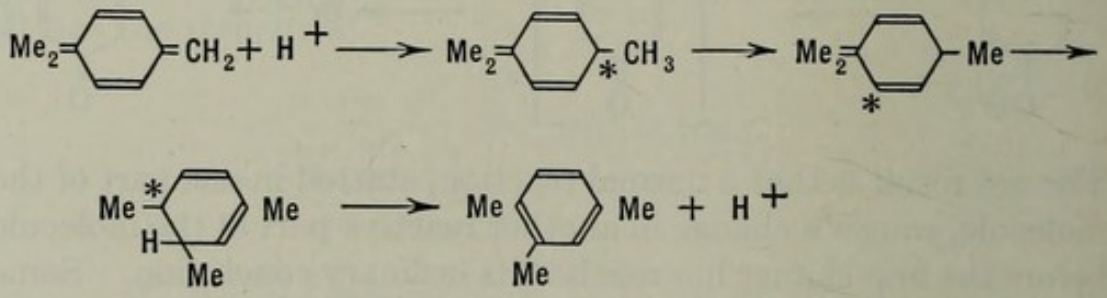




The methylene quinones usually undergo condensation to very complex products.

The **semibenzenes** resemble the quinones in many ways. A trace of acid transforms these to the isomeric aromatic compounds (Rep. 1922, 96).




This is a combination of an allylic shift and a pinacolone rearrangement caused by the addition of a proton




A more complex reaction but one involving the same types of change is the formation of pentamethylbenzene by the action of a trace of acid on 1,1,2,6-$Me_4$-4-methylene-cyclohexadiene-2,5.

## XVII. AROMATIC CARBOXYLIC ACIDS

These are known in great variety. In general they resemble the aliphatic acids in chemical properties. Those having the carboxyl attached directly to the aromatic ring have no alpha H and so resemble more closely the trisubstituted acetic acids. Like them they are usually solids. The most characteristic preparation of such acids is by the oxidation of side chains which removes all of the latter except the carbon attached to the ring. The product is stable to oxidation unless it contains some strongly *o,p*-orienting group such as OH or $NH_2$. When the carboxyl is attached to a side chain the properties are more nearly like those of the analogous aliphatic acids. Aromatic acids are known with practically all types of substituents in the nucleus or side chains. In general, the carboxyl derivatives of the aromatic series are slightly stronger acids than those of the aliphatic series.

### *A.* Benzoic Acid and Its Derivatives

**Benzoic acid,** carboxybenzene, benzene carboxylic acid, $C_6H_5CO_2H$, m. 121°, b. 250°, is found in many natural gums and balsams. It occurs characteristically in the urine of the herbivora as hippuric acid, $PhCONHCH_2CO_2H$. The preparation and reactions of benzoic acid are typical of acids having the carboxyl attached directly to the aromatic nucleus.

*Preparation.* 1. The most typical method is by the conversion of the methyl group of toluene to carboxyl by direct or indirect oxidation. This preparation is possible because of the stability of the benzene ring to any but the most vigorous oxidation.

*a.* Toluene can be oxidized to benzoic acid by refluxing with dilute nitric acid, chromic acid mixture, or alkaline permanganate. The process is slow because of the insolubility of the toluene in the aqueous reagents and its relative inactivity. These methods, however, have the advantage of giving very pure benzoic acid. This is highly desirable because of the use of "one tenth of one percent of benzoate of soda" as a preservative in certain food products. The most commonly used oxidant is chromic acid which can be regenerated electrolytically from the chromic salts formed.

$$PhCH_3 + Na_2Cr_2O_7 + 4\,H_2SO_4 \rightarrow PhCO_2H + Na_2SO_4 + Cr_2(SO_4)_3 + 5\,H_2O$$

*b.* When benzaldehyde is made from benzyl chloride by hydrolysis, and oxidation or by the hydrolysis of benzyl chloride, benzoic acid is always obtained as a by-product which can be separated by distillation and by washing with bicarbonate solution.

*c.* Benzotrichloride, $C_6H_5CCl_3$, obtained by chlorinating boiling toluene without a catalyst can be hydrolyzed to benzoic acid

$$C_6H_5CCl_3 + 2\,H_2O \rightarrow 3\,HCl + C_6H_5CO_2H$$

Benzoic acid prepared from chlorination products of toluene is likely to contain a trace of the more highly toxic *p*-chlorobenzoic acid.

2. The hydrolysis of benzonitrile, $C_6H_5CN$, which can be obtained in a variety of ways.

$$C_6H_5CN + 2\,H_2O \rightarrow C_6H_5CO_2H + NH_3$$

In general, aromatic nitriles are much more difficult to hydrolyze than their aliphatic analogs. In some cases the hydrolysis proceeds to the acid amide and then stops. Treatment with concentrated sulfuric acid, with a mixture of concentrated sulfuric acid and glacial acetic acid or with sulfuric acid and sodium nitrite, will usually complete the process.

3. Phenylmagnesium halides with $CO_2$ give benzoic acid. A similar method involves the action of $CO_2$ on phenyl bromide and sodium or the action of sodium on a mixture of phenyl bromide and ethyl chlorocarbonate. Treatment of benzene with ethylpotassium (EtK) and then with $CO_2$ gives benzoic and terephthalic acids (Gilman 1936).

4. The Friedel-Crafts reaction between benzene and phosgene or carbamic chloride in presence of $AlCl_3$ gives benzoyl chloride or benzamide which can be hydrolyzed to the acid.

The *reactions* of benzoic acid can be divided into those of the carboxyl group and of the benzene ring.

I. *Carboxyl reactions.*

*a. Salts* are formed in the usual way. Sodium benzoate is used as a food preservative. Calcium benzoate crystallizes with 3 $H_2O$ in glistening prisms. Sodium benzoate solution, with halogens, gives mixtures of *o*-, *m*-, and *p*-halogen-benzoic acids. Silver benzoate with iodine gives $CO_2$, phenyl benzoate and AgI. In presence of benzene, the organic products are iodobenzene (31%) and phenyl benzoate (32%). The Ag salt of *p*-toluic acid similarly gives 18% iodobenzene and 52% phenyl toluate (Birckenbach 1936).

*b. Esters* are best prepared by refluxing benzoic acid in the required alcohol with a trace of HCl gas or conc. $H_2SO_4$. The Me, Et and *n*-Pr esters b. 199.6°, 212.6° and 231°. Higher aliphatic esters, when distilled at atmospheric pressure, decompose to benzoic acid and the olefin. *Benzyl benzoate*, m. 21°, b. 324°, used as an antispasmodic, is usually prepared from benzaldehyde by the catalytic action of sodium benzylate, $PhCH_2ONa$, or $Al(OEt)_3$ (OS).

$$2\ PhCHO \rightarrow PhCO_2CH_2Ph$$

Aromatic esters are less reactive than aliphatic esters in hydrolysis and ammonolysis. This is not surprising as they are "tertiary" acids. Thus the reactivity of $Et_3CCO_2Et$ would probably be even less than that of $C_6H_5CO_2Et$.

**Benzoyl chloride,** $C_6H_5COCl$, b. 198°, can be made in the usual ways. Commercially it is made by chlorinating benzaldehyde, thus taking advantage of the absence of any alpha H. It is made in large amounts for the preparation of benzoyl peroxide. It is less reactive than ordinary aliphatic acyl halides. Benzoylation of OH and $NH_2$ compounds is usually carried out by the *Schotten-Baumann* method of using benzoyl chloride and a *base.*

$$ROH + PhCOCl + NaOH \rightarrow PhCO_2R + NaCl + H_2O$$

**Benzoyl bromide,** b. 219°, can be made by $PBr_3$ and benzoic acid. **Benzoyl iodide,** m. 3°, b. 135° (25 mm), is best made by passing HI gas through benzoyl chloride until no more HCl is displaced. It is very reactive. **Benzoyl fluoride,** b. 155°, is formed from the chloride and $KHF_2$. **Benzoyl cyanide,** $C_6H_5COCN$, m. 33°, b. 206°, is formed by distilling the chloride with $K_2Hg(CN)_4$ or by the successive action of nitrous acid and acetic anhydride on acetophenone.

$$PhCOCH_3 \xrightarrow{HNO_2} PhCOCH{=}NOH \xrightarrow{Ac_2O} PhCOCN.$$

It behaves like an acyl halide rather than a keto nitrile. With $NH_3$, aniline, diethylzinc and Zn and HCl it gives benzamide, benzanilide, phenyl ethyl ketone and benzaldehyde. With metallic sodium it gives a polymer, m. 95°, which reacts with NaOH to give sodium benzoate, NaCN and $NH_3$. Only with cold fuming HCl does it react like a nitrile to give benzoylformic acid, $PhCOCO_2H$.

**Benzoic anhydride,** $(C_6H_5CO)_2O$, m. 42°, b. 360°, is prepared by heating benzoyl chloride with anhydrous oxalic acid. Its reactions are like those of acetic anhydride.

**Benzoyl peroxide,** $(C_6H_5CO)_2O_2$, m. 108°, made by benzoyl chloride and sodium peroxide, is relatively stable. It is used as a

bleaching agent for wheat flour. *Perbenzoic acid*,

$$HO-O-COC_6H_5,$$

is obtained from the peroxide (OS).

$$(PhCO)_2O_2 + EtONa \rightarrow PhCO_2Et + PhCO_3Na$$

Its chloroform solution is an oxidizing agent (OS).

**Benzamide,** $C_6H_5CONH_2$, m. 130°, b. 290°, is readily made from benzoyl chloride and ammonium carbonate. Silver compounds are known of the forms PhCONHAg, orange, and

$$PhC(OAg)NH,$$

colorless (Titherly 1897).

**Benzanilide,** $C_6H_5CONHC_6H_5$, m. 161°, b. 119° (10 mm) is made by heating benzoic acid and aniline (OS).

**Benzoylhydrazine,** benzhydrazide, $C_6H_5CONHNH_2$, m. 112°, is easily made from hydrazine and ethyl benzoate.

**Benzazide,** benzoyl azoimide, $C_6H_5CON_3$, m. 30°, is formed from the hydrazide by nitrous acid. It is explosive on heating alone. When heated with water, it gives $N_2$, $PhNHCO_2H$ and $(PhNH)_2CO$. With alcohol it gives $PhNHCO_2R$ while with NaOEt it gives ethyl benzoate and sodium azide, $NaN_3$. When $N_2$ is evolved, the *Curtius rearrangement* takes place.

**Benzonitrile,** phenyl cyanide, $C_6H_5CN$, b. 191°, is obtained from

*a*. Benzamide with $PCl_5$ or $P_2O_5$.

*b*. Sodium benzene sulfonate fused with NaCN.

*c*. Benzene diazonium chloride and cuprous cyanide (Sandmeyer).

*d*. Benzoic acid distilled with $NH_4SCN$.

Its reactions are typical nitrile reactions. Thus with HCl, $NH_3$ and amines, and $H_2O_2$ it gives benzimino chloride, amidines and benzamide respectively. Reduction gives benzyl amine and hydrolysis gives benzoic acid. Ammonium sulfide gives *thiobenzamide*, $C_6H_5CSNH_2$, m. 116°.

### *B.* Substituted Benzoic Acids

These are known in great number. Some of the meta derivatives can be made by direct substitution. The three isomers of a monosubstituted benzoic acid can often be made in three general ways:

1. By oxidation of a substituted toluene by means of dilute nitric acid which converts the methyl to carboxyl.
2. By diazotizing an aminobenzoic acid and introducing the desired group.
3. By diazotizing a substituted aniline, replacing the diazonium group by CN, and hydrolyzing the resulting nitrile.

The *halogen benzoic acids* illustrate the first two methods and a few special ones in addition. The four *o-halogenbenzoic acids* are usually obtained by diazotizing anthranilic acid (prepared from naphthalene) and replacing the diazonium group by treatment with HF, $Cu_2Cl_2$, $Cu_2Br_2$ or KI. *o-Iodobenzoic acid*, m. 162°, is of special interest because of its ready conversion by treatment with chlorine in $CHCl_3$ solution and then with water to *o-iodosobenzoic acid*, $C_6H_4(IO)CO_2H$, m. 244° dec., which is converted by alkaline permanganate to *o-iodoxybenzoic acid*, $C_6H_4(IO_2)CO_2H$, which explodes at 233°. If *o-iodobenzoic acid* is needed in large amounts it will probably be made from phthalic anhydride through anhydro-*o*-hydroxymercuribenzoic acid (OS).

$$C_6H_4(CO)_2O \xrightarrow{HgCl_2} \xrightarrow{heat}$$

$$CO_2 + C_6H_4(HgO)CO \xrightarrow[ICl]{NaCl} HgCl_2 + C_6H_4ICO_2Na$$

A remarkable formation of *o*-halogenbenzoic acids is by the action of alcoholic KCN at 200°, on the *meta*-nitrohalogen benzenes (Richter 1871).

The four *m-halogenbenzoic acids* can be made by diazotizing *m*-aminobenzoic acid obtained by reducing the nitro compound formed by the direct nitration of benzoic acid. *m*-Chlorobenzoic acid can be made by direct chlorination by heating benzoic acid, $MnO_2$ and conc. HCl at 150°. *m*-Bromobenzoic acid is obtained by heating benzoic acid, bromine and water at 150°. *m*-Iodo-

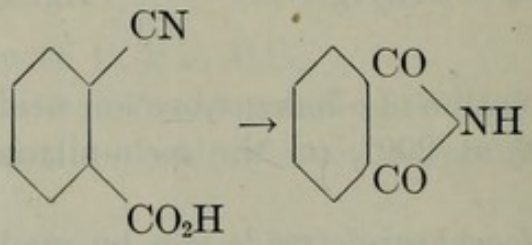
benzoic acid can be made by heating benzoic acid with $KIO_3$ and $H_2SO_4$ or by heating silver benzoate with iodine at 150°. The difficulty of these direct halogenations of benzoic acid well illustrates the fact that *meta directing groups make substitution in the benzene ring more difficult.*

The *m*-halogenbenzoic acids can also be made by the action of alcoholic KCN at 200° on the *para*-nitrohalogen benzenes (Richter 1871).

While the four *p-halogenbenzoic acids* can be made by diazotization of *p*-aminobenzoic acid prepared from the *p*-$NO_2$-compound obtained by oxidizing *p*-$NO_2$-toluene, it is better to make them by oxidizing with dil. nitric acid the *p*-halogentoluenes prepared either by direct halogenation or by diazotizing *p*-toluidine. *p*-Iodobenzoic acid has been made by the action of iodine on *p*-chloromercuribenzoic acid (OS).

**Polyhalogenbenzoic acids** are available. Thus *2,4-dibromobenzoic* acid, m. 167°, is obtained by oxidizing 2,4-$Br_2$-toluene with nitric acid while 2,4,6-$Br_3$-benzoic acid, m. 187°, is made by brominating *m*-aminobenzoic acid and then removing the $NH_2$ group by diazotization. *Pentabromobenzoic acid,* m. 235°, is made by heating with $Br_2$ at 200°, 3,4,5-$Br_3$-benzoic acid, m. 235° obtained by carefully brominating *p*-aminobenzoic acid and replacing the $NH_2$ by diazotization.

The three *cyanobenzoic acids,* $C_6H_4(CN)CO_2H$, are made by diazotizing the aminobenzoic acids and treating with $Cu_2(CN)_2$ made from KCN and $CuSO_4$. The *o*-acid melts about 180° changing to phthalimide.




Of the three *nitrobenzoic acids,* the *m*-acid is available by direct nitration of benzoic acid with fuming nitric acid. About 20 and 2% of the *o*- and *p*-acids are formed at the same time. The *o*- and *p*-acids are best prepared by oxidizing *o*- and *p*-nitrotoluenes with permanganate or dilute nitric acid. With *m*-nitrotoluene com-

mercially available, the *m*-acid could perhaps be made more cheaply by oxidizing it than by nitrating benzoic acid.

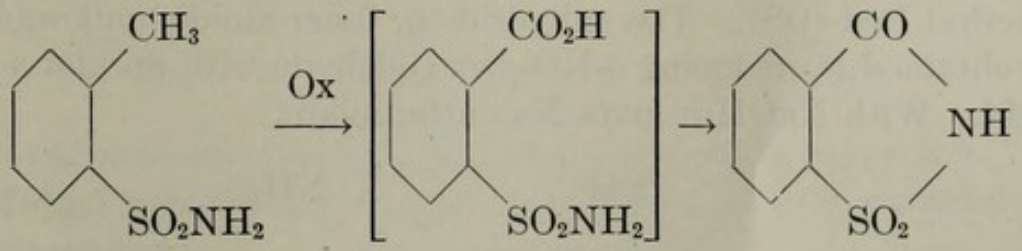
*Di-* and *tri-nitrobenzoic acids* are available by the standard reactions. *3,5-dinitrobenzoic acid*, m. 205°, is easily made by nitrating benzoic acid with a mixture of fuming nitric acid and sulfuric acid. This acid is valuable in identifying primary and secondary alcohols because of the relatively high melting points of its esters. *2,4-Dinitrobenzoic acid*, m. 183°, and *2,4,6-trinitrobenzoic acid*, m. 228°, are made by oxidizing the corresponding nitrotoluenes with chromic acid mixture (OS).

### *Sulfobenzoic Acids, Sulfonic Acids of Benzoic Acid*

The **m-acid** is obtainable by direct sulfonation of benzoic acid with fuming sulfuric acid. The acid sodium salt is relatively insoluble in NaCl solution.

***o*-Sulfobenzoic acid** is important because its imide is *saccharin*, large amounts of which are made to be used as a sweetening agent in place of carbohydrates. A solution of one part in three thousand of water is about as sweet as a one percent sucrose solution. The steps for its preparation follow:

Toluene is treated with chlorosulfonic acid to give a mixture of *o*- and *p*-toluene sulfonyl chlorides. The latter is a solid and most of it can be separated readily from the liquid *o*-compound. The latter is carefully purified and then converted to the amide. This is oxidized with permanganate. The resulting acid forms the internal benzosulfimide, *saccharin*.




The hydrolysis of saccharin with HCl gives acid ammonium *o*-sulfobenzoate (OS) which, with $SOCl_2$, gives the anhydride (OS) which can be converted to the free acid or used to make sulfonephthaleins just as phthalic anhydride is used.

***p*-Sulfobenzoic acid,** m. 200° dec. is made by sulfonating toluene and oxidizing the product with chromic acid mixture or

permanganate. It is purified as the acid barium salt and then converted to the free acid by the calculated amount of $H_2SO_4$.

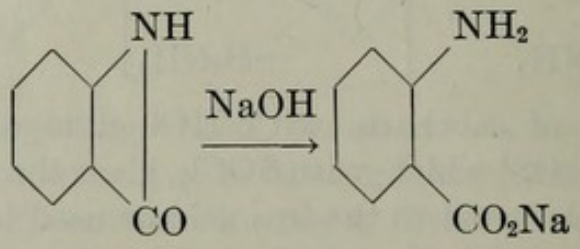
*Aminobenzoic Acids*

They are obtained by reducing the nitro compounds with such reagents as zinc and acid, ammonium sulfide, and alkaline ferrous hydroxide. Their reduction in alkaline solution is very easy because of the solubilizing effect of the carboxyl group. The aminobenzoic acids, as amphoteric substances, are soluble in either acid or basic solution.

$$H_2NC_6H_4CO_2^{\ominus} \xleftarrow{OH^{\ominus}} {}^{\oplus}H_3NC_6H_4CO_2^{\ominus} \xrightarrow{H^{\oplus}} {}^{\oplus}H_3NC_6H_4CO_2H$$

Diazotization gives internal diazonium, salts ${}^{\oplus}N_2C_6H_4CO_2^{\ominus}$, similar to those formed by the aminosulfonic acids. The $NH_2$-benzoic acids give the reactions of both their reactive groups including ready substitution *o*- and *p*- to the $NH_2$ group. When the carboxyl is *o*- or *p*- to the $NH_2$, it may be replaced during such a change. Thus the careful bromination of *p*-$NH_2$-benzoic acid gives the 2,6-$Br_2$ cpd. but vigorous treatment with an excess of $Br_2$ gives $CO_2$ and $Br_3$-aniline.

**Anthranilic acid,** *o*-aminobenzoic acid, m. 145°, is best made by the Hofmann reaction through the action of hypochlorite and alkali on phthalimide. It is the starting point for the preparation of indigo using naphthalene as the ultimate raw material. When diazotized and coupled with $Me_2$-aniline it gives the indicator Methyl Red (OS). The anhydride or inner amide, *anthranil* (I) is obtained by reducing *o*-$NO_2$-benzaldehyde with Sn and acetic acid. With NaOH it gives Na anthranilate.




(I)

Methyl anthranilate is used in perfumes.

***p*-Aminobenzoic acid** is important because its esters have local anesthetic properties. *Anesthesin, Butesin, Novocaine* (*Procaine*), and *Butyn* are salts of its ethyl, *n*-Butyl, β-dimethylaminoethyl, and γ-di-*n*-butylaminopropyl esters.

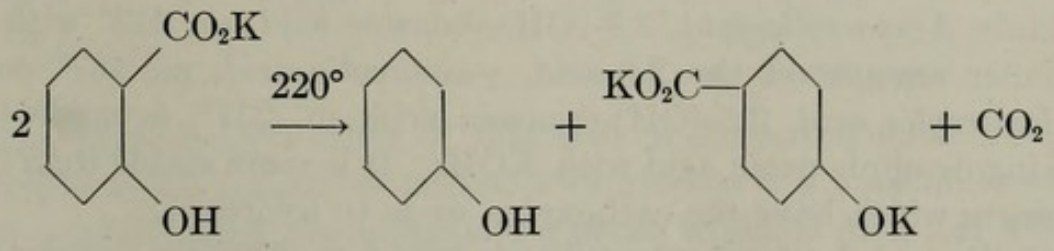
### *Phenolic Acids*

These have the properties of a phenol and a substituted benzoic acid. Thus with NaOH they give di-sodium salts but with carbonates they give mono-sodium salts, only the carboxyl reacting. The positions *o*- and *p*- to the hydroxyl have the usual reactivity toward substituting reagents. If the carboxyl is on one of these positions it also may be displaced. Thus treatment of salicylic acid with excess bromine water gives $CO_2$ and $Br_3$-phenylhypobromite.

**Salicylic acid, *o*-hydroxybenzoic acid,** m. 155°, is prepared by heating Na phenate with $CO_2$ under pressure at 130° (Kolbe). if K phenate is used below 150° the same result is obtained but at higher temperatures the *p*-compound results

$$C_6H_5ONa + CO_2 \rightarrow C_6H_5OCO_2Na \rightarrow C_6H_4(OH)CO_2Na$$

The mechanism of the reaction is indicated by the fact that K salicylate at 220° gives phenol and the di-K salt of *p*-OH-benzoic acid.




Salicylic acid and its compounds have antiseptic properties.

**Methyl salicylate,** $C_6H_5(OH)CO_2CH_3$, b. 223°, is artificial oil of wintergreen.

**Phenyl salicylate,** $C_6H_5(OH)CO_2C_6H_5$, m. 43°, is used as *Salol* in medicine. Because of its stability to acid, it passes unchanged through the stomach and undergoes alkaline hydrolysis in the intestine to give phenol and Na salicylate. It is prepared from salicylic acid, phenol and $POCl_3$.

***m*-Hydroxybenzoic acid,** m. 201°, is made by alkali fusion of sodium *m*-sulfobenzoate or by diazotization of *m*-aminobenzoic acid. The reactions of the $NH_2$ and $CO_2H$ groups are independent of each other. The carboxyl is not easily removed as it is when *o*- and *p*- to the OH group.

***p*-Hydroxybenzoic acid,** m. 213°, is made by the action of $CO_2$ under pressure on K phenoxide at 200° or by the action of carbon tetrachloride on phenol in presence of NaOH (Reimer, Tiemann). Its reactions are typical of its two reactive groups. Its methyl ether is *anisic acid*, $CH_3OC_6H_4CO_2H$, m. 184°, b. 280°.

**Protocatechuic acid,** 3,4-dihydroxybenzoic acid, m. 199°, is obtained by the alkaline fusion of various natural resins which probably contain depsides of this acid. It is obtained along with *pyrocatechuic acid*, 2,3-$(OH)_2$-benzoic acid, m. 204° when pyrocatechol is heated with ammonium carbonate. Its 3-Me ether is *vanillic acid*, m. 207°, which is formed by oxidizing the related aldehyde, vanillin. Its dimethyl ether is *veratric acid*, m. 181°, while its 3,4-methylene ether is *piperonylic acid*, m. 228° which is related to piperic acid. Capsaicin is a vanillyl amide,

$$Me_2CHCH=CH(CH_2)_4CONHCH_2C_6H_3(OH)OMe$$

(Rep. 1923, 98). *Gentisic acid*, 2,5-dihydroxybenzoic acid, m. 197°, is made by heating hydroquinone and $KHCO_3$ solution at 130°. Heating resorcinol with ammonium carbonate gives mainly *β-resorcylic acid*, 2,4-$(OH)_2$-benzoic acid, m. 213° with a smaller amount of the 2,6-acid, *γ-resorcylic acid*, m. 167° dec. *α-Resorcylic acid*, 3,5-$(OH)_2$-benzoic acid, m. 237°, is made by fusing disulfobenzoic acid with KOH. It is more stable than its isomers which have the carboxyl *o*- or *p*- to hydroxyl.

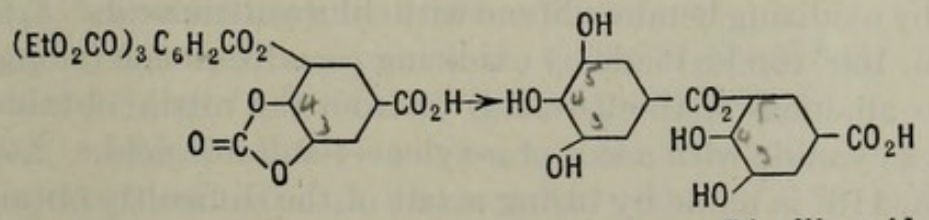
*Gallic acid*, 3,4,5-trihydroxybenzoic acid, m. 220° dec., occurs in nut galls, in tea, and as glucosides in tannins. It is obtained by hydrolysis of nut galls and certain tannins. On heating, it gives $CO_2$ and pyrogallol. Its chief use is in ink. Its reactions have been extensively studied because of its relation to the natural *depsides* (E. Fischer). These are esters formed from two or more molecules of the same or different phenolic acids. Thus the simplest di-depside is *p*-hydroxybenzoyl-*p*-hydroxybenzoic acid, $HOC_6H_4CO_2C_6H_4CO_2H$, m. 261°. The secret of success in these

studies is the protection of the hydroxyl groups so that they will not interfere with the reactions of the carboxyl groups. At first this was done by acetylation but later it was more successfully achieved by means of the carbethoxy group, $-CO_2Et$, introduced by means of chloroformic ester. The superiority of the latter group is due to its easier removal. Whereas the acetyl group can be removed only by vigorous treatment with HCl, the carbethoxy group can be removed by mild treatment with alcoholic ammonia. A means of protecting two adjacent hydroxyls is the action of phosgene which forms a carbonate. *m-Digallic acid*, *m*-galloylgallic acid, m. 285° can be made by the following steps which show its structure:

1. Gallic acid is treated with NaOH and $ClCO_2Et$ to give $(EtO_2CO)_3C_6H_2CO_2H$ which can then be converted to the acid chloride by cold $PCl_5$.

2. Gallic acid, NaOH, and $COCl_2$ give a carbonate involving the 3- and 4-hydroxyls but leaving the 5-OH free.

3. The acid chloride can be condensed with the free OH. The protecting groups can then be removed by treatment with alcoholic $NH_3$ without breaking the phenol ester linkage.




m-Digallic acid.

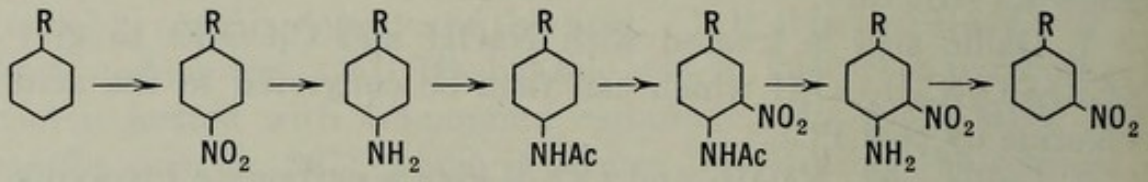
If the pentamethyl ether of this acid is converted to the acid chloride which is then condensed with glucose it is possible to obtain a methylated pentadigalloyl glucose which is identical with a methyl *tannin* obtained by methylating Chinese tannin with diazomethane.

The technique of Bergmann (p. 605) for protecting a group by the action of $PhCH_2OCOCl$ and removal of the protecting group by mild hydrogenation could undoubtedly be used in depside studies.

Simpler depsides occur in various lichens. For instance *lecanoric acid* is the di-depside of *orsellinic acid*, 4,6-dihydroxy-*o*-toluic acid, m. 176°. *Evernic acid*, m. 169° is the monomethyl ether of this di-depside.

*Alkyl Benzoic Acids*

The three *toluic acids* or methylbenzoic acids can be made by oxidation of the three xylenes with dilute nitric acid. In the case of the *p*-compound, *p*-cymene is more available than *p*-xylene and the oxidation removes mainly the isopropyl group because of the point of attack presented by its tertiary H. The toluic acids can also be made from the nitriles obtained by diazotizing the three toluidines. Higher *alkylated benzoic acids* can be made through the steps: hydrocarbon, nitro compound, amine, nitrile, acid. This gives only the *o*- and *p*-series. The *m*-series is harder to make.




This can then be converted to the amine, nitrile and acid of the *m*-series.

The six possible *xylic acids* or dimethylbenzoic acids are known. *Hemellitic acid*, 2,3-$Me_2$-benzoic acid, 2,3-xylic acid, m. 144° is made by oxidizing hemimellitene with dilute nitric acid. *3,4-xylic acid*, m. 166° can be made by oxidizing pseudocumene (along with smaller amounts of the 2,4-acid) or from the nitrile obtained by fusing a cyanide with a salt of *o*-xylene-4-sulfonic acid. *2,6-xylic acid*, m. 116° is made by fusing a salt of the difficultly obtainable *m*-xylene-2-sulfonic acid with a formate. *2,4-xylic acid*, m. 126° is the most readily available of these acids. Probably the best preparation is by the action of phosgene and $AlCl_3$ on *m*-xylene. *Mesitylenic acid*, 3,5-xylic acid, m. 166°, is made by oxidizing mesitylene with dilute nitric acid. *2,5-xylic acid*, isoxylic acid, m. 132°, is made from the amide obtained from *p*-xylene, $NH_2COCl$ and $AlCl_3$ in $CS_2$ solution.

The six possible *trimethylbenzoic acids* are made by oxidation of the three tetramethyl benzenes with dilute nitric acid. Prehnitene gives mainly *prehnitylic acid*, 2,3,4-$Me_3$-benzoic acid, m. 167°. From its mother liquors is obtained the isomeric *2,3,6-$Me_3$-benzoic acid*, m. 106°. Durene can give only one acid of this series, *durylic acid* (cumylic acid), 2,4,5-$Me_3$-benzoic acid, m. 150°.

Isodurene gives the three possible monobasic acids in nearly equal amounts. When the barium salts are crystallized the first to separate is that of *α-isodurylic acid*, 3,4,5-$Me_3$-benzoic acid, m. 215°. The acids are liberated from the mother liquors and are crystallized from ligroin. The first to separate is *β-isodurylic acid*, 2,4,6-$Me_3$-benzoic acid, m. 152°. From the mother liquors is obtained *γ-isodurylic acid*, 2,3,5-$Me_3$-benzoic acid, m. 127°.

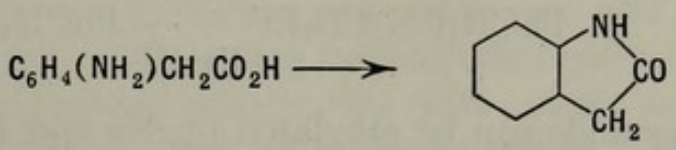
The three possible *tetramethylbenzoic acids* have been made. The 2,3,4,5-$Me_4$-acid, m. 165° is made by oxidizing $Me_5$-benzene. The *2,3,4,6-acid*, m. 140° is made by oxidizing the corresponding methyl ketone obtained from isodurene, acetyl chloride and $AlCl_3$ in $CS_2$, at low temperature. The *2,3,5,6-acid*, m. 179° is similarly made from phosgene and durene.

The complex relationships of symmetry and melting points are well illustrated by the polymethylbenzoic acids.

### *C.* Aryl-substituted Aliphatic Acids

These are known in nearly as large numbers as the substituted benzoic acids. Because they usually have one or two alpha H atoms and may have reactive groups both in the side chain and the ring, their chemistry is very complex.

**Phenylacetic acid,** α-toluic acid, $C_6H_5CH_2CO_2H$, m. 77°, b. 265°, is available from benzyl cyanide, $C_6H_5CH_2CN$, b. 232°, which is readily formed from benzyl chloride and a cyanide. The expected substitution products involving the α- and aryl hydrogens are known. They give the normal reactions. An exception is *o*-amino-phenylacetic acid which cannot exist in the free form but becomes oxindole, m. 120°.



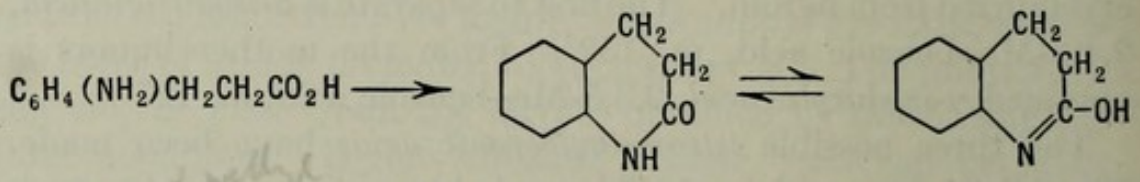

This is another example of the ease of ring closure when two mutually reactive groups are in the 1,5-position.

**β-Phenylpropionic acid, hydrocinnamic acid,**

$$C_6H_5CH_2CH_2CO_2H,$$

m. 48°, b. 280°, is obtained by the easy reduction of cinnamic acid

either by nascent or catalytic hydrogen. Its $\alpha$-amino derivative is phenylalanine, a protein decomposition product. When the $NH_2$ group is in the *o*-position, the free acid changes spontaneously to *hydrocarbostyril*, a dihydroquinoline derivative.




**α-Phenylpropionic acid, hydratropic acid,** $C_6H_5CH(CH_3)CO_2H$, b. 265°, is obtained by reducing atropic acid formed by dehydrating tropic acid.

Since phenyl halides do not react with substances like Na-malonic ester, *phenylethylmalonic ester*, $C_6H_5(Et)C(CO_2R)_2$, the intermediate for the important soporific, Luminal cannot be made from malonic ester. Several methods have been devised for its preparation.

1. Phenylacetic and oxalic esters are condensed and the phenyloxaloacetic ester is decomposed by heat.

$$EtO_2C(Ph)CH_2 + EtOCOCO_2Et \rightarrow$$
$$EtO_2C(Ph)CHCOCO_2Et \rightarrow CO + PhCH(CO_2Et)_2$$

Treatment with Na and EtBr gives the desired product although the yield is not good.

2. Benzylcyanide with sodamide in ether gives a sodium derivative which reacts with ethyl carbonate (Nelson, Cretcher 1928).

$$PhCH_2CN \xrightarrow{NaNH_2} \xrightarrow{Et_2CO_3}$$
$$PhCH(CN)CO_2Et \xrightarrow[EtOH]{HCl} PhCH(CO_2Et)_2, \text{ etc.}$$

3. Benzyl cyanide can be ethylated by Na and EtBr (Rising 1928).

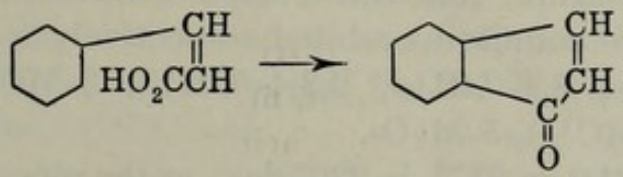
$$PhCH_2CN \xrightarrow[EtBr]{Na} PhEtCHCN \xrightarrow[ClCO_2Me]{Na}$$
$$PhEtC(CN)CO_2Me \xrightarrow[MeOH]{HCl} PhEtC(CO_2Me)_2$$

The phenylethyl acetonitrile does not condense with ethyl carbonate.

**Cinnamic acid,** *trans*-$\beta$-phenylacrylic acid, $C_6H_5CH=CHCO_2H$, m. 133°, b. 300°, occurs in natural balsams and resins and can be readily prepared by the Perkin reaction by heating benzaldehyde, sodium acetate and acetic anhydride. It gives the reactions of an alpha beta unsaturated acid and of a benzene compound. Nitration gives *o*- and *p*-nitro compounds. Fusion with KOH gives acetic and benzoic acids.

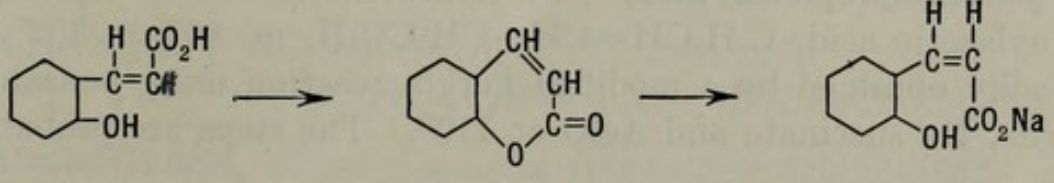
**Allocinnamic acid,** the *cis*-form, m. 68°, is prepared in a variety of ways but most readily by the catalytic reduction of phenylpropiolic acid. It exists in polymorphic forms as various isocinnamic acids, m. 59°, 38°, 80°, and possibly 131°.

Two **$\alpha$-bromocinnamic acids,** m. 120° and 131°, are obtained from cinnamic acid dibromide. Two $\beta$-bromocinnamic acids, m. 135° and 159°, are obtained by adding HBr to phenyl propiolic acid. The *cis* forms yield indenones with sulfuric acid.



***o*-Aminocinnamic acid,** obtained by the reduction of the *o*-$NO_2$ acid from the direct nitration of allocinnamic acid, spontaneously changes to carbostyril, $\alpha$-OH-quinoline, an example of the ease of 6-ring closure. This change also indicates the *cis* nature of the acid. The stereoisomeric *o*-$NH_2$-cinnamic acid does not change to a ring compound but gives ordinary cinnamic acid when its $NH_2$ group is replaced by H (Stoermer 1912).

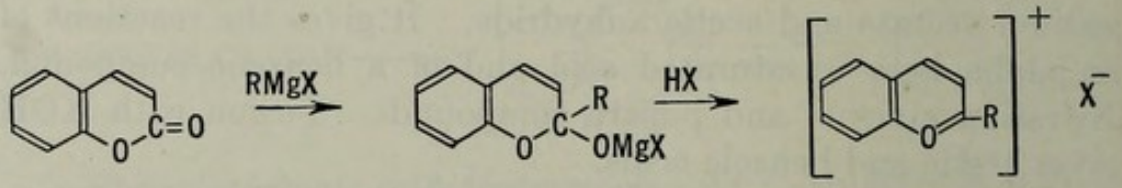
*trans*-*o*-Hydroxycinnamic acid, *coumaric* acid, is made by diazotizing the *o*-$NH_2$- acid or by the Perkin synthesis from salicylaldehyde. Vigorous dehydration with acetic anhydride gives *coumarin*, m. 67°, b. 290°, an inner anhydride. This dissolves in NaOH to give the salt of *coumarinic acid* the *cis*-*o*-OH-cinnamic acid.



Coumaric acid Coumarin Coumarinic acid

Coumarin is an important natural and artificial perfume and flavoring material. It is used with vanillin in artificial vanilla extract and in fixing odors in perfumes.

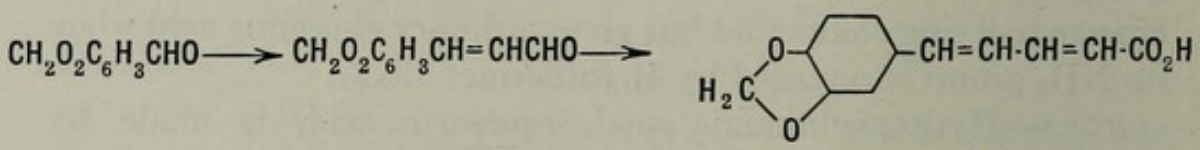
Coumarin, with Grignard reagents, gives a peculiar type of pseudo base.




A benzopyrilium salt

**Caffeic acid,** 3,4-$(OH)_2$-cinnamic acid, m. 220°, occurs in plant products notably in coffee as *chlorogenic acid*, a di-depside in which it is esterified with the 3-OH of quinic acid. The 3-Me-ether of caffeic acid is *ferulic acid*, m. 168°, while the 4-Me-ether is *hesperitinic acid*, or isoferulic acid, m. 228°. *Umbellic acid*, 2,4-$(OH)_2$-cinnamic acid readily changes to *umbelliferone*, m. 224°, a hydroxycoumarin. *Aesculetin, daphnetin, scopoletin, limettin,* and *fraxetin* are coumarins related respectively to the following cinnamic acids, 3,4-$(OH)_2$-, 2,3,4-$(OH)_3$-, 3-MeO-4-OH-, 2,4-$(MeO)_2$-, 2,3,4-$(OH)_3$-5-MeO-.

**Piperic acid** (I), m. 217°, b. 220° dec., as the piperidide *piperine*, is the chief constituent of pepper. Its synthesis from piperonal well illustrates the value of the aldol condensation and its modifications. The first step is a condensation with acetaldehyde and the second with Na acetate and $Ac_2O$.




(I)

**Atropic acid,** $\alpha$-phenylacrylic acid, $CH_2=C(C_6H_5)CO_2H$, m. 107°, b. 267° dec., is made by dehydrating tropic acid. Fusion with KOH gives formic and phenylacetic acids.

**β-Benzalpropionic acid,** $\gamma$-Phenylisocrotonic acid, $\gamma$-phenylvinylacetic acid, $C_6H_5CH=CH-CH_2CO_2H$, m. 86°, b. 302°, is readily obtained by a modified Perkin reaction using benzaldehyde, Na succinate and $Ac_2O$ at 110°. The steps are probably

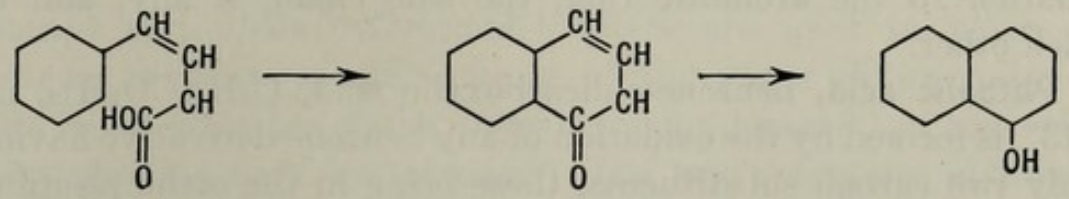
as follows:

$$PhCHO + \begin{matrix} CH_2CO_2Na \\ | \\ CH_2CO_2Na \end{matrix} \rightarrow PhCHOH—\underset{\displaystyle CH_2CO_2Na}{\underset{|}{CH}}—CO_2Na \rightarrow$$

$$PhCH—\underset{\displaystyle OCOCH_2}{\underset{|}{CHCO_2Na}} \rightarrow PhCH=CH—CH_2CO_2Na$$

(I)

**Phenylparaconic acid,** m. 99°, corresponding to (I) is a by-product. Further heating converts it to the unsaturated acid. The latter on refluxing for some time gives α-naphthol.



**Phenylpropiolic acid,** $C_6H_5C\equiv CCO_2H$, m. 137°, is made by eliminating 2 HBr from cinnamic acid dibromide or its ester. With $H_2O$ at 120° it gives $CO_2$ and $PhC\equiv CH$ while with sulfuric acid it gives $PhCOCH_2CO_2H$.

*Aryl Substituted Aliphatic Hydroxy and Keto Acids*

**Mandelic acid,** phenylglycollic acid, $C_6H_5CHOHCO_2H$, m. 118°, occurs in amygdalin and is made from benzaldehyde cyanohydrin (*mandelonitrile*), b. 170°.

**Phthalide,** m. 73°, b. 290°, is the inner ester of *o*-hydroxymethyl-benzoic acid obtained by the reduction of phthalic anhydride or phthalyl chloride with Zn and HCl.

**Tropic acid,** α-phenyl-β-hydroxypropionic acid,

$$HO\overset{\beta}{C}H_2\overset{\alpha}{C}H(C_6H_5)CO_2H,$$

m. 118°, obtained by the hydrolysis of its tropine ester, atropine, has been synthesized by reducing the condensation product of ethyl phenylacetate and ethyl formate.

$$PhCH_2CO_2Et + HCO_2Et \rightarrow HCOCHPhCO_2Et \rightarrow$$
$$HOCH=CPhCO_2Et \rightarrow HOCH_2CHPhCO_2Et$$

**Atrolactic acid,** α-phenyl-α-hydroxypropionic acid, m. 93°.

**Benzoylformic acid,** phenylglyoxylic acid, $C_6H_5COCO_2H$ is a typical ketonic acid obtained by hydrolyzing benzoyl cyanide with cold conc. HCl.

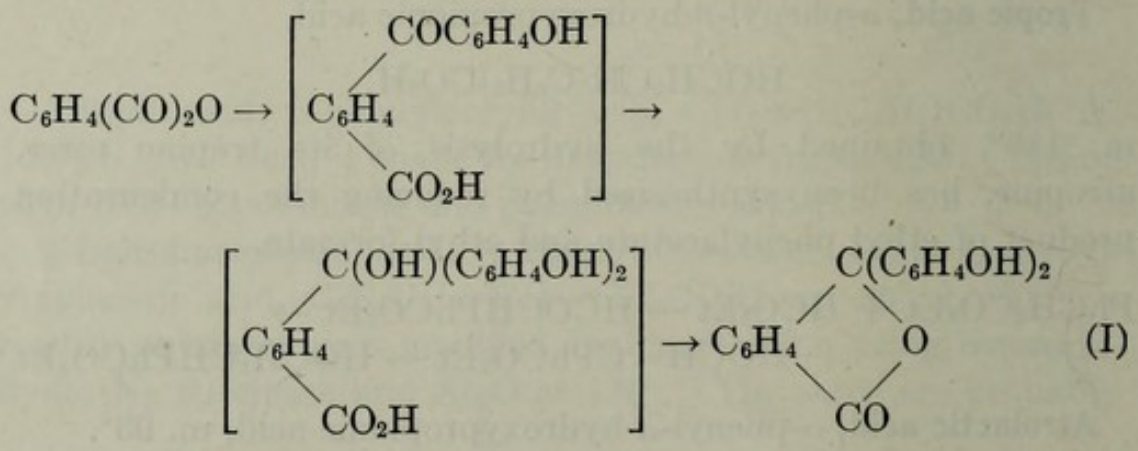
**Benzoylacetic acid,** $C_6H_5COCH_2CO_2H$, m. 103°, is obtained as its ester like acetoacetic ester by the condensation of Et benzoate and Et acetate by means of NaOEt. It and its ester resemble the other beta keto acids and their esters.

### *D.* Dibasic Aromatic Acids

These have been made in great number and variety. Their properties depend on the position of the two carboxyl groups in relation to the aromatic ring, the side chain, if any, and to each other.

**Phthalic acid,** benzene-*o*-dicarboxylic acid, $C_6H_4(CO_2H)_2$, m. 213°, is formed by the oxidation of any benzene derivative having only two carbon substituents, these being in the ortho position. Naphthalene can be oxidized to phthalic acid in a variety of ways, including the famous method of oxidizing with concentrated sulfuric acid in presence of mercuric sulfate, supposedly discovered by the accidental breaking of a thermometer during a sulfonation experiment. Sodium amalgam converts it to di-, tetra- and hexahydrophthalic acids which are known in all the theoretically possible stereiosomeric forms.

**Phthalic anhydride,** m. 130°, b. 284°, is made cheaply in large quantities by the catalytic oxidation of naphthalene vapor with air under carefully controlled conditions. In addition to the ordinary reactions of an acid anhydride, it reacts with the *p*-H of phenols. The formation of phenolphthalein (I) is typical




(I)

Similarly fluorescein is made from resorcinol. With aromatic hydrocarbons, phthalic anhydride condenses readily in presence of $AlCl_3$ to give substituted *o*-benzoylbenzoic acids which are important intermediates for making anthraquinones.

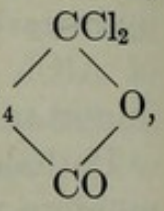
Phthalic anhydride reacts with alcoholic $NH_3$ to give ammonium phthalamate, $NH_2COC_6H_4CO_2NH_4$. Treatment of this substance or the free acid with hypohalites gives anthranilic acid.

Normal and acid esters of phthalic acid are known. The former are obtained in the usual way from the acid or anhydride and excess of alcohol refluxed with a small amount of HCl or $H_2SO_4$. These esters are stable and very high boiling. The dibutyl and di-2-ethylhexanol-1 esters are used in place of mercury in high vacuum pumps of the vapor diffusion type. The latter ester has vapor pressures considerably less than the corresponding ones for mercury. The acid esters are obtained by the direct action of the anhydride and an alcohol. These are still acids and form salts. The salts with optically active bases like brucine can be used for separating *d*- and *l*- forms of optically active alcohols (p. 121).

Nitration and sulfonation of phthalic anhydride, give the *3*- and *4-nitro*- and *3*- and *4-sulfo-phthalic acids*. The *3*- and *4*-isomers can be separated by differences in solubility, the former being less soluble. *3*- and *4-aminophthalic acids* can exist only as certain complex salts and as esters. Both free acids spontaneously lose $CO_2$ and give *m*-aminobenzoic acid. This is an unusual example of the activating effect of $NH_2$ on the *o*- and *p*-positions.

Heating the mercuric salt of phthalic acid gives $CO_2$ and anhydro-hydroxymercuri-benzoic acid (OS). Similarly 3-nitrophthalic acid gives the 2-mercuri-3-$NO_2$-benzoic acid derivative (OS) in which the 2-Hg can be replaced by halogen to give 2-halogen-3-$NO_2$-benzoic acids.

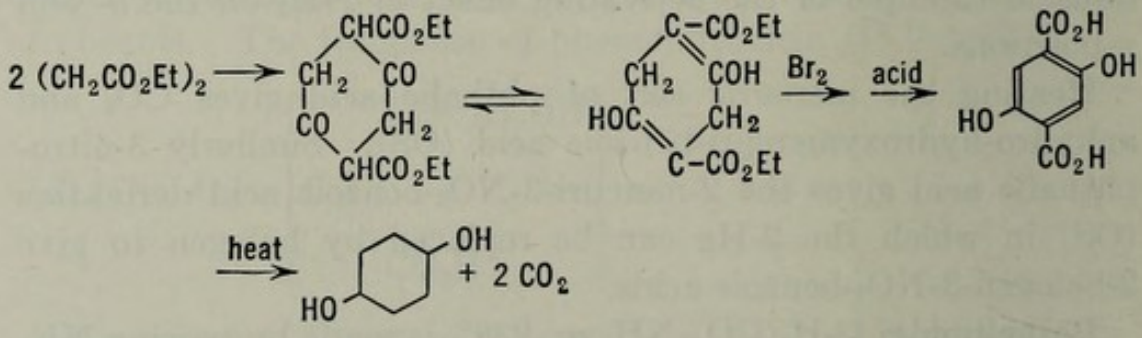
**Phthalimide,** $C_6H_4(CO)_2NH$, m. 238°, is made by passing $NH_3$ gas over hot phthalic anhydride. Its potassium compound is readily formed by adding conc. KOH to alcoholic phthalimide. It is the intermediate for the *Gabriel synthesis of primary amines.*

**Phthalyl chloride** exists in both the symmetrical form, $C_6H_4(COCl)_2$, m. 16°, and the unsymmetrical form,  , m. 89°.

Phthalic anhydride and $PCl_5$ give the first which is converted to the second by heating with pure $AlCl_3$ (OS). Apparently the $AlCl_3$ forms a more stable compound with the carbonyl group of the *unsym*-form than with either carbonyl of the true acid chloride form.

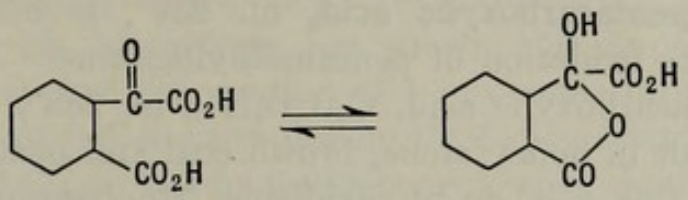
**Isophthalic acid,** benzene-1,3-dicarboxylic acid, m. 330°, is made by oxidizing *m*-xylene. It forms no anhydride. Its barium salt is readily soluble while those of the *o*- and *p*-phthalic acids are difficultly soluble. Its methyl ester melts at 68°. *Uvitic acid,* toluene-3,5-dicarboxylic acid, m. 290°, is obtained by oxidizing mesitylene.

**Terephthalic acid,** benzene-1,4-dicarboxylic acid, sublimes without melting. It is made by oxidizing *p*-toluic acid or *p*-cymene from spruce turpentine. Its Me and Et esters melt at 140° and 44° respectively. The theoretically possible stereoisomers of the di-, tetra- and hexahydroterephthalic acids have been made. Succinylosuccinic ester, obtained by the action of NaOEt on ethyl succinate is a derivative of dihydroterephthalic acid.




**Phthalonic acid,** *o*-carboxybenzoylformic acid, is a good example of ring-chain tautomerism (Rep. 1927, 114). For instance

it gives two dimethyl derivatives, only one of which gives a semicarbazone.



### *E.* Polybasic Aromatic Acids

All the theoretically possible acids are known.

**Benzenetricarboxylic acids. Hemimellitic acid,** the 1,2,3-acid, m. 203° dec., is made by permanganate oxidation of acenaphthene. On heating the Hg salt, the 2-carboxyl is lost to give anhydro-2-hydroxymercuri-isophthalic acid. The Hg can be replaced by halogen to give 2-derivatives of isophthalic acid. *Trimellitic acid*, the 1,2,4-acid, m. 216° dec., is made by oxidizing abietic acid or colophony (rosin) with dilute nitric acid. The isopropyl group and the aliphatic part of the molecule are oxidized leaving three carboxyl groups. *Trimesic acid*, 1,3,5-, m. 350°, is available by a great variety of reactions including the oxidation of mesitylene, the hydrolysis of the nitrile from *sym*-benzenetrisulfonates and NaCN, and the hydrolysis of the ester from the action of NaOEt on methyl formate and acetate. This is another example of successive aldol condensations which finally lead to a stable unreactive product.

$$HCO_2Et + CH_3CO_2Et \rightarrow HCOCH_2CO_2Et$$

$$2\ HCOCH_2CO_2Et \rightarrow EtO_2CCH_2CHOHCH(CO_2Et)CHO \rightarrow$$
$$EtO_2CCH_2CHOHCH(CO_2Et)CHOHCH(CO_2Et)CHO$$

The active carbonyl group is now in the 1,6-position to an $\alpha$-H. Their reaction closes the ring. The loss of $3\ H_2O$ from the secondary OH groups and the adjacent H atoms which are $\alpha$- to carbethoxyl groups gives *sym*-$C_6H_3(CO_2Et)_3$. In trimesic acid, the carboxyl groups have little influence on each other.

**Benzene tetracarboxylic acids** are obtained by oxidizing the $Me_4$-benzenes. The melting points given are taken in sealed tubes as heat causes anhydride formation with greater or less

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ease. *Prehnitic acid*, 1,2,3,4-, m. 237°; *mellophanic acid*, 1,2,3,5-, m. 238°, $Me_4$ ester, m. 130°; *pyromellitic acid*, 1,2,4,5, m. 264°.

**Benzene pentacarboxylic acid,** m. 230°, is made by cold permanganate oxidation of pentamethylbenzene. *Mellitic acid*, benzene hexacarboxylic acid, $C_6(CO_2H)_6$, m. 288°, occurs as its aluminum salt in honey stone, brown coal and peat. It can be made from this salt or by oxidizing $Me_6$-benzene with cold permanganate. It is also formed in the oxidation of graphite and willow charcoal with nitric acid. Heat removes one or more carboxyl groups.

## XVIII. HYDROCARBONS WITH TWO OR MORE SEPARATE BENZENE NUCLEI AND THEIR DERIVATIVES

### *A.* Diphenyl and Its Derivatives

**Diphenyl, biphenyl,** phenylbenzene, $C_6H_5C_6H_5$, m. 71°, b. 255°, is made commercially by heating benzene to a high temperature with the elimination of $H_2$. The by-products include *p*- and *m*-diphenylbenzenes and a little triphenylene (1,2,3,4-dibenzonaphthalene) (Bachmann 1927).

Diphenyl can also be made in the following ways, among others:

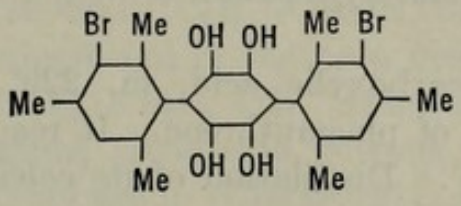
$$2\ PhBr + 2\ Na \rightarrow Ph-Ph \quad \text{(Fittig)}$$
$$2\ PhI + 2\ Cu \rightarrow Ph-Ph + Cu_2I_2 \quad \text{(Ullmann)}$$
$$2\ PhMgBr + 2\ CuCl_2 \rightarrow Ph-Ph + MgBr_2 + MgCl_2 + Cu_2Cl_2$$

An ether solution of $FeCl_3$ gives a 90% yield of diphenyl from PhMgBr. Because of its stability, diphenyl is used as a high temperature heat transfer medium.

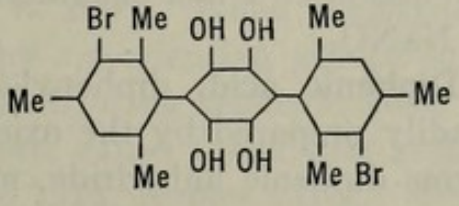
Great numbers of derivatives of diphenyl have been studied because of (1) its cheapness as an intermediate and (2) the peculiar isomerism of many of its *o,o'*-substitution products. Although these contain no asymmetric carbon, certain of them were early resolved into optical isomers. A simple example of such a resolvable substance is 6-$NO_2$-diphenyl-2,2'-dicarboxylic acid. At first it was believed that the isomerism indicated the existence of the two phenyl groups in two parallel planes (Kauffler 1907). The isomerism is actually due to a restricted rotation about the 1,1'-bond in compounds in which the substituents in

the 2,2′, 6,6′ positions are large enough to prevent free rotation (Turner, Kenyon, Mills; Rep. 1926, 119–26). The work of Adams and his co-workers has shown this hypothesis to be correct. A typical preparation of a resolvable diphenyl derivative is that of 6,6′-dinitro-diphenyl-2,2′-dicarboxylic acid from the action of Cu on 2-iodo-3-nitrobenzoic acid obtained from the mercuration product of 3-nitrophthalic acid.

In terphenyl compounds having the middle ring completely substituted a peculiar type of *cis-trans* isomerism is possible (Shildneck 1931). Complete ortho substitution by suitable groups in the end rings restricts rotation and makes isomerism possible as in the following pair of compounds




*cis*




*trans*

The *interference* of the Me and OH groups in the *o*-positions prevents free rotation and tends to hold the end rings in a plane at right angles to that of the middle ring.

Many higher analogs of diphenyl are known. For instance, sexiphenyl, $C_6H_5(C_6H_4)_4C_6H_5$, has been made as follows:

$$2\ PhN{=}NPh + Ph{-}Ph \xrightarrow[AlCl_3]{HCl}$$

$$2\ Ph{-}C_6H_4C_6H_4NH_2 \rightarrow 2\ ArI \xrightarrow[330°]{Ag} Ar{-}Ar$$

Diphenyl can be halogenated, nitrated and sulfonated in the usual way. Substitution takes place first in the 4- and 4′-positions and then in the positions ortho to the bond between the phenyl groups.

*Derivatives of Diphenyl*

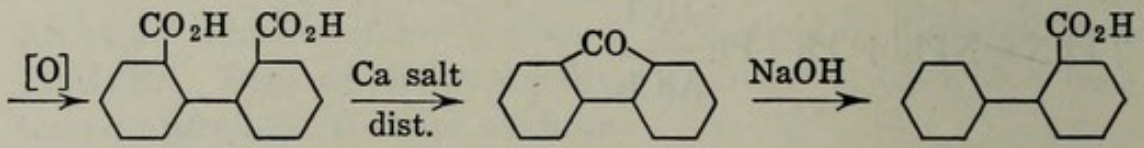
The univalent group, $C_6H_5{-}C_6H_4{-}$ is called *xenyl*. All the ordinary derivatives are known. Their chemistry closely parallels that of the phenyl compounds.

*4-Amino-diphenyl, p-xenylamine*, $C_6H_5C_6H_4NH_2$, can be made by nitration and reduction from diphenyl in the usual way or by the Friedel-Crafts reaction on azobenzene and benzene.

**Benzidine,** 4,4′-diaminodiphenyl, m. 128°, b. 400°, is obtained by the action of acids on hydrazobenzene. It forms a sparingly soluble sulfate. It and related substances such as *tolidine*, 3,3′-$Me_2$-benzidine, m. 128°, and *diansidine*, 3,3′-$(MeO)_2$-benzidine, m. 138°, made from *o*-nitrotoluene and *o*-nitrophenol are useful in making complex azo dyes. *Diphenyline*, 2,4′-diaminodiphenyl, m. 45°, is obtained in small amounts in the preparation of benzidine. Its sulfate is soluble as contrasted with that of benzidine. *N-Me₄-benzidine*, $Me_2NC_6H_4C_6H_4NMe_2$, is formed by the action of 1 mol of dimethylaniline hydrochloride with 1 mol of $NaNO_2$.

**Diphenic acid,** diphenyl-2,2′-dicarboxylic acid, m. 229°, is readily prepared by the oxidation of phenanthrene. It readily forms diphenic anhydride, m. 217°. Distillation of its calcium salt gives *fluorenone* (I).

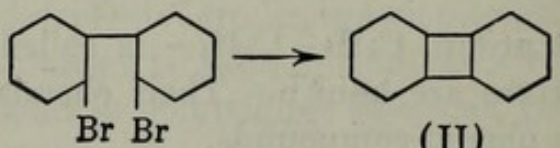
The other carboxylic acids of diphenyl are made by the usual processes for aromatic acids. The three monobasic acids are *o*-, *m*-, and *p*-phenylbenzoic acids, m. 114°, 162°, and 219°. The ortho acid can best be made by fusing fluorenone with a base. The preparation from phenanthrene takes the following steps:




(I)

The chemistry and stereochemistry of diphenyls. Rev. 1933, *12*, 261. Rep. 1933, 255–263.

**Diphenylene,** $(C_6H_4)_2$, (II) has been made from 2,2′-$Br_2$-diphenyl and Na. Its nature is shown by M.W. determinations and its oxidation to phthalic acid (Dobbie 1911).




(II)

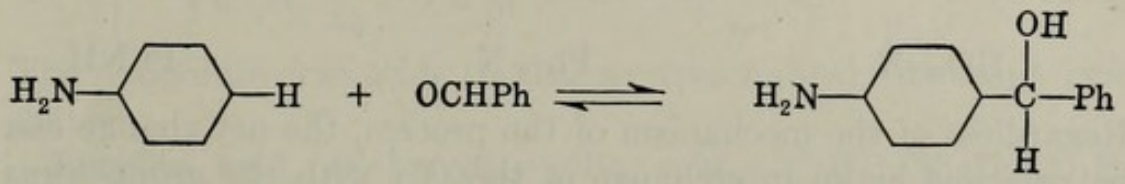
***p*-Diphenylbenzene,** $C_6H_5C_6H_4C_6H_5$, m. 205°, is obtained among other products from *p*-$Br_2$-benzene, bromobenzene and Na. *sym*-Triphenylbenzene, $C_6H_3(C_6H_5)_3$, m. 170° can be made by the action of HCl gas on acetophenone.

### *B.* Diphenylmethane

$(C_6H_5)_2CH_2$, m. 26°, b. 262°, is made from benzyl chloride, benzene and $AlCl_3$. It can similarly be made from benzene and $CH_2Cl_2$, and by the action of sulfuric acid on a mixture of benzene and methylal, $H_2C(OMe)_2$, or benzene and benzyl alcohol. The methylene H atoms are highly reactive as would be expected from their being $\alpha$- to two phenyl groups. Replacement by bromine is easy. The resulting monobromide is hydrolyzed to benzhydrol, $(C_6H_5)_2CHOH$, m. 69°, b. 299°. When benzhydrol is substituted in the para position by *o*,*p*-orienting groups such as $NH_2$, $NMe_2$, OH, OMe, etc., substituting reagents such as bromine, nitric acid, nitrous acid, etc. cause a splitting at the carbinol group (Clarke 1911, Esselen 1914, Kohler 1916).

$$PhCHOHC_6H_4NH_2 \xrightarrow{Br_2} PhCHO + C_6H_4Br_3NH_2$$

This change can be regarded as the removal of a product of the reversal of an aldol condensation by which the benzhydrol could be formed from benzaldehyde and the amine or phenol.




The dye intermediate, Michler's hydrol, is *pp'*-$(Me_2N)_2$-benzhydrol.

***p*-Diaminodiphenylmethane,** $(H_2NC_6H_4)_2CH_2$, and its $N-Me_4$ derivative are readily obtained from formaldehyde with aniline or $Me_2$-aniline. In the first case intermediate steps can be distinguished.

$$PhNH_2 + H_2CO \rightarrow PhN{=}CH_2 \xrightarrow[PhNH_3Cl]{PhNH_2} (H_2NC_6H_4)_2CH_2$$

**Diphenylmethane-*o*-carboxylic acids** are important intermediates in making anthraquinones. ***o*-Benzylbenzoic acid,** m. 114°, is readily obtained by NaxHg reduction of *o*-benzoylbenzoic acid. Sulfuric acid readily closes a 6-ring to form anthrone which gives anthraquinone on oxidation.

Oxidation of diphenylmethane gives *benzophenone*, $(C_6H_5)_2CO$, b. 305° which exists in polymorphic forms m. 48°, 26°, and 51°. It is better prepared from the hydrolysis of $Ph_2CCl_2$ prepared from benzene, $CCl_4$ and $AlCl_3$ (OS). Its oxime melts at 142° (OS). The reactions of benzophenone and its substitution products are those which would be expected of a ketone with no $\alpha$-H. Thus it is split by sodamide.

$$Ph_2CO + NaNH_2 \rightarrow PhCONH_2 + [PhNa] \xrightarrow{H_2O} C_6H_6$$

Unsymmetrically substituted benzophenones may form isomeric oximes. Thus anisyl phenyl ketone gives two oximes, one of which on Beckmann rearrangement with $PCl_5$ or AcCl gives PhCONHAn and the other AnCONHPh. These can be identified by hydrolysis to benzoic acid and anisidine and to anisic acid and aniline respectively.

$$MeOC_6H_4{-}\overset{\displaystyle Ph}{\underset{\displaystyle N{-}OH}{C}} \rightarrow HO{-}\overset{\displaystyle Ph}{\underset{\displaystyle N{-}C_6H_4OMe}{C}} \rightleftharpoons O{=}\overset{\displaystyle Ph}{\underset{\displaystyle NHC_6H_4OMe}{C}}$$

$$MeOC_6H_4{-}\overset{\displaystyle Ph}{\underset{\displaystyle HO{-}N}{C}} \rightarrow MeOC_6H_4{-}\overset{\displaystyle OH}{\underset{\displaystyle Ph{-}N}{C}} \rightleftharpoons MeOC_6H_4C{=}O \quad \underset{\displaystyle PhNH}{|}$$

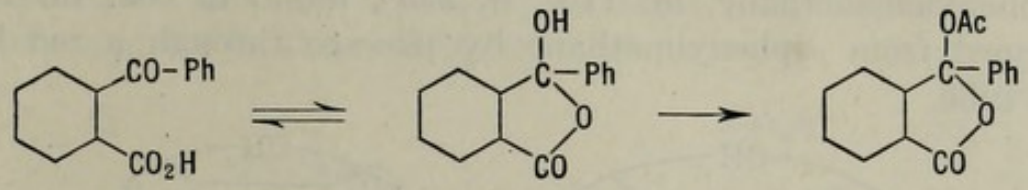
Regardless of the mechanism of the process, the net change can be regarded as an interchange of the OH with the group *trans* to it (Rep. 1922, 95).

Michler's ketone, an important dye intermediate, is made by phosgene and dimethylaniline. No $AlCl_3$ is needed.

$$2\ PhNMe_2 + COCl_2 \rightarrow CO(C_6H_4NMe_2)_2$$

**Benzophenone carboxylic acids** can be made by oxidizing the homologs of benzophenone. The *o*-cpd, ***o*-benzoylbenzoic acid,** m. 127°, is readily available as an intermediate in anthraquinone manufacture from benzene, phthalic anhydride and $AlCl_3$. As

a gamma keto acid it exists in equilibrium with a lactone-hemiacetal form as is evidenced by its acetylation.




Reduction by NaxHg changes benzoylbenzoic acids to benzylbenzoic acids. The most important reaction of *o*-benzoylbenzoic acid is its easy ring closure with $H_2SO_4$ or $P_2O_5$ at 180° to give anthraquinone (Gleason 1929).

**1,1-Diphenylethane,** $(C_6H_5)_2CHCH_3$, b. 286°, is made from paraldehyde, benzene and $H_2SO_4$ or from benzene, a curpous chloride catalyst and acetylene (Nieuwland). 1,1-Diphenylethylene, $(C_6H_5)_2C{=}CH_2$, b. 277°, is made from PhMgBr and ethylacetate (OS). It polymerizes very readily in the presence of acids. It reacts with metallic potassium to give a compound which with water or acid gives 1,1,4,4-tetraphenylbutane (Schlenk 1914). This reaction is entirely like the bimolecular reduction of a carbonyl compound to give a pinacol. Electronically

$$K\cdot + \underset{\underset{Ph}{\cdot\cdot}}{\overset{\overset{Ph}{\cdot\cdot}}{C}}\!:\!:\!\underset{\underset{H}{\cdot\cdot}}{\overset{\overset{H}{\cdot\cdot}}{C}} \rightarrow K:\underset{\underset{Ph}{\cdot\cdot}}{\overset{\overset{Ph}{\cdot\cdot}}{C}}:\underset{\underset{H}{\cdot\cdot}}{\overset{\overset{H}{\cdot\cdot}}{C}}\cdot \rightarrow \xrightarrow{H_2O} Ph_2CHCH_2CH_2CHPh_2$$

The potassium first adds to give a "free radical," two of which unite.

**Benzilic acid,** diphenylglycollic acid, $(C_6H_5)_2C(OH)CO_2H$, m. 150°, is obtained by the action of benzil and a base. The oxidation of benzoin to benzil and the rearrangement of the latter can be carried out in one operation (OS).

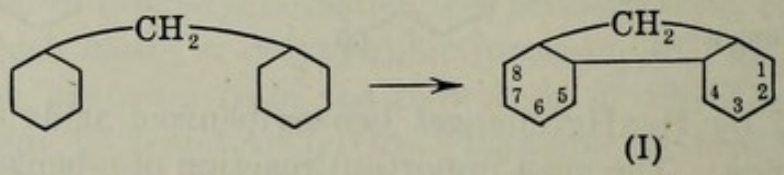
$$3\ PhCHOHCOPh + NaBrO_3 + 3\ NaOH \rightarrow 3\ Ph_2C(OH)CO_2Na + NaBr + 3\ H_2O$$

Benzilic acid is readily reduced to diphenylacetic acid,

$$(C_6H_5)_2CHCO_2H,$$

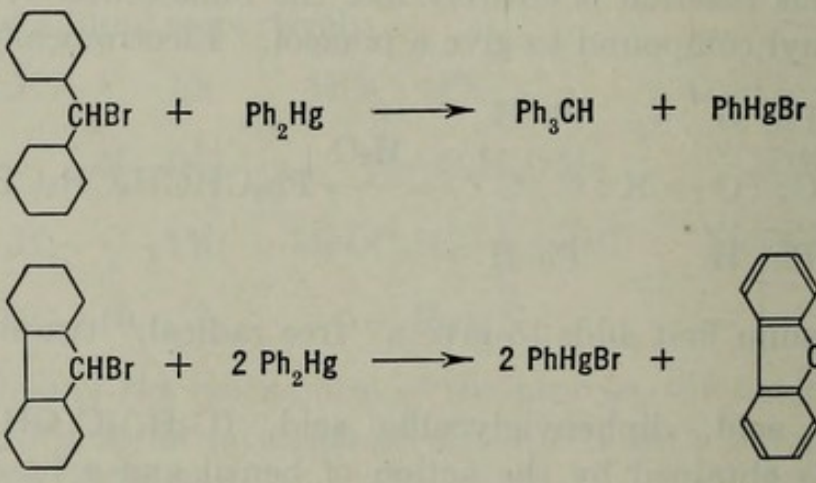
m. 145° by HI formed by red P, $I_2$ and glacial acetic acid (OS).

Related to diphenylmethane and to diphenyl is fluorene (I), diphenylenemethane, m. 116°, b. 295°, found in coal tar and formed from diphenylmethane by passage through a red hot Fe tube.




(I)

It is readily oxidized to fluorenone, diphenylene ketone, m. 84°, which can be reduced to *fluorenyl alcohol*, 9-fluorenol, m. 153°. Fusion of the ketone with KOH gives diphenyl-2-carboxylic acid. 9-Bromofluorene shows a marked contrast to the analogous diphenylbromomethane. While the latter reacts with alcoholic KOH and with diphenylmercury to give metatheses producing diphenylmethyl ethyl ether and triphenylmethane, the former with both reagents gives bis-diphenylene-ethylene (II), red crystals, m. 188°.



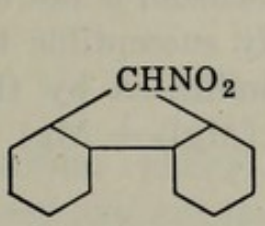

9-Br-fluorene

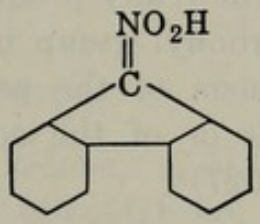
II

Thus this bromide acts as a bromide of a dibenzocyclopentadiene rather than a phenylated methyl bromide. The red hydrocarbon is also formed by the action of $PbO_2$ on fluorene at 330°. Fluorene with $SeO_2$ gives only 5% fluorenone whereas diphenylmethane under identical conditions gives 87% benzophenone (Postovskii 1935).

Phenanthrenequinone, with alkali, gives the benzilic acid

rearrangement to give *diphenylene glycollic acid*, (9-hydroxyfluorene-9-carboxylic acid), m. 162°. 9-Nitrofluorene has been prepared in the true and acinitro forms from fluorene, ethyl nitrite and KOEt (Rep. 1908, 91).



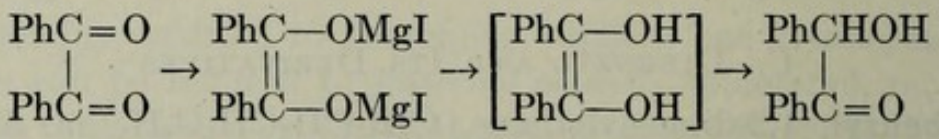




### *C.* Dibenzyl and Its Derivatives

**Dibenzyl,** 1,2-diphenylethane, $C_6H_5CH_2CH_2C_6H_5$, m. 53°, b. 284°, is best made by ethylene chloride, benzene and $AlCl_3$. It can be oxidized catalytically to benzaldehyde. *Stilbene*, trans-1,2-diphenylethylene, $C_6H_5CH=CHC_6H_5$, m. 125°, b. 307°, can be made in a variety of ways including the action of toluene on PbO at a red-heat and by the action of benzylmagnesium chloride with benzaldehyde. The alcohol first formed is dehydrated with great ease because both the OH and H are $\alpha$- to phenyl. *Isostilbene*, b. 143° (20 mm) is the *cis* form.

**Stilbene dibromide,** $C_6H_5CHBrCHBrC_6H_5$, m. 237°, reacts with alcoholic KOH to give first bromostilbene and then *tolan*, diphenylacetylene, $C_6H_5C\equiv CC_6H_5$, m. 62°, b. 300°. With some reagents, which might be expected to give replacement of the Br atoms, stilbene dibromide instead gives up bromine. Thus with KSH it gives stilbene. Similarly with di-*p*-tolylmercury it gives stilbene and tolyl bromide. With silver acetate, stilbene dibromide gives two isomeric diacetates which on hydrolysis form *hydrobenzoin* and *isohydrobenzoin*, the *racemic* and *meso* forms respectively of 1,2-$Ph_2$-glycol, $C_6H_5CHOHCHOHC_6H_5$, m. 138° and 119°. Tolan on reduction gives *sym*-diphenylethane. Oxidation with $SeO_2$ gives a 35% yield of benzil (Postovskii 1935). *Benzoin*, phenylbenzoylcarbinol, $C_6H_5CHOHCOC_6H_5$, m. 134°, is made from benzaldehyde and NaCN solution (OS). Its great ease of reduction is probably due to an enediol form, $PhC(OH)=C(OH)Ph$. *Benzil*, dibenzoyl, $C_6H_5COCOC_6H_5$, yellow crystals, m. 95°, is obtained by oxidizing benzoin with nitric acid or with an alkaline copper solution (OS).

Reduction of benzil gives all the theoretically possible compounds namely benzoin, PhCOCHOHPh, hydrobenzoin, PhCHOHCHOHPh, desoxybenzoin, $PhCH_2COPh$, diphenylethane, etc. The last two products are obtained by reduction with HI. The ready production of benzoin is not an indication that one carbonyl group is unusually susceptible to reduction. The mechanism of the process is indicated by the action of alkali metals or of the equivalent ($MgI_2$ + Mg) combination (Gomberg 1927)

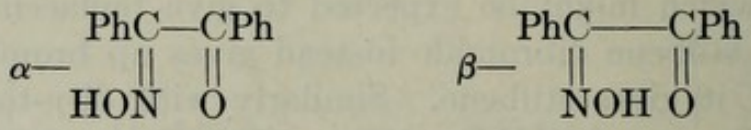


Thus the reaction is initiated by a 1,4-addition to the system, O=C−C=O.

Heating benzil with alcoholic KOH gives the *benzilic acid rearrangement* to form potassium benzilate, $Ph_2C(OH)CO_2K$. The conversion of benzoin to benzil and then to benzilic acid can be combined by heating the former with $NaBrO_3$ + NaOH (OS).

Ammonium cyanide (NaCN + $NH_4Cl$) splits benzil to give benzamide and benzaldehyde cyanohydrin.

**Benzil monoxime** exists in two forms, α-, m. 134°, β-, m. 113°. The following are the configurations



These are based on a variety of evidence including the formation of metallic derivatives of the α-form, the greater volatility of the β-form (due to a chelate ring, Sidgwick 1925) and the formation of the benzoyl derivative of the β-oxime from triphenylisoxazole and $O_3$ (Meisenheimer 1921) (Rep. 1922, 8; 1925, 106; 1926, 127). Three forms of *benzildioxime* are definitely known: α-, m. 237°, β-, m. 207°, γ-, m. 163°, (Rep. 1921, 88; 1922, 95; 1924, 111–15; Ponzio 1932, 1933). A δ-form has been reported but not confirmed (Atack 1921, Meisenheimer 1924).

Various substituted benzils have been prepared in colorless as well as in the ordinary yellow forms (Irvine 1907, Rep. 1922, 109).

The colorless forms react only slowly with 1,2-diamines while the yellow forms react rapidly to give quinoxalines. The condition may be a peculiar bond tautomerism

$$\underset{\text{Yellow}}{\text{ArCOCOAr}} \rightleftharpoons \underset{\text{Colorless}}{\text{ArC(—O—)=CAr}}$$

**Desoxybenzoin,** phenyl benzyl ketone, $C_6H_5COCH_2C_6H_5$, m. 55°, is best made from benzene, phenylacetyl chloride and $AlCl_3$ (OS). PhCOCHPh is the *desyl group*. The $CH_2$ group in desoxybenzoin shows the same reactions as that group in 1,3-dicarbonyl cpds. such as malonic and acetoacetic esters. Thus it gives a sodium cpd. and condenses with aldehydes in presence of catalysts such as piperidine (Knoevenagel) and adds to the conjugated system in $\alpha\beta$-unsaturated carbonyl cpds. (Michael) (Ionescu 1932).

### *D.* Triphenylmethane and Its Derivatives

**Triphenylmethane** compounds are readily formed. Just as one phenyl group activates an $\alpha$-carbon group, so two phenyl groups on the same carbon have an even more pronounced effect on $\alpha$-groups. This may be illustrated by the stepwise action of $CCl_4$ with benzene in presence of $AlCl_3$

$$CCl_4 \rightarrow PhCCl_3 \rightarrow Ph_2CCl_2 \rightarrow Ph_3CCl$$

Each chloride is much more reactive than the preceding one. The last chloride forms a very stable compound with $AlCl_3$ (p. 840). The introduction of another phenyl group is not possible by any ordinary process. A similar result is found with benzaldehyde and benzene in presence of acid condensing agents.

$$PhCHO \rightarrow PhCHOHPh \rightarrow Ph_3CH$$

Groups like OH, $NH_2$, $NR_2$, etc. which activate *p*-H make such triphenylmethane condensations even easier.

**Triphenylmethane, tritane,** $(C_6H_5)_3CH$, m. 93°, b. 360°, can be made from $CHCl_3$ and benzene by the Friedel-Crafts reaction

but is better made from carbon tetrachloride (OS). The reaction mixture is decomposed with ether.

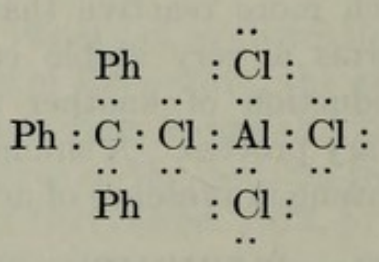
$$Ph_3CCl.AlCl_3 + Et_2O \rightarrow Ph_3CH + EtCl + MeCHO + AlCl_3$$

The tertiary H is easily replaced by halogen, by OH by means of oxidizing agents, and by metallic potassium on heating. In contrast to this reactivity of the tertiary H is the conversion by cold fuming nitric acid to the trinitro compound, $HC(C_6H_4NO_2)_3$, m. 207°. Reduction gives the *p*-triamino compound, para-leucaniline which, on oxidation, gives pararosaniline. Oxidation of the trinitro compound with chromic acid gives the corresponding carbinol.

A peculiar formation of tritane which shows the inadequacy of the simpler conception of steric hindrance is by the action of sodium diphenylmethyl with diphenyl sulfoxide.

**Triphenylchloromethane, trityl chloride,** $(C_6H_5)_3CCl$, m. 112°, b. 310°, is readily prepared from triphenylcarbinol. It gives the reactions of a tertiary chloride. In addition, it reacts on boiling with alcohol to give triphenylmethyl ethyl ether. The ease of introducing the *trityl* group in place of a primary alcoholic hydroxyl is utilized in making trityl derivatives of carbohydrates. Introduction of one such group in place of the H of the terminal $-CH_2OH$ often gives a fairly high melting solid. The process is carried on in cold pyridine solution.

Trityl chloride forms a very stable compound with $AlCl_3$ which is interesting electronically.



This compound is the main product of the action of $CCl_4$ with benzene and $AlCl_3$. It reacts with ether to give triphenylmethane (OS).

Trityl chloride acts like an inorganic chloride with silver nitrate and conc. $H_2SO_4$ to give AgCl and HCl gas respectively.

Tritylmagnesium chloride can be obtained in excellent yields under carefully controlled conditions (Gilman 1929).

**Trityl bromide,** $(C_6H_5)_3CBr$, m. 152°, is best made by the action of bromine on $Ph_3CH$.

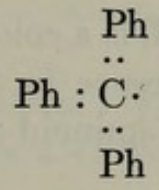
**Triphenylcarbinol,** trityl alcohol, $(C_6H_5)_3COH$, m. 159°, is readily available from benzophenone and PhMgBr. It is a typical tertiary alcohol except that, of course, olefin formation is not possible. Dehydration readily gives the ether. The reactivity of the OH is seen from the ready reaction with formic acid to give tritane and $CO_2$.

**Triphenylmethyl amine,** trityl amine, $(C_6H_5)_3CNH_2$, m. 105° is made from $NH_3$ and a trityl halide. The $NH_2$ is easily removed by hydrolysis. Boiling with alcohol replaces it by OEt.

**Triphenylmethyl,** $(C_6H_5)_3C-$, (Gomberg 1900) is obtained by the action of metals on trityl halides in absence of air or by reducing agents like vanadous chloride (Conant 1923) with the halides or the carbinol. It absorbs oxygen to give a peroxide, $Ph_3C-O-O-CPh_3$. The *free radical* exists in equilibrium with hexaphenylethane.

$$2\ Ph_3C \rightleftharpoons Ph_3C-CPh_3$$

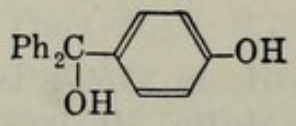
Electronically, the free radical is neutral but unstable because it has an *odd* electron.



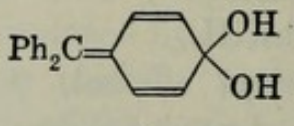
Since 1900 a tremendous mass of information has been developed about *tervalent* carbon and *free radicals* as illustrated by triphenylmethyl and related substances.

**Hydroxytriarylcarbinols** present a type of tautomerism which is of the utmost importance in the triphenylmethane dyes. Thus *p*-hydroxytriphenylcarbinol can be obtained in a yellow form, m. 140°, which loses water readily to give fuchsone or in a

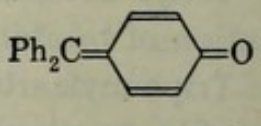
colorless form, m. 159°, which loses water only slowly (Anderson 1928).



colorless

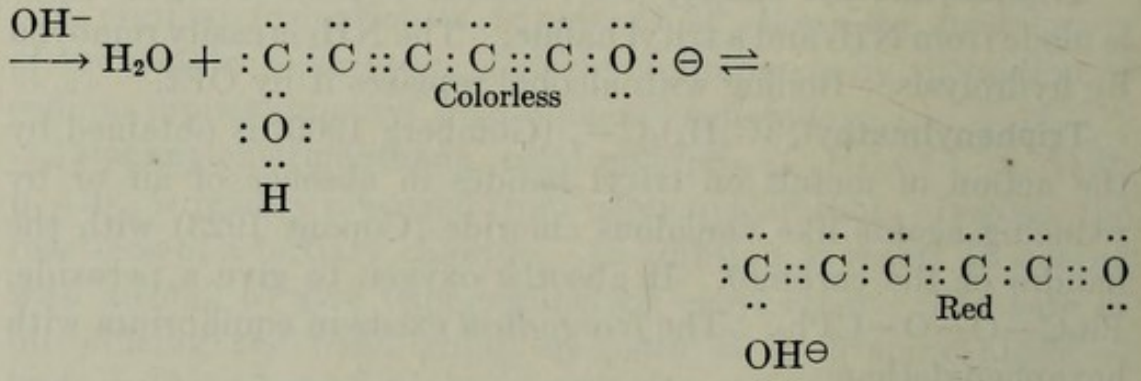


colored



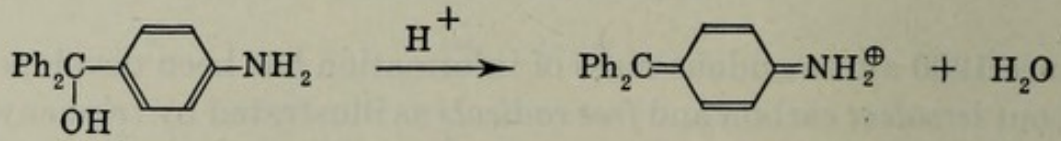
Fuchsone

Bases turn the colorless form red at once. The $OH^-$ ion removes the $H^+$ from the phenolic hydroxyl. This causes a shift of electrons in the 6-atom chain to liberate the tertiary hydroxyl.




$H^+$ ions add to the $:C::O:$ system to give $:C:O:H$ thus reversing the change. This series of changes shows that the hydroxytrityl alcohol, in common with the related acid tritane dyes, is a pseudo acid.

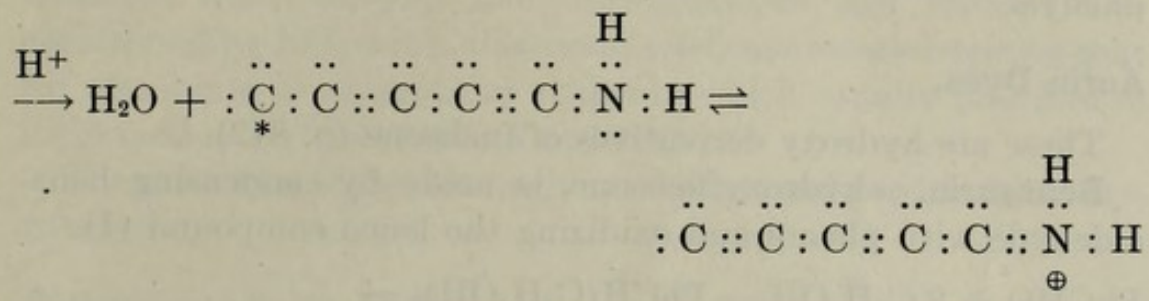
***p*-Aminotriphenylcarbinol,** is a colorless compound which turns red with acids. The difference in the two compounds is that between the benzenoid and quinoid structures.



colorless colored

The colored compounds are salts of *fuchsonimine.* The electronic shift in the 6-atom chain is entirely analogous to that in the corresponding phenolic compound except that in this case the change is initiated by $H^+$ instead of by $OH^-$. The tertiary

hydroxyl is removed by the $H^+$ ion and the electron shift follows



Hydroxyl ions reverse the change by adding to the C *. Thus aminotrityl alcohol and the related basic tritane dyes are *pseudo-bases.*

### *E.* Triphenylmethane Dyes

The colored compounds of the monohydroxy- and monoamino-triphenylcarbinols are not useful as dyes because they contain no *auxochrome groups.* This lack can be overcome by additional acidic or basic groups such as OH, $NH_2$, $NMe_2$ etc. These not only fix the dye to the mordant or the fiber but modify its shade as well.

The dyes are closely related to colorless tritane derivatives. These are called *leuco-compounds.* Oxidation converts them to the corresponding tertiary alcohols which readily change from the colorless benzenoid forms to the quinoid dyes. These colorless alcohols are *pseudo acids* or *pseudo bases* because with bases or acids *they give salts of different structure from the parent substances.*

The triphenylmethane dyes fall in two main groups, the acid and the basic types.

1. Acid dyes. These contain a *quinone* grouping with additional acid groups. They are used with mordants to give colored *lakes.*

*a.* Aurins are related to hydroxytriphenylmethane.

*b.* Phthaleins have a carboxyl or sulfonic acid group in one of the rings ortho to the methane carbon.

2. Basic dyes. These contain a *quinonimine* grouping with additional basic groups. These dye silk and wool directly.

*a.* Malachite green and related dyes have two of the phenyl groups substituted with basic groups.

*b.* Rosaniline or magenta dyes have basic groups in all three phenyls.

**Aurin Dyes.**

These are hydroxy derivatives of fuchsone (p. 842).

**Benzaurin,** *p*-hydroxyfuchsone, is made by condensing benzaldehyde with phenol and oxidizing the leuco compound (I).

$$PhCHO + 2\,C_6H_4OH \rightarrow PhCH(C_6H_4OH)_2 \rightarrow$$

$$[PhC(OH)(C_6H_4OH)_2] \rightarrow C(C_6H_5)(C_6H_4OH)=C_6H_4=O$$

(I)

**Aurin,** pararosolic acid, is the corresponding dihydroxy compound. It can be made in a variety of ways, the commonest of which is the heating of phenol with oxalic acid and $H_2SO_4$

$$3\,C_6H_5OH + H_2C_2O_4 \rightarrow$$

$$CO_2 + 2\,H_2O + \underset{\text{Leucaurin}}{CH(C_6H_4OH)_3} \rightarrow \underset{\text{Aurin}}{(HOC_6H_4)_2C=C_6H_4=O}$$

The first step may be an aldol condensation involving a *p*-H and "nascent" carbon monoxide or, more probably, a similar condensation with one carbonyl group of the oxalic acid.

$$\begin{matrix} & O \\ & \| \\ C & -OH \\ | & \\ CO_2H & \end{matrix} + C_6H_5OH \rightarrow \left[\begin{matrix} (HO)_2C & -C_6H_4OH \\ | & \\ CO_2H & \end{matrix}\right] \rightarrow$$

$$CO_2 + H_2O + HOC_6H_4CHO$$

**Corallin yellow** is sodium aurin. Heating aurin with water under pressure gives phenol and 4,4′-$(OH)_2$-benzophenone, a reversal of the aldol condensation.

**Rosolic acid** is aurin with a methyl *o*- to one hydroxyl. It was discovered by the oxidation of a mixture of phenol and *o*- and *p*-cresols, the methyl of the latter forming the methane carbon. A common oxidizing mixture is arsenic acid dissolved in sulfuric acid.

**Chrome violet** is the sodium salt of aurin-tricarboxylic acid obtained from salicylic acid, formaldehyde and $H_2SO_4$. The corresponding $NH_4$ salt is *aluminon*, a delicate colorimetric reagent for aluminum in presence of elements which usually interfere in its detection (Winter 1929, Yoe 1932).

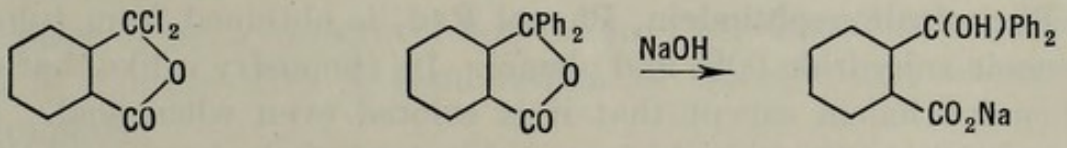
The reduction of the aurins gives the *leuco* compounds, hydroxytritanes.

*Phthalein or Eosin Dyes.*

The parent substance is tritane-*o*-carboxylic acid,

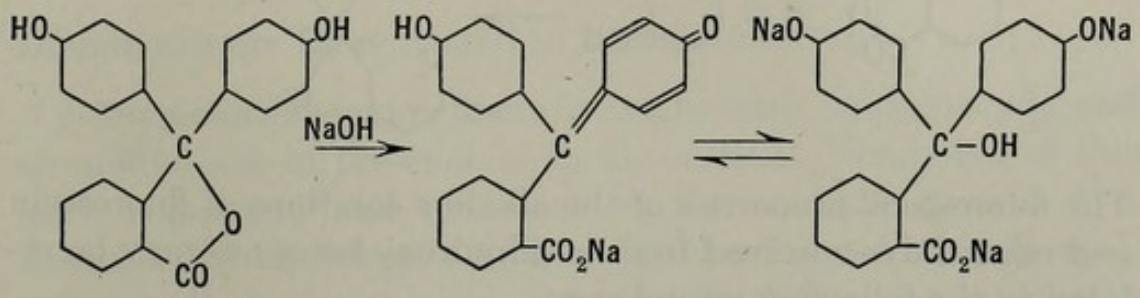
$$Ph_2CHC_6H_4CO_2H,$$

m. 162° which can be made by reducing *phthalophenone*, m. 115°, the lactone of the corresponding tertiary carbinol. Phthalophenone (I) is made from phthalyl chloride and benzene in presence of $AlCl_3$. The symmetrical chloride is converted to the unsymmetrical by the action of the $AlCl_3$ (OS).




(I)

Phenol phthalein is the corresponding di-*p*-OH cpd. formed by condensing phthalic anhydride with phenol in presence of sulfuric acid, oxalic acid or stannic chloride. It is colorless but gives characteristic purple-red salts with bases. With excess of strong conc. base it becomes colorless again.




Colorless Colored Colorless

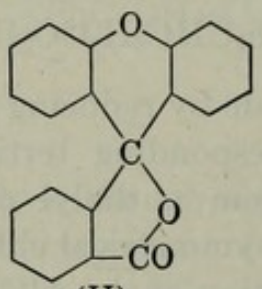
The change is due to $OH^-$ as illustrated with *p*-hydroxytritane (p. 842).

Phenolphthalein gives an oxime, m. 212°, a diacetyl cpd., m. 143° and colorless and red alkyl derivatives. With Zn dust and a base, it is reduced to *phenolphthalin* (the leuco compound) the alkaline solution of which is colorless but is readily oxidized to a red solution of a phenolphthalein salt.

The laxative properties of phenolphthalein are due to impurities of anthraquinone derivatives.

Salts of phenolphthalein (Dehn 1932).

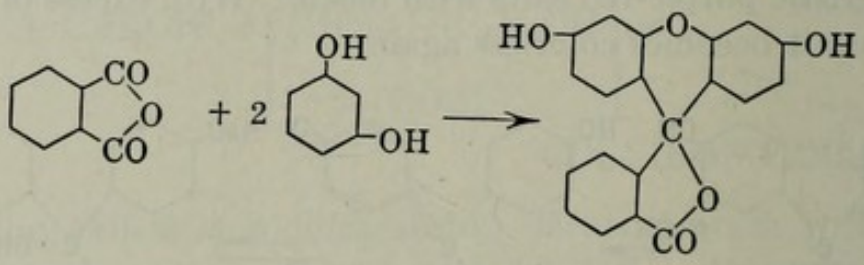
**Fluoran** (II) is a by-product of the preparation of phenolphthalein. It forms oxonium salts.



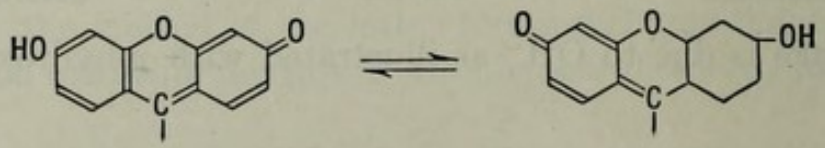

(II)

**Phenolsulfonephthalein, Phenol Red,** is obtained from sulfobenzoic anhydride (OS) and phenol. Its chemistry is like that of phenolphthalein except that it is colored even when acid. It thus exists as the quinoid free acid instead of the benzenoid lactone. Its tetrabromo cpd., *Bromophenol Blue,* exists in colorless lactoid form as well as the blue quinoid form.

**Fluorescein,** dihydroxyfluoran, resorcinolphthalein, is formed from phthalic anhydride and resorcinol heated at 200°.




The fluorescent properties of the alkaline solutions of fluorescein and related dyes derived from *m*-dihydroxy benzenes may be related to the following interchange



This change consists merely in the removal of $H^+$ from the phenolic hydroxyl and its addition to the carbonyl oxygen of the quinoid system with the resulting shift of electrons along the 11-atom system terminated by the 2 oxygen atoms.

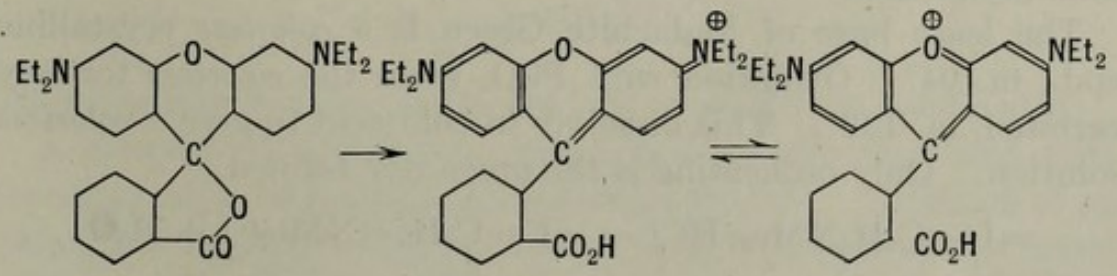
Fluorescence, Ahr. 1906, 102 pp.

Four Br atoms can be introduced into the positions ortho to the hydroxyls of fluorescein. The K salt of this compound is *eosin*. Halogenated phthalic anhydrides can be used to give fluoresceins. Thus a variety of dyes containing up to 8 atoms of halogen can be prepared. Such dyes include erythrosin, Rose Bengal, phloxin, etc.

**Mercurochrome** is the sodium salt of hydroxymercuri-dibromofluorescein. Since the Hg is ortho to a phenolic OH it is readily removed by acid.

**Gallein** is tetrahydroxyfluoran obtained from pyrogallol and phthalic anhydride.

**Rhodamines** are fluoran derivatives having two $R_2N$ groups in place of the hydroxyls of fluorescein. *Rhodamine B* is typical as a chloride with a combination of quinoid and oxonium groupings.




**Diaminotritane Dyes** related to malachite green.

***p*-Diaminotriphenylmethane** is made from benzaldehyde and an aniline salt in presence of $ZnCl_2$ or HCl. Oxidation of this leuco compound and formation of the chloride gives a dye, *Benzal Violet* or *Döbner's Violet*. Its chemistry is entirely analogous to that of the aurin dyes, the C=NH group taking the place of the C=O group of the quinoid system. In the case of the amino compounds, salts are formed with acids by the

production of an ion containing the $C=NH_2^+$ or $C=NR_2^+$ grouping.

$$PhCHO + 2\,C_6H_5NH_2 \rightarrow PhCH(C_6H_4NH_2)_2 \rightarrow PhC(OH)(C_6H_4NH_2)_2 \rightarrow$$

Leuco base — Color base

$$PhC(C_6H_4NH_2)=C_6H_4=NH \rightarrow PhC(C_6H_4NH_2)=C_6H_4=NH_2^{\oplus}Cl^{\ominus}$$

Dye

The change from color base to dye by $H^+$ ions and the reverse change by $OH^-$ ions is as illustrated for *p*-aminotritane (p. 842).

The corresponding N-tetramethyl derivative is *Malachite Green*, prepared by heating benzaldehyde with dimethylaniline and $ZnCl_2$ or $H_2SO_4$ and oxidizing the resulting leuco cpd. and converting it to the chloride. It is used as a double compound with $ZnCl_2$ or oxalic acid. It is also known as *Victoria Green* and *Bitter Almond Oil Green*. *Brilliant Green* is the corresponding tetraethyl compound. *Acid Green* is a sulfonic acid of the analogous compound from benzaldehyde and methylbenzylaniline. *Victoria Green 3 B* is made from dichlorobenzaldehyde and dimethylaniline.

The *leuco* base of Malachite Green is a *colorless* crystalline cpd., m. 94°. Oxidation with $PbO_2$ gives the *colorless* tertiary carbinol, m. 132°. This dissolves in cold acid to give a *colorless* solution. Only on heating is the green dye formed.

$$=C(OH)-C_6H_4NMe_2.HCl \rightarrow =C=C_6H_4=NMe_2Cl + H_2O$$

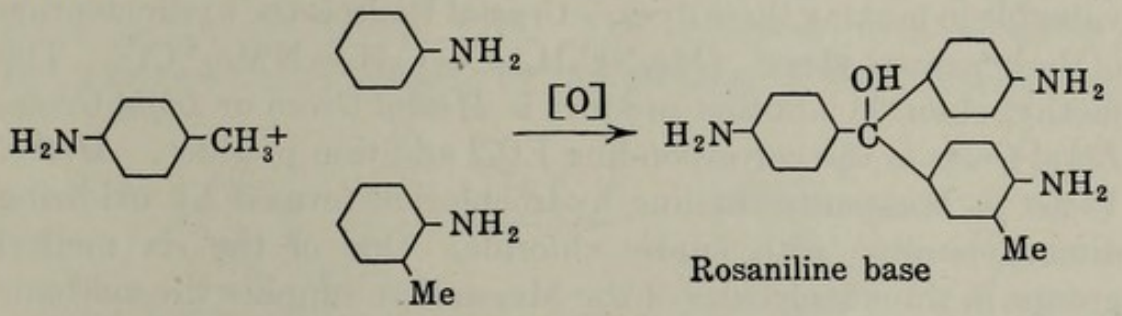
Colorless — Green

The colorless salt is the ordinary amine hydrochloride while the green quinoid salt is the salt of the stable cation obtained by rearrangement of the pseudo base, the tertiary carbinol.

**Triaminotritane Dyes Related to Rosaniline.**

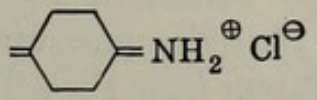
These were the original "aniline dyes" obtained by oxidizing crude aniline with arsenic acid. The *p*-toluidine in the mixture supplied the tritane carbon for union by condensation with *p*-H

in the aniline and *o*-toluidine present. The result was *fuchsine* or *magenta* a salt of rosaniline, *p*-triaminodiphenyl-*m*-tolylmethane. This was originally obtained as *Mauve* or *Mauvein* by Perkin in 1856 as the first artificial dye. He obtained it in an attempt to make quinine by the action of chromic acid on crude aniline.




Rosaniline base

The chief improvement in the original process has been the use of milder oxidizing agents notably nitrobenzene and nitrotoluenes. "Aniline for Red" is crude aniline containing toluidines and consequently suitable for making magenta. Reduction of the color base converts the C(OH) to CH giving leucaniline. Treatment of the color base with HCl gives the dye which contains the quinoid grouping




Diazotization can be used to convert rosaniline to rosolic acid.

A solution of fuchsine is decolorized by sulfurous acid with formation of a rather unstable addition product. Addition of an aldehyde causes the transfer of the sulfurous acid to the latter with the regeneration of the violet-red color of the dye (Schiff's Reagent for aldehydes).

**Parafuchsine,** (I), is the hydrochloride of *pararosaniline,* the quinonimine form of tri-*p*-aminophenylcarbinol obtained by oxidizing a mixture of *p*-toluidine and aniline. Nitrobenzene or nitrotoluene can be used as the oxidizing agent.

$$2\,C_6H_5NO_2 + 4\,C_6H_5NH_2 + 3\,CH_3C_6H_4NH_2 + 3\,HCl \rightarrow 4\,H_2O + 3\,(H_2NC_6H_4)_2C{=}C_6H_4{=}NH.HCl$$

(I)

Pararosaniline and rosaniline can also be made by oxidizing mix-

tures of *p*-diaminodiphenylmethane and aniline and *o*-toluidine respectively.

**Methyl violets** are N-methylated rosaniline dyes made by methylating the dyes or by preparing them from $Me_2N$-cpds. in place of aniline and the toluidines. Michler's Ketone, Michler's Hydrol and the related di-*p*-dimethylaminophenylmethane are valuable in making these dyes. *Crystal Violet* is the hydrochloride of the hexamethyl cpd., $(Me_2NC_6H_4)_2C=C_6H_4=NMe_2^{\oplus}Cl^{\ominus}$. The methyl chloride addition product is *Methyl Green* or *Light Green*. *Ethyl Green* is the corresponding EtCl addition product. *Methyl Violet* is $Me_5$-pararosaniline hydrochloride formed by oxidizing dimethylaniline with cupric chloride. One of the six methyl groups in three molecules of the $Me_2$-aniline supplies the methane carbon of the dye. It is probably the most important tritane dye.

**Phenylated rosanilines** shift in color to violet and then blue. *Triphenyl fuchsine*, *Aniline Blue*, *Diphenylamine Blue*, *Spirit Blue*, is obtained in a variety of ways including the action of diphenylamine with oxalic acid or formaldehyde. Sulfonic acids of the rosanilines are water-soluble dyes such as *Water Blue* and *Patent Blue*.

**Tetraphenylmethane,** $C(C_6H_5)_4$, m. 285°, b. 431°, can be made from trityl chloride and phenylmagnesium bromide in about 5% yield or by the following steps from the action of phenylhydrazine and trityl bromide (Gomberg 1897).

$$\rightarrow Ph_3CNHNHPh \xrightarrow{\text{Air}} Ph_3CN=NPh \xrightarrow{130^\circ} N_2 + Ph_4C$$

The attempt to prepare the analogous completely phenylated ethane led to the discovery of triphenylmethyl by Gomberg and the opening up of the whole chapter of free radical chemistry. The great stability of tetraphenylmethane is noteworthy.

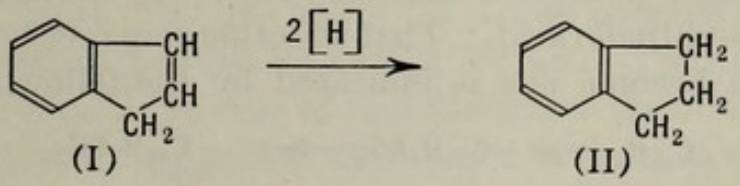
**Phenylated ethanes.** All possible ones have been prepared. Only the hexa cpd. dissociates into free radicals.

**Tetraphenylethylene,** $(C_6H_5)_2C=C(C_6H_5)_2$, m. 221°, b. 425°, is readily obtained from benzophenone dichloride heated with zinc or with diphenylmethane. It adds $H_2$ (Zartman 1932) and $Cl_2$ normally but does not add HX or bromine. With the latter it gives 9,10-diphenylphenanthrene in 25% yield (Schoepfle 1932).

## XIX. AROMATIC COMPOUNDS WITH CONDENSED RINGS

The simplest of these is indene, a fusion of a benzene and a cyclopentadiene ring.

**Indene** (I), b. 180°, is obtained from coal tar. It adds bromine readily to give a dibromide. Oxidation gives phthalic acid. Sulfuric acid gives a polymer. Treatment with Na and alcohol gives *hydrindene* (II), b. 177°. The reduction of the C=C by this means is made possible by the presence of the benzene ring.

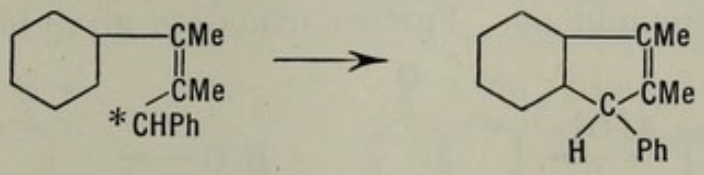



(I) (II)

The formation of substituted indenes is very easy from substances containing the grouping Ph−CR=CR−C(OH)$R_2$ in which R may be alkyl, aryl or H (Koelsch 1932–4). Often a rearrangement takes place before the ring closure. Thus the product of the action of MeMgX with benzalpropiophenone readily gives 1-Ph-2,3-$Me_2$-indene with acids.

Ph−C(OH)(Me)C(Me)=CHPh →

Ph−$\overset{*}{C}$(Me)C(Me)=CHPh →

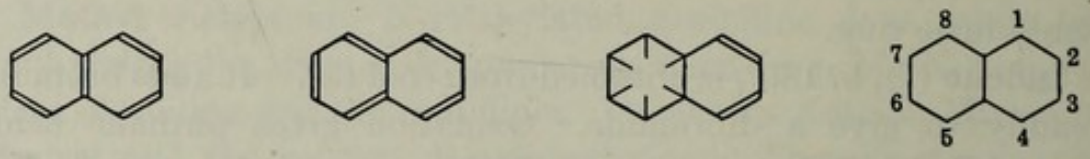



### *A.* Naphthalene and Its Derivatives

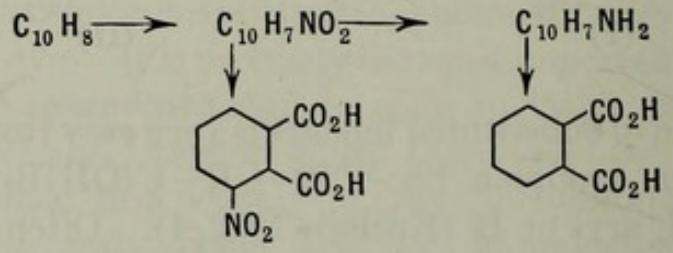
Just as an open chain of at least six carbon atoms tends to form a six-membered ring under suitable conditions, a compound with at least ten carbon atoms may form a substance having two six-membered rings, two of the carbons forming part of both rings.

**Naphthalene,** $C_{10}H_8$, m. 80°, b. 218°, is the largest single constituent of coal tar, occurring up to 6% in it. The structure

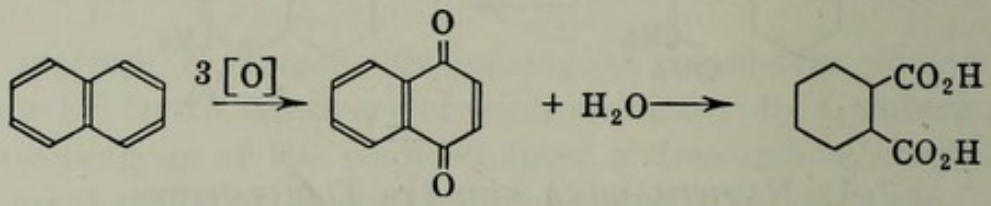
of naphthalene involves the same uncertainty as to the fourth valence of carbon as is presented by benzene.



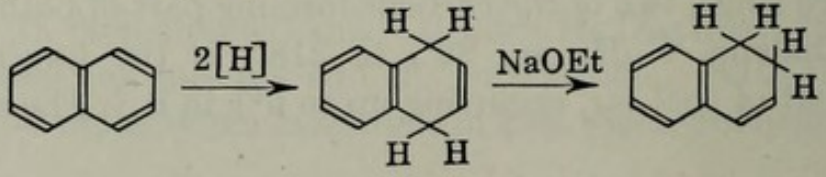

Much study has been given to the problem (Kohlrausch 1935, Fieser 1935, Fries 1936). Usually the non-committal double hexagon formula is used. The presence of a benzene ring with two carbons in the *o*-position is shown by the ready oxidation of naphthalene to *o*-phthalic acid. That the other ring is either a benzene ring or can become one is indicated by the following changes.




Thus, in one case the part not containing the N substituent was oxidized leaving the other part as a benzene ring while in the other case the part containing the N group was destroyed leaving the unsubstituted part also as a benzene ring. Naphthalene forms a yellow crystalline compound with picric acid, m. 149°. Naphthalene is more readily oxidized than benzene. The first step in the oxidation can be achieved by $CrO_3$ in acetic acid to give $\alpha$-naphthoquinone. Further oxidation gives phthalic acid.




It is also more easily hydrogenated than benzene. Addition of Na to an alcoholic solution of naphthalene gives 1,4-*dihydronaphthalene*, m. 25°, b. 212°, a result of 1,4-addition. Heating with NaOEt gives the 1,2- cpd.

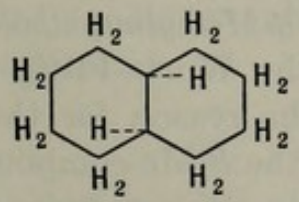


This is a typical benzene compound with unsaturated side chain. One mol of $Br_2$ adds readily to give a dibromide, m. 74°, which easily loses 2 HBr to give naphthalene again. Cautious oxidation converts $H_2$-naphthalene to *o*-phenylene diacetic acid,

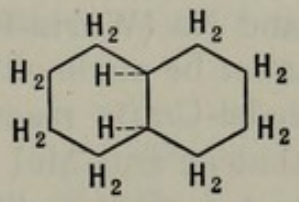
$$C_6H_4(CH_2CO_2H)_2,$$

m. 150. More vigorous oxidation gives phthalic acid. When 1,4-$H_2$-naphthalene is heated at 100° with NaOEt the double bond shifts to give 1,2-$H_2$-naphthalene, which on careful oxidation gives *o*-$C_6H_4(CO_2H)CH_2CH_2CO_2H$. It is not possible to go beyond the dihydro stage with Na and an alcohol. Thus this peculiar hydrogenation in the case of naphthalene is possible only because the ends of a conjugated system are both $\alpha$- to a benzene ring.

Hydrogenation with a nickel catalyst gives 1,2,3,4-*tetrahydronaphthalene, tetralin*, m. −30°, b. 207°, an important cheap solvent. This substance contains a true benzene ring with four alicyclic $CH_2$ groups forming another ring attached in the *o*-positions. Oxidation gives phthalic acid. Bromine substitutes in the alicyclic ring. The monobromide and dibromide lose 1 and 2 HBr giving dihydronaphthalene and naphthalene readily. These processes take place so easily that a good way to convert bromine to HBr is to drop it into an excess of boiling tetralin. The aromatic ring of tetralin can be nitrated and sulfonated. Ordinarily the catalytic hydrogenation of naphthalene stops at the $H_4$ stage. More vigorous treatment gives *decahydronaphthalene, decalin*, bicyclo(4.4.0)decane, *cis*, b. 193°, d. 0.895; *trans*, b. 185°, d. 0.870. Pt black gives mainly the *cis* form while Ni gives mainly the *trans* form (Rep. 1924, 92).



trans



cis

Synthetic decalin derivatives are usually *trans* while the natural di-cyclic sesqui-terpenes are usually related to the *cis* form.

(Rep. 1932, 153). Decalin cannot be nitrated or sulfonated. Oxidation gives deep seated changes ending in $CO_2$ and $H_2O$.

Naphthalene can also *add* $Cl_2$ or 2 $Cl_2$ more readily than can benzene. Dry chlorine gas acts on solid naphthalene to give *naphthalene tetrachloride*, $C_{10}H_8Cl_4$, m. 182°. Bases convert it to a mixture of dichloronaphthalenes. Naphthalene gives all the *substitution reactions* of which benzene is capable. In general it resembles toluene in ease of substitution. Whereas benzene gives only one monosubstitution product naphthalene can give two. The 1,4,5, and 8 positions are like each other as are the 2,3,6, and 7 positions but the two sets of four are different from each other. The first four are called $\alpha$- as they are in that position to the other ring while the other four are $\beta$-. Considering one ring of naphthalene as the ring in which substitution is to take place, it is found to have side chains $-CH=CH-$ much like the side chain in cinnamic acid which gives only *o*- and *p*-substitution. Thus it is not surprising that the direct introduction of a group into naphthalene takes place in one of the $\alpha$-positions which are *ortho* to the side chain rather than in a $\beta$-position which is *meta*. The only exceptions are the sulfonation of naphthalene at high temperatures and the Friedel-Crafts reaction both of which give $\beta$-substitution.

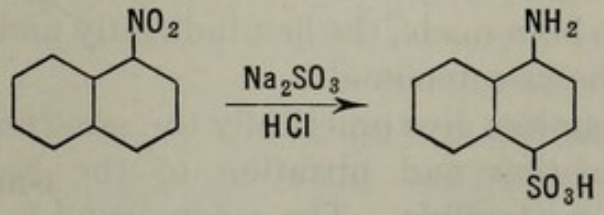
Of disubstituted naphthalenes, *ten* isomers are possible when the groups are alike and *fourteen* when they are different. The 1 : 8-position is the *peri* position and resembles the *o*-position in making possible anhydride formation and other changes involving the formation of 5- and 6-membered rings including carbons 1,9, and 8. The methylnaphthalenes are obtained from coal tar. No satisfactory synthesis has ever been devised for them. *$\alpha$-Methylnaphthalene*, m. −22°, b. 243° can be made from $\alpha$-bromonaphthalene, MeI and Na (Wurtz-Fittig). *$\beta$-Methylnaphthalene*, m. 35°, b. 245°, cannot be made either by the Wurtz-Fittig reaction or by the Friedel-Crafts reaction. The reason for the failure of $\beta$-Br-naphthalene and MeI to give the $\beta$-Me-compound is probably due to too great a difference in the reactivity of the two halides. Thus $\beta$-Br-naphthalene, ethyl bromide and Na give $\beta$-ethyl-naphthalene, b. 251°. The failure of the Friedel-Crafts reaction may be from a similar reason. Naphthalene alone acts

readily with $AlCl_3$ to form dinaphthyls and other compounds. With ethyl chloride and $AlCl_3$ it gives β-Et-naphthalene. Methylnaphthalenes are used as a standard high knocking fuel for Diesel engines.

**Agathalene,** is 1,2,5-trimethylnaphthalene. *Sapotalene* is the 1,2,6-cpd. Because of their relation to the terpenes, all the possible trimethylnaphthalenes have been synthesized (Ruzicka 1932). 1-Methyl-7-ethylnaphthalene has been made from artemesin (Rep. 1932, 156). *Cadalene,* 1,6-dimethyl-4-isopropylnaphthalene and *eudalene,* 1-methyl-7-isopropylnaphthalene are related to the terpenes.

All ten possible *dichloronaphthalenes* have been made. In most cases they have been obtained by replacing $NH_2$ by Cl or H and $SO_2Cl$ by Cl in suitable naphthalene intermediates of the dye industry. The melting points of the isomers follow: 1,2-, 37°; 1,3-, 61°; 1,4-, 68°; 1,5-, 107°; 1,6-, 49°; 1,7-, 64°; 1,8-, 88°; 2,3-, 120°; 2,6-, 136°; 2,7-, 114°. They well illustrate the complex relations of constitution and melting points.

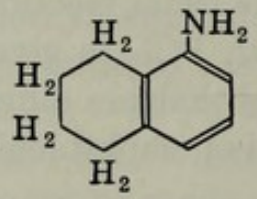
The chlorination of naphthalene gives nearly pure *α-chloronaphthalene,* b. 259°. About 5% of the *β-cpd.*, m. 57°, b. 266°, is also formed and can be separated by suitable crystallization (Britton 1933). It is best obtained from β-naphthylamine by diazotization. Further chlorination gives polychloro compounds, first oils and then waxes (Halowax). When free of HCl these waxes have valuable dielectric properties. *α-Nitronaphthalene,* $C_{10}H_7NO_2$, m. 59°, b. 304°, is readily obtained by direct nitration. No β-compound is formed. It gives the usual reactions of nitro compounds. In addition, it reacts with $PCl_5$ to give α-chloronaphthalene. In this reaction nitronaphthalenes differ from the nitrobenzenes. α-Nitronaphthalene gives naphthionic acid by the Piria reaction.



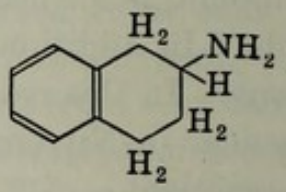
Further nitration gives 1,5- and 1,8-$(NO_2)_2$-naphthalene, m. 217° and 173°. 1,3-$(NO_2)_2$-naphthalene, m. 145°, is made by acetylating α-naphthylamine, dinitrating, hydrolyzing and treating a sulfuric acid solution of the resulting 2,4-$(NO_2)_2$-naphthylamine with ethyl nitrite to replace the $NH_2$ by H. *β-Nitronaphthalene*, m. 79°, b. 165° (15 mm.) can only be made indirectly. Diazotized β-naphthylamine with $NaNO_2$ and cuprous oxide gives the β-nitro compound.

*α-Naphthylamine*, $C_{10}H_7NH_2$, m. 50°, b. 301°, is made by reducing the nitro compound. Its reactions are like those of aniline. It has a very vile odor. *β-Naphthylamine*, m. 112°, b. 294°, is made from β-naphthol by heating with $NH_3$ and various catalysts such as $ZnCl_2$. The replacement of OH by $NH_2$ is much easier than in the benzene series. β-Naphthylamine differs from the α-compound in being odorless. It is also more stable, especially to oxidation. The two naphthylamines behave quite differently with Na and an alcohol. The α-compound adds 4 H on the ring not containing the $NH_2$ group to give *ar-tetrahydro-α-naphthylamine*, b. 273°, (I), so-called because it is an aromatic amine capable of diazotization and other typical aromatic amine reactions. It resembles aniline closely, including its weak basic properties. The β-compound adds 4 H mainly on the ring containing the $NH_2$ to give *ac-tetrahydro-β-naphthylamine*, b. 246°, (II), so-called because it is a typical alicylic amine. Instead of giving a diazonium salt it gives a stable nitrite which melts at 140° and decomposes at 190° to $N_2$, $H_2O$, and dihydronaphthalene. It is a strong enough base to absorb $CO_2$.

(I)




(II)




***ac*-$H_4$-α-naphthylamine**, b. 243°, and ***ar*-$H_4$-β-naphthylamine**, b. 274° have also been made, the first indirectly and the latter as a by-product of the *ac*-compound.

The naphthylamines give practically the same reactions as does aniline. Bromination and nitration of the acetnaphthalides proceed as with acetanilide. The α-compound is substituted in

the 4- position("*p*-") while the β-cpd. is substituted in the 1-position ("*o*-").

The *sulfonation* of naphthalene is easier than that of benzene. Conc. acid at 80° gives a mixture of naphthalene-α- and -β-sulfonic acids, the former predominating. The separation is easy by means of the Ca or Ba salts, those of the α-acid being more soluble. The sulfonic acid group is more readily replaced in fusion reactions than with benzene sulfonic acid. For instance, the sulfonyl chlorides on fusion with $PCl_5$ have the $SO_2Cl$ group replaced by Cl. The α-acid when heated with conc. sulfuric acid gives the β-acid. Thus sulfonation at 160° gives almost entirely the β-acid. This is the usual process since the α-substitution products of naphthalene are available by a variety of processes whereas the β-compounds are practically all made through the β-sulfonic acid. The conversion of the α- to the β-acid is not a true rearrangement but rather a result of hydrolysis, the β-acid being less readily hydrolyzed.

$$\alpha\text{-}C_{10}H_7SO_3H + H_2O \rightleftharpoons H_2SO_4 + C_{10}H_8 \rightleftharpoons \beta\text{-}C_{10}H_7SO_3H + H_2O$$

Four *naphthalene disulfonic acids* are readily available. Chlorosulfonic acid, $ClSO_3H$, in the cold, gives a *1,5-* and a *1,6-acid* from naphthalene and naphthalene-β-sulfonic acid respectively. Sulfonation of naphthalene with conc. sulfuric acid at 200° gives a mixture of the *2,6-* and *2,7-acids*. Five other disulfonic acids of naphthalene have been made. The only missing member of the ten theoretically possible isomers is the 2,3-acid.

Of the fourteen possible *naphthalene trisulfonic acids*, the *1,3,6-* and *1,3,7-acids* are obtained by direct sulfonation of naphthalene and of the 2,6-disulfonic acid while the *1,3,5-*, *1,4,5-*, and *2,3,6-acids* are made indirectly.

Of the twenty-five theoretically possible *tetrasulfonic acids* of naphthalene, the *1,3,5,7-* and *1,3,6,8-acids* are known.

The appearance of a sulfonic acid group in the 1-position in most of the polyacids indicates the high activity of the α-position even after several groups have entered the molecule. The predominance of β-groups is because of the greater stability of the β-sulfonic acids under the necessarily drastic conditions required to introduce several groups. The wetting agent, Nekal, consists of

alkylnaphthalene sulfonic acids. The action of naphthalene sulfonic acids with formaldehyde gives various complex synthetic tanning materials (syntans, Leukanol, etc.)

Six *nitronaphthalene sulfonic acids* are obtainable by nitrating the sulfonic acids of naphthalene, the $\alpha$-acid giving the *1,4-*, *1,5-*, and *1,8-acids* and the $\beta$-acid giving the *1,3-*, *1,6-*, and *1,7-acids*, the $NO_2$ group being 1- in each case. The 1,2-acid is not formed apparently because the meta-directing influence of the sulfonic acid group overbalances the reactivity of an $\alpha$-position *ortho* to it.

Six *nitronaphthalene disulfonic acids* are obtained by nitration of the following disulfonic acids to give the indicated products, the $NO_2$ group being numbered first:

2,6- → 1,3,7-; 2,7- → 1,3,6-;
1,4- → 1,5,8-; 1,6- → 1,3,8-;
1,5- → 1,4,8- and 2,4,8-.

The last product is remarkable as involving the entrance of a group other than $SO_3H$ into a beta position. Evidently the *meta*-effect of the sulfonic acid group partly counterbalances the reactivity of the $\alpha$-positions. Of course, the 1,5-disulfonic acid necessitates the entrance of a nitro group either para to the sulfonic acid (in an $\alpha$-position) or meta (in a $\beta$-position).

*1-Nitronaphthalene-3,6,8-trisulfonic acid* is made by the nitration of 1,3,6-naphthalene sulfonic acid (see preparation of H Acid).

*1,8-Dinitronaphthalene-3-sulfonic* acid is obtained by nitrating the acid chloride of 1,6-Nitronaphthalene sulfonic acid. The dinitration of naphthalene-2,7- and -1,5-disulfonic acids illustrates the principles of orientation in naphthalene compounds. In the first case two $\alpha$-positions are meta to the two sulfonic groups. The result is 1,8-dinitronaphthalene-3,6-disulfonic acid, the parent substance of the important intermediate, *H acid*. In the second case one nitro group occupies an $\alpha$-position *para* to the sulfonic acid group and the other takes the $\beta$-position *meta* to the other group, the product being *1,6-dinitronaphthalene-4,8-disulfonic acid*.

**Naphthylamine monosulfonic acids** are known corresponding to 13 of the 14 possible isomers, the missing one being the 2,3-acid.

Six of them can be made by reducing the nitro acids. The 1,2-acid can be made by heating Na naphthionate to 250°. *Naphthionic acid*, the most important of these acids is α-naphthylamine-4-sulfonic acid, made by direct sulfonation of the amine. Next in importance are *Peri acid*, 1,8-, Cleve's acids, α-naphthylamine-6- and -7-monosulfonic acids, and *Laurent's acid*, 1,5-. Less important is *Broenner's acid*, 2,6-. The *naphthylamine disulfonic* acids are made by reducing the nitro compounds and by sulfonating the naphthylamines. The important α-naphthylamine derivatives are the 6,8-(*Epsilon acid*) and the 4,8-disulfonic acids. The β-naphthylamine cpds. in order of importance are the 5,8-, the 5,7-, the 4,8- and the 6,8- (*Amino G acid*) disulfonic acids.

Both *naphthols*, $C_{10}H_7OH$, are found in coal tar and can be made by fusion of the naphthalene sulfonates with NaOH. *α-Naphthol*, m. 96°, b. 280° and *β-Naphthol*, m. 123°, b. 286° resemble the phenols but have their OH groups more readily replaceable by treatment with $NH_3$ and $PCl_5$. Pure α-naphthol free from any trace of the β-cpd. can be made by heating α-naphthylamine with dil. $H_2SO_4$ in an autoclave. *ar-Tetrahydro-α-naphthol*, m. 69°, b. 263°, can be made by diazotizing the corresponding amine or from the action of Na and alcohol on α-naphthol. The corresponding *ac*-compound is a liquid. β-Naphthol with amyl alcohol and Na gives mainly *ac-$H_4$-β-naphthol*, b. 262° with a smaller amount of the *ar*-compound, m. 59°, b. 276°. In both cases the *ar*-compounds are true phenols and the *ac*-compounds true alcohols. Both naphthols are oxidized to dinaphthols by $FeCl_3$. *β-Naphthyl methyl ether, nerolin*,

$$C_{10}H_7OCH_3,$$

m. 72°, b. 274°, is a perfume material.

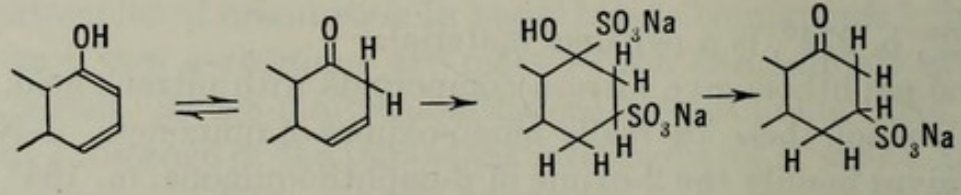
The naphthols give nitroso compounds with nitrous acid. As with phenol, these are really mono-oximes of quinones. α-Naphthol gives mainly the 2-oxime of β-naphthoquinone, m. 164° dec., with a lesser amount of the 4-oxime of α-naphthoquinone, m. 194°. *Nitroso-β-naphthol*, m. 109°, the 1-oxime of β-naphthoquinone is used in determining Fe and Co because it does not give precipitates with Al, Cr, Mn and Ni.

The *nitration* of α- and β-naphthol gives respectively the 4- and

1-nitro-compounds. 2,4-Dinitro-α-naphthol is *Martius Yellow* or *Naphthalene Yellow* while its 7-sulfonic acid obtained from α-naphthol-2,4,7-trisulfonic acid and nitric acid is *Naphthol Yellow S* or *Fast Yellow*. It cannot be made by sulfonating the dinitro compound.

The direct *sulfonation* of *α-naphthol* under various conditions gives the *2-* and *4-* (Neville-Winther acid) *sulfonic acids*, the *2,4-* and 4,6-*disulfonic acids*, and the *2,4,7-trisulfonic acid*. The latter loses the 4-group on treatment with sodium amalgam and acid to give the *2,7-disulfonic acid*. The *5*-sulfonic acid and the 3,6-disulfonic acid of α-naphthol are obtained by the action of NaOH at high temperature on naphthalene-1,5-disulfonic and 1,3,6-trisulfonic acids respectively. Many other α-naphthol sulfonic acids have been made by diazotizing the corresponding $NH_2$ acids. Thus the *1,8-acid* is obtained. It readily gives an anhydride 1,8-naphtholsulfone, "naphsultone," m. 154°, b. 360°. With cold fuming sulfuric acid this compound gives *α-naphthol-2,4,8-trisulfonic acid*. With nitric acid, this gives 2,4-dinitro-α-naphthol-8-sulfonic acid. The direct sulfonation of *β-naphthol* gives the 6-sulfonic acid (*Schaeffer's acid*) (Engel 1930), the *8-sulfonic acid* (*Croceic acid*), the *1-sulfonic acid*, the *3,6-disulfonic acid* (*R acid*) and the *6,8-disulfonic acid* (G. acid).

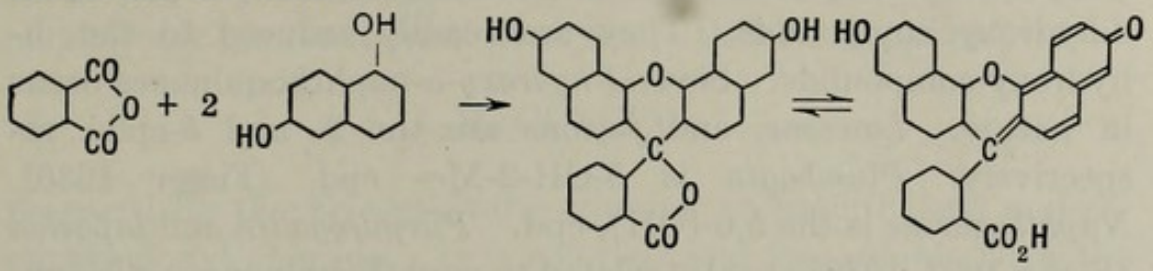
The tautomerism of naphthols is shown by the action of $NaHSO_3$ with 1,5- and 2,7-$(OH)_2$-naphthalenes (Rep. 1922, 108). The α-cpd. adds 2 $NaHSO_3$. Boiling with water removes 1 $NaHSO_3$ and gives sodium 5-OH-1-ketotetrahydronaphthalene-3-sulfonate.




The β-cpd. adds only 1 $NaHSO_3$. This can be converted by $NH_3$ and heat to 2-$NH_2$-7-OH-naphthalene.

1,6-Dihydroxynaphthalene gives a fluorescein with phthalic anhydride (Koenigs, Rep. 1914, 114). The colorless and colored

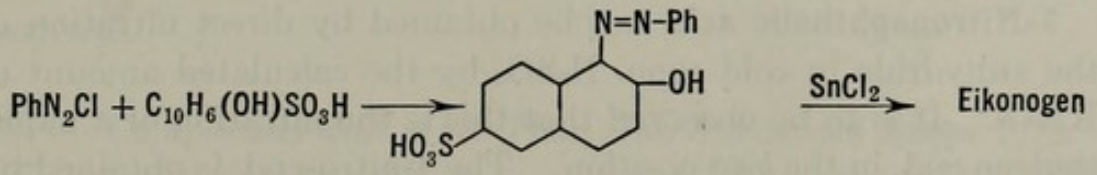
forms are as follows:



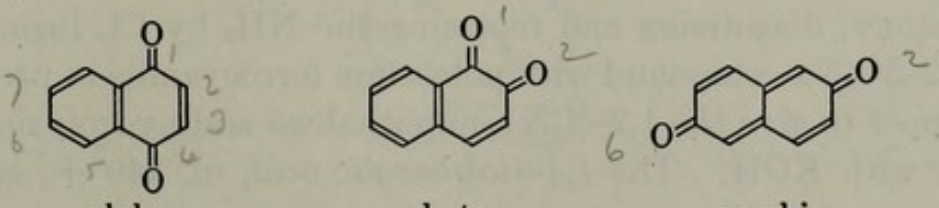
Even the free acid exists in the colored quinoid form when free of solvent.

**Chromotropic acid,** 1,8-$(OH)_2$-naphthalene-3,6-disulfonic acid, is obtained by heating H acid with KOH to replace $NH_2$ by OH.

**Aminonaphthols** are like the amino phenols in preparation and properties. The commonest are the 1,4-; 1,8-; 2,1-; and 2,7-compounds, the OH being numbered first. Various mono and disulfonic acids of the aminonaphthols are important dye intermediates. The most important of these is *H acid, 8-amino-α-naphthol-3,6-disulfonic acid* which can be made in a variety of ways including fusion with NaOH of 1-aminonaphthalene-3,6,8-trisulfonic acid made by reducing the nitration product of the common naphthalene-1,3,6-trisulfonic acid. Less important intermediates are *Gamma acid*, 1-OH-7-$NH_2$-3-$SO_3H$-, *J acid*, 1-OH-6-$NH_2$-3-$SO_3H$-, *Chicago acid*, 1-$NH_2$-8-OH-2,4$(SO_3H)_2$- and the 1-$NH_2$-2-OH-4-$SO_3H$ acid. An important photographic developer is sodium 1-amino-2-naphthol-6-sulfonate, *Eikonogen*. One method of preparation is from Schaeffer's acid and benzene diazonium chloride.



**Naphthaquinones.** Three are known, the α- or *1,4-*, the β- or *1,2-* and the *amphi-* or 2,6-naphthaquinones. They are yellow or red crystalline compounds resembling the benzoquinones.

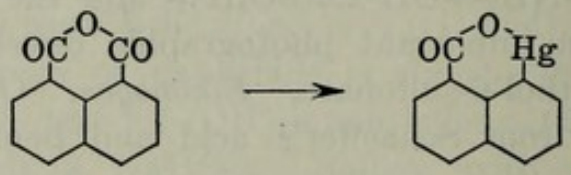


alpha beta amphi

They are made by oxidizing the corresponding amino hydroxy or dihydroxy compounds. They are readily reduced to the dihydroxy compounds. Several *hydroxy-α*-naphthoquinones occur in nature. *Lawsone,* and *juglone* are the 2- and 5-cpds. respectively. *Plumbagin* is 5-OH-2-Me- cpd. (Fieser 1936). *Naphthazarine* is the 5,6-$(OH)_2$-cpd. *Purpurogallin* and *lapachol* (Fieser 1927, 1936) are also related to naphthoquinone. *β*-Naphthoquinone-4-sulfonic acid is used to estimate amino acid nitrogen in blood. (Folin 1922.) An example of a *β*-naphthoquinoid cpd. is the fluorescein from phthalic anhydride and 1,6-$(OH)_2$-naphthalene (p. 861).

*Naphthalene Carboxylic Acids*

*α*- and *β*-naphthoic acids, m. 161° and 184°, are made by the usual methods. The best known of the dibasic acids is *naphthalic acid,* the peri acid, naphthalene-1,8-dicarboxylic acid, m. 270°, made by oxidizing acenaphthene. It behaves like phthalic acid in many ways. It forms a cyclic anhydride and imide and reacts with mercuric acetate with replacement of one carboxyl by HOHg- which forms an inner salt with the other carboxyl.




**3-Nitronaphthalic acid** can be obtained by direct nitration of the anhydride in cold conc. $H_2SO_4$ by the calculated amount of $KNO_3$. It is to be observed that this is the nitration of a naphthalene cpd. in the *beta* position. The 4-nitro-cpd. is obtained by oxidizing 4-$NO_2$-acenaphthene.

**Naphthalene-1,2-dicarboxylic acid,** m. 178° dec., can be made by heating Na naphthionate in refluxing naphthalene to give the 1,2-isomer, diazotizing and replacing the $NH_2$ by Cl, fusing the 1-Cl-2-$SO_3Na$-compound with potassium ferrocyanide in presence of copper to give the 1,2-$(CN)_2$-naphthalene and hydrolyzing the latter with KOH. The *1,4-dicarboxylic acid,* m. 240°+, can be

made similarly from naphthionic acid. The *2,3-dicarboxylic acid*, m. 235° dec., is made from diethylnaphth-2,3-indandione,

$$C_{10}H_6(CO)_2CEt_2,$$

prepared by the Friedel-Crafts reaction on naphthalene and diethylmalonyl chloride. It is colorless and less soluble than the yellow 1,2-compound which is formed in small amounts. Treatment with KOH opens the indandione ring and oxidation with nitric acid converts the resulting $Et_2$-acetyl-naphthoic acid to the 2,3-dibasic acid. These dibasic acids resemble phthalic acid in forming anhydrides and in having the carboxyl readily replaceable by Hg. This is also true of their nitro derivatives. Replacement of the Hg by H, halogen and other groups gives many synthetic possibilities.

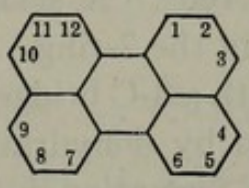
**1,4,5-Naphthalenetricarboxylic acid,** is readily made by oxidizing an acyl derivative of acenaphthene (Fieser 1932). Its anhydride melts at 274°. Treatment of this with MeOH and $H_2SO_4$ gives the monomethyl ester, m. 222°, without changing the anhydride grouping.

**1,4,5,8-Naphthalenetetracarboxylic acid** is obtained by oxidizing *peri*-succinoylacenaphthene (Fieser 1932). It gives a diimide which forms a characteristic yellow Na salt.

*αα-*, *ββ-*, and *αβ-dinaphthyls*, $(C_{10}H_7)_2$, are known. The first two melt at 160° and 187°. They can be obtained in good yield by the action of ethereal $FeCl_3$ solution on the naphthyl Grignard reagents.

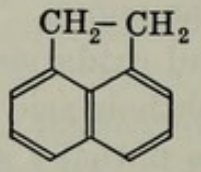
### *Compounds with More Than Two Condensed Rings*

*Perylene* is a di-naphthylene many derivatives of which have been made.

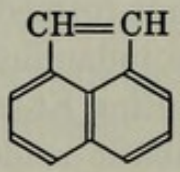


### *B.* Acenaphthene and Related Compounds

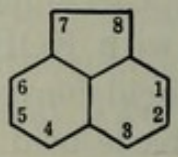
**Acenaphthene,** (I), m. 95°, b. 277°, found in coal tar, is a naphthalene with a bridge of two $CH_2$ groups in the *peri* position. At red heat it loses 2 H to form acenaphthylene (II) m. 93°. The latter has been isolated from the solid products of the pyrolysis of natural gas (Campbell 1936)



(I)

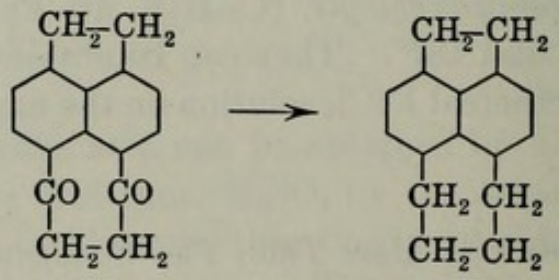


(II)




The fact that II is bright yellow while I is colorless illustrates the effect of an accumulation of conjugated double linkages. Oxidation of acenaphthene gives acenaphthoquinone which is really not a quinone but a 7,8-diketo compound. Further oxidation gives naphthalic acid and then hemimellitic acid.

The reactivity of the 3- and 4-positions in acenaphthene is shown by the condensation with succinic anhydride to give a seven-membered ring in perisuccinoylacenaphthene (III), m. 208°, and the corresponding hydrocarbon, *peri*-tetramethyleneacenaphthene (IV) m. 138° (Fieser 1932).

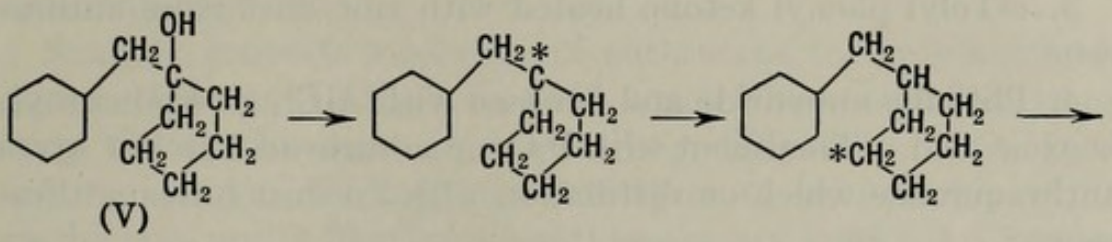


III IV

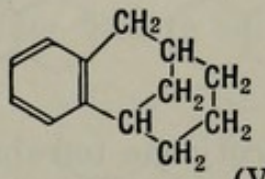
The reduction is by the Wolff-Kishner procedure using hydrazine hydrate and NaOEt at 160°. A scale model (Organospheres, Steiger) shows no strain in the 7-ring.

A tetralin derivative with a 3-C bridge across the meta positions in the *ac*-ring is obtained by dehydrating 1-benzylcyclohexanol (V). (Cook 1936.) Its formation is another example of the

shift of a reactive spot in a molecule to a position which makes possible the closure of a 6-ring.



(V)

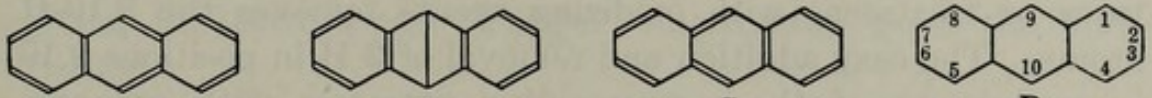


(VI)

(VI) is 2,3-benzo-(1.3.3)-bicyclo-nonene-2. A scale model (Organospheres) shows practically no strain.

### *C.* Anthracene

Anthracene is found in coal tar up to about one per cent. It is readily separated in a fraction containing carbazole and phenanthrene. Distillation with KOH retains the first as its nonvolatile N-K derivative. Phenanthrene can be removed by $CS_2$ from the distillate.



A. B. C. D.

No one of the formulas A, B, and C expresses completely the peculiar properties of anthracene but all of them taken together seem to do so. This is probably a perfect case of *resonance* between several electronic formulas (Pauling 1935). Anthracene is so peculiar that it is worthwhile to give various syntheses which have a bearing on its structure and properties.

1. Benzyl chloride heated with water at 200° gives it, dibenzyl and other products

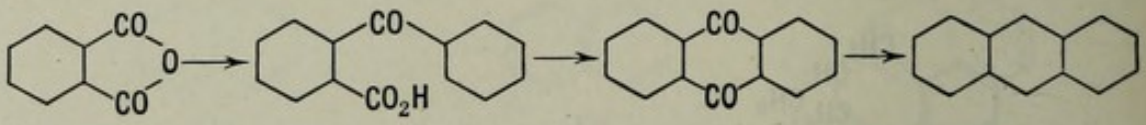
$$4\ PhCH_2Cl \rightarrow C_{14}H_{10} + PhCH_2CH_2Ph + 4\ HCl$$

Probably the first product is 9,10-dihydroanthracene which readily loses its two extra H atoms.

2. *o*-Bromobenzyl bromide with Na gives $H_2$-anthracene which is changed to anthracene on mild oxidation.

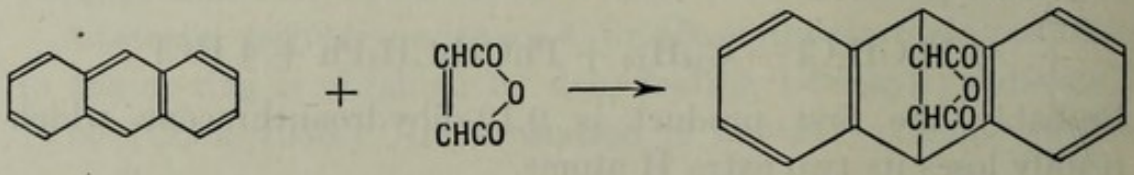
3. *o*-Tolyl phenyl ketone heated with zinc dust gives anthracene.

4. Phthalic anhydride and benzene with $AlCl_3$ give *o*-benzoylbenzoic acid. Treatment with $P_2O_5$ or sulfuric acid at 180° gives anthraquinone which on distillation with Zn dust forms anthracene.



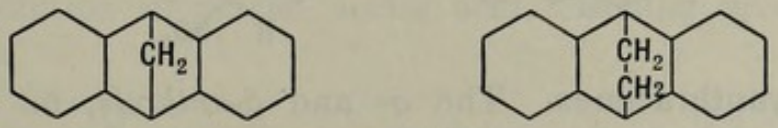

5. The formation of anthracene from acetylene tetrabromide, benzene and $AlCl_3$ has been used as evidence for the existence of a para bond in the middle ring. It should be remembered, however, that $AlCl_3$ is very effective in breaking bonds and establishing new ones.

*Properties.* Anthracene, $C_{14}H_{10}$, m. 218°, b. 342°, forms colorless crystals which have a remarkable blue fluorescene. This probably depends on the excitation of a transformation between forms A and C possibly through B. Reduction readily gives 9,10-dihydroanthracene, m. 107°, in which the end rings are definitely like benzene. It is not fluorescent. High temperatures or treatment with oxidizing agents removes the 9,10-H atoms. The easy addition and removal of 2 H in positions 9,10 is reminiscent of the corresponding processes with quinone. Hence form B is called the quinone form. Addition takes place at 9,10- rather than at 1,4 in A or at 5,8 in B because the 9,10-positions are alpha to a true benzene ring in both cases. The best argument for the existence of a conjugated system between 9 and 10 as in A and C rather than of a para bond as in B is the fact that anthracene acts as the conjugated diene in the Diels-Alder reaction with maleic anhydride giving a bridge in the 9,10 position to form a new six-membered ring in the usual way.

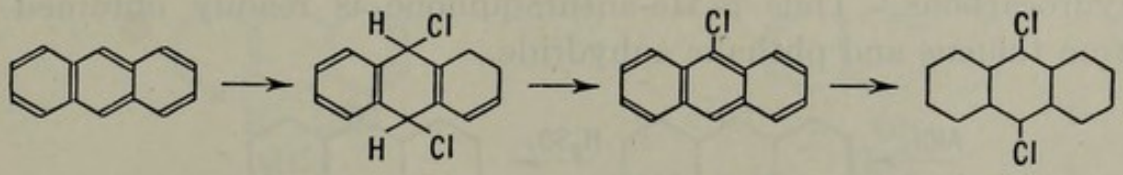


Further hydrogenation of $H_2$-anthracene gives $C_{14}H_{16}$ and $C_{14}H_{24}$. Mild oxidation also attacks the 9,10-positions giving anthraquinone.

Sunlight converts a solution of anthracene to the less soluble *para-anthracene*, $(C_{14}H_{10})_2$, m. 244°, which is more stable in many ways than anthracene. It is relatively difficult to oxidize it to anthraquinone. On melting, it reverts to anthracene. 9,10-methylene- and 9,10-ethylene-anthracene are known. They are ordinary aromatic compounds except that oxidation removes the 9,10-bridge to give anthraquinone.



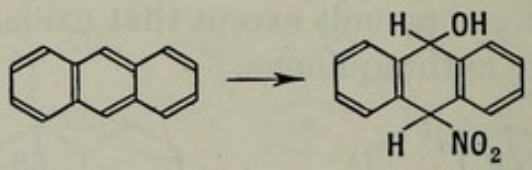

**Derivatives of Anthracene.** Three mono-substitution products are possible, the $\alpha$-(1,4,5 or 8), the $\beta$-(2,3,6 or 7) and the $\gamma$-(9, or 10). The structures of such products are determined by oxidation, a $\gamma$-derivative giving anthraquinone, and the $\alpha$- and $\beta$-derivatives giving the corresponding $\alpha$- and $\beta$-substituted anthraquinones and then 3- and 4-substituted phthalic acids respectively unless the nature of the group is such as to favor the destruction of the ring to which it is attached (OH, $NH_2$). Anthracene adds $Cl_2$ in the 9,10-position. Bases remove 1 HCl giving 9-Cl-anthracene. Further chlorination gives the 9,10-$Cl_2$-cpd.




Bromination in $CS_2$ solution gives 9,10-$Br_2$-anthracene, m. 221°. Alcoholic KOH reduces it to anthracene with the formation of MeCHO. Anthracene with pure $Br_2$ gives dibromoanthracene tetrabromide, m. 180° dec., which changes on heating to tribromo-anthracene, m. 169°, and on treatment with alcoholic KOH to *$Br_4$-anthracene*, m. 254°. That 2 Br in each of these last compounds occupy the 9,10-positions is shown by their conversion respectively to monobromo and dibromo-anthraquinone.

Cautious *sulfonation*, avoiding oxidation to anthraquinone, gives *α*- and *β-anthracene sulfonic acids*, the former predominating. It and its salts are more soluble than the *β*-compounds. Anthracene disulfonic acids are also available.

All attempts at the *nitration* of anthracene result in its oxidation to anthraquinone. The first step in the process may be the addition of nitric acid to the 9,10-system to give "*anthracene nitrate*," m. 127° dec.

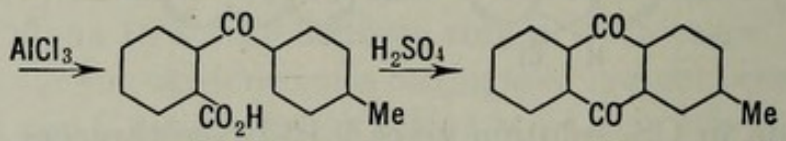



**Hydroxyanthracenes.** The *α*- and *β-anthrols*, m. 153° and dec. 200° respectively, are obtained from the sulfonic acids by alkaline fusion. 9-hydroxy- and 9,10-dihydroxyanthracenes are obtained from anthraquinone.

**Anthraquinone,** 9,10-diketo-9,10-dihydroanthracene, $C_{14}H_8O_2$, m. 285°, b. 380°, occurs repeatedly in anthracene chemistry because of the ease of its formation and its great stability. Commercially it is made in large amounts as a dye intermediate.

1. By oxidizing anthracene with chromic acid or catalytically by air.

2. From phthalic anhydride (Gleason 1929). This method has been used for making a great variety of substituted anthraquinones from suitably substituted phthalic anhydride and aromatic hydrocarbons. Thus *β*-Me-anthraquinone is readily obtained from toluene and phthalic anhydride.

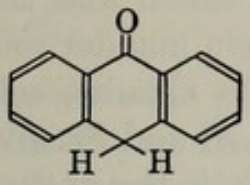



Sometimes the ring closure of the substituted *o*-benzoylbenzoic acid is difficult. It can then be reduced to the corresponding benzylbenzoic acid in which the ring can be closed more readily. The resulting anthrone can then be oxidized to the desired anthraquinone.

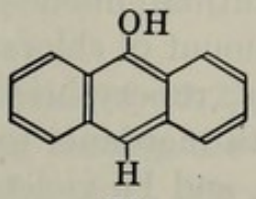
2. A preparation which indicates its ketonic nature is by the distillation of calcium phthalate.

Anthraquinone can be split by fusion with alkali to give two molecules of a benzoate. This is like the splitting of benzophenone by NaOH to give benzene and Na benzoate.

Reduction of anthraquinone by HI gives anthracene and its 9,10-$H_2$-cpd. Treatment with Sn and HCl in glacial acetic acid reduces one CO to $CH_2$ to give *anthrone* (I), 9-keto-9,10-$H_2$-anthracene, m. 155° (OS). It can also be obtained from *o*-benzylbenzoic acid and $H_2SO_4$ at 80°. Anthrone dissolves in hot dilute bases. Acidification precipitates the enol form anthranol (II), γ-OH-anthracene, 9-OH-anthracene, m. 120°. This gives a yellow solution in glacial acetic acid. Boiling gives colorless anthrone.

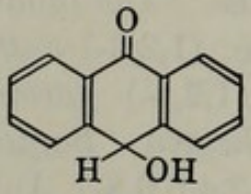


(I)

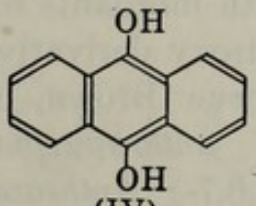


(II)

Solutions of (II) are fluorescent while those of (I) are not. Bromination of (I) followed by hydrolysis gives *oxyanthranol* (III), m. 167°, which is converted almost completely by alcoholic HCl to 9,10-$(OH)_2$-anthracene, *anthrahydroquinol* (IV) m. 180°, which can also be made by reducing anthraquinone with Zn and NaOH or by heating anthracene in HOAc with $PbO_2$.



(III)



(IV)

As would be expected, (IV) gives fluorescent solutions while (III) does not. (IV) is readily oxidized, even by air, to anthraquinone.

Monohalogen anthraquinones are not obtainable by direct halogenation. The β-compounds can be made from phenyl halides and phthalic anhydride.

Two *dibromoanthraquinones*, m. 245° and 275° are obtainable, one by direct bromination at 160° and the other by the oxidation of $Br_4$-anthracene.

*Nitration* of anthraquinone gives *mono-* and *di-nitro*-derivatives, m. 230° and 260°.

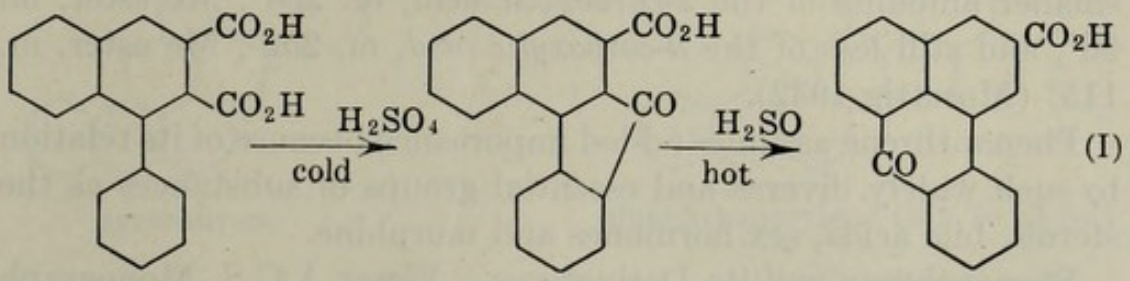
*Sulfonation* is difficult, requiring 40% oleum at 160°. The product is *anthraquinone-β-sulfonic acid*, with the 2,6- and 2,7-disulfonic acids and about 5% of the α-acid. Mercuric sulfate catalyzes the formation of the *α-acid* and makes sulfonation possible under milder conditions. The by-products are then the *1,5-* and *1,8-disulfonic acids*. The sulfonic acid group is readily hydrolyzed from the α-position of anthraquinone. Alkaline fusion of the sulfonic acids is accompanied by air oxidation to give an extra hydroxyl group. This ease of oxidation is utilized in preparing *alizarin*, 1,2-dihydroxyanthraquinone, m. 289°, by fusing anthraquinone-β-sulfonic acid with alkali and the calculated amount of chlorate. Alizarin occurs in madder root as the glucoside, ruberythric acid, $C_{26}H_{28}O_{14}$. Its alkaline solution is used with mordants to give colored *lakes*, Al and Sn giving red, Ca blue, and Fe violet black. *Anthrarubin* is the anthranol obtained by reducing alizarin. Many other dihydroxyanthraquinones are known. The most important are the following: (1,3-) *xanthothopurpurin*, m. 264°, (1,4-) *quinizarin*, m. 195°, (1,5-) *anthrarufin*, *rufol*, m. 265°, dec., (1,8-) *chrysazin*, *chrysazol*, m. 225° dec., (2,3-) *hystazin*, *hystazarin*, m. 280°, (2,6-) anthraflavinic acid, m. 330°+, (2,7-) isoanthraflavinic acid, m. 330°+.

Many important dyes are related to alizarin and are similarly used with mordants to form insoluble lakes. The following are polyhydroxy derivatives of anthraquinone: (1,2,3-) *anthragallol*, Anthracene Brown, (1,2,4-) *purpurin*, (1,2,6-) *flavopurpurin*, (1,2,7-) *anthrapurpurin*, (1,2,6,8-) *Alizarin Bordeaux B*, (1,2,3,5,6,7-) *Anthracene Brown SW*, (1,2,4,5,6,8-) Anthracene Blue WR. Many more complex alizarin dyes, especially those containing sulfonic acid groups, are known, Certain dyes are identified by the alizarin name without being related to it. Thus *Alizarin Yellow C* is gallacetophenone, 2,3,4-$(OH)_3$-acetophenone obtained from pyrogallol and acetic acid, *Alizarin Yellow A* is 2,3,4-$(OH)_3$-benzophenone, Alizarin Black S or naphthazarin is 3,4-$(OH)_2$-α-naphthoquinone, and *Alizarin Green G* and *B* are oxazin dyes formed from sulfonic acids of β-naphthoquinone and aminonaphthols.

*Tectoquinone* is β-Me-anthraquinone. *Rubiadin* is 2-Me,1,3-$(OH)_2$-anthraquinone and *munjistin* is the same with Me oxidized to carboxyl.

Das Anthracen und die Anthrachinone, J. Houben, 890 pp., Thieme, Leipzig 1929.

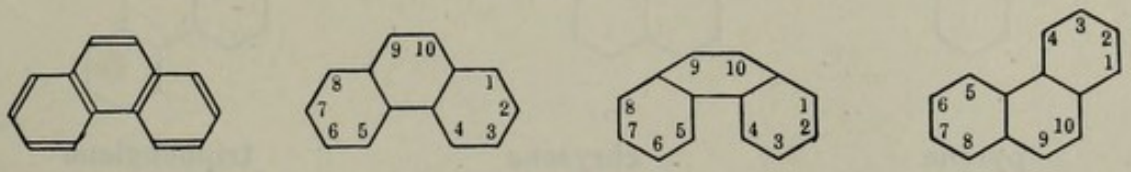
**Benzanthrone** can be made from its carboxylic acid (I) which is obtained in the following steps (Rep. 1918, 87).




This represents the closing of a 5-ring involving the 2,2′-positions in a diphenyl and the opening of that ring leaving the carboxyl group in the phenyl instead of the naphthyl group. Then follows closure to give the more stable 6-ring of benzanthrone.

## *D.* Phenanthrene

**Phenanthrene,** $C_{14}H_{10}$, m. 99°, b. 340°, an isomer of anthracene occurs with that substance in coal tar. It is a diphenyl with the 2,2′-positions bridged by a $-CH=CH-$ group thus forming three condensed benzene rings.




Like anthracene it gives fluorescent solutions. It is more difficult to oxidize and to reduce than anthracene. The first product of hydrogenation is a tetrahydro compound. Its system of conjugated double bonds cannot assume a quinone arrangement like that possible in the middle ring of the latter. Oxidation gives *phenanthraquinone*, 9,10-diketo-9,10-dihydrophenanthrene, m. 200°, which is really a diketone rather than a true quinone. Reduction with sulfurous acid is possible giving *phenanthraquinol* or 9,10-$(OH)_2$-phenanthrene. Vigorous oxidation of phenan-

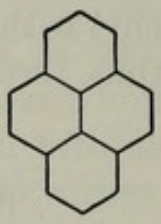
threne or its quinone or quinol gives *diphenic acid*, diphenyl-2,2′-dicarboxylic acid.

Halogens, nitro and sulfonic acid groups can be introduced directly into phenanthrene (Fieser 1929). *Phenanthrene-1-carboxylic acid*, m. 233°, Me ester, m. 57°, can be made from the 1-sulfonic acid (Fieser 1932). Phenanthrene with oxalyl chloride gives mainly the *3-carboxylic acid*, m. 269°, Me ester, m. 95°, with smaller amounts of the *2-carboxylic acid*, m. 258°, Me ester, m. 96°, and still less of the *9-carboxylic acid*, m. 252°, Me ester, m. 115° (Mosettig 1932).

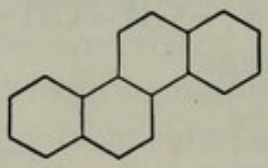
Phenanthrene assumes added importance because of its relation to such widely diverse and essential groups of substances as the sterols, bile acids, sex hormones and morphine.

Phenanthrene and its Derivatives. Fieser A.C.S. Monograph 1936.

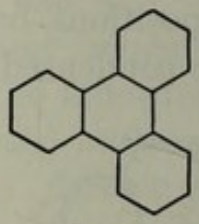
More complex hydrocarbons having condensed benzene nuclei are known in large numbers. Some of these come from coal-tar, others from the stupp-fat obtained in the working up of mercury ores at Idria and many more by synthetic methods which have been stimulated by the discovery of carcinogenic hydrocarbons (Cook).



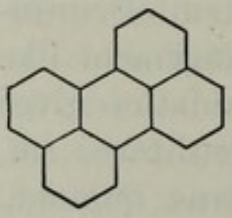
pyrene
$C_{16}H_{10}$
m. 150°



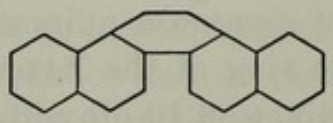
chrysene
$C_{18}H_{12}$
m. 251°



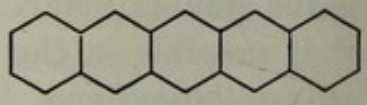
triphenylene
$C_{18}H_{12}$



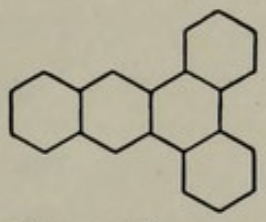
perylene



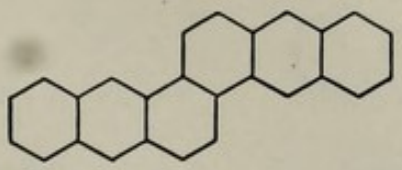
picene
$C_{22}H_{14}$
m. 364°, b. 520



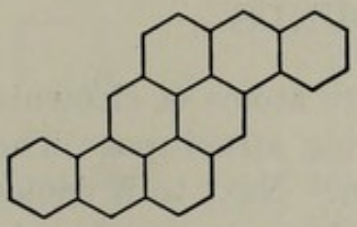
pentacene



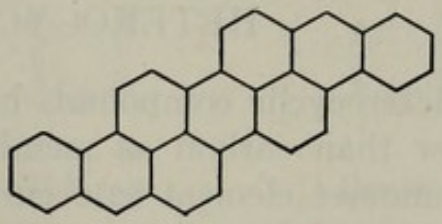
dibenzanthracene–$\alpha\gamma$



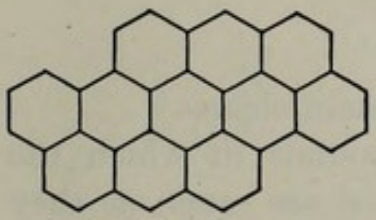
dibenzochrysene (bk)



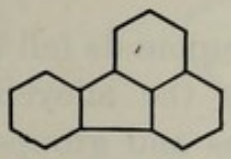
pyranthrene



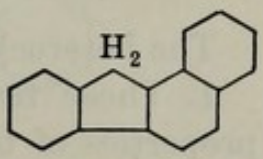
dinaphthoperylene (3, 2, 1–cd, lm)



dinaphthocoronene



fluoranthene
idryl, $C_{16}H_{10}$
m. 110°




chrysofluorene

Everest, "Higher Coal-Tar Hydrocarbons," Longmans, Green and Co., 1927

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# PART IV

## HETEROCYCLIC COMPOUNDS

Heterocyclic compounds have one or more atoms of elements other than carbon as members of their ring structures. The commonest element so occurring is nitrogen. Next to it comes oxygen and then sulfur. Many other elements are less commonly found as members of rings.

### I. CLASSIFICATION

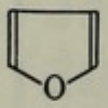
The heterocyclic compounds fall in two main classes.

1. Those resembling the alicyclic compounds in which the properties of the atoms and groups involved are much as they would be in an open chain structure.

2. Those containing a conjugation of unsaturated groups or atoms which give an effect like that in benzene. Such compounds as pyridine, pyrrole, thiophene and furan show many aromatic properties which are destroyed on partial or complete hydrogenation much as happens with benzene.

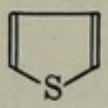
Many heterocyclic compounds have condensed rings, that is, pairs of rings having two atoms in common. Sometimes both rings are heterocyclic but very often one is a benzene ring.

The most important 5-membered *heterocyclic systems* are listed below. In each case an angle represents a CH group



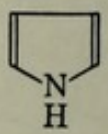

Furan

$C_4H_4O$



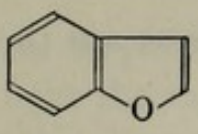

Thiophene

$C_4H_4S$



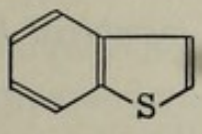

Pyrrole

$C_4H_5N$



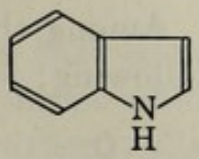
Coumarone

$C_8H_6O$



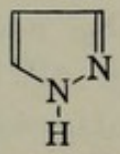
Benzothiophene

$C_8H_6S$



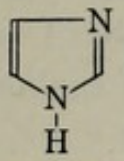
Indole

$C_8H_7N$



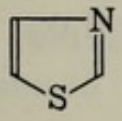
Pyrazole

$C_3H_4N_2$



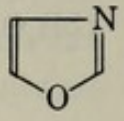
Imidazole
Glyoxalin

$C_3H_4N_2$



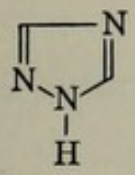
Thiazole

$C_3H_3NS$

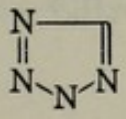


Oxazole

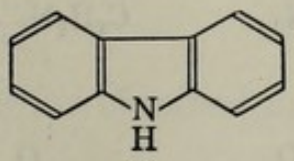
$C_3H_3ON$



Triazole
$C_2H_3N_3$



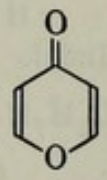
Tetrazole
$CH_2N_4$



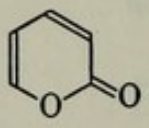
Carbazole
Dibenzopyrrole

In each of these 5-membered rings there are three points of unsaturation, the two double bonds and an atom capable of an -onium valence. These are conjugated as in benzene. This conjugation obscures the individual unsaturation much as in benzene. Thus the double bonds in these compounds have about the same inactivity as those in benzene. Moreover, the "unsaturation" of the hetero-atom has largely disappeared. Thus pyrrole is a very weak base. Thiophene fails to give the addition compounds with substances like MeI and $HgCl_2$ which are characteristic of open chain sulfides. This failure is not due to the presence of the isolated double bonds for vinyl sulfide readily gives the compound $(CH_2=CH)_2S.HgCl_2$. In accordance with these analogies to benzene, all these heterocyclic compounds show aromatic properties in varying degrees (Gilman).

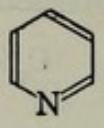
Among the important *6-membered heterocyclic systems* are the following:



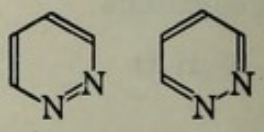
γ-Pyrone
$C_5H_4O_2$



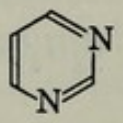
α-Pyrone
$C_5H_4O_2$



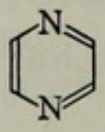
Pyridine
$C_5H_5N$



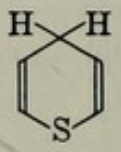
Pyridazine
$C_4H_4N_2$



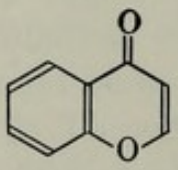
Pyrimidine
$C_4H_4N_2$



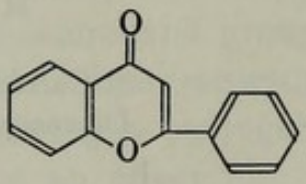
Pyrazine
$C_4H_4N_2$



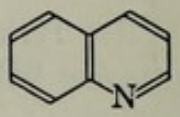
Penthiophene
$C_5H_6S$



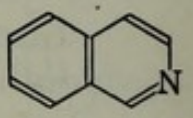
Chromone
$C_9H_6O_2$



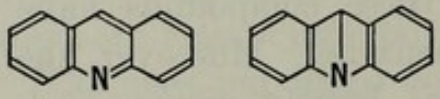
Flavone
2-phenylchromone



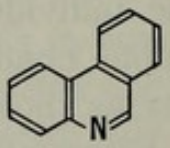
Quinoline
$C_9H_7N$



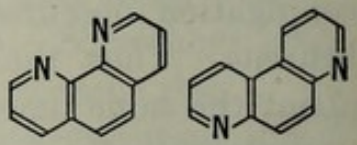
Isoquinoline
$C_9H_7N$



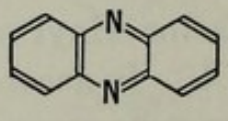
Acridine
Dibenzopyridine
$C_{13}H_9N$



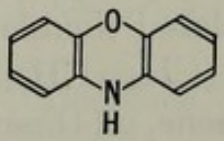
Phenanthridine
3,4-Benzoquinoline



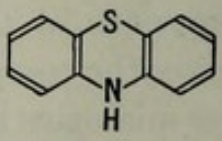
Phenanthrolines
1,10- 4,7-



Phenazine
$C_{12}H_8N_2$



Phenoxazine
$C_{12}H_9ON$



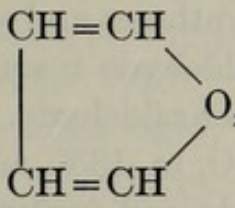
Phenthiazine
$C_{12}H_9NS$

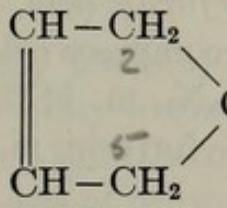
An inspection of these heterocyclic formulas shows that some have the characteristic conjugated unsaturation of benzene while others have that of quinone and still others have neither. The analogy of acridine and phenazine to anthracene is confirmed by the reactions of these substances.

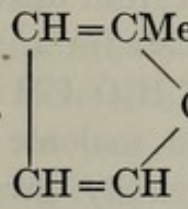
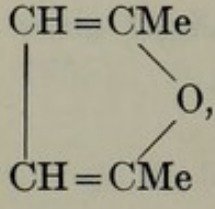
In numbering the positions in heterocyclic compounds, the hetero atom is usually No. 1 even though substitution on it may be impossible. Exceptions are carbazole in which the N is No. 9 and the analogs of anthracene in which the atoms of the middle ring are No. 9 and No. 10.

## II. FIVE-MEMBERED RINGS

### *A.* Furan and Derivatives

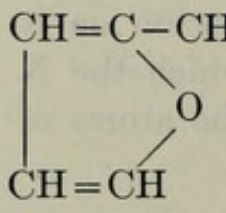
**Furan,** furfurane,  , b. 32°, is obtained in various thermal decompositions as in wood distillation. It is readily prepared by heating furan-2-carboxylic acid (OS). It is stable to Na and NaOH but is resinified by strong acids.

**2,5-Dihydrofuran,**  , b. 67°, is made by heating erythritol with formic acid, a process analogous to the production of allyl alcohol from glycerol.

**2-Methylfuran,** sylvane,  , b. 65°, and *2,5-Me₂-furan,*  , b. 94°, are contained in wood tar and in the products

of distilling sucrose with lime. The latter can also be made from acetonylacetone with $ZnCl_2$ or $P_2O_5$. This change may be regarded as a simple dehydration of the dienol. Conc. HCl resinifies the methylfurans violently. Dilute HCl at 270° changes $Me_2$-furan to acetonyl acetone.

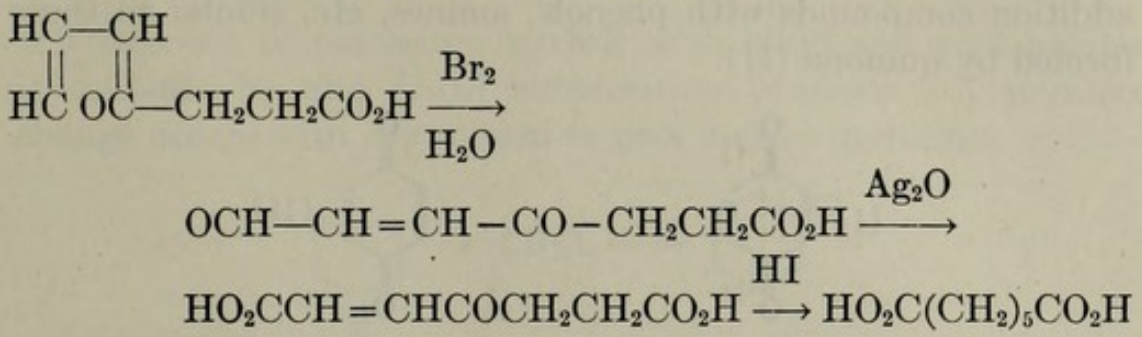
**Furfural,** furfurol, furol, α-furaldehyde, α-furfuraldehyde,



, b. 162°, is obtained by the action of mineral acids on pentoses and pentosans which occur in large amounts in vegetable products such as oat hulls, cornstalks, corn cobs, bran and the like. Commercially it is made in large amounts by the action of sulfuric acid with oat hulls (Quaker Oats Company). It is used for various syntheses and as a selective solvent for petroleum refining. The aldehyde reactions of furfural are almost exactly like those of benzaldehyde. Thus KCN gives *furoin*, $C_4H_3O.CHOHCO.C_4H_3O$, m. 135°, analogous to benzoin. From a mixture of benzaldehyde and furfural KCN gives *benzfuroin*, $C_4H_3O.CHOHCO.C_6H_5$, m. 139°. These on oxidation give *furil*, $(C_4H_3O.CO)_2$, m. 162°, and *benzfuril*, $C_4H_3O.COCOC_6H_5$, m. 41°. *Furil* with alkali gives *furilic acid*, difurylglycollic acid, $(C_4H_3O)_2C(OH)CO_2H$, which decomposes below 100°. Ammonia gives *furfuramide*, $(C_4H_3O.CH)_3N_2$, m. 117°, which is converted by alkalis or heat to the isomeric furfurin, m. 116°, corresponding to hydrobenzamide and amarin.

**Furylacrylic acid,** *trans* $C_4H_3O.CH=CHCO_2H$, m. 141°, is made by the Perkin reaction from furfural, NaOAc and $Ac_2O$ at 170°. This and the *allo* or *cis* form, m. 103°, are obtained by heating furalmalonic acid, $C_4H_3O.CH=C(CO_2H)_2$, m. 205° dec. obtained by warming furfural, malonic acid and HOAc. Reduction of furylacrylic acid readily gives β-furylpropionic acid. This with $Br_2$ water followed by oxidation with $Ag_2O$ gives

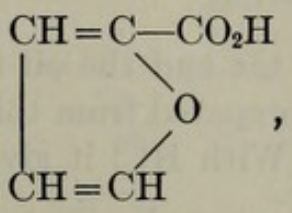
*furonic acid*, a keto unsaturated dibasic acid which is reduced by HI to pimelic acid (Baeyer 1877).



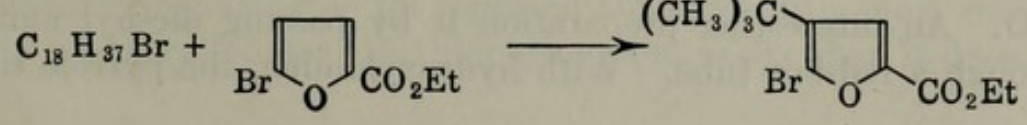
The first step consists in 1,4-addition of bromine, followed by hydrolysis to give the 1,4-keto-aldehyde. Furylacrylic acid with alcoholic HCl gives acetone diacetic ester, $CO(CH_2CH_2CO_2Et)_2$ (Marckwald 1888).

Furfural, through the Perkin reaction with *n*-butyric anhydride and salts, gives $\alpha$-ethyl-$\beta$-furylacrylic acid incorrectly called furylangelic acid (Carter 1928).

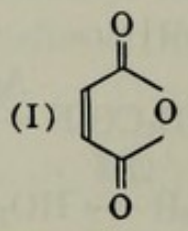
**Furoic acid,** pyromucic acid, furan-2-carboxylic acid,



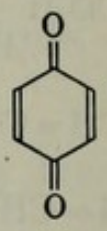
m. 133°, was originally made by heating mucic acid but is now prepared from the readily available furfural either by cautious oxidation or by the Cannizzaro reaction. While many of its reactions resemble those of benzoic acid it differs in being readily oxidized, for instance, by permanganate. With dry bromine it gives a *tetrabromide*, m. 160° dec. which with alcoholic KOH gives *3,4-* and *3,5-dibromofuroic acids*, m. 192° and 168°. Mono- and tri-bromofuroic acids have also been made. 5-Bromo-furoic ester gives a remarkable reaction with $AlCl_3$ and alkyl halides. Thus *n*-AmCl, *n*-Hex-Br and *n*-octadecyl bromide all give the same product, ethyl 4-tertiary-butyl-5-bromo-2-furoate (Gilman 1935). A yield of 46% was obtained from the $C_{18}$ bromide.



Maleic anhydride (I) may be regarded as the quinone of furan. This relation is indicated by its formation of colored addition compounds with phenols, amines, etc. similar to those formed by quinone (II).



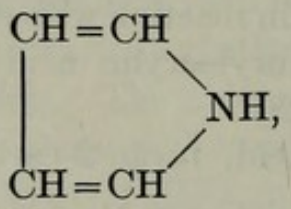

(I)




(II)

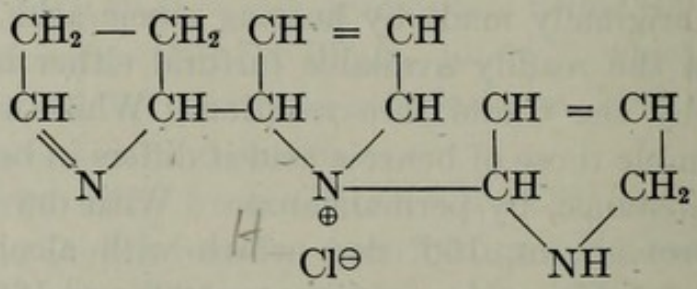
Orientation in the furan series has been studied intensively. Gilman, Rev. *11*, 330 (Gilman 1934, 1935).

### *B.* Pyrrole




b. 131°

This is found in coal tar and the oil from the preparation of bone black. It is best prepared from this bone oil. It does not form salts with acids. With HCl it gives a trimer (Rep. 1927, 159).

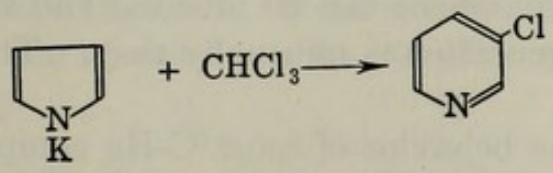



The imino H of pyrrole is replaceable by metals, alkyl and acyl. It can be purified by heating with solid KOH and distilling the other bases from the residue of the solid potassium compound. NaOH does not act on it and even metallic Na acts very slowly. Pyrrole can be synthesized by heating ammonium mucate with glycerol at 200° and by heating furoic acid with $ZnCl_2$-$2NH_3$ and CaO. An interesting preparation is by passing diethyl amine through a red-hot tube. With hydroxylamine, the pyrrole ring

opens and forms the dioxime of succinic dialdehyde,

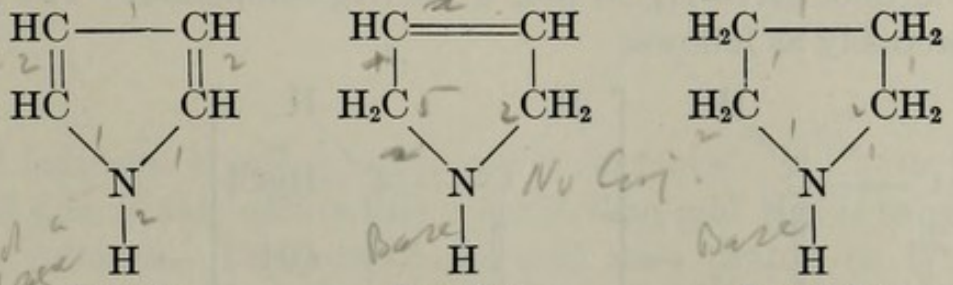
$$HON=CH(CH_2)_2CH=NOH.$$

Treatment of potassium pyrrole with alkyl and acyl halides gives both N- and C-($\alpha$) substitution products. A peculiar change occurs with chloroform to give 3-chloropyridine.



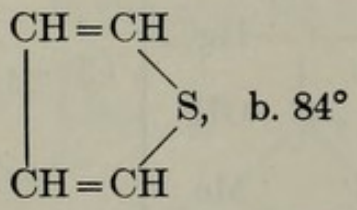

Iodine and a base give *tetraiodopyrrole*, iodole, dec. 150°, which has been used as an antiseptic of the iodoform type.

Pyrrole with zinc and acetic acid gives dihydropyrrole or *pyrroline*, b. 91°. Further reduction with HI gives tetrahydropyrrole or *pyrrolidine*, b. 86°. The effect of conjugation in masking the basic properties of the N in pyrrole is shown by the fact that its $H_2$- and $H_4$-derivatives are strong bases.




Pyrrolidine is best prepared by reducing succinimide with Na and alcohol. Pyrrole forms the basis of the coloring matters in hemoglobin and in chlorophyll.

### *C.* Thiophene



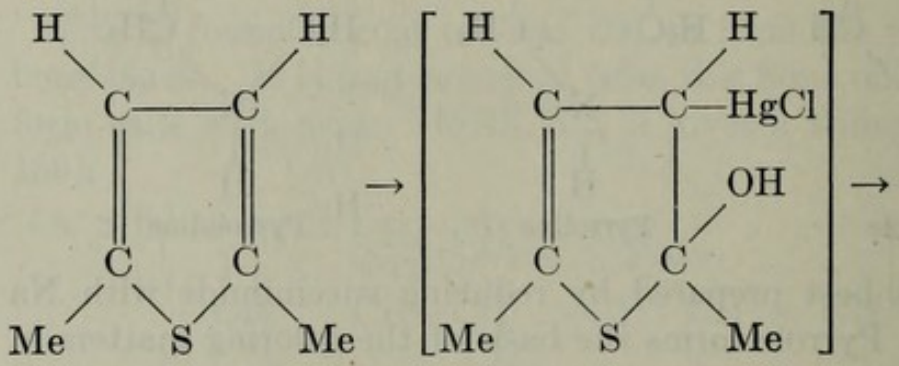

b. 84°

This occurs with benzene (b. 80.5°) in coal tar. It can be removed from benzene by repeated shakings with conc. sulfuric acid which sulfonates the thiophene more easily than it does the

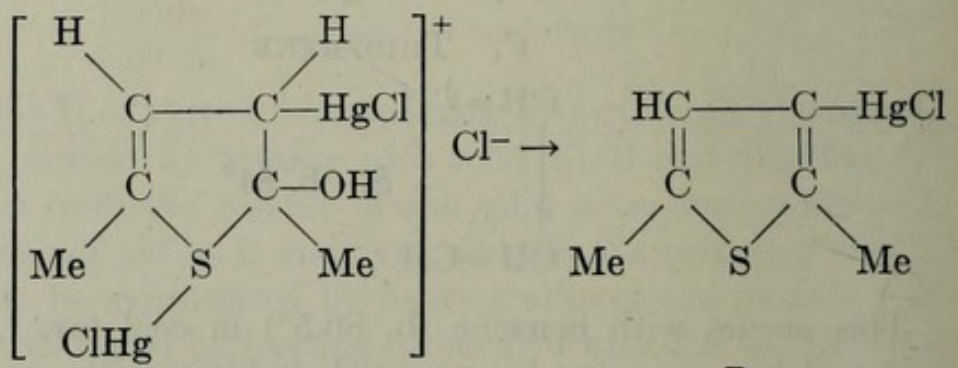
benzene. It can also be removed by refluxing with mercuric acetate which mercurates the thiophene with great ease and the benzene slowly, if at all, under these conditions. The best *preparation* of thiophene is probably by heating sodium succinate with $P_2S_3(OS)$. It is also obtained by passing acetylene and $H_2S$ over $Al_2O_3$ at 400°, and by passing diethyl sulfide through a red-hot tube. Thiophene can be nitrated and sulfonated in the $\alpha$-position. Mercuration is unusually easy. The Hg enters the $\alpha$-position.

Contrary to the behavior of most C-Hg compounds, $\alpha$-chloromercurithiophene reacts metathetically with acetyl chloride to give $\alpha$-acetylthiophene, *acetthienone*.

The behavior of $\alpha\alpha'$-disubstituted thiophenes with mercuric chloride and sodium acetate throws light on the mechanism of mercuration and the effect of ring conjugation. The first product analyses for an addition product of one molecule each of thiophene, basic mercuric chloride and mercuric chloride. Boiling with alcohol gives $HgCl_2$ and a 3-ClHg-compound. The steps are probably as follows:



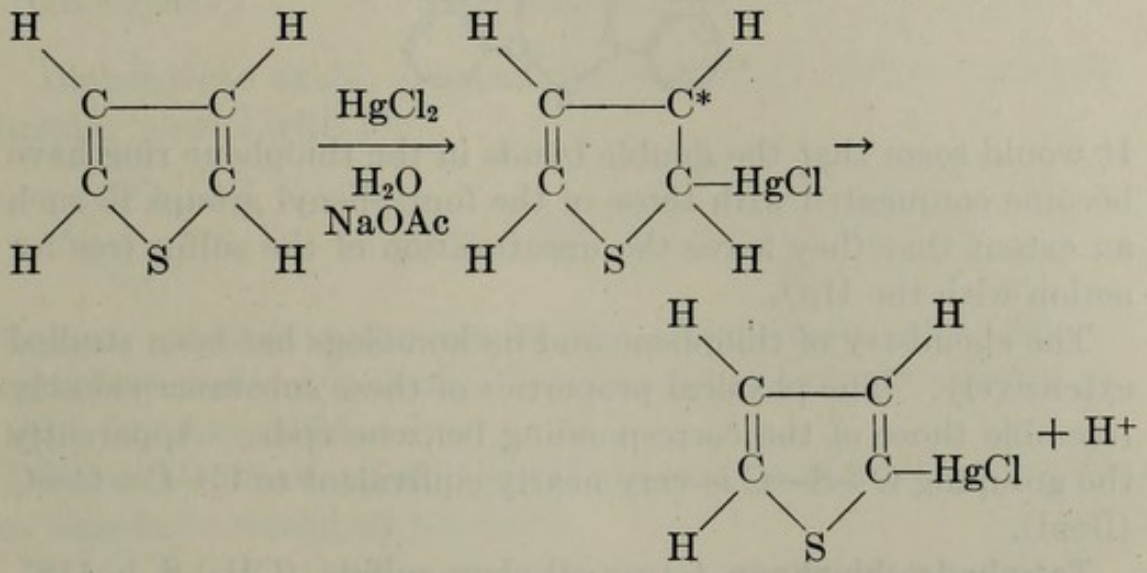

A. B.




C. D.

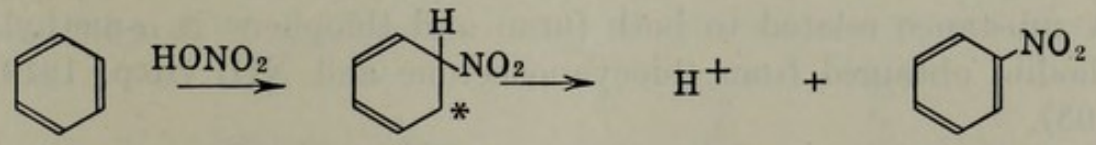
The S atom in A is incapable of forming an addition compound

with $HgCl_2$ because its unsaturation is inactivated by conjugation with the two double bonds. As soon as a molecule of B has formed, its sulfur no longer is conjugated as part of the cyclic unsaturation and can add a molecule of mercuric chloride. Long boiling removes $H_2O$ from C giving D in which the S is again part of the ring conjugation and so incapable of holding the $HgCl_2$. With thiophene itself, the process probably takes place much like the action of chlorine with isobutylene (p. 41).



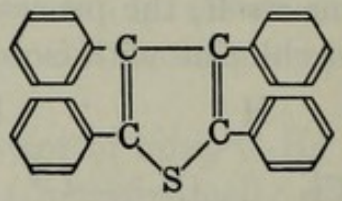

The * indicates a carbon with only 6 electrons. If $Cl^-$ or $OH^-$ should add to this carbon the S could then add $HgCl_2$ to give a stable product. The loss of the $\alpha$-H as a proton or $H^+$ ion with regeneration of the conjugated unsaturation makes the process seem one of simple substitution. In the case of the 2,5-disubstituted thiophenes, such as A, the less active $\beta$-H is not expelled quickly enough to prevent the two bimolecular processes which produce B and C.

Similar steps are probably involved in the nitration and sulfonation of benzene. In this case, the tendency to reestablish




the ring conjugation is so great that there is no possibility of the addition of the $OH^-$ to the electronically deficient carbon. Thus a relatively slow bimolecular process is excluded by a very rapid monomolecular process.

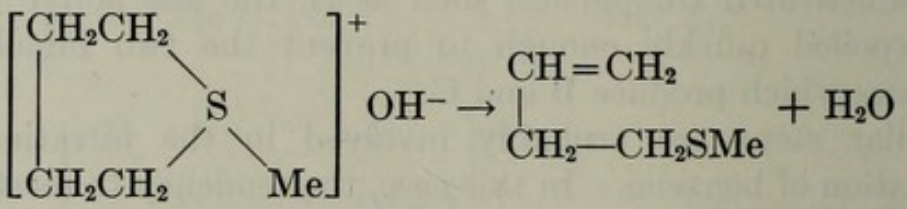
Whereas open chain and saturated cyclic sulfides are easily oxidized to sulfones the sulfur in thiophene and its ordinary homologs is not attacked by oxidizing agents unless the ring is broken. A notable exception is the ready formation of a sulfone by the action of $H_2O_2$ on *tetraphenyl thiophene, thionessal,* m. 184°, formed by the action stilbene and sulfur.



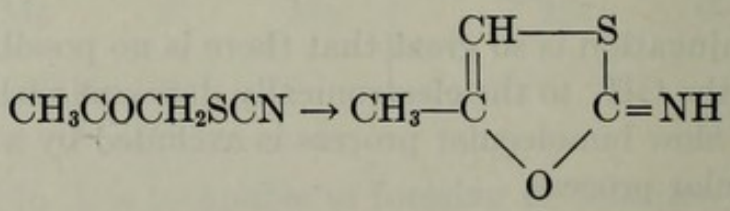
It would seem that the double bonds in the thiophene ring have become conjugated with those of the four phenyl groups to such an extent that they leave the unsaturation of the sulfur free for action with the $H_2O_2$.

The chemistry of thiophene and its homologs has been studied extensively. The physical properties of these substances closely resemble those of the corresponding benzene cpds. Apparently the grouping C—S—C is very nearly equivalent to C—C=C—C (Reid).

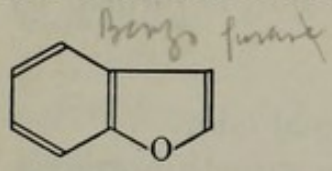
**Tetrahydrothiophene,** tetramethylene sulfide, $(CH_2)_4S$, b. 118°, is readily made from $Br(CH_2)_4Br$ and $Na_2S$. It acts as an ordinary sulfide giving a sulfone, and addition products with MeI, $HgCl_2$, etc. Treatment of the sulfonium iodide with a base and heat opens the ring as in the exhaustive methylation of cyclic amines.



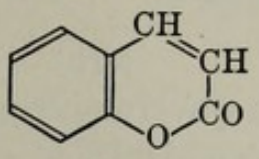
A substance related to both furan and thiophene is α-methylrhodim obtained from thiocyanoacetone and $NH_3$ (Rep. 1919, 105).



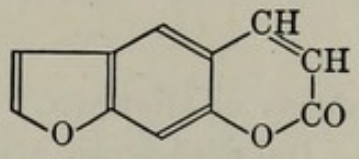
**Coumarone,** benzofuran, b. 170°, occurs in coal-tar and has been synthesized in various ways. Many coumarone derivatives occur in plants. Thus *xanthotoxin* is a combination of coumarone and coumarin structures (Späth 1936).



Coumarone

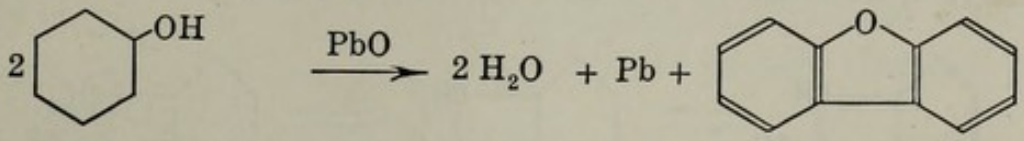


Coumarin



Xanthotoxin

**Diphenylene oxide,** dibenzofuran, m. 87°, b. 288°, is made by heating phenol with PbO.

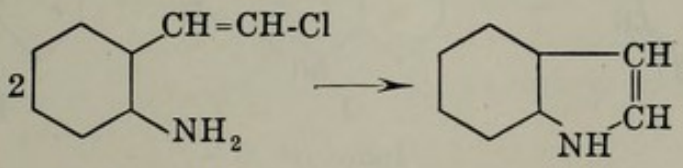


Because of the occurrence of the dibenzofuran grouping in morphine many of its derivatives have been prepared (Robinson 1936, Mosettig 1936).

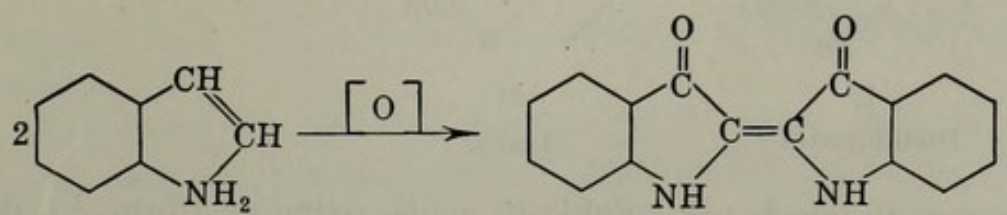
**Benzothiophene,** m. 31°, b. 221°, resembles naphthalene much as thiophene resembles benzene.

### *D.* Indole and Its Derivatives

**Indole,** benzopyrrole, (I), m. 52°, is of great importance as the parent substance of indigo. It has been synthesized in many ways, one of the simplest of which is the action of NaOEt on *o*-amino-ω-chlorosytrene.

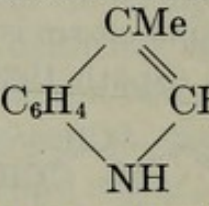


Like pyrrole, it is very feebly basic and can have its imino H replaced by alkyl, acyl and K. Oxidation with ozone gives indigo.



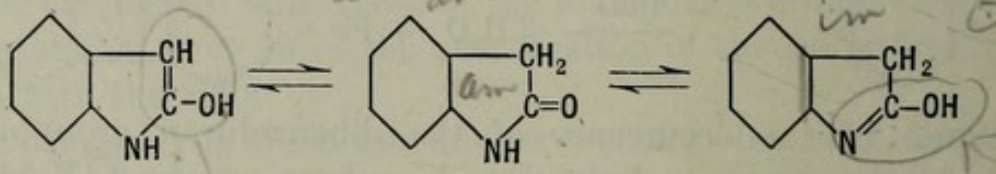
Indigo

This is a bimolecular oxidation analogous to the bimolecular reductions which give pinacols from ketones.

**Skatole,** 3-methylindole,  , m. 95°, is formed by decay of albumen. It has an overpowering fecal odor.

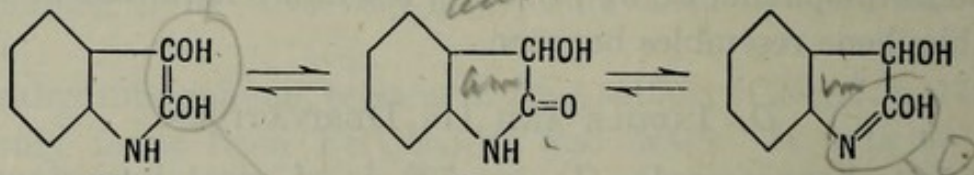
Indole-3-acetic acid has been identified as the growth-hormone, hetero-auxin (Kögl 1934). Many analogous substances have been tested for their growth-promotion activity (Rep. 1935, 425–30).

Oxygen derivatives of indole are widely known.



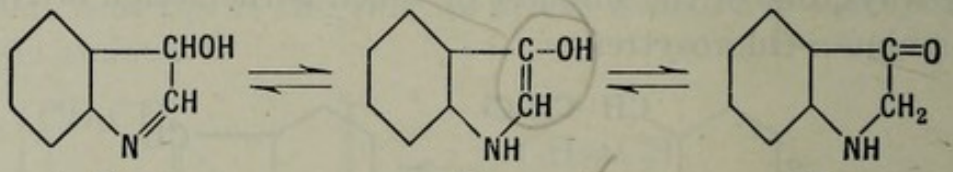
A B C

Oxindole



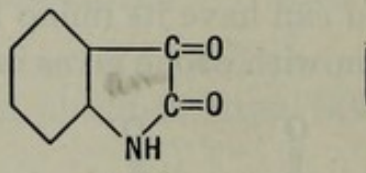
D E F

Dioxindole



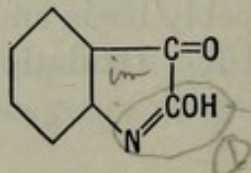
G J K

Indoxyl



L

Pseudoisatin



M

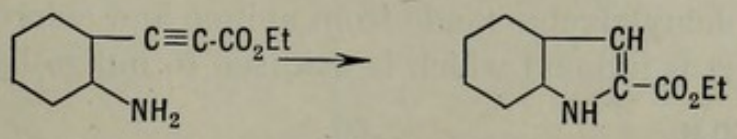
Isatin

Whereas indole is not soluble in acids, oxindole (form A), diox-

indole (form D) and indoxyl are soluble. Oxindole (form C), dioxindole (form F) and indoxyl (form J) are also soluble in bases while isatin is soluble only in bases. Forms B, E and L are ordinary acid amide forms while forms C, F and M are tautomeric acidic forms of the amides in which the grouping C=NPh plays the part of the C=O of a carboxyl group. The solubility of indoxyl in bases is surprising. Apparently the grouping C=C in the aromatic pyrrole ring acts like the C=O in a carbonyl group. This is the same as saying that the hydroxyl is phenolic in nature. Form G of indoxyl is readily subject to hydrolysis to give an amino hydroxyaldehyde which probably accounts for the great instability of indoxyl. The presence of OH in forms A, D and J apparently interferes with the conjugation of the nitrogen unsaturation in the pyrrole ring and thus restores its basic properties.

**Oxindole,** 2-hydroxyindole, (A, B, C, p. 886), m. 120°, the lactam of *o*-aminophenylacetic acid, is made by reducing *o*-nitrophenylacetic acid or dioxindole. It can be easily oxidized to dioxindole. This easy oxidation is due to the enol form A which can be changed to form E by the addition of a positive hydroxyl at the 3-position and the expulsion of $H^+$ from the 2-OH. As has been noted above, oxindole is amphoteric.

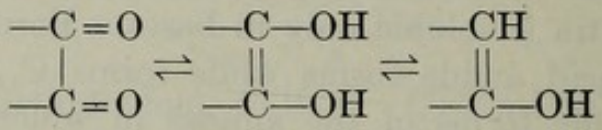
**Indoxyl,** 3-hydroxyindole, (G, J, K, p. 886), m. 85°, while isomeric with oxindole differs radically from it in being very unstable. It is readily oxidized to indigo by air in basic solution and by ferric chloride in acid solution. Derivatives of both J. and K. are known. *Indoxylic acid,* 3-hydroxyindole-2-carboxylic acid, subl. 123°, can be obtained as the ethyl ester by reducing ethyl *o*-$NO_2$-phenylpropiolate, the amino group adding internally to the triple bond.



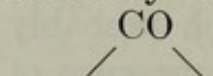

The acid loses $CO_2$ to give indoxyl which is readily oxidized to indigo.

**Dioxindole,** 2,3-dihydroxyindole, (D, E, F, p. 886), m. 180° can be made by reducing isatin. Further reduction gives oxindole. It is also formed by oxidizing oxindole. The reactive

groups in the oxidation-reduction series of isatin ⇌ oxindole ⇌ dioxindole are



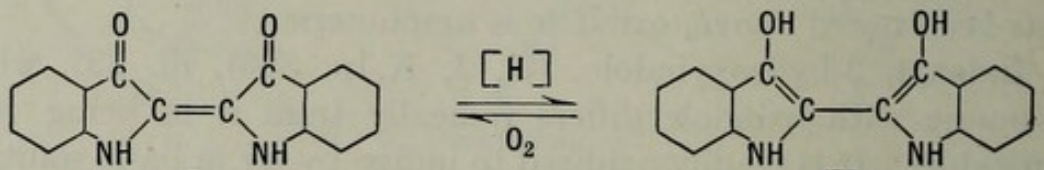
**Isatin,** diketodihydroindole, m. 201°, exists in form M (p. 886). It is readily made by oxidizing indigo, oxindole, dioxindole or indoxyl. Reduction gives dioxindole and then oxindole rather than the isomeric indoxyl. Isatin has been synthesized in many ways. Treatment with $PCl_5$ gives *isatin chloride,*



m. 180° dec., O-Ethers of isatin and N-alkyl derivatives of pseudoisatin (L, p. 886) are known.

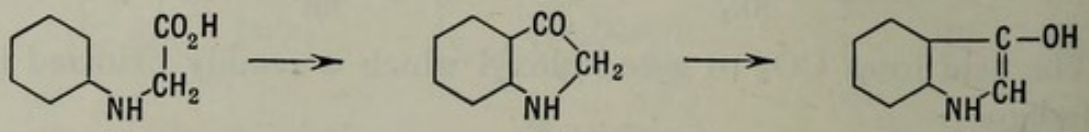
### *E.* Indigo and Related Compounds

**Indigo** (I) is the oldest known dye. The indigo plant contains a glucoside of indoxyl, *indican.* It is very insoluble but is changed by reduction to soluble *indigo white* (II) which can be oxidized readily back to the insoluble blue indigo. This gives the method of indigo or vat dyeing.



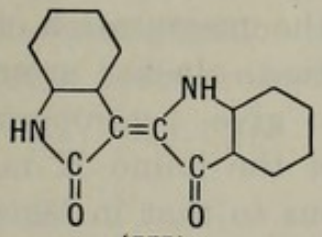
(I) (II)

Mono- and disulfonic acids of indigo are readily formed. The Na salt of the latter is *indigo carmine.* Many syntheses of indigo have been developed. The most important of these is the *phenylglycine process* which involves the fusion with $NaNH_2$ and NaOH of phenylglycine made from aniline and chloroacetic acid. The product is indoxyl which is oxidized to indigo by air.

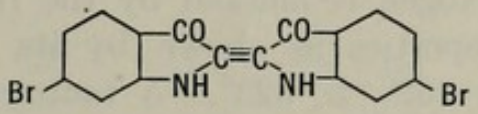


Many dyes involving modifications of the indigo molecule are known. *Indirubin* (III) is made by alkaline condensation of isatin and indoxyl, the 3-carbon of the former becoming attached

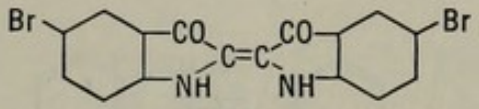
to the 2-carbon of the latter. Imperial purple, royal purple, or Tyrian purple was obtained from a species of Mediterranean shellfish. It has been shown to be a dibromo indigo (IV). The direct bromination of indigo gives (V). Thioindigo has S in place of the NH groups in indigo (VI).



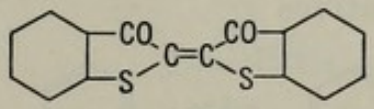

(III)




(IV)



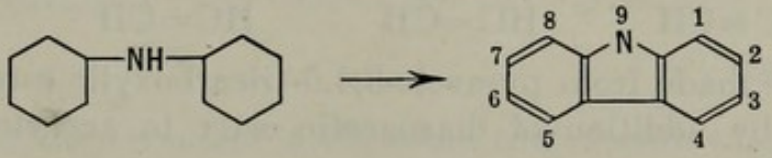

(V)




(VI)

*F.* Carbazole (VII), m. 245°, b. 355°

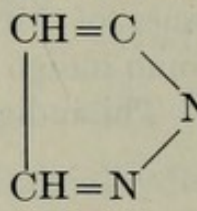
This is dibenzopyrrole or the 2,2′-imide of diphenyl. It occurs in coal tar. It can be made by heating diphenylamine in a red hot tube.



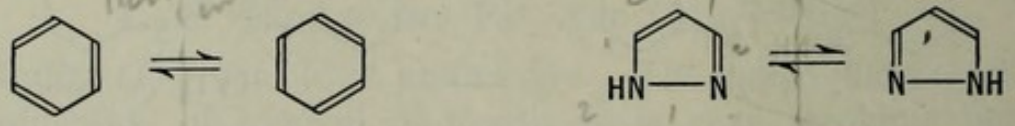

(VII)

The conjugation of the nitrogen with the two benzene rings increases the stability of the compound, decreases the ability of the N to unite with $H^+$ and increases its tendency to lose $H^+$. Its formation of a K cpd. with KOH is used in separating it from crude anthracene. Oxidation of carbazole gives a variety of products (Rep. 1921, 126). Silver oxide gives N-N-dicarbazyl, a colorless compound which gives colored solutions containing considerable amounts of the bivalent nitrogen free radical (Branch 1920). Nitration gives 1- and 3-nitro compounds (Morgan 1932). A partly hydrogenated carbazole grouping is found in strychnine. Carbazole is used in making the valuable vat dye Hydrone Blue.

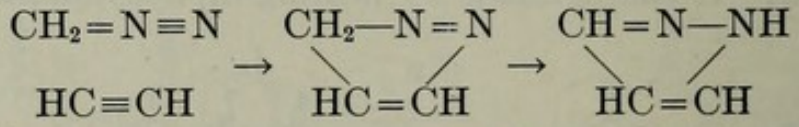
### *G.* Pyrazole and Related Compounds

**Pyrazole,**  NH, m. 70°, b. 185°, is a stable weak base.

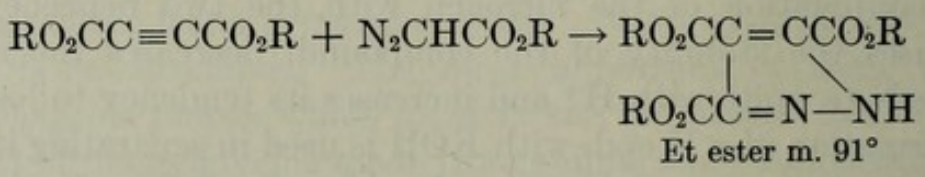
As in the case of pyrrole and its analogs, the unsaturation of the nitrogen is masked by the ring conjugation. It has aromatic properties as shown by its nitration to give *4-nitropyrazole*, m. 162°, b. 323°. A tautomeric shift of the imino H makes possible a shift of bonds entirely analogous to that in benzene. Undoubtedly this sets up a resonance which accounts for the aromatic properties and the high stability of pyrazole and its derivatives



Pyrazole can be made from diazomethane and acetylene in cold ether solution. This involves a peculiar addition of a 1,3-type if ordinary formulas are used.

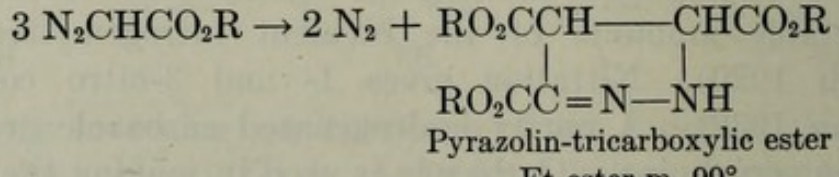


It can also be made from pyrazole-3,4,5-tricarboxylic ester prepared either by addition of diazoacetic ester to acetylene dicarboxylic ester,



Et ester m. 91°

or by the action of $Br_2$ on the corresponding pyrazoline ester obtained by heating diazoacetic ester alone

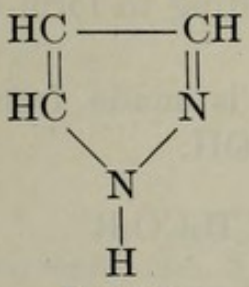


Pyrazolin-tricarboxylic ester
Et ester m. 99°

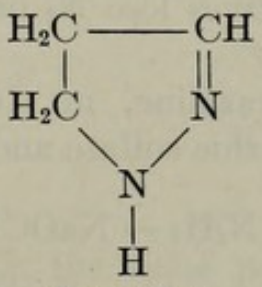
The action of $Br_2$ in producing a double bond is typical of a

dihydroaromatic compound. The ester is hydrolyzed to *pyrazole-3,4,5-tricarboxylic acid*, m. 233°, which on higher heating gives pyrazole. The aromatic nature of the pyrazole ring is further shown by the production of this acid by the permanganate oxidation of 3,4,5-$Me_3$-pyrazole, the three methyl groups being oxidized to carboxyl groups without changing the nucleus.

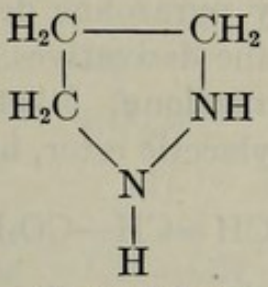
The hydrogenation products of pyrazole are no longer aromatic but show basic properties.



Pyrazole



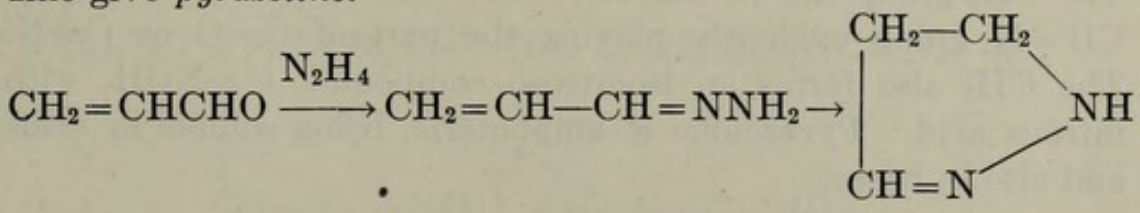
Pyrazoline
b. 144°



Pyrazolidine

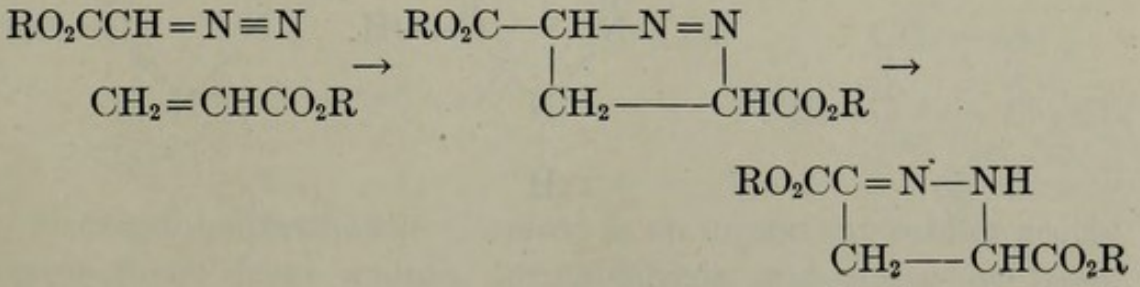
Pyrazolines are obtainable by a variety of reactions including:

1. The action of hydrazine or one of its derivatives with an $\alpha\beta$-unsaturated aldehyde or ketone. Thus acrolein and hydrazine give *pyrazoline.*

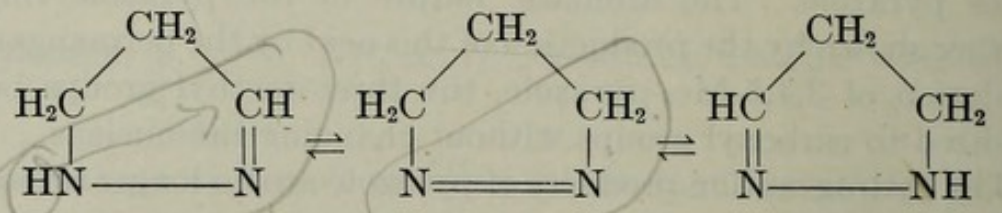


The last step consists in the usual ring closure when an active H is in the 1,5-relation to a double bond.

2. The addition of aliphatic diazo compounds to $\alpha\beta$-unsaturated esters. The *3,5-dicarboxylic ester*, Me ester, m. 94°, is formed from diazoacetic ester and acrylic ester while the *4,5-dicarboxylic ester*, Me ester, m. 97°, is formed from diazomethane and maleic or fumaric ester. The former process shows that the N adds to the $\alpha$-carbon.

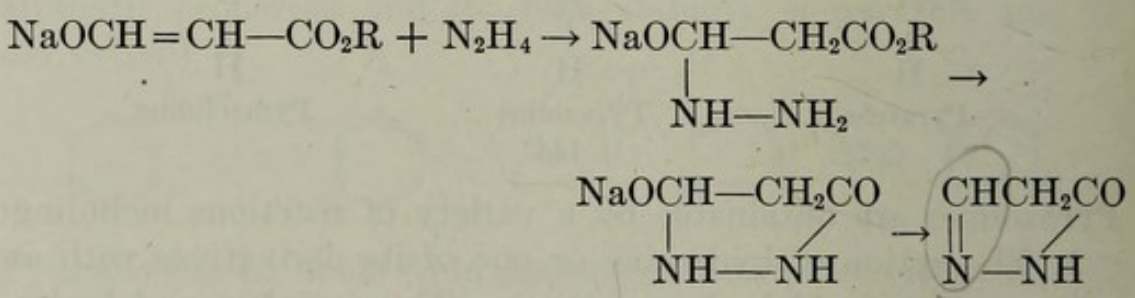


The 3- and 5-positions in pyrazolines are identical, because of the peculiar tautomerism which is possible.

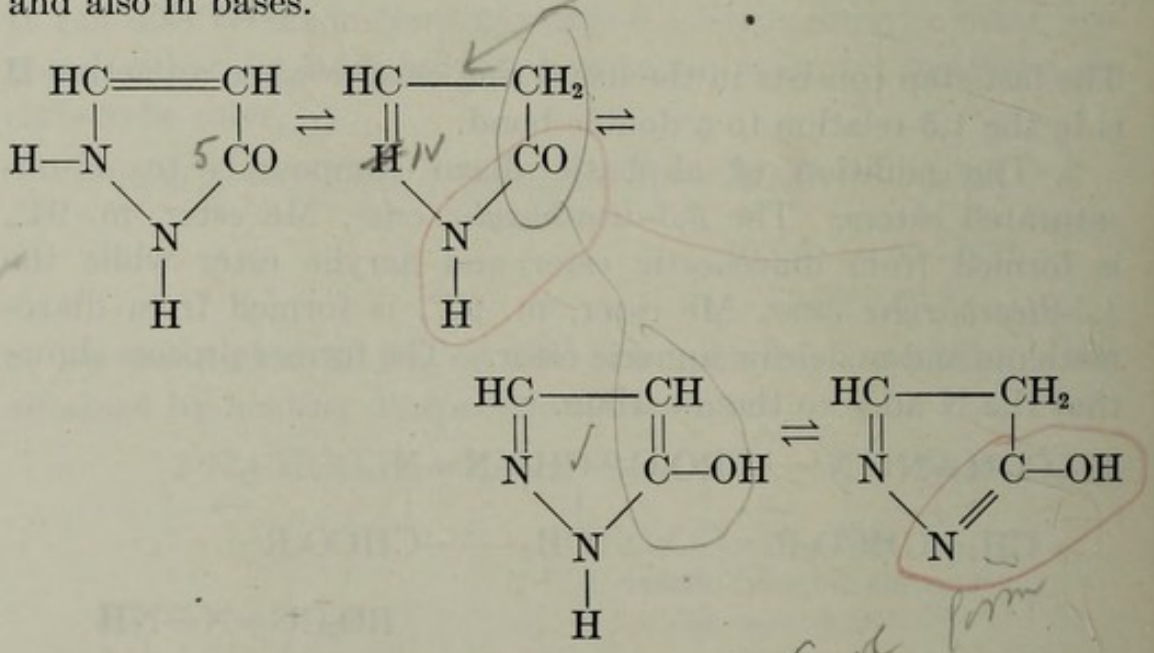


Many pyrazoline derivatives lose $N_2$ on heating to form cyclopropane derivatives.

**Pyrazolone,** 5-ketopyrazoline, m. 165°, is made from Na formylacetic ester, hydrazine sulfate and NaOH.

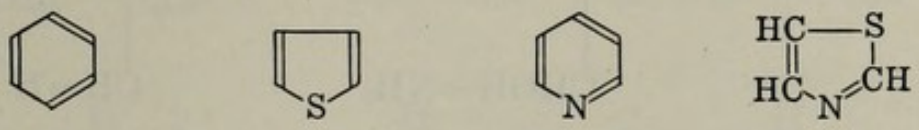


The $CH_2$ group can be alkylated like that in 1,3-diketones, the $CH=N$ group evidently playing the part of $C=O$ or $C\equiv N$. The $CH_2$ also forms an isonitroso compound, $C=NOH$, with nitrous acid. Pyrazolone is amphoteric, being soluble in acids and also in bases.



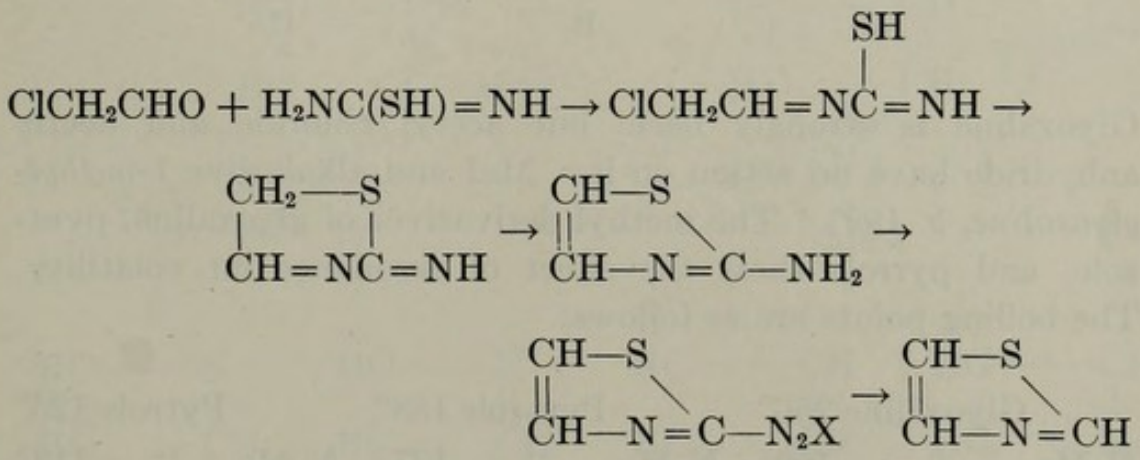
The first form is evidently responsible for the basic properties. The enol form is a hydroxyl derivative of pyrazole, an aromatic compound, and so has phenolic properties. *1-Phenyl-3-methylpyrazolone*, m. 127°, is made from phenylhydrazine and ethyl acetoacetate. Methylation gives *1-phenyl-2,3-dimethylpyrazolone* or *antipyrine*, m. 113°, an important febrifuge.

**Thiazole** (I) b. 117°, closely resembles pyridine in much the way that thiophene resembles benzene.

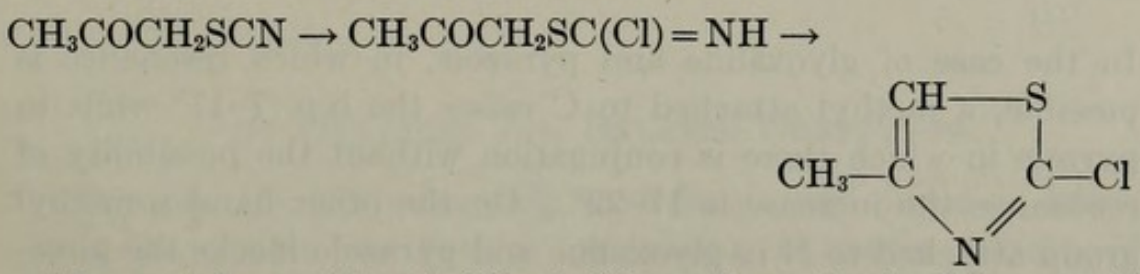


(I)

In each case the S plays the same part as $-CH=CH-$ in determining physical and chemical properties. It is made by heating with alcohol the diazonium salt of *2-aminothiazole*, m. 90°, a typical aromatic amine like aniline, obtained from chloroacetaldehyde and thiourea.

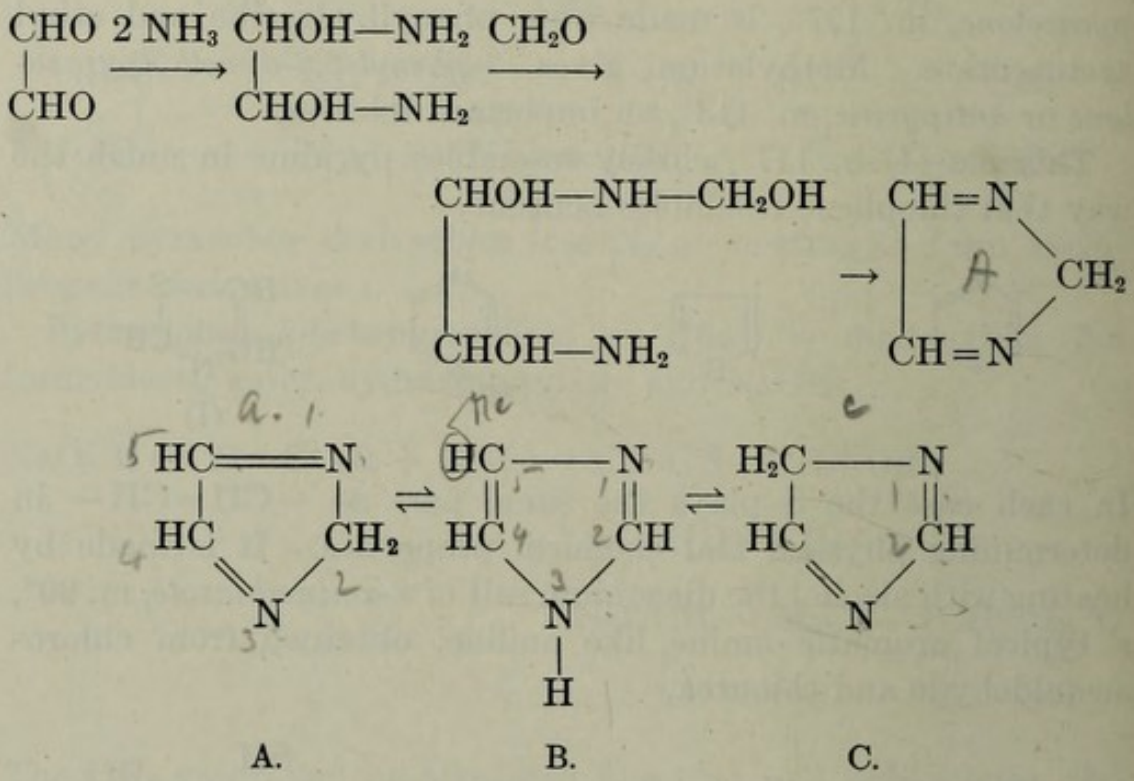


Thiocyanoacetone with HCl gives 2-Cl-4-Me-thiazole (Rep. 1919, 105)



Mercaptobenzothiazole (*Captax*) is an important rubber accelerator made from aniline, formaldehyde and sulfur or from aniline, carbon disulfide and an organic oxidizing agent such as nitrobenzene.

**Glyoxaline, imidazole,** (A, B, C), m. 90°, b. 256°, is made from glyoxal, formaldehyde and $NH_3$.

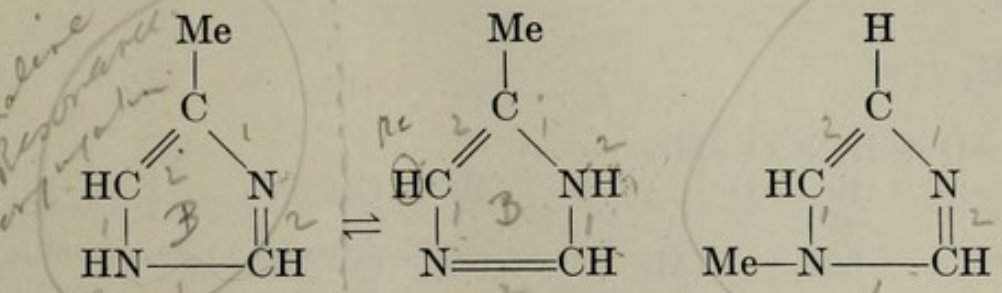


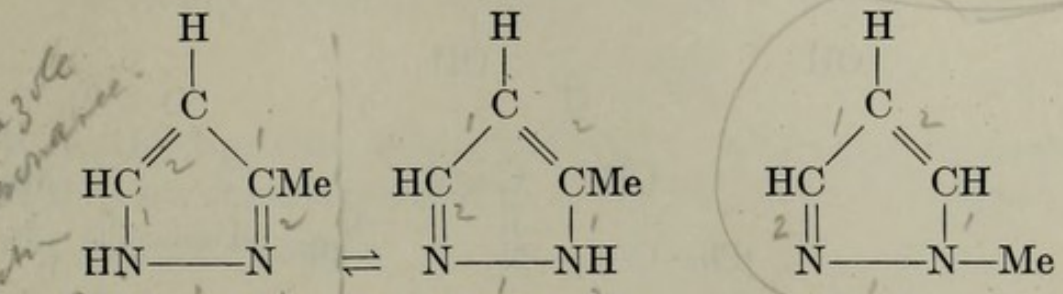
Glyoxaline is strongly basic but acetyl chloride and acetic anhydride have no action on it. MeI and alkali give *1-methyl-glyoxaline, b. 199°*. The methyl derivatives of glyoxaline, pyrazole, and pyrrole show the effect of resonance on volatility. The boiling points are as follows:

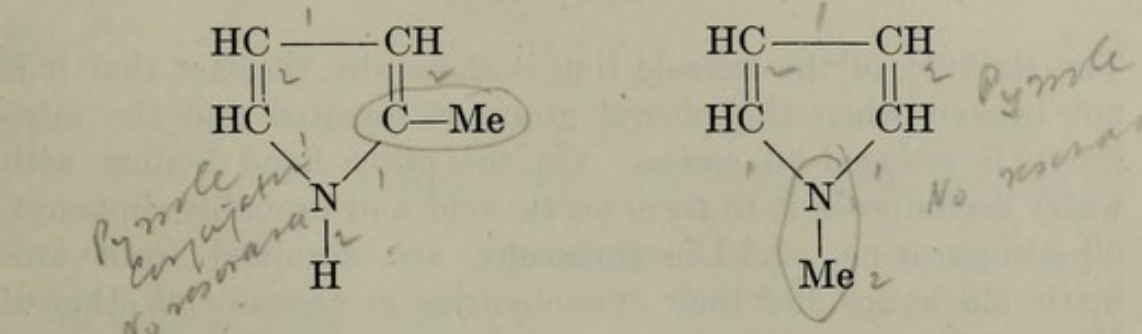
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Glyoxaline | 256° | | Pyrazole | 188° | | Pyrrole | 126° |
| N-Me | " | 199° | N-Me | " | 127° | N-Me | " | 113° |
| 5-Me | " | 263° | 5-Me | " | 205° | 2-Me | " | 148° |
| 2-Me | " | 267° | | | | 3-Me | " | 143° |

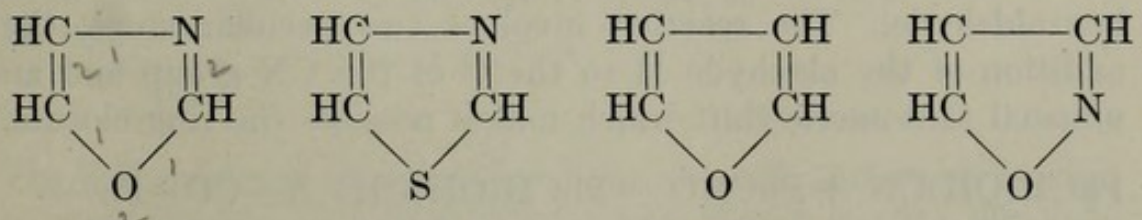
In the case of glyoxaline and pyrazole, in which resonance is possible, a methyl attached to C raises the b.p. 7–17° while in pyrrole in which there is conjugation without the possibility of resonance the increase is 17–22°. On the other hand a methyl group attached to N in glyoxaline and pyrazole blocks the possi-

bility of resonance and *lowers* the b.p. 57° and 61° respectively whereas in pyrrole it lowers it only 13°.







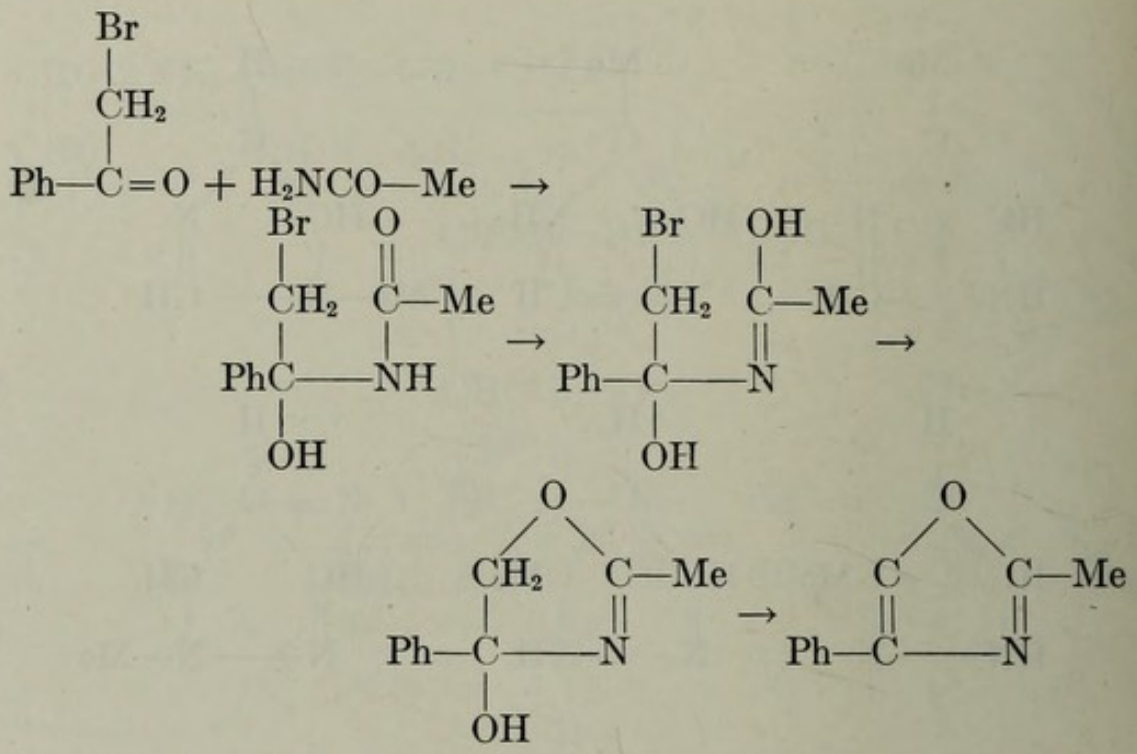


Oxazole (I) Thiazole Furan Isoxazole (II)

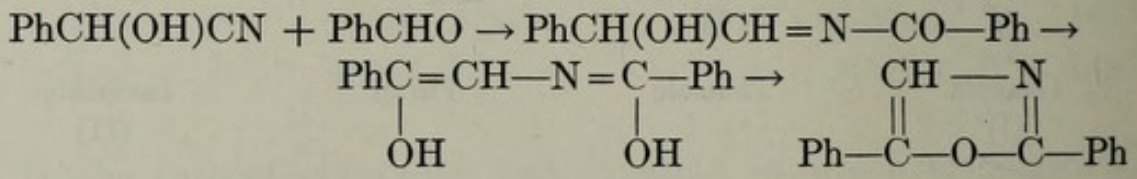
## *H.* Oxazoles and Related Compounds

**Oxazole** (I), corresponding to thiazole and furan is known only in certain derivatives containing aromatic groups. *2-*

*Methyl-4-phenyloxazole,* m. 45°, b. 242°, is readily made by heating acetamide and bromoacetophenone at 130°.



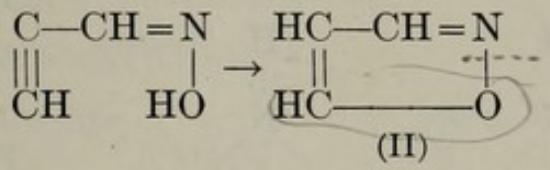
The stability of the oxazole ring is shown by the fact that it is not broken when the phenyl group is nitrated and the nitro group is reduced to amino. On the other hand boiling with water decomposes it to form acetic acid and probably diphenyldihydropyrazine. 2,5-Diaryloxazoles are obtained from aromatic aldehydes and their cyanohydrins in presence of ethereal HCl. *2,5-Diphenyloxazole,* m. 74°, b. 360°+, is thus made from benzaldehyde. The reaction involves two peculiar steps, the addition of the aldehyde H to the C of the CN group and an unusual tautomeric shift which makes possible the ring closure.



**4,5-Diphenyloxazole,** m. 44°, is obtained from benzoin, KCN and $H_2SO_4$.

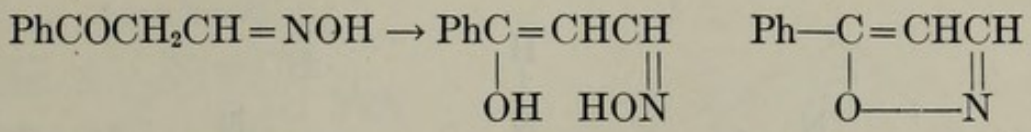
Isoxazoles have been studied extensively. Isoxazole, (II), b. 95°, is made from propargylic aldehyde and hydroxylamine.

The oxime, having an active H in the 1,5-relation to a triple bond undergoes ring closure.

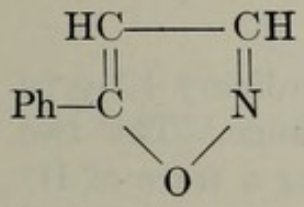


(II)

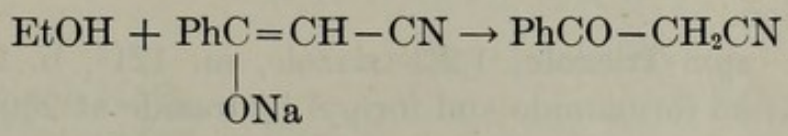
NaOEt opens the ring to give $NaOCH=CH-C\equiv N$. The monoximes of β-ketoaldehydes and β-diketones give 5- and 3,5-substituted isoxazoles.

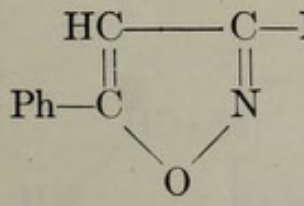


When the 3-position is free, the ring is readily split by bases as in the case of isoxazole itself. If the 3-position is occupied, the ring is stable to bases.



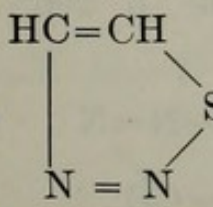
+ NaOEt →





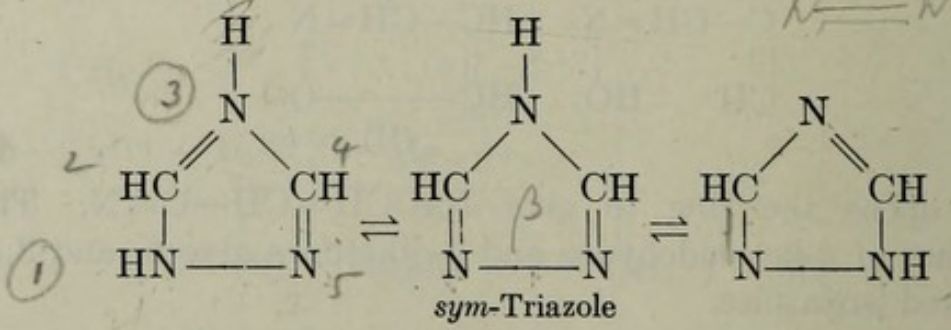
+ NaOEt → no action.

The 3-H evidently makes possible an unusual tautomeric change to give the α-cyanoketone which is removed by the alkali as an enolate.

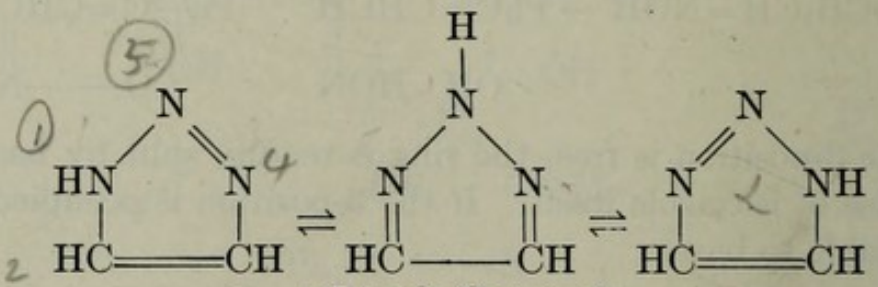
**Thiodiazole,**  S, b. 158°, does not have a disagreeable odor, is stable to acids but is decomposed by bases. It is very weakly basic.

## *I.* Triazoles

Two types are known.



*sym*-Triazole

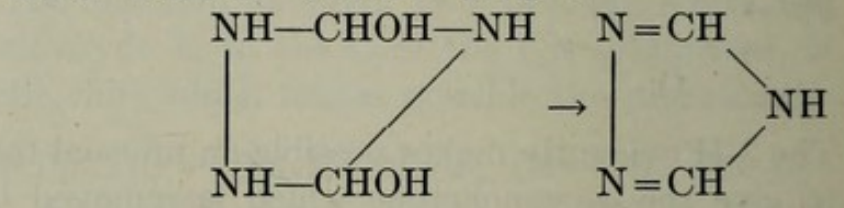


*v*-Triazole, Osotriazole

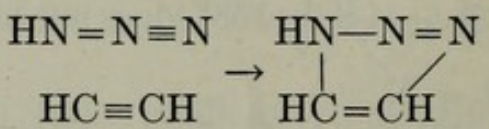
The tautomerism of the *sym*-triazole is of the ordinary 1,3-type while in the osotriazole it involves a 1,5-change. The two changes are probably both bimolecular involving a trace of $H^+$ ion.

***sym*-Triazole,** 1,2,4-triazole, m. 121°, b. 260°, can be made from formamide and formyl hydrazide at 260°

$$HCO—NHNH_2 + HCO—NH_2 \rightarrow$$



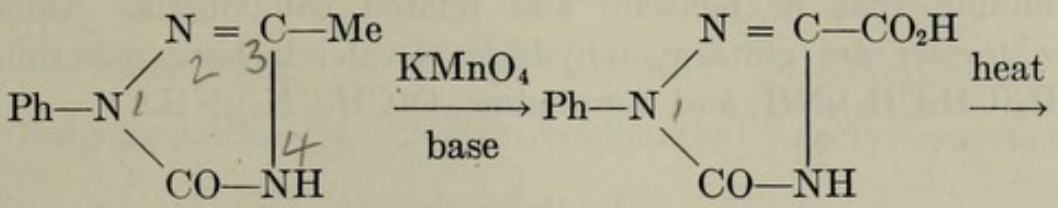
***v*-Triazole,** osotriazole, 1,2,3-triazole, b. 206°, can be made from acetylene and hydrazoic acid.



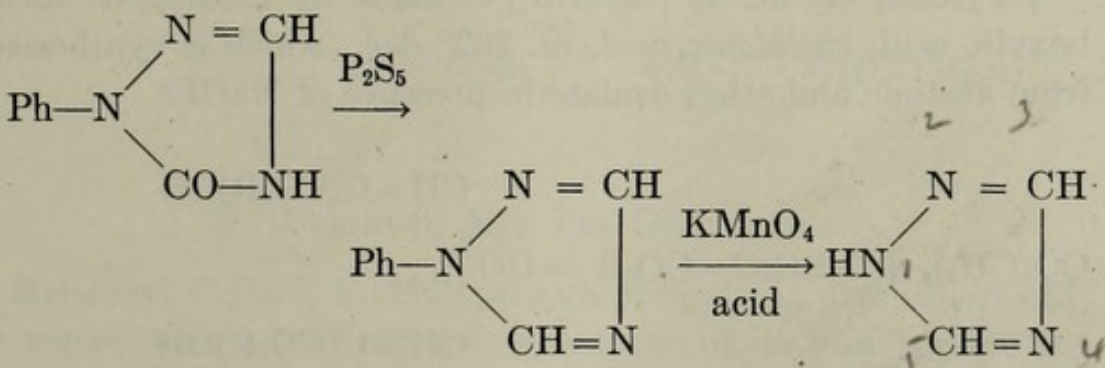
The chemistry of the triazoles, especially the stability of the

conjugated rings, is shown by the following changes:

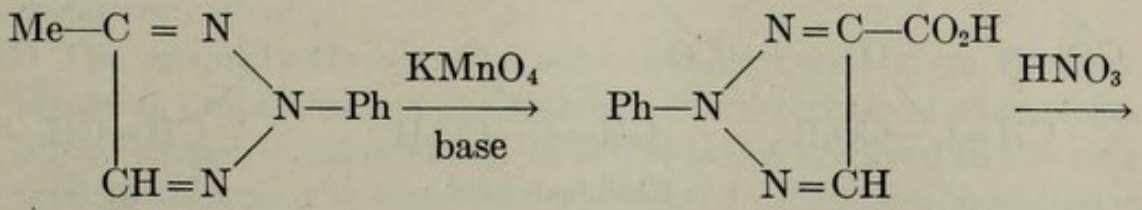
$$MeCO{-}NH{-}CO_2R + PhNHNH_2 \xrightarrow{55^\circ} PhNH{-}N{=}CMe{-}NHCO_2R \rightarrow$$

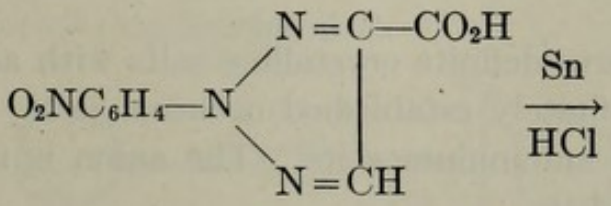


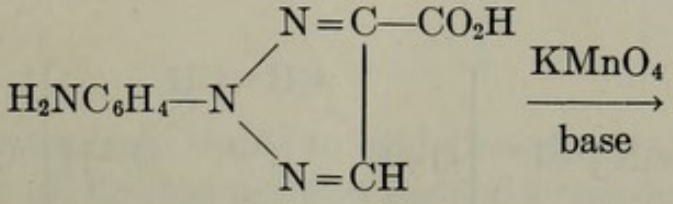
1-Ph-3-Me-1,2,4-triazolone-5

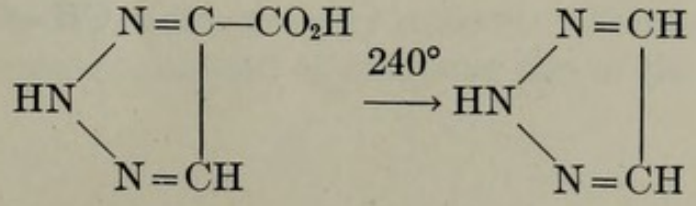


$$MeCOCHO + PhNHNH_2 \rightarrow Me{-}C(=NNHPh){-}CH{=}NNHPh \xrightarrow[FeCl_3]{\text{dil. HCl}}$$







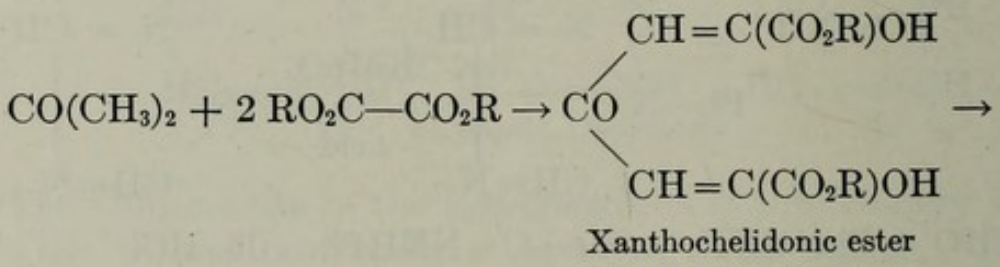


## III. SIX-MEMBERED HETEROCYCLIC RINGS

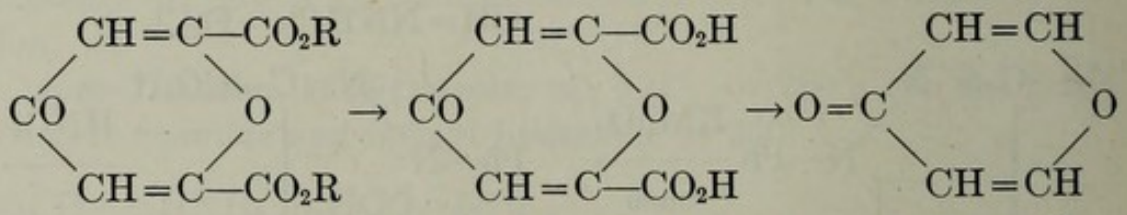
These fall into two groups, the saturated rings which show no properties different from their aliphatic analogs and the unsaturated rings, especially those with ring conjugation resembling that of benzene and related compounds. Among the former are glutaric anhydride, δ-valerolactone, piperidine $CH_2(CH_2CH_2)_2NH$, and morpholine, $O(CH_2CH_2)_2NH$.

### *A.* Pyrones

**γ-Pyrone,** (I) m. 32°, b. 315°, is made by heating its dicarboxylic acid, *chelidonic acid*, m. 262° dec., which is synthesized from acetone and ethyl oxalate in presence of NaOEt.

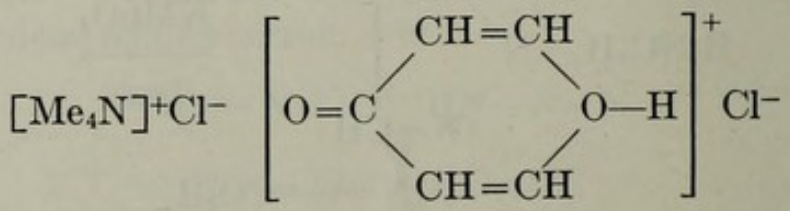



Xanthochelidonic ester

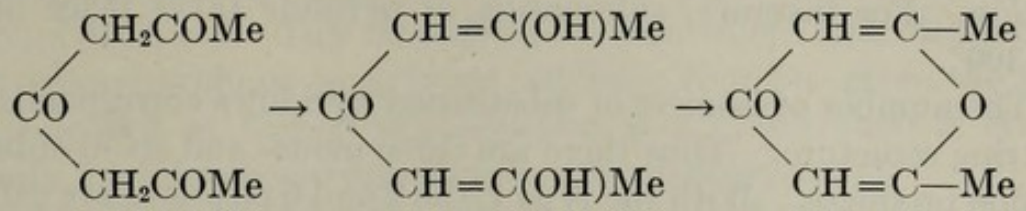



Chelidonic acid γ-Pyrone (I)

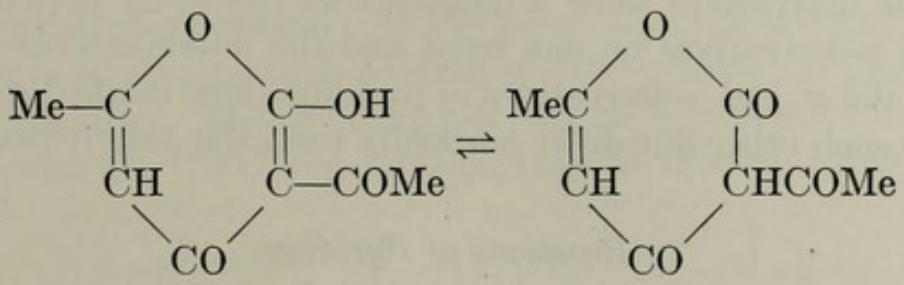
The γ-pyrones form definite crystalline salts with acids. These were the first definitely established *oxonium salts*. These salts are analogous to ammonium salts. The anion is not attached by a valence bond.



**αα-Dimethyl-γ-pyrone,** m. 132°, b. 250°, is made by heating diacetylacetone obtained from phosgene and Cu acetoacetic ester.



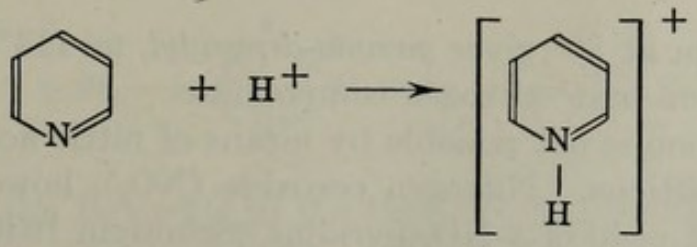
**Dehydroacetic acid** is 2-hydroxy-6-methyl-3-acetyl-γ-pyrone.



*B.* Pyridine and Its Derivatives

**Pyridine,** $C_5H_5N$, b. 116°, occurs in coal tar and can readily be separated by acid extraction because of its basic properties. It can be purified by effective fractional distillation or by crystallization of its difficultly soluble ferrocyanide. It has a disagreeable odor which makes it valuable as a constituent of mixtures for denaturing alcohol.

The conjugated system of three double bonds gives the ring aromatic properties and the stability characteristic of such rings. Since the salt forming ability of the N is not involved in the ring unsaturation as it is in pyrrole and related substances, pyridine is a base and forms pyridonium ions.



Pyridine is even more stable to oxidation than is benzene. Its homologs are oxidized to pyridine carboxylic acids.

Substitution reactions with pyridine are very difficult. This is presumably because the reagent, instead of attacking one of the

double bonds as in benzene, attaches itself to the highly reactive nitrogen and forms a relatively stable compound without substitution. For instance, sulfonation of pyridine takes place only at 300°.

The number of isomers of substituted pyridines corresponds to its ring structure. Thus there are three mono- and six di-substitution products. With the N as 1, the 2 and 6 positions are called *alpha*, the 3 and 5 *beta* and the 4 *gamma*. In the same way that benzene derivatives show a difference in reactivity between the *o*- and *p*-derivatives on one hand and the *m*-derivatives on the other, the $\alpha$- and $\gamma$-derivatives of pyridine show marked similarities to each other but differ markedly from the $\beta$-derivatives.

### *Reactions of Pyridine*

*A*. Those of the N atom.

1. $H^+$ ions unite with it to give pyridonium ions. Concentrated nitric and sulfuric acids merely form salts without any substituting action even at fairly elevated temperatures.

2. Methyl iodide and many other alkyl halides react to form N-alkyl pyridonium ions, and halide ions. The quarternary salt thus formed with MeI reacts when heated with a base to give methyldihydropyridine.

3. Halogens form dihalides, $C_5H_5NX_2$.

*B*. Reactions of the ring.

1. Oxidation is very difficult.

2. Reduction is very easy. Alcohol and Na, catalytic hydrogenation, or electrolytic reduction give hexahydropyridine, *piperidine*.

3. Sodium at 80° gives *gamma-dipyridyl*, m. 114°, and several basic and non-basic nitrogen compounds.

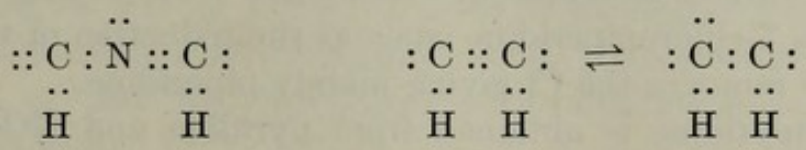
4. Nitration is not possible by means of nitric acid under any known conditions. Nitrogen peroxide ($NO_2$), however, at 120° gives a 10% yield of $\beta$-$NO_2$-pyridine (Schorigin 1936).

5. Sulfonation takes place at 300° to give pyridine-$\beta$-sulfonic acid. This is like the sulfonation of aniline in concentrated sulfuric acid solution to give the *m*-acid. The sulfonic acid group can be replaced by OH or CN by the usual fusion reactions.

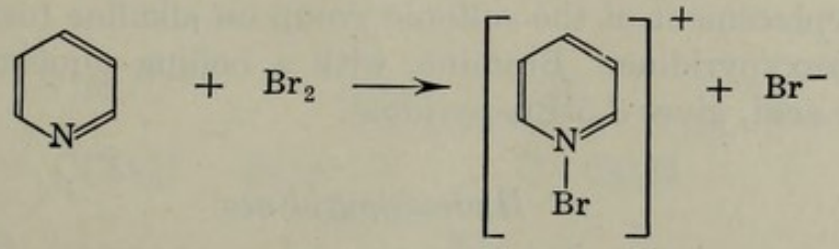
6. Chlorine and water simply give the hypochlorite of pyridine. In presence of bases, chlorine destroys the ring with the formation of $N_2$, $CHCl_3$ etc. Dry chlorine gives mainly pyridine dichloride and chloropyridines to a lesser extent. Bromine gives the dibromide but at higher temperatures in a sealed tube it gives mainly 3,5-dibromopyridine and a little 3-Br-pyridine.

7. Heating with $NaNH_2$ gives 2-amino- and 2,6-diamino-pyridine in which the $NH_2$ group has the properties of that in aniline.

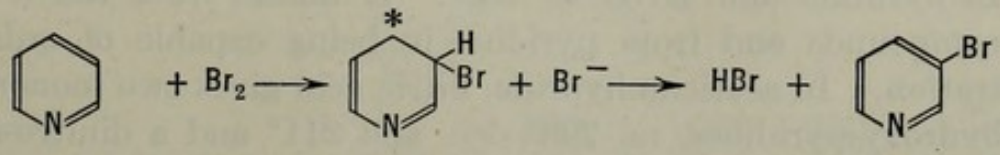
**Halogenated pyridines.** As has been seen, the activity of the N atom in combining with halogen interferes with the halogenation of the ring. The situation can best be shown electronically. The N and the C=C unsaturation may be shown as follows:



The competing processes would then be A and B (an atom with only 6 electrons being indicated by *):

A. 

In this case the Br with 6 electrons adds to the unshared pair of electrons of the N atom.

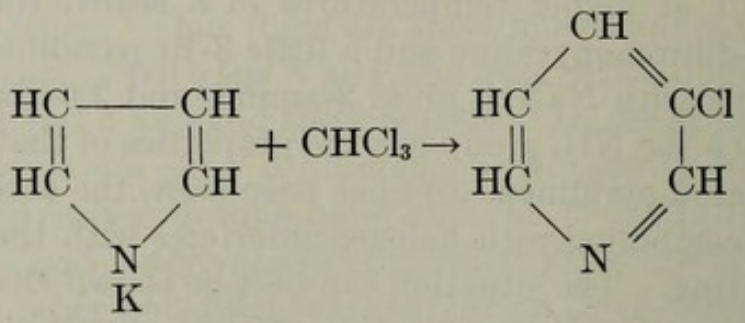
B. 

In this case the Br* adds to the lone electron pair of the active form of the C−C double bond. At ordinary temperatures only process A takes place. At high temperatures the N-dibromide is unstable and process B appears.

*α*- and *γ-chloropyridines*, b. 168° and 148°, are best made from $PCl_5$ and the corresponding hydroxypyridines. The chlorine

resembles that in the *o*- and *p*-chloro-nitrobenzenes in being replaceable by OH, $NH_2$, OR, SH etc.

**β-Chloropyridine,** b. 149°, is obtained by the remarkable action of pyrrole potassium with $CHCl_3$, $CCl_4$, chloral, etc.



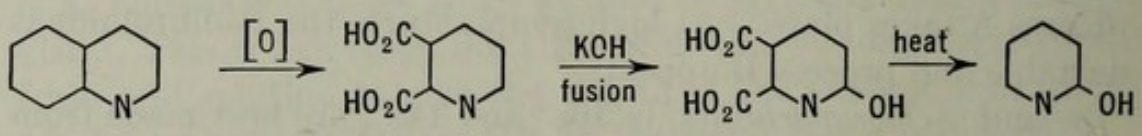

The γ-Cl cannot be replaced. Reduction with $Na_xHg$ or Zn and HCl gives 3-chloropiperidine whereas the reduction of the 2- and 4-isomers removes the Cl giving mainly piperidine.

β-Nitropyridine is obtained from pyridine and $NO_2$ at 120° (Schorigin 1936). It shows the reactions of nitrobenzene.

**Pyridine-3-sulfonic acid** is obtained by sulfonation at 330–350°. It shows the expected properties, including amphoteric reactions and replacement of the sulfonic group on alkaline fusion to give 3-hydroxypyridine. Bromine, with a boiling aqueous solution of the acid, gives 3,5-$Br_2$-pyridine.

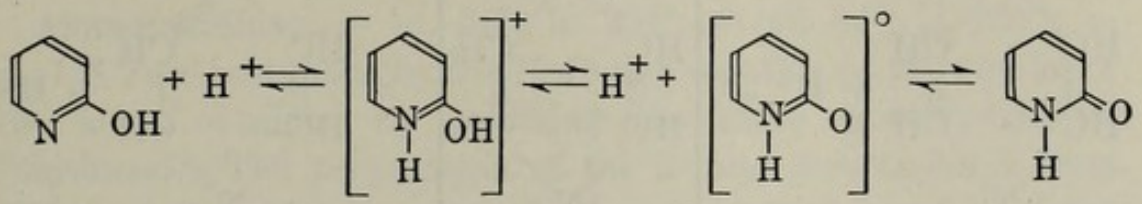
### *Hydroxypyridines*

They show phenolic properties in being soluble in bases and giving colors with $FeCl_3$. Only the *β-compound,* m. 129°, is readily obtainable, being formed from the sulfonic acid or from 3-Br-pyridine and KOH at 160°. It differs from the α- and γ-compounds and from pyridine in being capable of ordinary nitration. In acetic anhydride, nitric acid gives two mononitro-3-hydroxy-pyridines, m. 298° dec. and 211° and a dinitro-3-hydroxypyridine, m. 133°. *α-Hydroxypyridine,* m. 107°, b. 281°, is made from quinoline by the following steps:

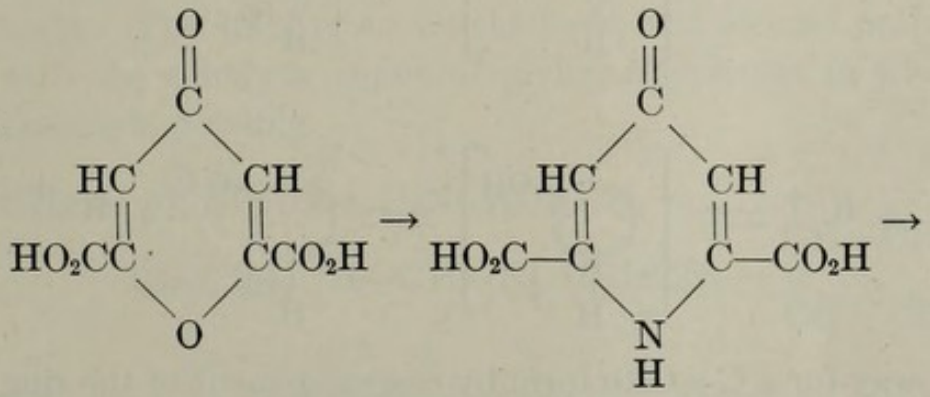


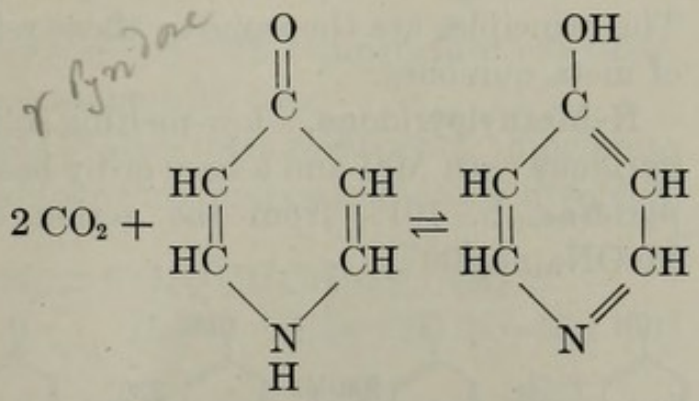

Quinolinic acid

It probably exists mainly as *α-pyridone*, 2-keto-1,2-dihydropyridine. The ready change to this keto form is due to the tendency of the N to unite with $H^+$ ion and is a good illustration of the bimolecular nature of tautomerization.



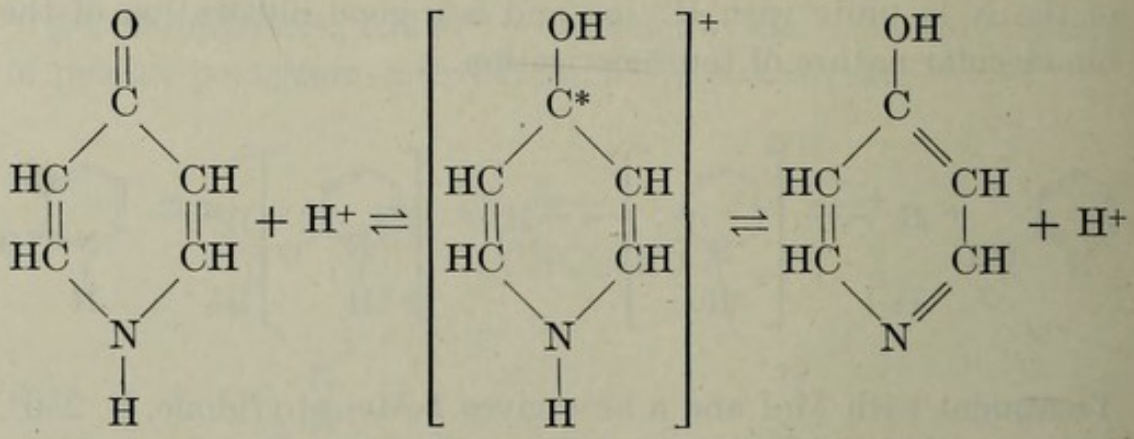
Treatment with MeI and a base gives 1-Me-α-pyridone, b. 250°. This reacts with $PCl_5$ to give 2-Cl-pyridine. *γ-Hydroxypyridine, γ-pyridone*, m. 148°, b. 350°+, is made by heating *chelidamic acid*, 4-hydroxypyridine-2,6-dicarboxylic acid, pyridone-2,6-dicarboxylic acid, m. 220° dec. which is readily obtained from $NH_3$ and chelidonic acid.



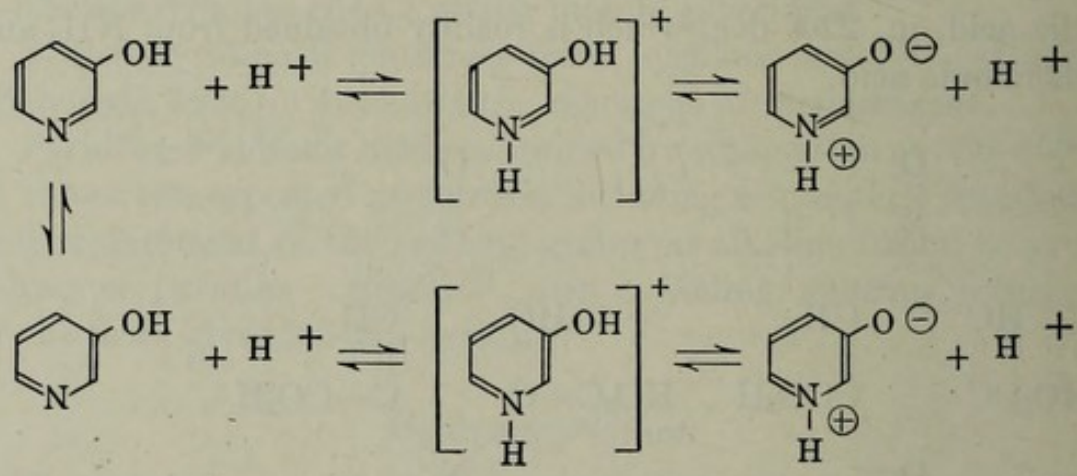


The change of the pyridone form to the hydroxypyridine form is

another example of the addition to $H^+$ to give a tautomeric change.

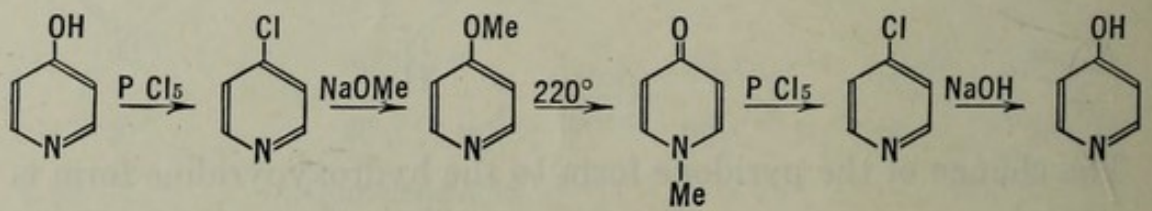


The accuracy of this conception receives support from the failure of 3-hydroxypyridine to give a pyrone form.



There is no way for a C=O to form by rearrangement of the ring unsaturation, which is so easy with the $\alpha$- and $\gamma$-compounds. The principles are the same as those related to the non-existence of meta quinones.

**N-Methylpyridone,** a low-melting solid, is obtained by treating pyridone with MeI and a base or by heating, at 200°, *4-methyoxypyridine*, b. 191°, from the action of 4-chloropyridine with MeONa at 100°.



The action of $PCl_5$ with pyridone is much like that with acetone in which the chief product is $MeCCl=CH_2$. In each case, the reaction may be due to the "enol" form or to the loss of HCl from a dichloride. In the case of the N-Me-pyridone, a mechanism like the latter process is indicated.

**Aminopyridines,** $\alpha$- m. 56°, b. 204°; $\beta$- m. 64°, b. 252°; $\gamma$- m. 158°, are best made by the Hofmann reaction on the amides of the acids obtained by oxidizing the three methylpyridines (picolines). The preparation of the 2- and 4-compounds from $NH_3$ and the chloro-compounds is unimportant because of the difficulty in making the latter. Sodamide with pyridine gives *2-$NH_2$-* and *2,6-$(NH_2)_2$-pyridines.* The $NH_2$ group can be diazotized and replaced by other groups or coupled to give dyes.

**Pyridine homologs** are obtained in great variety from coal tar and from bone oil. *Picolines,* methylpyridines, $\alpha$- b. 129°, $\beta$- b. 143°, $\gamma$- b. 143°, resemble pyridine in general. *$\alpha$-Picoline* is formed when acetaldehyde-ammonia is heated with acetaldehyde. The aldol or crotonaldehyde first formed probably reacts with the aldehyde ammonia giving a molecule in which 1,6-ring closure is possible.

$$CH_3CH=CHCHO + H_2NCHOHCH_3 \rightarrow$$

$$CH_3CH=CH-CH=NCHOHCH_3 \rightarrow \begin{matrix} CH-CH_2-CHCH_3 \\ \| \qquad\quad | \\ CH-CH=N \end{matrix}$$

The resulting dihydropicoline readily changes to picoline on mild oxidation.

**β-Picoline** is obtained by various high temperature reactions.

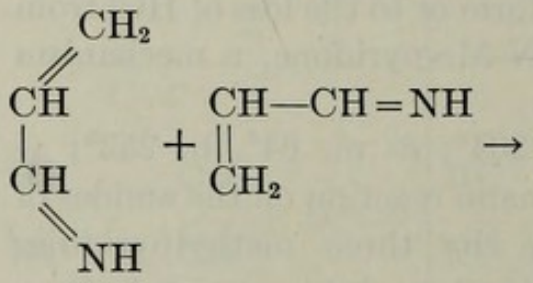
1. Decomposition of strychnine with lime.

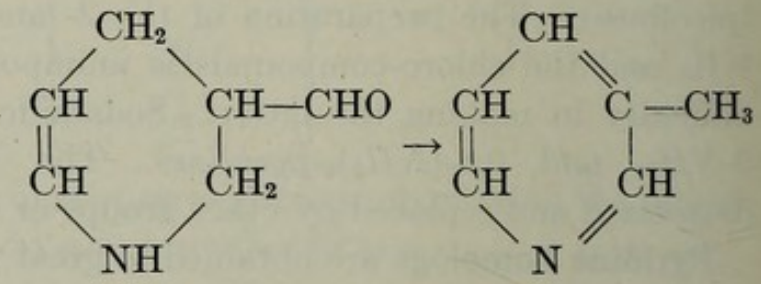
2. From acrolein ammonia or glycerol in presence of ammonium phosphate and $P_2O_5$. The following processes may be involved.

$$(A)\ CH_2=CHCHO + NH_3 \rightleftharpoons CH_2=CHCH(OH)NH_2 \rightleftharpoons H_2O + CH_2=CHCH=NH\ (B)$$

A Diels-Alder reaction with (*B*) as the conjugated diene and (*A*) as the $\alpha\beta$-unsaturated carbonyl compound would give an

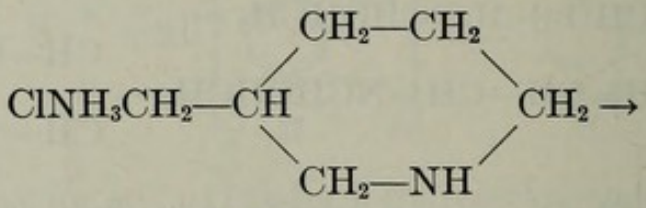
aldehyde of a tetrahydropyridine which would readily undergo internal oxidation and reduction.

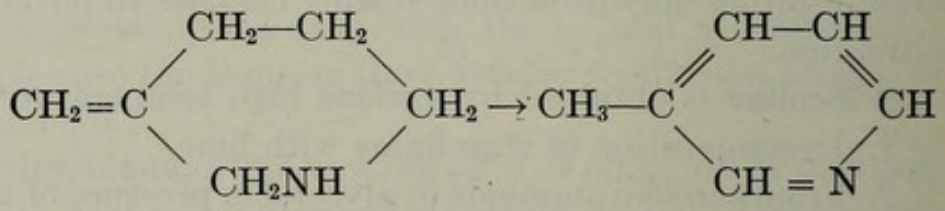




3. From trimethylene diamine hydrochloride. An 8-membered ring may form first and then undergo ring-narrowing as happens in the change of cyclohexane to methylcyclopentane or the ring may close in the 1,6-position by the following steps;

$$2\,NH_2(CH_2)_3NH_2 \xrightarrow{HCl} ClNH_3(CH_2)_3NH(CH_2)_3NH_3Cl \xrightarrow{HCl}$$





Oxidation of the picolines gives the three pyridine carboxylic acids.

The methyl group of *α-picoline* differs from that in its isomers by giving α-H reactions in condensing with aldehydes and ketones. Thus the grouping $N=C-CH_3$ resembles $O=C-CH_3$. The stability given by the pyridine ring makes possible reactions which could not take place with this grouping in simpler com-

pounds. Thus α-picoline and paraldehyde at 260° give *α-allylpyridine*, b. 190°. Similar condensations can be had with methylal, acetone and phthalic anhydride.

**α- and γ-Picolines** are also formed by rearrangement when pyridine-methyl iodide is heated to 300°. This is closely analogous to the formation of *o*- and *p*-toluidines from N-Me-anilines. α- and γ-Ethylpyridines, b. 148° and 166°, are similarly prepared. When pyridine compounds with higher alkyl halides are decomposed, rearrangements may occur within the alkyl group. Thus the *n*-propyl iodide compound gives isopropylpyridines. *α-n*-propylpyridine, *conyrine*, is obtained by dehydrogenating its hexahydroderivative, the alkaloid *coniine*. It is synthesized from propenylpyridine made from α-picoline and acetaldehyde.

**Dimethylpyridines, lutidines,** 2,4- b. 157°, 3,4- b. 164°, 2,6- b. 142°, are found in coal tar and bone-oil. *Trimethylpyridines, collidines* are known. The 2,4,6- or *sym*-collidine, b. 172°, is made from acetoacetic ester and aldehyde-ammonia or from acetamide and acetone at 250°. In both cases the aldol condensation produces molecules capable of 1,6-ring closure. The second case gives a pyridine directly without any dehydrogenation. The mesityl oxide formed from the acetone reacts with the acetamide in the simplest possible way.

$$(CH_3)_2C{=}CH{-}CO{-}CH_3 \rightarrow$$

$$CH_3{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}N{-}CO{-}CH_3 \rightarrow \quad CH{=}C(CH_3)N$$

$$CH_3{-}C{=}CH{-}C{=}\!\!\!\!\diagup\!\!\!\!\diagdown$$

The final ring closure is a cyclic aldol condensation involving H which is α- to the conjugated system C=C−C=N instead of merely α- to C=O.

**Pyridine carboxylic acids** are made in general by:

1. Oxidation of alkylpyridines. In some cases more complex side chains are removed leaving one or more carboxyl groups. Thus nicotine and quinoline give nicotinic and quinolinic acids respectively.

2. By partial decarboxylation of dibasic acids. The carboxyl nearer to the N is removed more easily.

The *monobasic acids* are *picolinic*, α-, m. 135°, *nicotinic*, β- m. 231°, and *isonicotinic*, γ- m. 309° (sealed tube).

All six possible pyridine dicarboxylic acids are known: *quinolinic*, 2,3- m. 190°, *lutidinic*, 2,4- m. 235°, *dipicolinic*, 2,6- m. 226°, *isocinchomeronic*, 2,5- m. 236°, *dinicotinic*, 3,5- m. 323°, and *cinchomeronic*, 3,4- m. 266°.

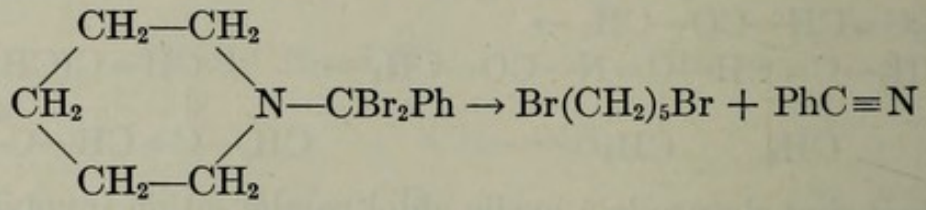
### *Hydrogenated Pyridines*

The di-, tetra, and hexa-hydro compounds of pyridine and its derivatives are known. They all readily revert to pyridine. Their dehydrogenation is extraordinarily easy as compared with that of hydro-benzene derivatives.

**Piperidine,** hexahydropyridine, pentamethylene imine,

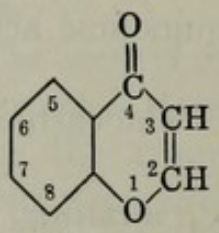
$$(CH_2)_5NH,$$

b. 106°, is a strong base made by hydrogenating pyridine in a variety of ways. On a large scale this is usually done electrolytically. Piperidine occurs in the alkaloid of pepper, *piperine*, which is the piperidide of piperic acid. Piperidine gives the reactions of a secondary aliphatic amine. Exhaustive methylation gives first $CH_2=CH(CH_2)_3NMe_2$ and then $CH_3CH=CHCH=CH_2$, the latter being a rearrangement product of the expected 1,4-diene. Piperidine is a source of pentamethylene compounds (v. Braun). The benzoyl compound is treated with $PBr_5$ and distilled.

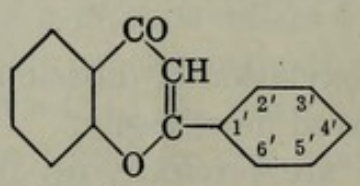



### *C.* Chromone and Derivatives

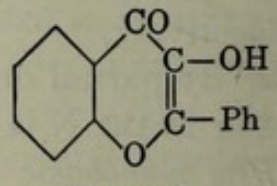
**Chromone,** benzpyrone, m. 59° and *flavone*, 2-phenylbenzpyrone, m. 97° are parent substances of many natural vegetable colors and dyes.




Chromone




Flavone




Flavonol

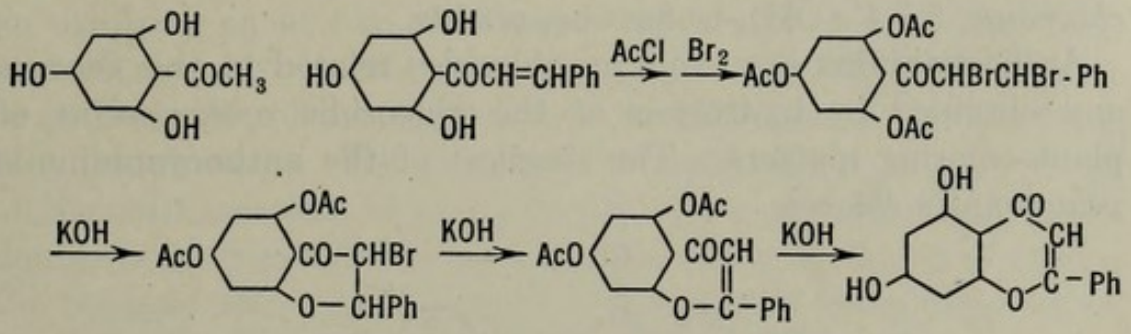
Benzo γ pyrone

*Chromane*, the parent substance of chromone, is made from PhONa and $(CH_2)_3Br_2$ or $Cl(CH_2)_3OH$. First an ether is formed and then the ring is closed by heating with $ZnCl_2$ or Zn.

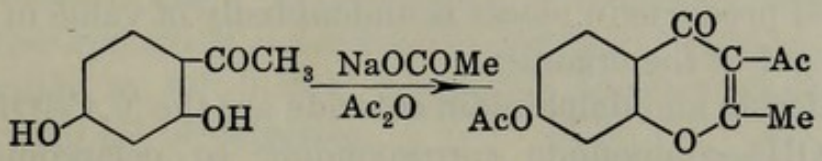
Some of the important natural products related to these parent substances are the following.

1. Related to flavone. *Chrysin*, 5,7-$(OH)_2$-; *luteolin*, 5,7,3′,4′-$(OH)_4$-; *quercitin*, 3,5,7,3′,4′-$(OH)_5$; *myrcetin*, 3,5,7,3′,4′,5′-$(OH)_6$-; *rhamnetin*, 3,5,3′,4′- $(OH)_4$-7-MeO-; *rhamnazin*, 3,5,4′-$(OH)_2$-7,3′-$(MeO)_2$-flavone. *Hesperetin* is 3,7,3′-$(OH)_3$-4-Me-2,3-$H_2$-flavone.

A general method of synthesis for many flavones is from poly-hydroxy-chalcones obtained from suitably substituted benzaldehydes and acetophenones by the Claisen reaction. One OH must be ortho to the CO so as to make possible the closing of the pyrone ring. The synthesis of chrysin would involve the following steps:




Hydroxyacetophenones can take part in a Perkin type reaction with acid anhydrides and Na salts of aliphatic and aromatic acids to give chromones and flavones respectively. With aliphatic acids an acyl group appears in the 3-position but not with the aromatic acids (Robinson 1925–)

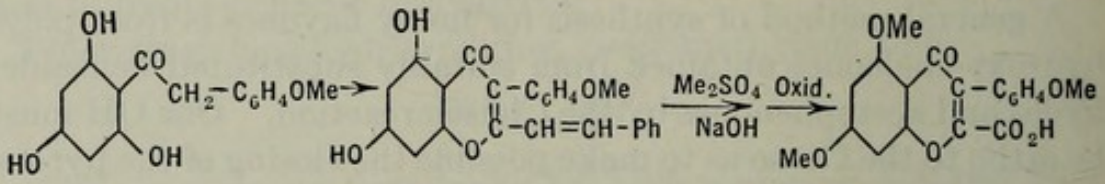



2-Me-3-acetyl-7-acetoxychromone

Similarly resacetophenone, with sodium anisate and anisic anhydride, gives 7-OH-4′-MeO-flavone, *pratol*.

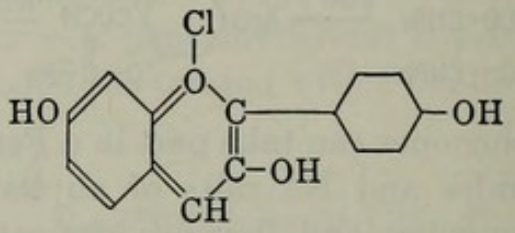
2. Related to flavanol (3-OH-flavone). If suitable ω-methoxy acetophenones are used, the products have MeO- in the 3-position and on demethylation give *flavanols*. The following naturally occurring substances have been made in this way: *galingin*,

5,7-$(OH)_2$-; *datiscetin*, 5,7,2′-$(OH)_3$-; *kaempherol*, 5,7,4′-$(OH)_3$-; *fisetin*, 7,3′,4′-$(OH)_3$-; *quercitin*, 5,7,3′,4′-$(OH)_4$-; *morin*, 5,7,2′,4′-$(OH)_4$-; *quercetazetin*, 5,6,7,3′4,′-$(OH)_5$-; *gossypetin*, 5,7,8,3′,4′-$(OH)_5$-; *myricetin*, 5,7,3′,4′,5′-$(OH)_5$-flavanol. A further modification of the Perkin reaction is used to give *isoflavones* (3-phenylchromones, p. 910). A polyhydroxy phenyl benzyl ketone, having OH ortho to the CO, is heated with Na cinnamate and cinnamic anhydride. The methylene group supplies the $\alpha$-H atoms while the cinnamic compounds supply the carbonyl group.




Decarboxylation and demethylation give *5,7,4′-(OH)$_3$-3-phenylchromone*, 5,7,4′-$(OH)_3$-isoflavone, *genista*.

**Anthocyanidins** are oxonium chlorides related to the *flavanes* and obtained by hydrolysis of the glucosidic *anthocyanins* of plant coloring matters. The simplest of the anthocyanidins is *pelargonidin chloride*.



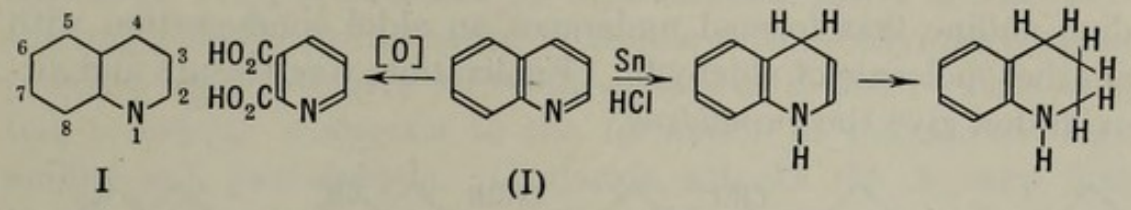

The chlorine is really ionic. The oxonium base is strong enough to keep the hydrolysis to a minimum. The limited hydrolysis of this and related products in plants is undoubtedly of value in the control of the pH of the organism.

**Cyanidin chloride** and **delphinidin chloride** are the 3′,4′-$(OH)_2$- and 3′,4′,5′-$(OH)_3$-compounds corresponding to pelargonidin. *Myrtillidin chloride* and *oenidin chloride* are the 7- and 3′,4′-methyl ethers of delphinidin chloride (Robinson 1928–).

### *Quinoline and Related Compounds*

**Quinoline,** $C_9H_7N$, (I) b. 239°, occurs in coal-tar and bone-oil, is obtained by alkaline decomposition of certain alkaloids and can be synthesized in a great variety of ways from aniline and from

ortho substituted anilines. It possesses the properties to be expected of a benzene and a pyridine ring.



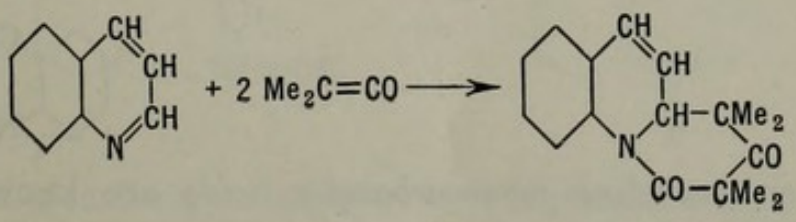

I (I)

Seven mono-substituted quinolines are possible because of its unsymmetrical structure. The positions numbered 2 to 8 are also known as $\alpha$-, $\beta$-, $\gamma$-, $a$-(ana-), $p$-, $m$-, and $o$-. The position of side chains is determined by oxidation to carboxylic acids or by synthesis.

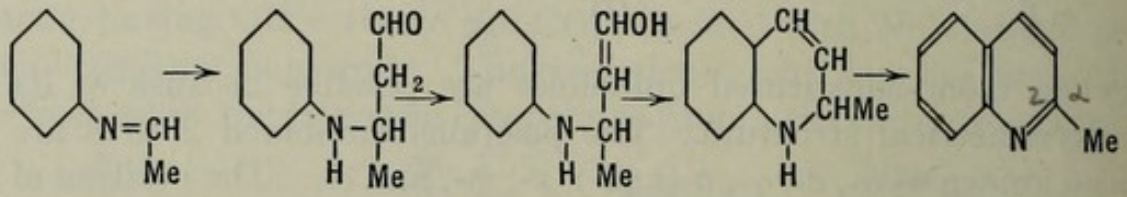
The most important synthesis of quinoline is that of Skraup which employs aniline and glycerol heated with sulfuric acid and an oxidizing agent like nitrobenzene or arsenic acid (OS). The process may involve the formation of acrolein, the 1,4-addition of aniline to acrolein, ring closure and oxidation of the resulting dihydroquinoline. The same result would follow the action of aniline with acrolein to give a Schiff's base, a product having a double bond in position to give ring closure with the $o$-position in the benzene ring. In fact, such a ring closure takes place when N-allylaniline is heated with PbO. Substituted anilines can also be used in the Skraup synthesis.

**Quinolonium salts** are analogous to pyridonium salts. Quinoline is readily reduced to *dihydroquinoline*, m. 161°, by metals and acids. The process is readily continued to give *tetrahydroquinoline*, b. 245°. Its N-ethyl derivative is *cairolin*, a febrifuge. Further reduction involving the benzene ring to give decahydroquinoline, m. 48°, b. 204°, is possible only by vigorous hydrogenation with HI or catalysts.

Quinoline forms a remarkable compound with 2 mols of dimethyl ketene.

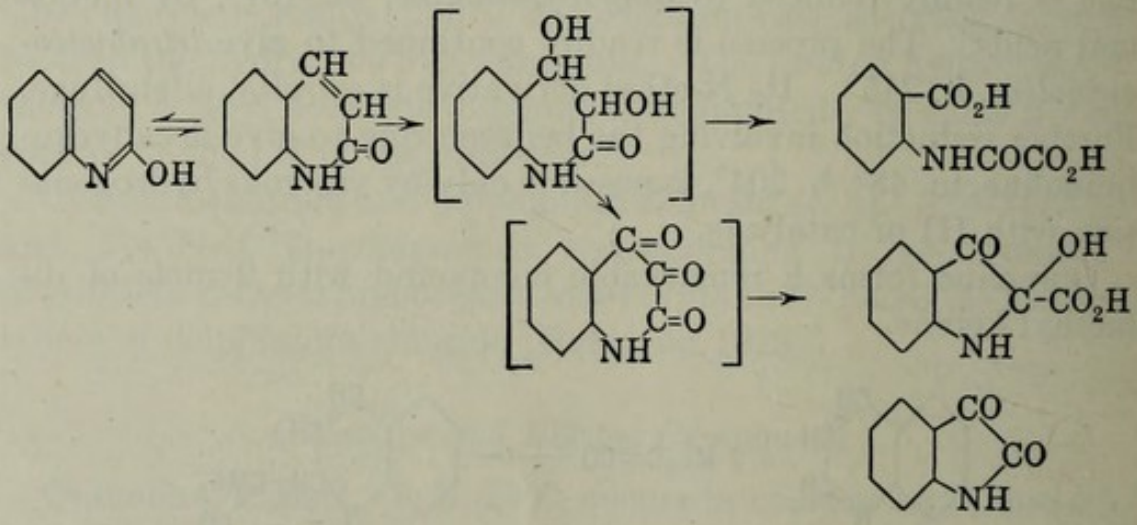


The most important methyl quinoline is the α- or 2-isomer, *quinaldine*, b. 246°, which occurs in coal-tar and can be synthesized by heating aniline and paraldehyde with HCl. The ethylidine aniline first formed undergoes an aldol condensation with another molecule of aldehyde. Enolization, ring closure and air-oxidation give the *quinaldine*.




Quinaldine shows the peculiar reactions noted with α-Me-pyridine, the H atoms of the Me group having α-H properties and consequently, giving condensation reactions with aldehydes, ketones and other active carbonyl compounds. Thus phthalic anhydride gives *Quinoline Yellow*, $C_9H_6NCH(CO)_2C_6H_4$, the disulfonic acid of which is *Quinoline Yellow* S. $CrO_3$ and $H_2SO_4$ convert quinaldine to quinoline-α-carboxylic acid while permanganate gives pyridine-2,3,6-tricarboxylic acid. The *cyanine dyes* which are used as sensitizers in photography are obtained from quinaldine and similar substances.

**Carbostyril,** 2-hydroxyquinoline, m. 200°, is obtained from *o*-aminocinnamic acid and 50% $H_2SO_4$. It has phenolic properties. Oxidation with alkaline $KMnO_4$ gives isatin and oxalylanthranilic acid.

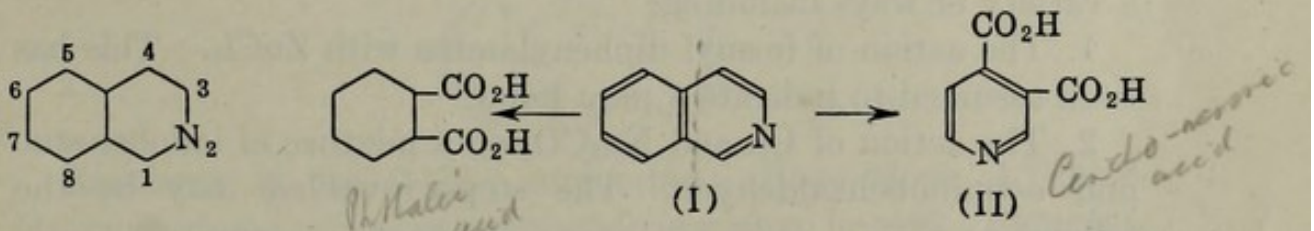



All seven *quinoline monocarboxylic acids* are known. The

2-acid, *quinaldinic* acid, m. 156°, and the 4-acid, *cinchoninic* acid, m. 254°, are made by oxidizing quinaldine and cinchonine. The *3-acid*, m. 275°, is obtained by a remarkable series of reactions starting with the condensation of aniline with *n*-butyraldehyde in presence of HCl to give *2-Pr-3-Et-quinoline*, b. 293°. This reaction is exactly analogous to the formation of quinaldine from aniline and paraldehyde. Oxidation attacks the 2-group first giving 3-Et-quinoline-2-carboxylic acid which is readily decarboxylated to 3-Et-quinoline, b. 267°, which gives the 3-acid on oxidation. The *7-acid*, m. 247°, is made by oxidizing 7-Me-quinoline obtained by the Skraup synthesis from *m*-toluidine and *m*-nitrotoluene. The 5-, 6-, and 8-acids, m. 320°+, 292°, and 187°, can be made by the Skraup synthesis using amino- and nitrobenzoic acids with glycerol and sulfuric acid.

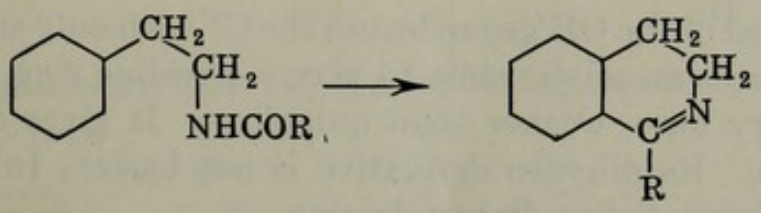
**Quinic acid,** 6-methoxyquinoline-4-carboxylic acid, m. 280°, is obtained by oxidizing quinine. *Acridinic acid*, quinoline-2,3-dicarboxylic acid, from the oxidation of acridine, loses $CO_2$ at 130° to give quinoline-3-carboxylic acid.

**Isoquinoline,** (I) m. 24°, b. 240°, is $\beta\gamma$-benzopyridine while quinoline is $\alpha\beta$-penzopyridine. Its structure is proved by its oxidation to give phthalic acid and cinchomeronic acid (II).




It is best separated from crude quinoline from coal tar by alternate crystallization of the sulfates and fractional distillation of the bases.

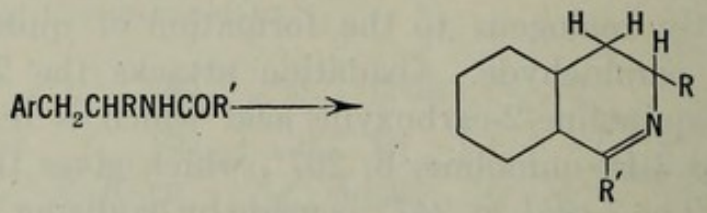
The N-acyl derivatives of $\beta$-arylethylamines undergo ring closure to give 3,4-dihydro-isoquinolines.




A method of making a variety of such acylamines starts with the

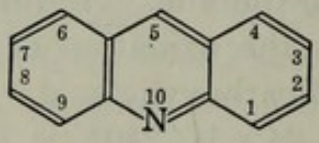
unsaturated ketones readily obtained by condensing an aromatic aldehyde and a ketone.

$$ArCH{=}CRCOR' \rightarrow ArCH_2CHRCOR' \rightarrow ArCH_2CHRC(NOH)R' \rightarrow$$




These reactions are of great importance in alkaloid syntheses.

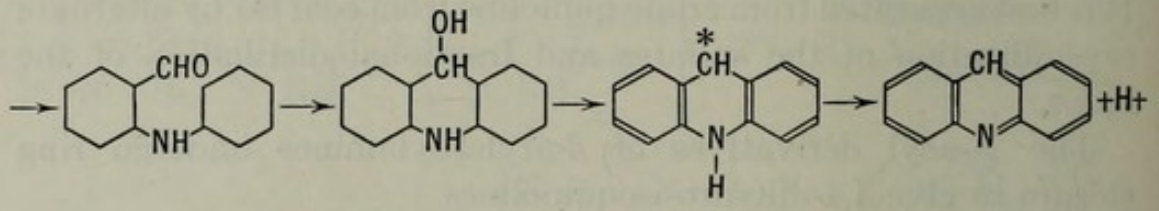
**Acridine,** m. 108°, b. 346°, 2,3,5,6-dibenzopyridine, occurs in crude anthracene from coal tar. It shows analogies to pyridine and to anthracene. The evidence for a para bond in the middle ring is about like that for one in anthracene.




It can be oxidized to quinoline-2,3-dicarboxylic acid and to pyridine-2,3,5,6-tetracarboxylic acid. It has been synthesized in a variety of ways including:

1. The action of formyl diphenylamine with $ZnCl_2$. This has been assumed to indicate a para bond.

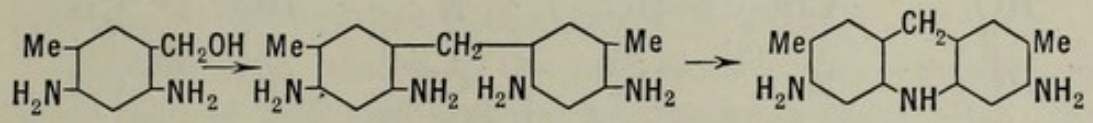
2. The action of Cu and $Na_2CO_3$ on a mixture of iodobenzene and *o*-aminobenzaldehyde. The steps involved may be the following:




The removal of the OH group leaves the C* with only six electrons which induces an allylic shift to give a pyridine ring. Acridine is a tertiary base, weaker than quinoline. It gives *acridonium compounds.* Its dihydro derivative is not basic. In structure, the latter is related to diphenylamine.

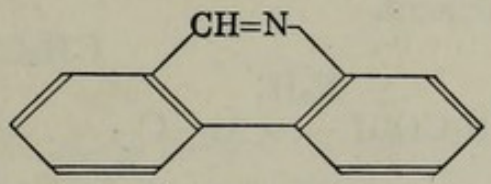
Aminoacridines are used as acridine dyes such as *Acridine Yel-*

*low*, 2,8-$(NH_2)_2$-3,7-$Me_2$-acridine hydrochloride, which is made from *m*-toluylene diamine and formaldehyde. The condensation takes place in the position *o,p*- to the two amino groups.



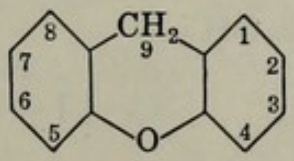
Oxidation gives the dye. *m*-Aminodimethylaniline similarly gives *Acridine Orange*. By using benzaldehyde in place of formaldehyde, 5-phenyl derivatives, *Benzoflavine* and *Acridine Orange R Extra*, respectively, are obtained.

**Phenanthridine** bears the same relation to phenanthrene that

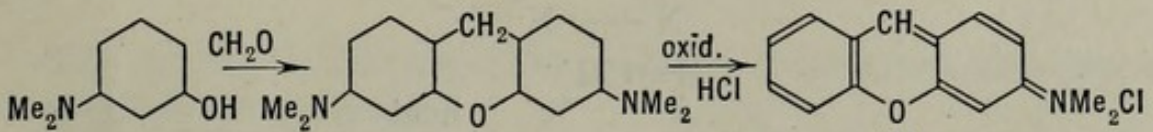


acridine does to anthracene. It occurs in coal tar and can be made by heating formaminodiphenyl, benzylidene aniline or N-Me-carbazole. The tendency to form the conjugated pyridine ring is notable.

**Xanthene,** m. 100°, b. 315°

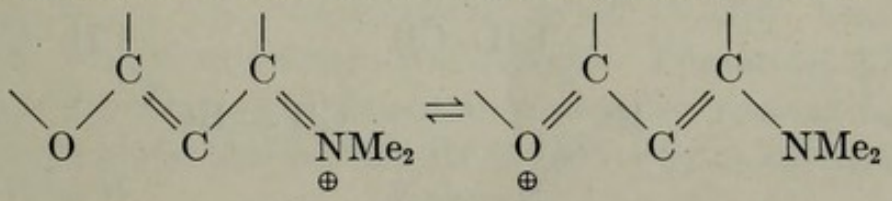


**Xanthone** is the 9-keto compound. *Euxanthone*, 1,7-dihydroxyxanthone occurs as a glucoside in mango leaves. *Pyronine*, formorhodamine, (I), is made from formaldehyde and *m*-dimethylaminophenol.

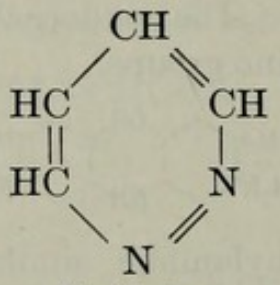


(I)

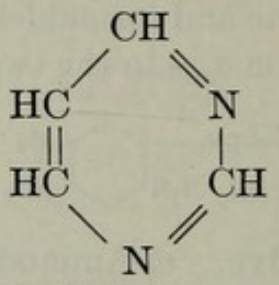
It is in equilibrium with the corresponding oxonium salt



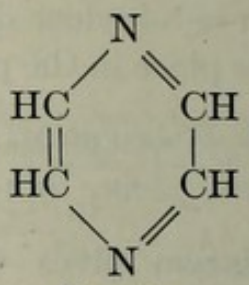
## *E.* The Diazines



Pyridazine
b. 208°

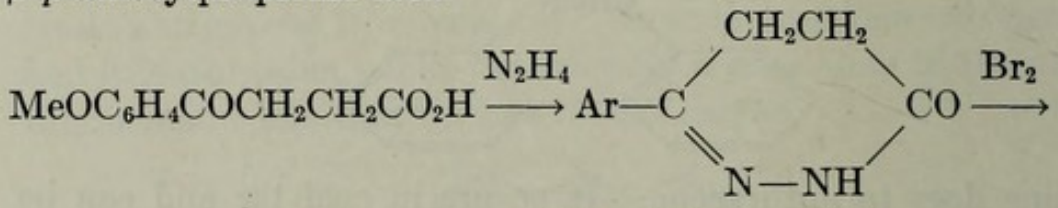


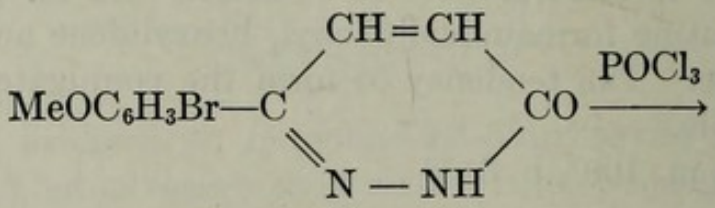
Pyrimidine
m. 22°, b. 124°

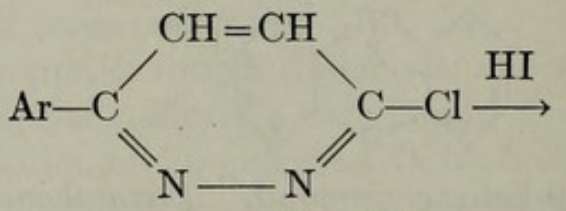


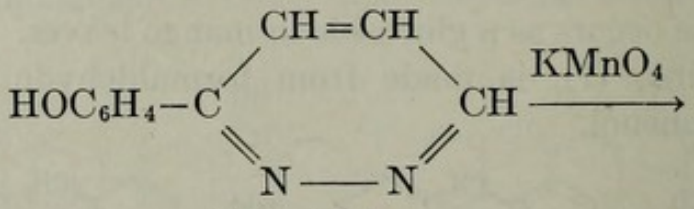
Pyrazine
m. 47°, b. 118°

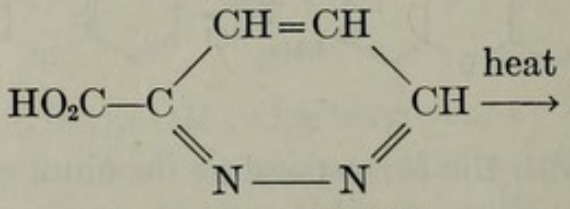
The preparation of *pyridazine* involves the following steps starting with anisole, succinic anhydride and $AlCl_3$ to give *β-p*-anisoylpropionic acid.

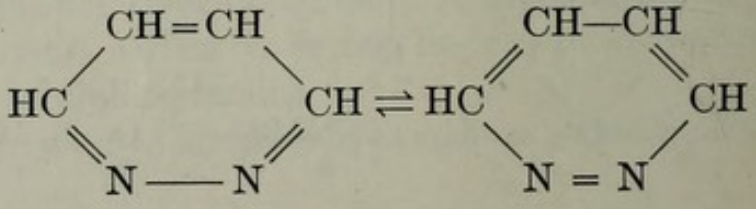






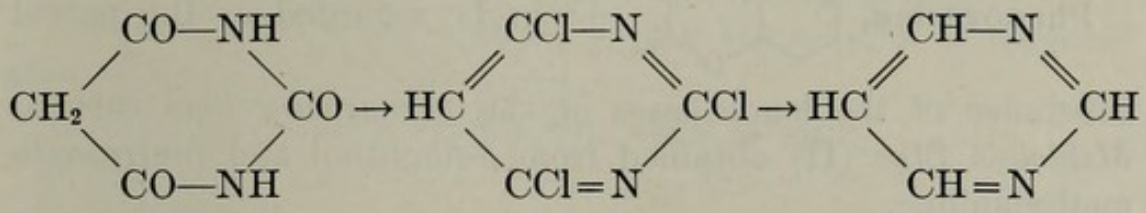




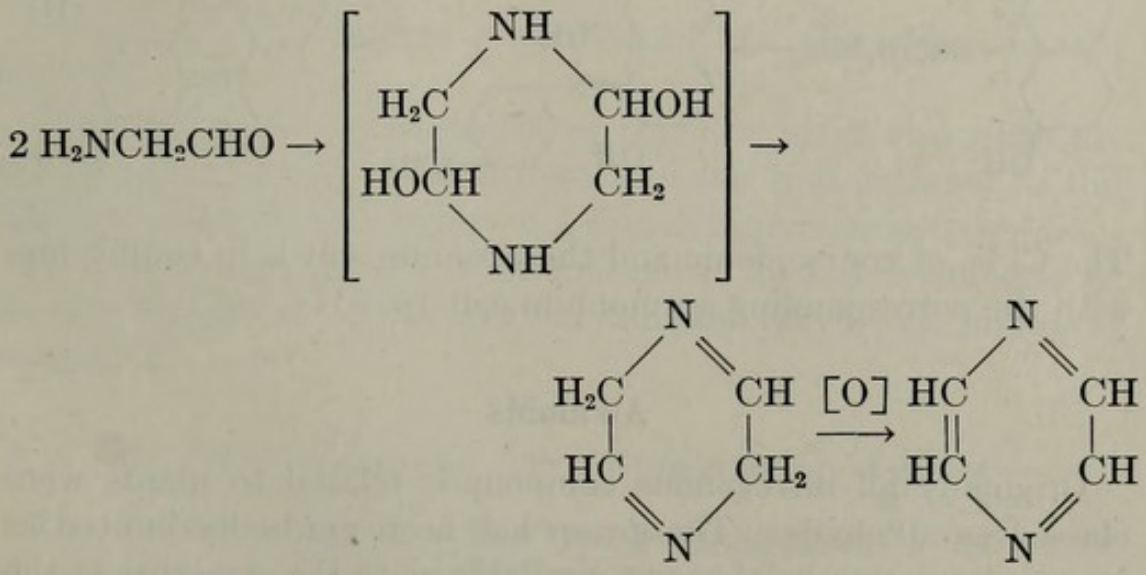


Many of these reactions serve to emphasize the analogy of pyridazine to pyridine and to illustrate its aromatic nature. Its surprisingly high boiling point is like those of pyrazole (188°) and imidazole (256°) rather than those of its isomers.

**Pyrimidine** is related to the purines and their oxygen derivatives such as uric acid and the barbituric acids (p. 528). It can be prepared by the action of Zn dust and water on the 2,4,6-$Cl_3$-derivative obtained from barbituric acid and $POCl_3$




**Pyrazine** can be made from its carboxylic acids and by oxidation of aminoacetaldehyde with $HgCl_2$ and a base.

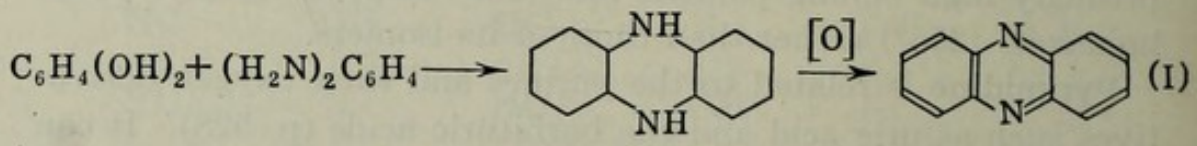



The last step is like that of the oxidation of dihydro derivatives of acridine and anthracene.

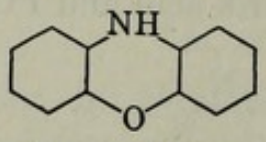
**Piperazine,** diethylenediimine, hexahydro-pyrazine, m. 104°, b. 145°, is made from ethylene dichloride and ammonia.

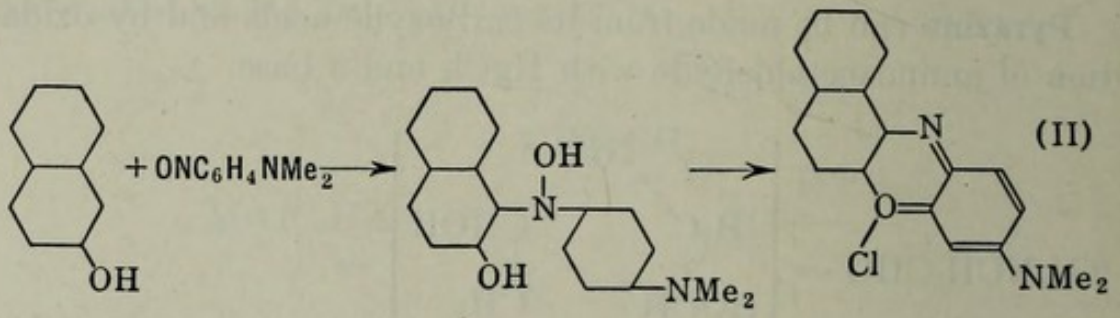
*Quinoxaline,* 2,3-benzopyrazine, m. 30°, b. 226°, can be made from *o*-phenylene diamine and glyoxal. *Phenazine,* (I) 2,3,5,6-dibenzpyrazine, m. 171°, is obtained as yellow crystals by heating nitrobenzene, aniline and NaOH at 140° or by oxidizing the color-

less dihydro compound obtained by heating pyrocatechol and *o*-phenylene diamine.




*Phenazine dyes* contain OH or $NH_2$ groups.

**Phenoxazine,**  can be regarded as the parent substance of the leuco bases of the *phenoxazine dyes* such as *Meldola's Blue* (II) obtained from β-naphthol and *p*-nitrosodimethylaniline.




The Cl is, of course, ionic and the oxonium salt is in equilibrium with the corresponding ammonium salt (p. 917).

## Alkaloids

Originally all nitrogenous compounds related to plants were classed as alkaloids. The group has been gradually limited as more information has become available as to the structure of the individual compounds. The alkaloids are mainly complex basic compounds which occur in plants as salts with organic hydroxy acids such as malic, citric, tannic and quinic acids.

Simple alkaloids such as coniine and nicotine contain only C, H and N and are volatile. The majority also contain oxygen and are crystalline. Most of them are tertiary amines. All are optically active.

The alkaloids are apparently built up by relatively simple re-

actions involving α-H atoms, carbonyl, amino and hydroxyl groups, including ring formation (Robinson, Rep. 1917, 135; 1919, 155).

Alkaloids give precipitates with reagents such as phosphomolybdic acid, potassium mercuric iodide solution, $KI_3$ solution and tannin. Much knowledge on the structure of individual alkaloids has been achieved by a great variety of processes including the following:—

1. Acetylation to give the number of *hydroxyl* groups.
2. Suitable treatment with HI to give the number of *methoxyl* groups (Zeisel) and *NMe* groups.
3. Determination of $-NH_2$ and $=NH$ groups.
4. Hydrolysis.
5. Oxidation.
6. Exhaustive methylation.
7. Degradation to more stable substances by heating with alkalies or with zinc dust.

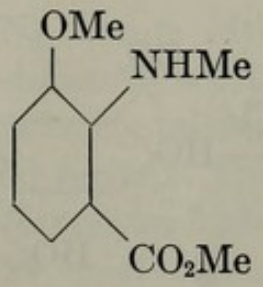
Formulas and physical properties of the alkaloids. Lange, 462–75.

The simpler alkaloids consist of one ring or of two rings attached as in diphenyl. In a few cases the N is external to the ring but usually it forms part of a ring as in pyrrole and pyridine.

**Aconitine,** $C_{34}H_{45}O_{11}N$, is exceptional in that it is an ester of *aconine* which is apparently an aminopolyhydroxy aliphatic compound.

### *A.* Derivatives of Aryl Substituted Amines

The simplest alkaloid of this type is *damascenine*, a derivative of anthranilic acid (Rep. 1912, 154; 1916, 157).




It has narcotic properties.

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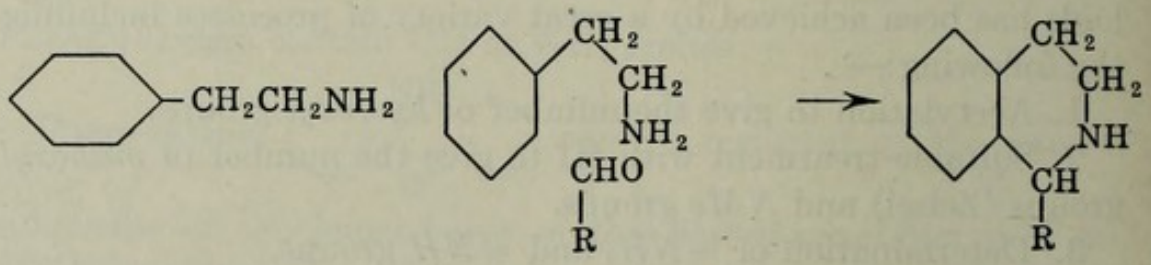
A benzyl amine derivative is *capsaicin*, the active principle of paprika. It is the vanillyl amide of a decylenic acid, 4-(OH)-3(OMe)-$C_6H_3CH_2NHCO(CH_2)_4CH=CHCHMe_2$.

β-Phenylethylamine derivatives occur as such in important alkaloids and serve as building units for the numerous isoquinoline alkaloids.




**Tyramine,** β-*p*-hydroxyphenylethylamine,

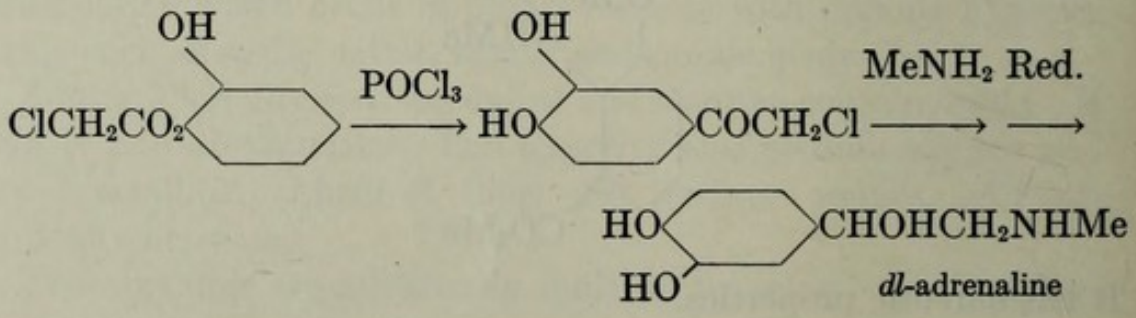
$$HOC_6H_4CH_2CH_2NH_2,$$

m. 161°, forms in the decay of proteins containing tyrosine. It has been synthesized. *Hordenine* (anhaline), m. 118°, is its $NMe_2$ derivative. *Mescaline* is 3,4,5-trimethoxyphenylethylamine, $(MeO)_3C_6H_2CH_2CH_2NH_2$. *Ephedrin* (I) m. 40°, occurs in laevorotatory form. The *dl*-form has been synthesized in a variety of ways. One of the simplest and best is by the catalytic reduction of phenyl methyl diketone in presence of methylamine.

$$PhCOCOMe + MeNH_2 \xrightarrow{+H_2} \underset{\textit{dl}\text{-ephedrin}}{PhCHOHCH(NHMe)Me} \quad (I)$$

**Pseudoephedrin,** m. 118°, differs from its stereoisomer in the configuration of the α-carbon.

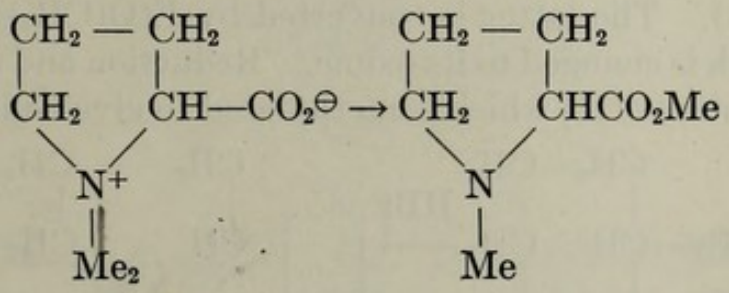
**Adrenaline,** suprarenin, the hormone of the suprarenal glands, has been synthesized as follows, starting with pyrocatechol and chloroacetyl chloride



Tartaric acid is used to separate the *d*- and *l*-forms. The latter is the natural form and is some fifty times as effective in raising the blood pressure. The *d*-form is racemized by heating and the resulting *dl*-mixture is further separated.

### *B.* Derivatives of Pyrrole

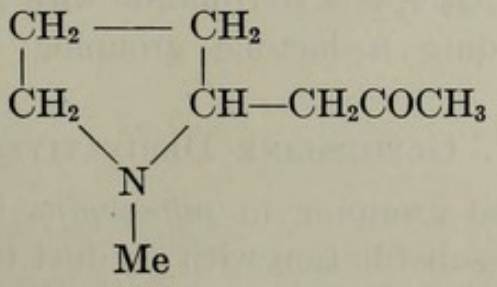
**Stachydrine** (I), m. 235°, is the betaine of *hygric acid*, N-methylpyrrolidine-α-carboxylic acid. Distillation gives the methyl ester.



(I)

**Betonicine,** dec. 244°, and *turicine*, m. 249°, are stereoisomers of 4-OH-stachydrine.

**Hygrine,** $C_8H_{15}ON$, is N-Me-α-pyrrolidylacetone

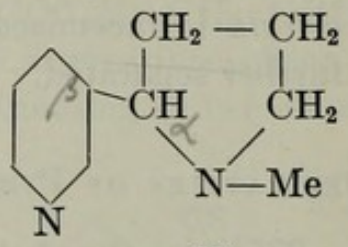


Oxidation gives hygric acid.

**Cuskhygrine,** $C_{13}H_{24}ON_2$, occurs with hygrine but is readily separated by means of its difficultly soluble nitrate. It is believed to be a disubstituted acetone containing two N-Me-α-pyrrolidyl groups instead of one as in hygrine. The substitution takes place αα-rather than αα′-. It forms two hydrazones (Rep. 1920, 126).

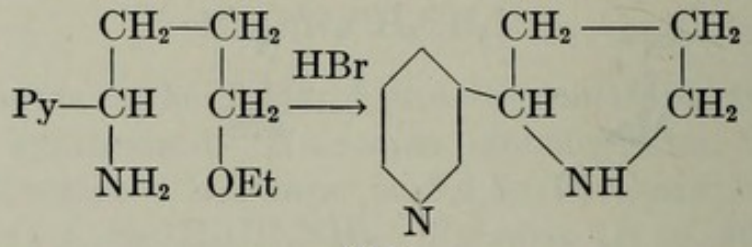
**Nicotine,** $C_{10}H_{14}N_2$, the chief alkaloid of tobacco, is α-(β-pyridyl)-N-Me-pyrrolidine, (II) b. 247°. Suitable oxidative deg-

radations give pyridine-$\beta$-carboxylic acid (nicotinic acid) and N-Me-pyrrolidine-$\alpha$-carboxylic acid, (Hygric acid).



(II)

Of several nicotine syntheses only one will be given. This is from pyridine through its $\beta$-sulfonic acid and $\beta$-cyano compound (Craig 1933). The latter is converted by $EtO(CH_2)_3MgBr$ to a ketone which is changed to its oxime. Reduction and ring closure give nornicotine (III) which is methylated to give *r*-nicotine.



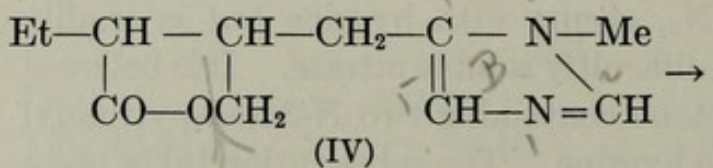
(III)

**Myosmine** is (III) with two less H in the pyrrolidine ring (Späth 1936).

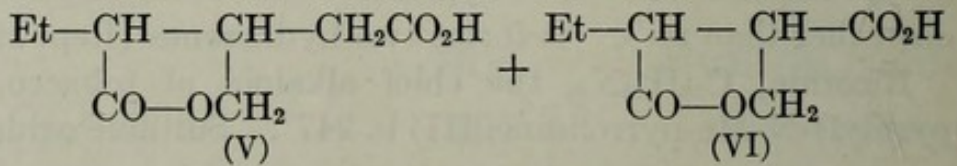
**Carpaine,** $C_{14}H_{25}O_2N$, is a pyrrolidine with an $\alpha$-side chain of 10 carbons including a lactone grouping. Oxidation gives suberic acid.

### *C.* Glyoxaline Derivatives

The fundamental grouping in *pilocarpine* (IV), $C_{11}H_{16}N_2O_2$, m. 34°, is shown by distillation with Zn dust to form 1-Me- and 1,5-$Me_2$-glyoxoline. Oxidation gives homopilopic (V) and pilopic acids (VI)



(IV)

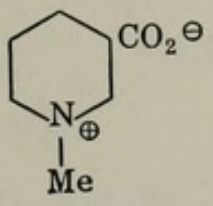


(V) (VI)

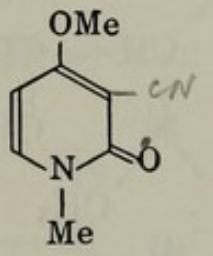
Pilocarpine has been synthesized (Preobrashenski 1935–6).

*Derivatives of Pyridine and Piperidine*

**Trigonelline** is the betaine of pyridine-β-carboxylic acid

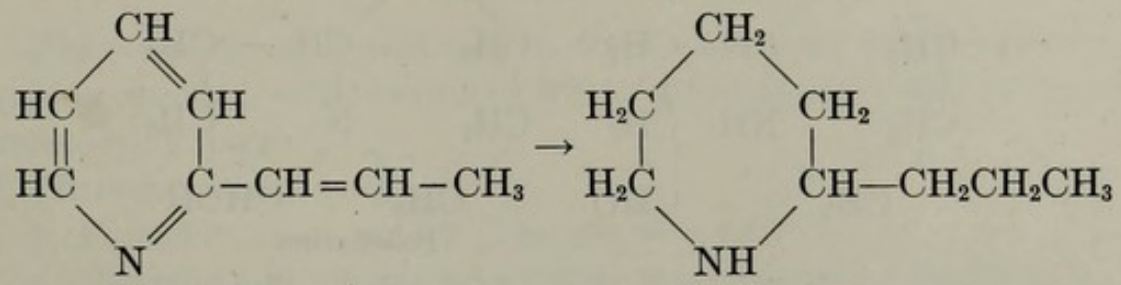



**Ricinine,** of the castor bean is N-Me-3-cyano-4-methoxy-α-pyridone (Rep. 1923, 153).




Poison hemlock contains various alkaloids including coniine, its N—Me derivative, γ-coniceine, δ-coniceine, conhydrine and pseudoconhydrine.

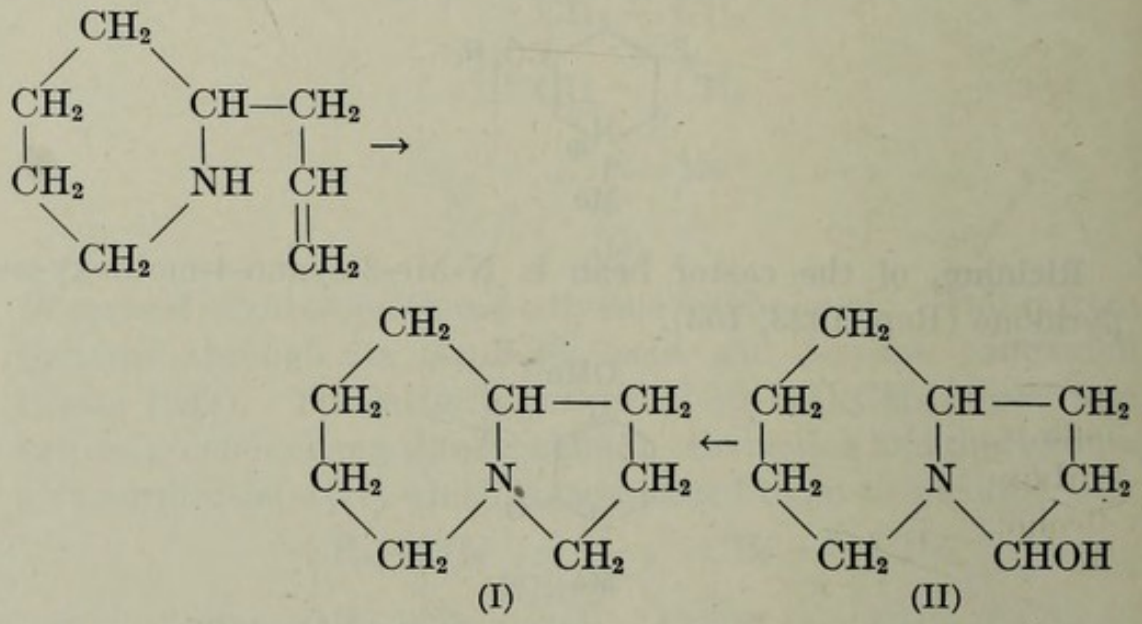
**Coniine** is α-*n*-propylpiperidine, b. 167°. Reduction by HI at high temperature gives *n*-octane and oxidation gives pyridine-α-carboxylic acid. The synthesis is easy by the action of Na and alcohol on α-propenylpyridine obtained from α-Me-pyridine and MeCHO.




Coniine

The ready reduction of even the side chain is a good example of the activating effect of the N. Heating with zinc dust gives α-propylpyridine or *conyrine.* Synthetic *dl*-coniine can be resolved by means of *d*-tartaric acid. *γ-Coniceine,* b. 174°, is Δ2-2-propyl-tetrahydropyridine. *δ-Coniceine* (I) is a fusion of a piperidine and a pyrrolidine ring (Rep. 1909, 102). It can be regarded as the cyclization product of an allylpiperidine or the

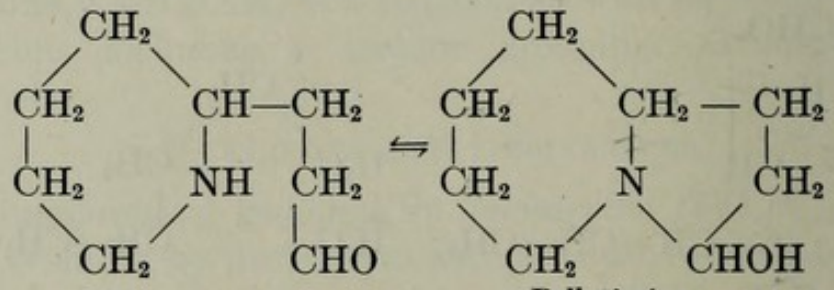
reduction product of the cyclic form (II) of the aldehyde pelletierine.



(I) (II)

**Conhydrine** has an $\alpha$-hydroxyl group in the side chain of coniine whereas *pseudoconhydrine* is 5-OH-coniine.

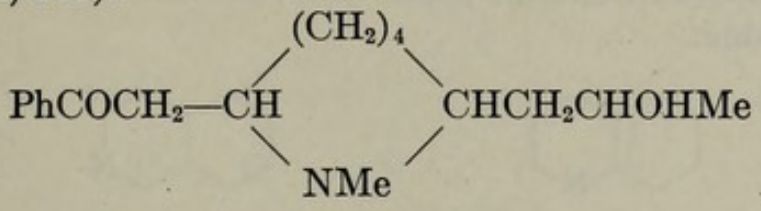
**Pelletierine** (II) and **isopelletierine** have $-CH_2CH_2CHO$ and $-CH_2COCH_3$ respectively in place of the propyl group of coniine. Since pelletierine does not react with nitrous acid it is believed to exist in a cyclic form (Rep. 1918, 109).



Pelletierine

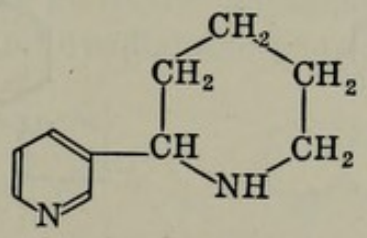
**Pseudopelletierine** (p. 935) has a $-CH_2COCH_2-$ bridge between the $\alpha$-positions of N-Me-piperidine and thus contains a fusion of a piperidine and a $\gamma$-piperidone ring. *Lobeline* (lobelidine) is an N-Me-piperidine substituted in one $\alpha$-position by $PhCOCH_2-$ and in the other by $PhCHOHCH_2-$. Related are *lobelanine* and *lobelanidine* which have respectively 2 $PhCOCH_2-$ and 2 $PhCHOHCH_2-$ in the $\alpha$-positions. The corresponding *nor*-compounds contain a free NH group (Rep. 1929, 169).

*Lobinine* is related to these alkaloids but has a 7-membered ring (Rep. 1931, 165).




The betel nut (areca-nut) contains *guvacine*, 1,2,5,6-$H_4$-pyridine-3-carboxylic acid, m. 293°, *arecaine* or *arecaidine*, its NMe compound, m. 232°, and their methyl esters, *guvacoline* and *arecoline* respectively.

**Anabasine** is β-(α-piperidyl)-pyridine (Orekhov 1934)




**Piperine,** m. 128°, the piperidide of piperic acid, occurs in pepper, 3,4-$(CH_2O_2)C_6H_3CH=CHCH=CHCONC_5H_{10}$. Other pungent materials such as *capsaicin*, *spilanthol* and *pellitorine* have also been shown to be substituted amides of unsaturated acids (Rep. 1930, 202).

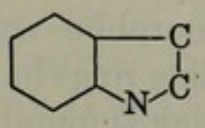
## *E.* Complex Alkaloids

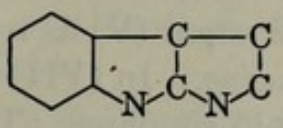
*These contain condensed ring systems.* In some, the N appears in only one ring, while in others it functions as part of two or three heterocyclic rings.

I. Nitrogen in one ring.

1. Fusion of rings with 2 C atoms in common.

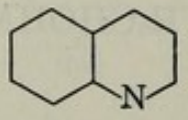
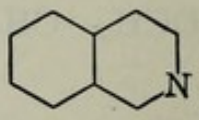
*a.* Benzene and pyrrole give indole and isoindole. Strychnine, and brucine are related to the former. A benzene ring and two pyrrolidine rings form the parent substance of eserine.



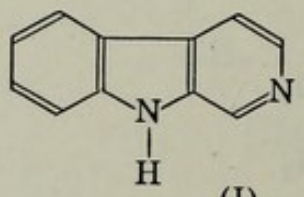




*b.* To benzene and pyridine, correspond quinoline and isoquinoline. From the former are derived the cinchona alkaloids and to

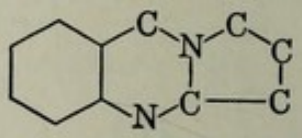
the latter are related many important groups of alkaloids including the anhalonium group, papaverine, narcotine, berberine and even morphine.

*c.* A fusion of the benzene, pyrrole and pyridine rings corresponds to *harmane* (I) the parent substance of harmine and harmaline. Fusion of a benzene, a pyrimidine and a pyrrole ring gives the basis of vasicine (II).



(I)



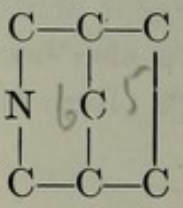
(II)

2. Fusion of rings with 3 C atoms in common. Using 5- and 6-membered rings the following might be possible.

(I)

(II)

(III)



(IV)

(V)

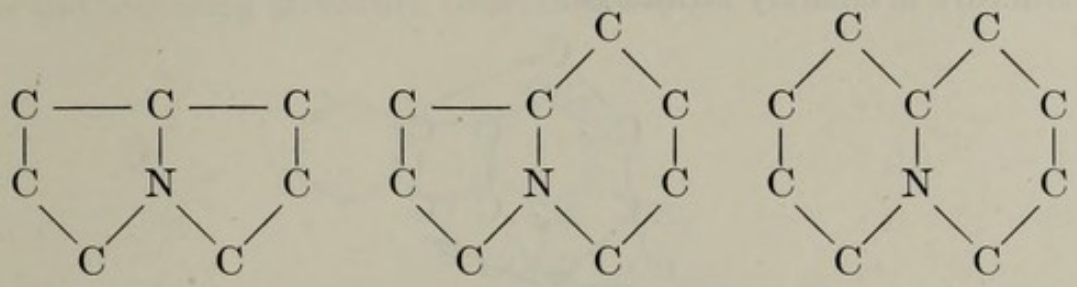
(VI)

(VII)

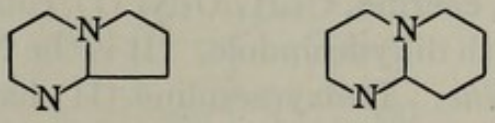
Only (I) involves any considerable strain. In (V) and (VI) there is no strain. System (V) as related to morphine and thebaine is called *mornuclidine.* In (VII) two pyridine rings have the $\gamma$- and both $\beta$-carbons in common. This grouping is found in sparteine, cytisine and anagyrine.

II. Nitrogen common to two or three rings.

1. Fusion with N and 1 C common to both rings.

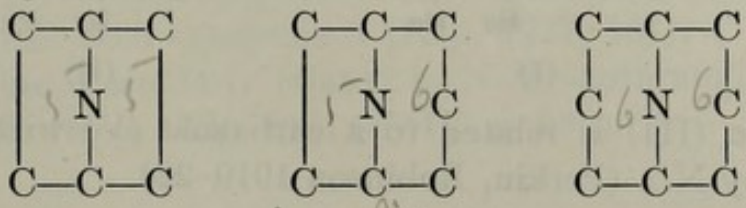


The second exists as δ-coniceine. Related to the last are lupinine, berberine, corydaline and sparteine. The first involves considerable strain and the last none at all. The fusion of *two* N-rings in similar ways gives the combinations found in vasicine and in rutaecarpine and evodiamine respectively.



2. Fusion with N and 2 C common to both rings. This can happen in two ways, the N having either two or three of its valences involved in ring formation.

*a*. Two valences of N in ring combination.



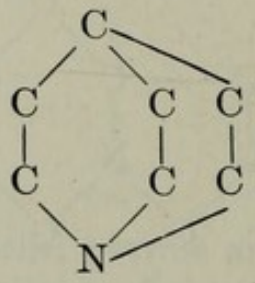
Again, a condensation of two pyrrolidine rings is apparently impossible but a combination of a pyrrolidine and a piperidine ring involves little strain and gives such important alkaloids as atropin and cocaine. Two piperidine rings can be fused without any strain giving the parent substance of pseudopelletierine.

*b*. Three valences of N in ring combination. None of the possibilities is found in known alkaloids.

3. Fusion with N and 3 C common to two rings.

In the *quinuclidine* portion of such important alkaloids as cinchonine and quinine the N forms part of three condensed

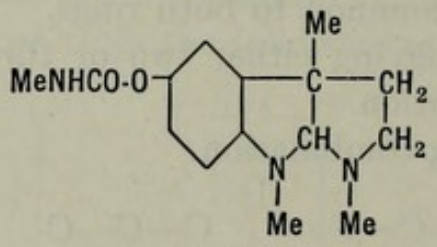
piperidine rings which have it and the γ-C in common. This structure is entirely strainless.



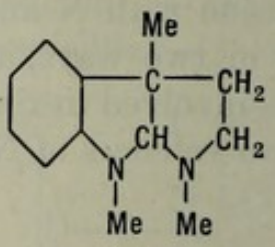
### *F.* Alkaloids Containing Pyrrole Rings Fused with Other Rings

The strychnine alkaloids belong to this class since they are related to indole. Because of their importance they will be considered separately.

**Physostigmine, eserine,** $C_{15}H_{21}O_2N_3$ (I), contains a pyrrolidine ring condensed with dihydroindole. It is the N-Me-carbamate of the phenol, *eseroline.* Deoxyeseroline (II) has been synthesized from dimethyloxindole (Julian 1934).

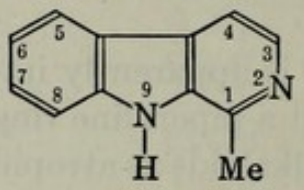


(I)

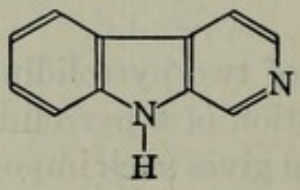


(II)

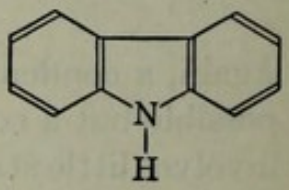
**Harmine** (III) is related to a carbazole (V) with the 2-CH replaced by N. (Perkin, Robinson 1919–22).



(III)

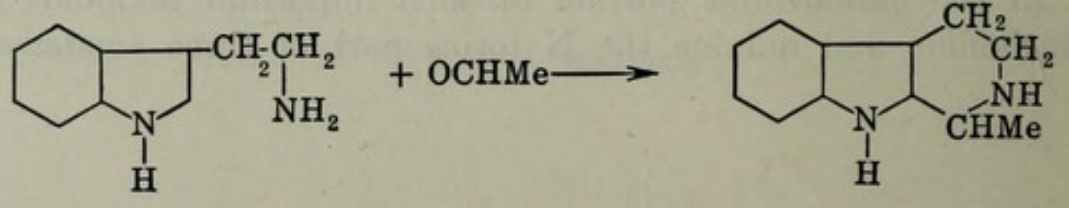


(IV)

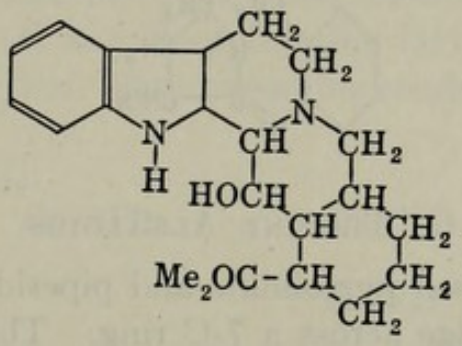


(V)

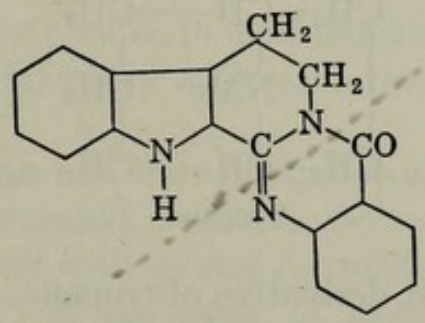
The parent substance is carboline or 2,9-pyrindole (IV). *Harmaline* is 3,4-dihydroharmine. Tetrahydroharmine can be prepared readily from acetaldehyde and 3-β-aminoethylindole at room temperature at pH 5–7 (Hahn 1934, Rep. 1934, 267).



**Yohimbine,** $C_{21}H_{26}O_3N_2$ is related to harmine and probably has the following structure (Scholz 1935)

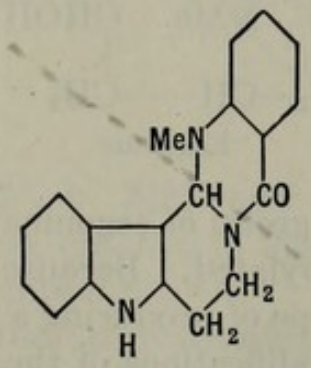


**Rutaecarpine** combines pyrrole, pyridine and pyrimidine rings with two benzene rings.



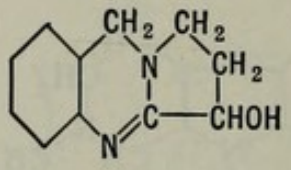
Hydrolysis gives anthranilic acid and 1-keto-1,2,3,4-$H_4$-carboline. The latter has been synthesized (Rep. 1927, 161).

**Evodiamine** is similarly related to N-Me-anthranilic acid and 3,9-pyrindole (Rep. 1921, 142) (cf. IV, p. 930).



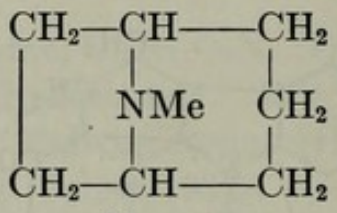
**Vasicine,** peganine, $C_{11}H_{12}ON_2$, contains a benzpyrimidine

nucleus fused through $C_2$ and $N_3$ with a pyrrolidine ring. (R. Robinson, Rev. Bio. 1935, 503; Adams 1935).




### *G.* Tropine Alkaloids

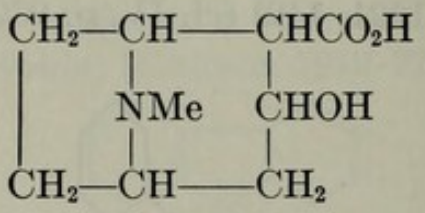
These contain fused pyrrolidine and piperidine rings with the N serving as a bridge across a 7-C ring. They can also be regarded as piperidine derivatives with a $-CH_2CH_2-$ bridge between the alpha positions.




Tropane

Tropine is the $\gamma-OH$ derivative of tropane.

Coca leaves contain cocaine, cinnamoyl cocaine, benzoyl ecgonin, and $\alpha$- and $\beta$-truxilline, all related to ecgonine (tropine carboxylic acid) and also *tropacocaine*, the benzoic ester of pseudotropine.

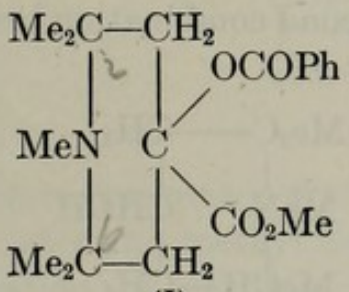



Ecgonine

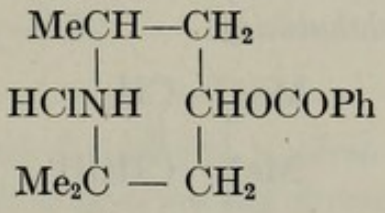
In *cocaine* the carboxyl group of ecgonine is methylated and the hydroxyl group is benzoylated. Because of its value as a local anesthetic and in the hope of producing a substitute which is not habit-forming, many modifications of the cocaine molecule have been made. $\alpha$-Cocaine, which has no anesthetic action, is made from tropinone by the cyanohydrin synthesis and thus has the $-OCOPh$ and $-CO_2Me$ groups both on the $\gamma-C$ of the piperi-

dine ring. Putting other alcohol groups in place of methyl in cocaine has little effect on its action. Very few acids besides benzoic acid give anesthetic compounds with ecgonine.

Alpha Eucaine (I) and Beta Eucaine (II) are made from triacetoneamine and from diacetoneamine condensed with acetaldehyde.




(I)

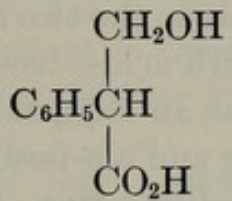



(II)

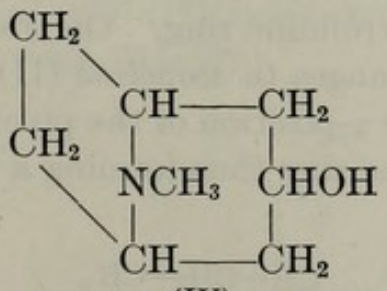
Useful substitutes for cocaine in local anesthesia are the *p*-aminobenzoates of the alkamines such as novocaine (procaine) and Butyn.

**Cinnamoyl cocaine** has the cinnamoyl group in place of the benzoyl group in cocaine. $\alpha$- and $\beta$-Truxilline are esters of ecgonine methyl ester with $\alpha$- and $\beta$-truxillic acids.

**Atropin,** m. 115°, is the ester of *dl-tropic acid,* $\alpha$-phenylhydracrylic acid, m. 118°, (III) and tropine (IV).




(III)



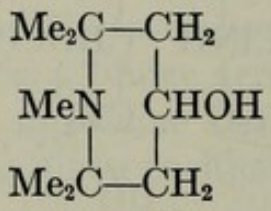

(IV)

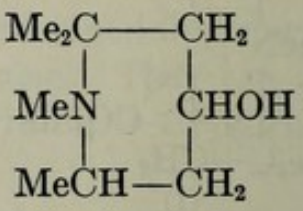
**Tropine** (IV), m. 63°, b. 233°, and *pseudotropine,* m. 108°, b. 241°, are stereoisomers, differing in the configuration of the OH group. Both are optically inactive.

**Tropinone** is the ketone corresponding to (IV). It has been synthesized from succinic and acetone dicarboxylic esters and methylamine, a remarkable example of ring closure. *Tropeines* are esters of tropine. Certain of these have mydriatic action (dilation of pupil of the eye) similar to that of atropine. *Homa-*

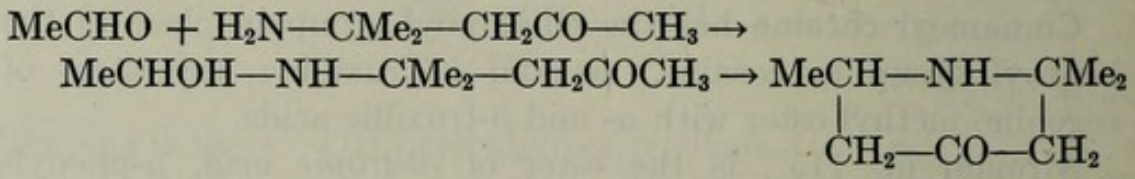
*tropine* and *pseudoatropine* are tropine esters of mandelic acid and atrolactic acid respectively. *Hyoscyamine*, m. 108°, is the tropine ester of *l*-tropic acid.

Substitutes for atropine have been made not only from tropine but from synthetic substances containing somewhat similar groupings. Thus the mandelic esters of the following two substances have mydriatic action, the second combination being used as *Euphthalmine.*



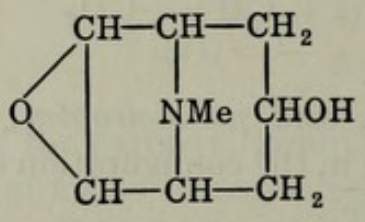


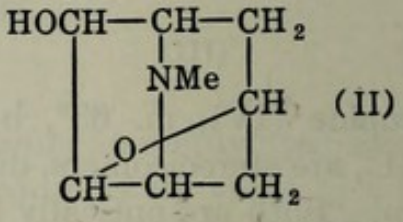
The first is made by methylating and reducing triacetonamine while the second is made by similar processes on the condensation product of acetaldehyde and diacetoneamine.



**Scopolamine,** hyoscine, is the tropic ester of *scopine*, (I) a tropine molecule with an epoxy group between the two $\beta$-positions of the pyrrolidine ring. On treatment with acids, bases or heat, this rearranges to *scopoline* (II) which has an oxygen bridge between the $\gamma$-position of the piperidine ring and a $\beta$-position in the pyrrolidine ring thus forming a tetrahydrofuran ring (Rep. 1922, 160)

(I)



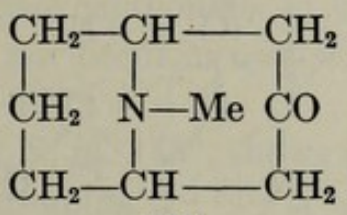


(II)

### *H.* Alkaloids Containing a Fusion of Two Piperidine Rings

*Pseudopelletierine* (III), N-Methylgranatonine, may be regarded as a cyclo-octanone ring with a symmetrical N-Me bridge

or as a fused structure combining an N-Me-piperidine and an N-Me-$\gamma$-piperidone, the N-Me and the two $\alpha-$C atoms being common to both rings.

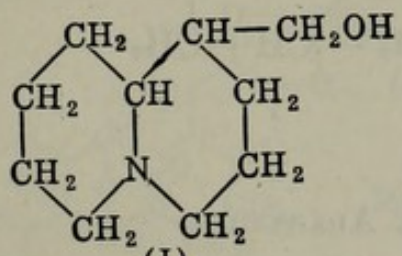


(III)

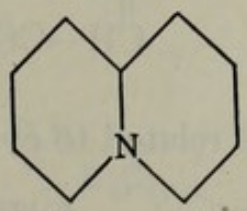
It has been synthesized from glutaric dialdehyde, acetone dicarboxylic ester and methyl amine. It is also readily obtained by condensation of phenylacetaldehyde, acrolein, acetone dicarboxylic acid and methyl amine in dilute solution below room temperature (Blount 1936). *Isopelletierine*, instead of having a $-CH_2COCH_2-$ bridge across the $\alpha$-positions of an N-Me piperidine, simply has the group $-CH_2COCH_3$ in one $\alpha$-position of piperidine and is thus related closely to coniine.

## *I.* Lupine Alkaloids

These contain two piperidine rings with the N and one $\alpha-$C in common (II). *Lupinine* (I) m. 69°, has not been synthesized but the parent substance, *norlupinane* (II) has been made in several ways (Karrer 1928, Rep. 1933, 231–239).



(I)

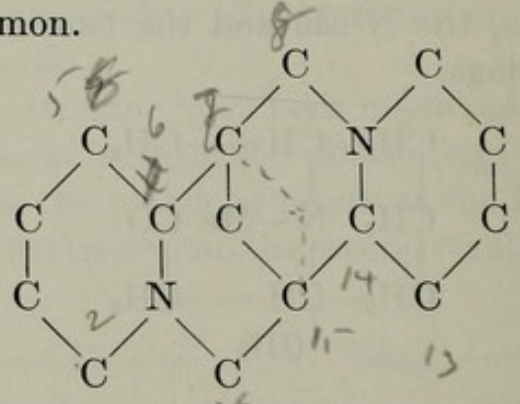


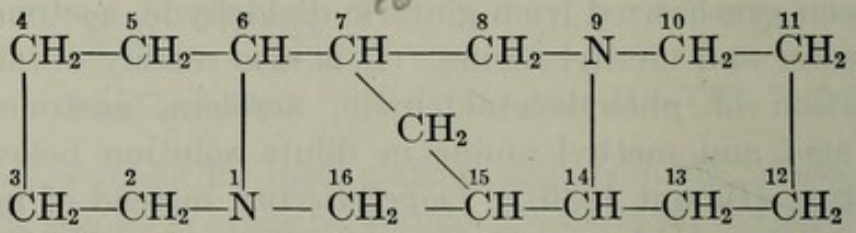
(II)

**Sparteine** and related alkaloids contain the lupinane system (II) (Ing. 1933; Clemo, 1933; Rep. 1934, 270; R. Robinson, Rev. Bio. 1935, 498; Couch 1936).

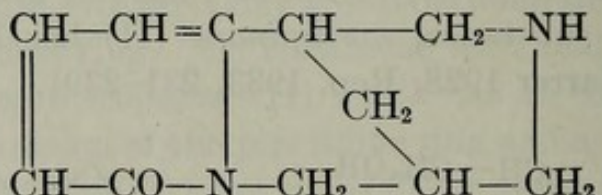
**Sparteine,** $C_{15}H_{26}N_2$, b. 326°, consists of a four-ring system each half of which contains a lupinane grouping of two piperidine rings with the N and an alpha carbon in common. The middle of the

system contains two piperidine rings with the γ- and both β-carbons in common.





**Lupanine,** $C_{15}H_{24}ON_2$, is 2-ketosparteine and *anagyrine*, $C_{15}H_{20}ON_2$, is 2-keto-3,4,5,6-tetra*de*hydrosparteine. Catalytic reduction of anagyrine gives lupanine while further reduction gives sparteine. *Monolupine*, $C_{16}H_{22}ON_2$, is a C—Me anagyrine (Couch 1936). *Cytisine*, $C_{11}H_{14}ON_2$ (III) (Ing 1933, Rep. 1933, 235; Späth 1936) differs from anagyrine by not having carbons 10–13.

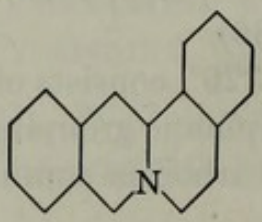


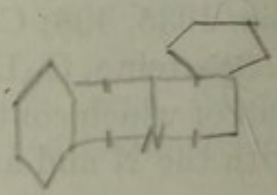
(III)

*Matrine* is related to cytisine.

### *J.* Berberine Alkaloids

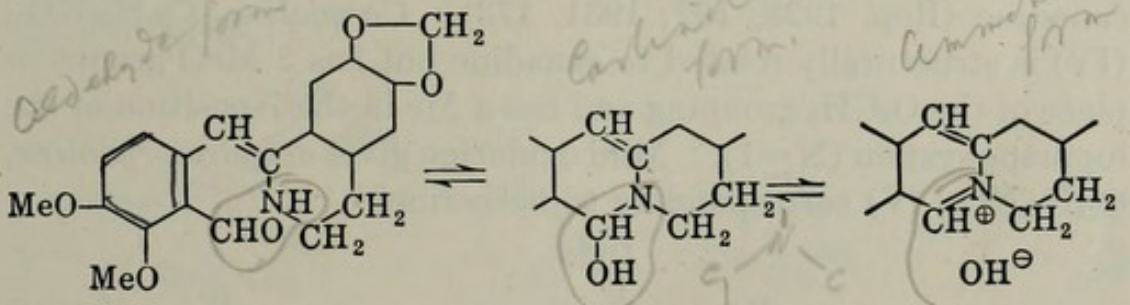
These contain the lupinane system (p. 935 II) with two benzene rings fused, one in linear and the other in angular combination. The skeleton is as follows:



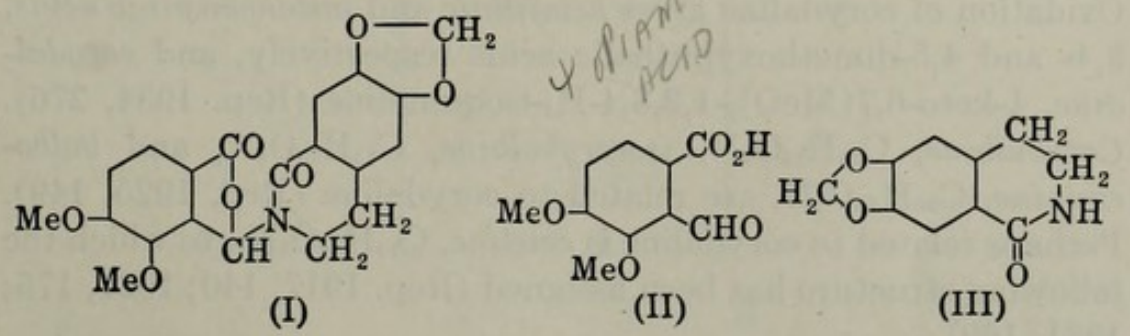


They can also be regarded as di-isoquinoline combinations in which the N is common to both isoquinoline groups and one carbon serves as $C_1$ and $C_3$ respectively in the two systems. The corresponding *paraberberine* compounds in which the four rings are linearly combined do not occur in nature and are very difficultly prepared (Rep. 1926, 170).

**Berberine,** $C_{20}H_{19}O_5N$, m. 145°, shows a peculiar tautomerism. Since it contains the grouping O—C—N—C it can also react in an aldehyde form. It moreover acts as a quarternary ammonium compound. These relations are shown in the following formulas for berberine



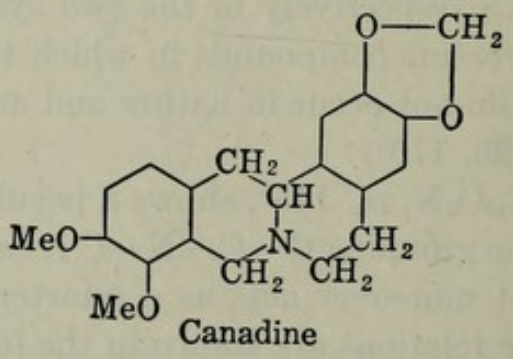
Mild oxidation converts the CHOH to CO giving oxyberberine. Another product involves the breaking of the double bond to give a carboxyl and a ketone. The former gives a lactone with the OH forming *berberal* (I). This on hydrolysis gives *pseudo-opianic acid* (II) and *noroxyhydrastinine* (III)



(I) (II) (III)

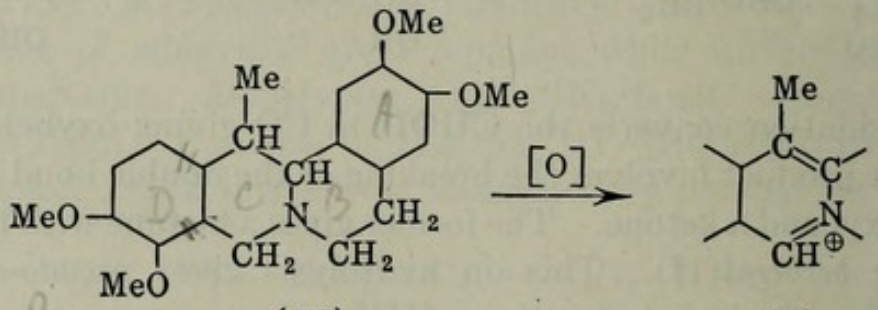
**Protoberberine** is the berberine molecule without substituents in the aromatic rings. *Coptisine* is 2,3,9,10-bismethylenedioxy-protoberberine (Rep. 1926, 167). *Palmatine* similarly has four —OMe groups (Rep. 1927, 168; 1929, 178). *Canadine,* $C_{20}H_{21}O_4N$, can be made by reduction of berberine and is called

tetrahydroberberine. It contains no double bond nor hydroxyl in the lupinane system. Oxidation gives berberine.



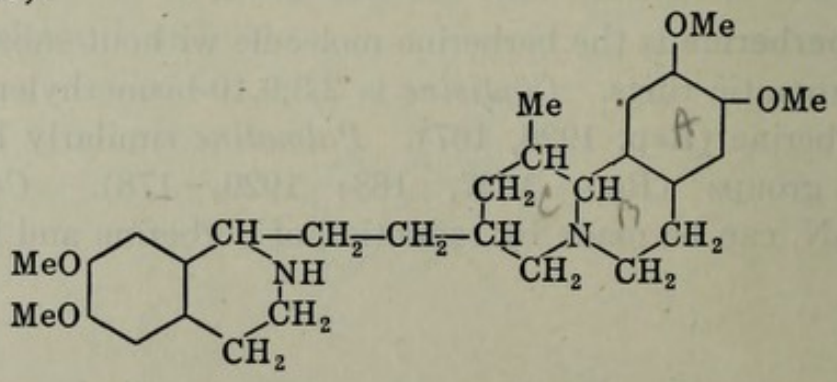

Canadine

**Isocorypalmine, sinactine** and **$H_4$-berberrubine** are related to canadine (Rep. 1928, 192; 1931, 173). *Corydaline*, $C_{22}H_{27}NO_4$, (IV) is structurally related to canadine but has 2 MeO groups in place of the $O_2CH_2$ grouping and has a Me in the 7-position of the lupinane system (N = 1). Mild oxidation gives *dehydrocorydaline*, $C_{22}H_{25}NO_5$, (V) corresponding to berberine.




(IV) (V)

Oxidation of corydaline gives *hemipinic* and *metahemipinic acids*, 3,4- and 4,5-dimethoxyphthalic acids respectively, and *corydaldine*, 1-keto-6,7(MeO)$_2$-1,2,3,4-$H_4$-isoquinoline (Rep. 1934, 276). *Corybulbine*, $C_{21}H_{25}O_4N$, *isocorybulbine*, $C_{21}H_{25}O_4N$, and *bulbocapnine*, $C_{20}H_{19}O_4N$, are related to corydaline (Rep. 1925, 149). Perhaps related to corydaline is *emetine*, $C_{29}H_{40}O_4N_2$, to which the following structure has been assigned (Rep. 1917, 140; 1927, 175; 1931, 169).

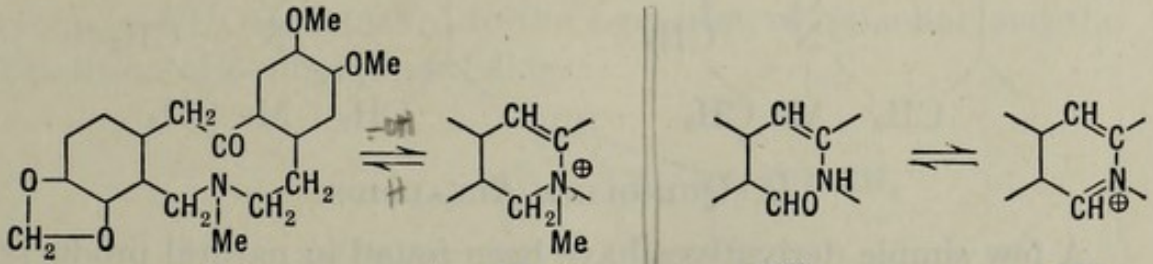


**Psychotrine,** $C_{28}H_{36}O_4N_2$, and **cephaeline,** $C_{28}H_{38}O_4N_2$, are related to emetine.

### *K.* Cryptopine Alkaloids

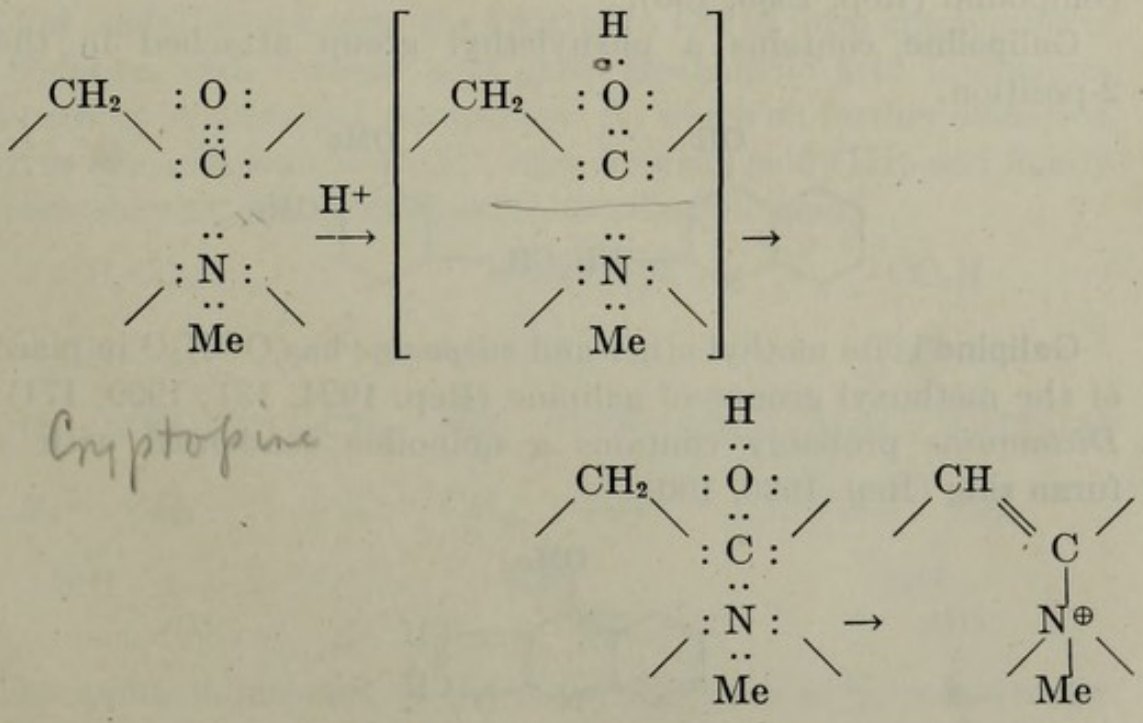
These contain a 10-membered ring such as would be obtained by breaking the bond between N and C in the middle of the lupinane section of the berberine molecule (Rep. 1926, 168).

**Cryptopine,** $C_{21}H_{23}NO_5$, m. 219° has formula (I) while *protopine,* $C_{20}H_{19}NO_5$, m. 208° differs from it only in having a methylene ether grouping in place of the two MeO groups. Acids cause ring closure to give salts of (II). This change is entirely analogous to the conversion of the aldehyde form of berberine (III) to a salt of (IV).

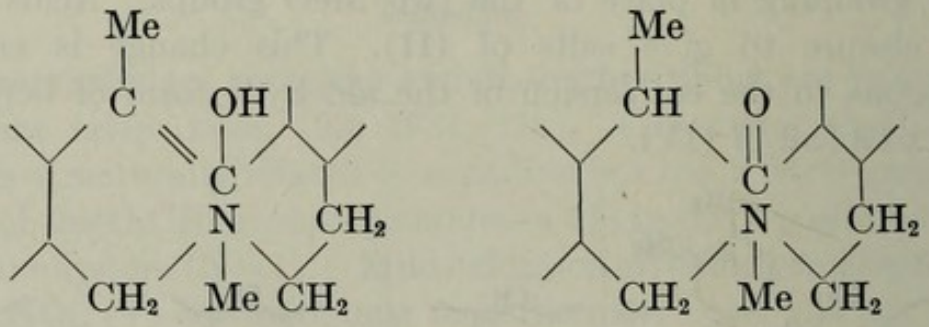



(I) (II) (III) (IV)

The mechanism of the action of $H^+$ ion is readily illustrated electronically. The addition of the proton to the oxygen of the



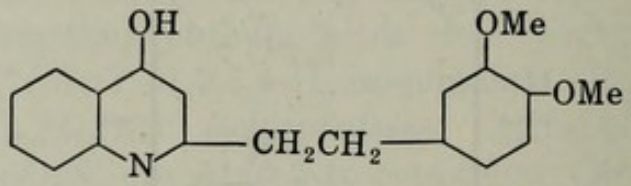
carbonyl group leaves its carbon with only 6 electrons. Since this carbon can readily approach the N in space it shares the open electron pair of the latter forming a new C—N linkage and leaving the N as a positive quarternary ammonium ion. *Corycavidine* is like cryptopine but with the $O_2CH_2$ and two OMe in opposite rings and a Me on the carbon between the ring and the CO group. *Corycavine* and *corycavamine* are enol and keto forms of a similar homolog of protopine. The central portions of their molecules have the following structures:



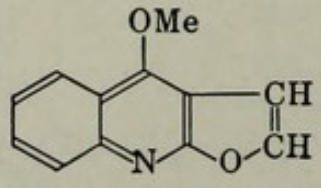

## *L.* Quinoline Alkaloids

A few simple derivatives have been found in natural products such as angostura bark which gives 2-*n*-amylquinoline, the corresponding 4-methoxy compound and even small amounts of quinoline and 2-Me-quinoline as well as the N-Me-2-keto-dihydro compound (Rep. 1930, 190).

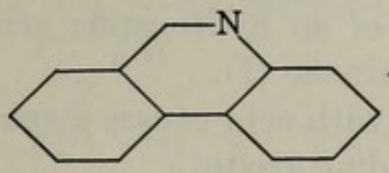
**Galipoline** contains a phenylethyl group attached in the 2-position.




**Galipine** is its methyl ether and *cusparine* has $OCH_2O$ in place of the methoxyl groups of galipine (Rep. 1924, 131; 1929, 171). *Dictamnine* probably contains a quinoline condensed with a furan ring (Rep. 1930, 190)



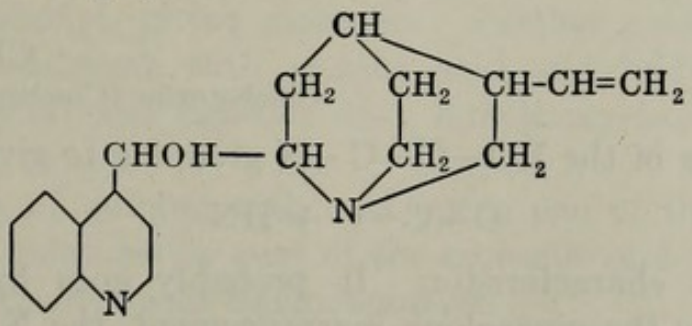
**Tazettine,** $C_{18}H_{21}O_5N$, is related to both quinoline and isoquinoline since it contains a phenanthridine skeleton (Rep. 1934, 276–7).



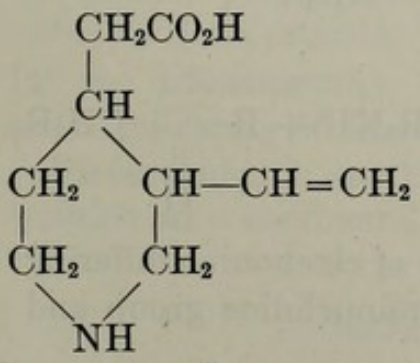
## *M.* Cinchona Alkaloids

These are the most important quinoline alkaloids although their properties are more dependent on the *quinuclidine* part of the molecule, a fusion of three piperidine rings, than on the quinoline portion.

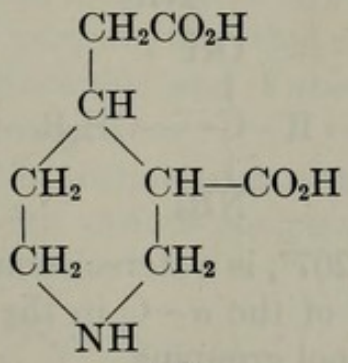
**Cinchonine,** $C_{19}H_{22}N_2O$, m. 264°, consists of a secondary alcohol group, $-CHOH$, attached to the 4-position of quinoline and the 2-position of 5-vinylquinuclidine.



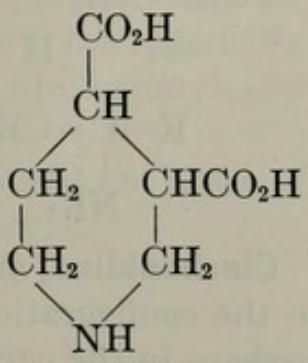
Mild oxidation converts the CHOH to CO to form *cinchoninone.* Oxidation with chromic acid gives cinchoninic acid (quinoline-4-carboxylic acid) and *meroquinene* (I) which on further oxidation gives *cincholoiponic acid* (II), then loiponic acid (III) and finally *cinchomeronic acid* (pyridine-3,4-dicarboxylic acid).



(I)



(II)

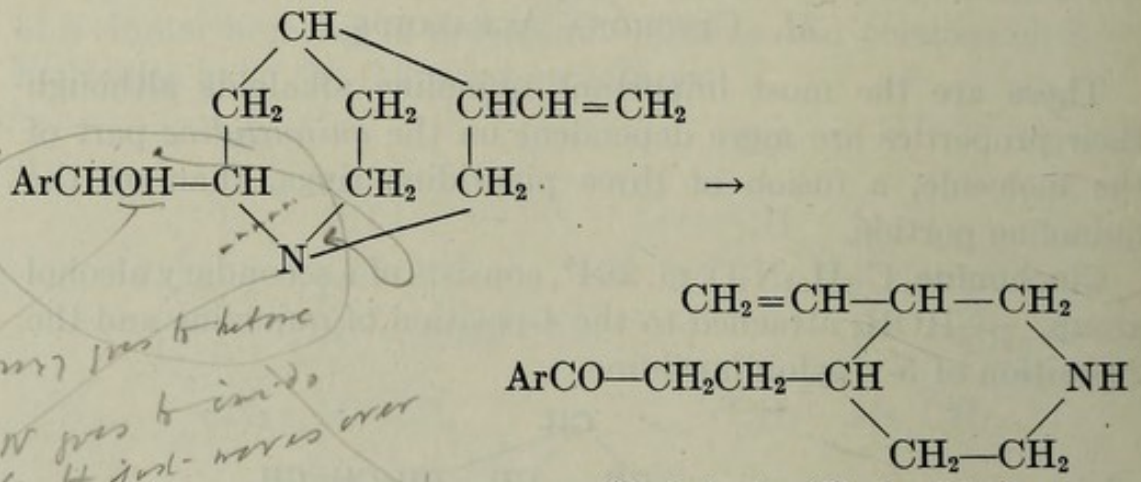


(III)

The quinuclidine part of the molecule can also be removed by

treating cinchoninone with amyl nitrite to form cinchoninic acid and the oxime of 5-vinyl-2-quinuclidone. The same product is obtained from cinchonine and from quinine (Rep. 1910, 136). It is really an amide of an hydroxamic acid and is hydrolyzed readily to give meroquinene (I).

Heating cinchonine with acid causes a splitting between the N and $C_2$ of the quinuclidine group.

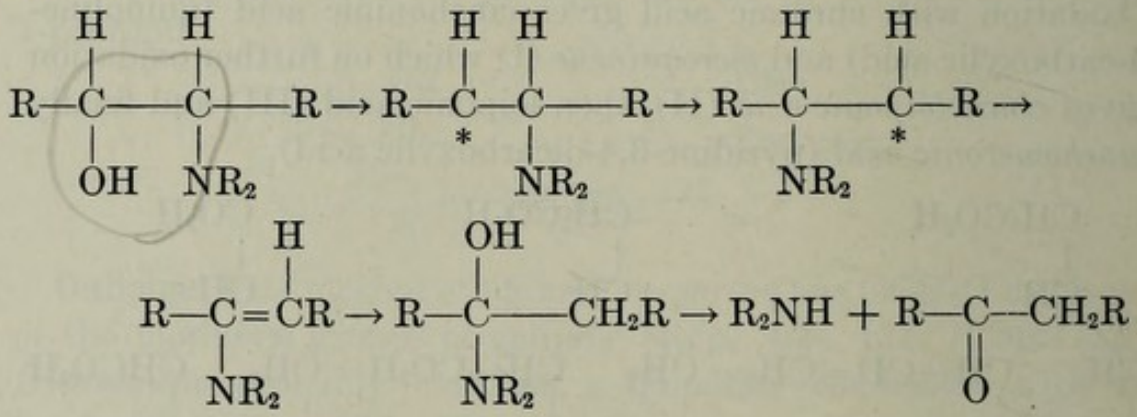



Cinchotoxine (Cinchonicine)

This breaking of the HO−C−C−N grouping to give

$$O=C-C + HN$$

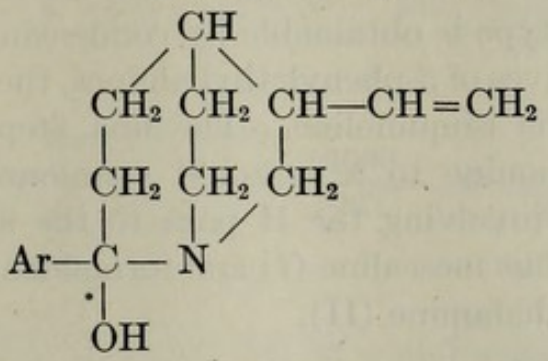
fragments is characteristic. It probably goes by the same mechanism as the pinacolone rearrangement, the N shifting instead of the $CH_3$.




**Cinchonidine,** m. 207°, is a stereoisomer of cinchonine differing in the configuration of the $\alpha$−C in the quinuclidine group and perhaps in the carbinol grouping.

**Hydrocinchonine,** m. 277°, and *hydrocinchonidine,* m. 229°, occur with cinchonine and are readily prepared by catalytic

reduction in which the vinyl group is changed to ethyl. *hetero-Cinchonine* is the result of the transfer of the linkage of $C_2$ from the quinuclidine N to the carbinol C with the widening of one piperidine to form a 7-ring (Rep. 1934, 273)



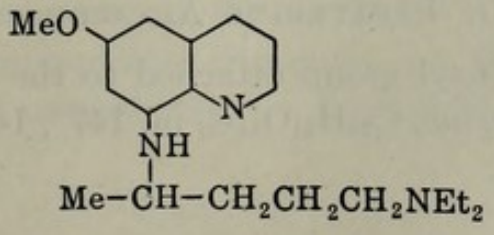
This change is like that which gives cinchotoxine except that the primary shift is that of a C instead of N.

**Quinine,** $C_{20}H_{24}O_2N_2$, m. 177°, is 6-methoxycinchonine. Oxidation converts the CHOH to CO giving *quininone*, the vinyl group to carboxyl, giving *quitenine*. Further oxidation of the ketone or treatment with nitrous acid and hydrolysis gives meroquinene (I) and *quininic acid*, 6-methoxy-4-quinoline carboxylic acid.

Treatment of quinine with acid opens one of the piperidine rings in the quinuclidine part of the molecule and forms *quinotoxine* entirely analogous to cinchotoxine.

**Quinidine,** m. 171°, **hydroquinine,** m. 172°, and **hydroquinidine,** m. 167° are related to quinine as are the corresponding compounds to cinchonine (p. 942). *Cupreine*, m. 202°, is 6-hydroxycinchonine. Methylation converts it to quinine. *Hydrocupreine* is best made by demethylating hydroquinine with HCl at 150°. From it are prepared ethers, homologs of hydroquinine which are valuable disinfectants. *Optoquin*, the ethyl ether, has specificity for the *pneumococcus*. *Eucupine* and *Vuzine* are isoamyl and sec-octyl ethers of dihydrocupreine.

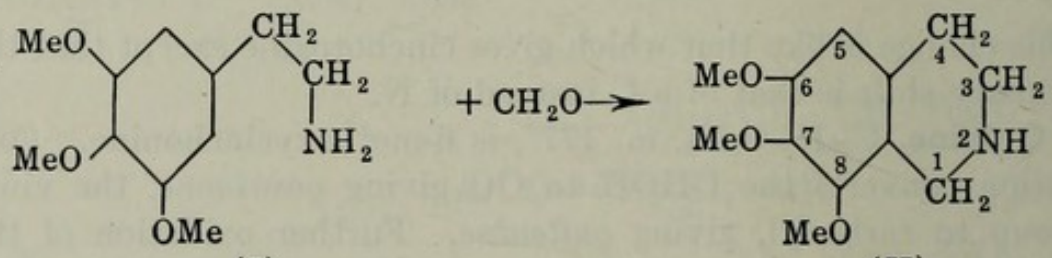
**Plasmoquin,** a synthetic antimalarial drug used in place of quinine as a compound with various complex acids.



**Atebrin** is an acridine derivative containing the same side chain (Rep. 1934, 273).

### *N.* Isoquinoline Alkaloids

The simplest type is obtainable by condensing aldehydes with hydroxy derivatives of β-phenylethyl amines, the aldehyde carbon forming $C_1$ of the isoquinoline. The first step is the ordinary addition of an amine to a carbonyl compound. The next is 1,6-ring closure involving the H para to the activating OH or OMe group. Thus mescaline (I) and formaldehyde react readily to give O-Me-anhalamine (II).




(I) (II)

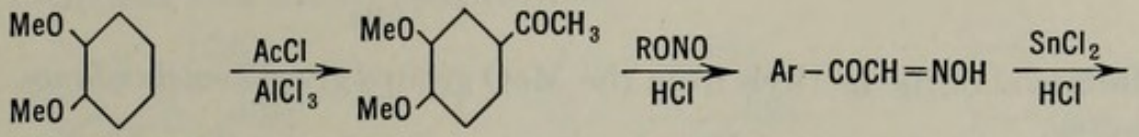
Pellotine Me ether can be made by methylating the product of ring closure of acetyl mescaline (Rep. 1922, 162). Some of the important simple *tetrahydro-isoquinolines* follow:

| Name | Substituents, Position | | | | |
|---|---|---|---|---|---|
| | 1- | 2 (N)- | 6- | 7- | 8- |
| Norsalsoline | Me | | OH | OH | |
| Salsoline | Me | | OH | OMe | |
| Carnegine | Me | Me | OMe | OMe | |
| Pellotine | Me | Me | OMe | OMe | OH |
| Anhalonidine | Me | | OMe | OMe | OH |
| Anhalamine | | | OMe | OMe | OH |
| Anhalidine | | Me | OMe | OMe | OH |
| Anhalonine | Me | | OMe | O—$CH_2$—O | |
| Lophophorine | Me | Me | OMe | O—$CH_2$—O | |

### *O.* Papaverine Alkaloids

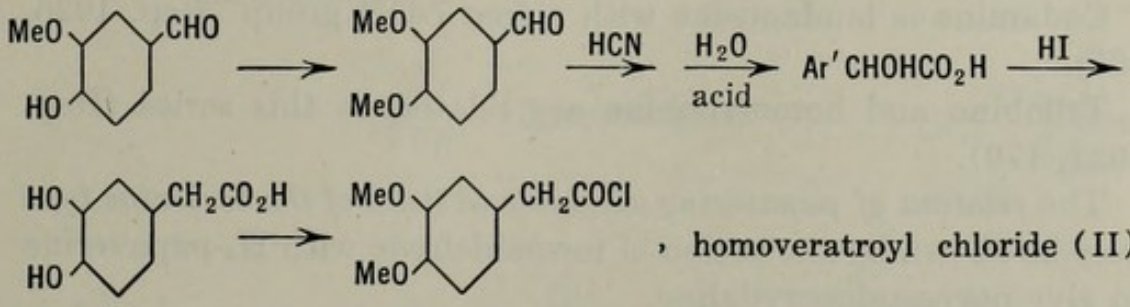
These have a benzyl group attached to the 1-position of isoquinoline. *Papaverine*, $C_{20}H_{21}O_4N_2$, m. 147°, 1-(3′,4′-dimethoxy-

benzyl)-6,7-dimethoxy-isoquinoline, and its 1,2- and 3,4-dihydro and 1,2,3,4-tetrahydroderivatives have been synthesized in a variety of ways. The original synthesis of Pictet and Gams (1909) has not been greatly improved. This starts with veratrole and vanillin



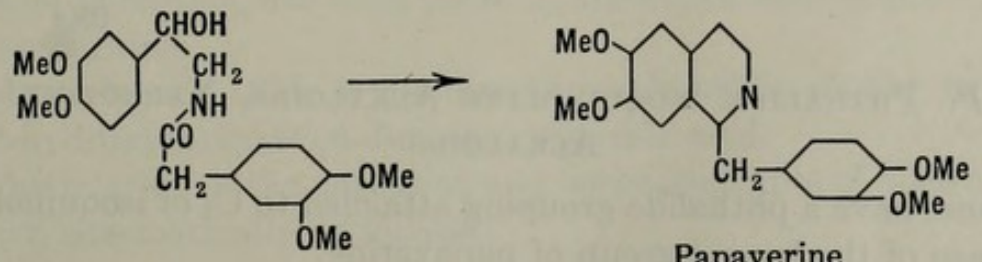

Veratrole

$ArCOCH_2NH_2.HCl$, hydrochloride of ω-aminoacetoveratrone (I)




, homoveratroyl chloride (II)

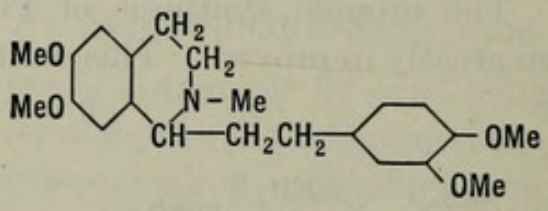
Compounds (I) and (II) in presence of a base condense to give the expected keto acid amide which can be readily reduced to the corresponding secondary alcohol. Treatment of this with $P_2O_5$ in xylene closes the isoquinoline ring giving a 30% yield of papaverine.




Papaverine

**Papaveraldine** has the $CH_2$ of papaverine oxidized to CO. Thus it is a 1-benzoylisoquinoline derivative. *Pavine* is 1,2-$H_2$-papaverine. *Laudanosine*, m. 89°, is N-Me-1,2,3,4-$H_4$-papaverine. *Laudanine* (laudanidine, tritopine), m. 166° is *dl*-laudanosine with the 3′-OH unmethylated. *Laudanidine* is its *l*-form.

**Homolaudanosine** is like laudanosine but has $-CH_2CH_2$ between the rings instead of $CH_2$ (Rep. 1934, 276)



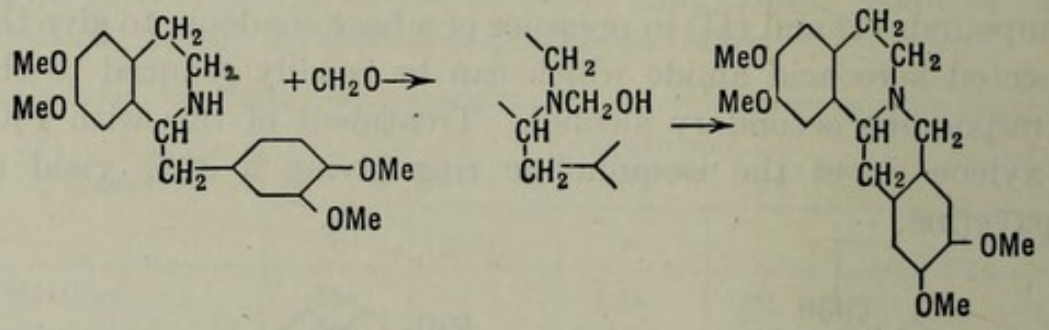

Removal of the methyls from the MeO groups gives *homolaudanosoline.*

**Coclaurine** has 7,4′-$(OH)_2$-6-MeO instead of the 4 MeO groups in $H_4$-papaverine. (Rep. 1930, 193). Combination of two molecules by two ether linkages gives oxycanthine (p. 950).

**Codamine** is laudanosine with a free 7-OH group (Rep. 1926, 165).

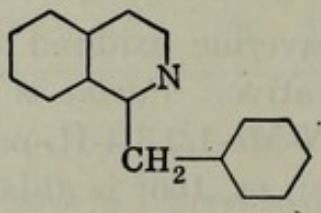
**Trilobine** and **homotrilobine** are related to this series (Rep. 1931, 170).

The *relation of papaverine alkaloids to those of the berberine type* may be shown by the action of formaldehyde with $H_4$-papaverine to give norpseudocorydaline.

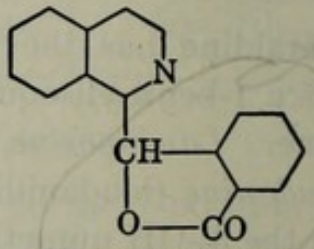



## *P.* Phthalide Isoquinoline Alkaloids, Narcotine Alkaloids

These have a phthalide grouping attached to $C_1$ of isoquinoline in place of the benzyl group of papaverine.

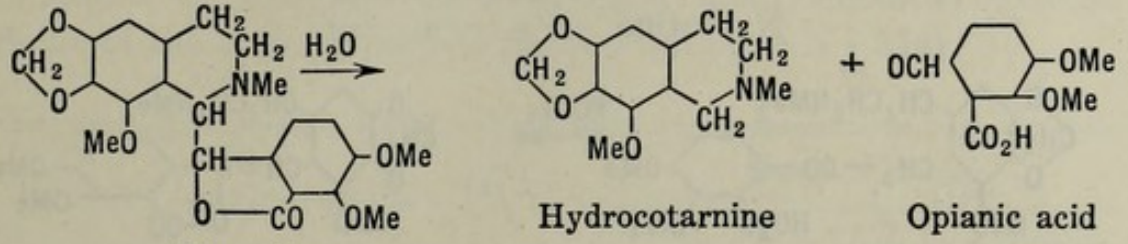



Papaverine type

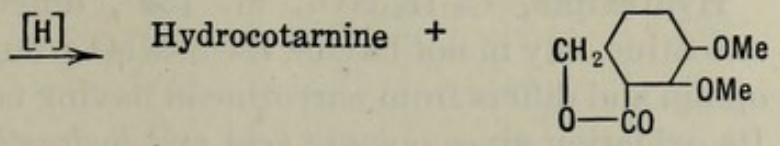



Narcotine type

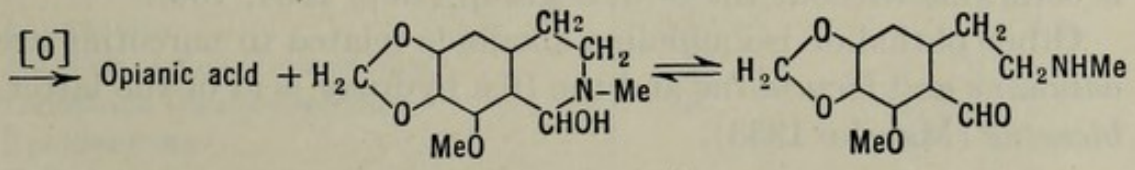
**Narcotine,** $C_{22}H_{23}O_7N$, m. 176°, one of the abundant opium alkaloids, is related to laudanosine but has a methylene ether grouping in place of the 6,7-$(MeO)_2$ and has an additional OMe in the 8-position and a lactone ring between the 2′-position and the benzyl carbon. Its hydrolysis at 140°, and its oxidation and reduction indicate its constitution.




Narcotine




Meconin

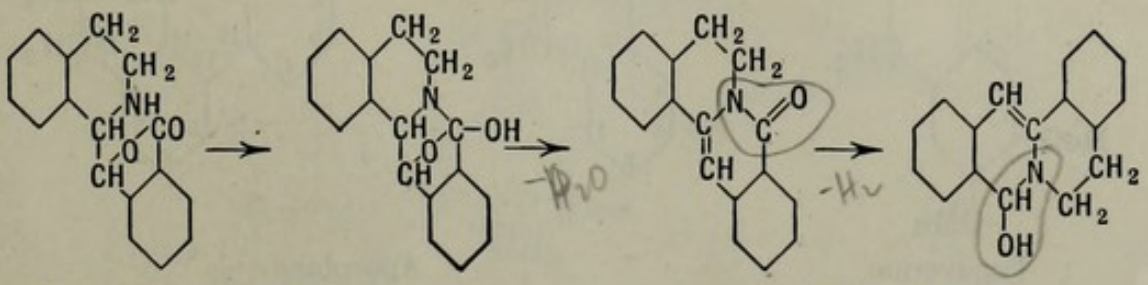



Cotarnine

Cotarnine gives open chain compounds with hydroxylamine, acetone, etc., and ring compounds with HCl, HCN, etc. *Gnoscopine, dl*-narcotine, has been made by the condensation of meconin and cotarnine.

**Meconin,** m. 101°, is 5,6-dimethoxyphthalide or the lactone of 2-hydroxymethyl-5,6-dimethoxybenzoic acid.

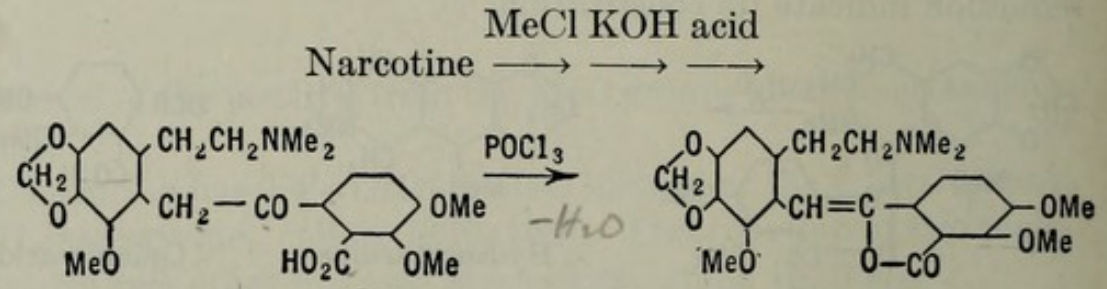
The relation of the narcotine and berberine types of alkaloids is shown schematically as follows:




Narcotine type

Berberine type

**Narceine,** $C_{23}H_{27}NO_8.3H_2O$, m. 171°, is made by the action of alkalies on the MeCl cpd. of narcotine. The $-O-C-C-N$ grouping is broken at the C—N linkage as in the splitting of ephedrine (p. 922) and in the conversion of the cinchona alkaloids to toxines (p. 942). Narceine with $POCl_3$ gives *aponarceine*



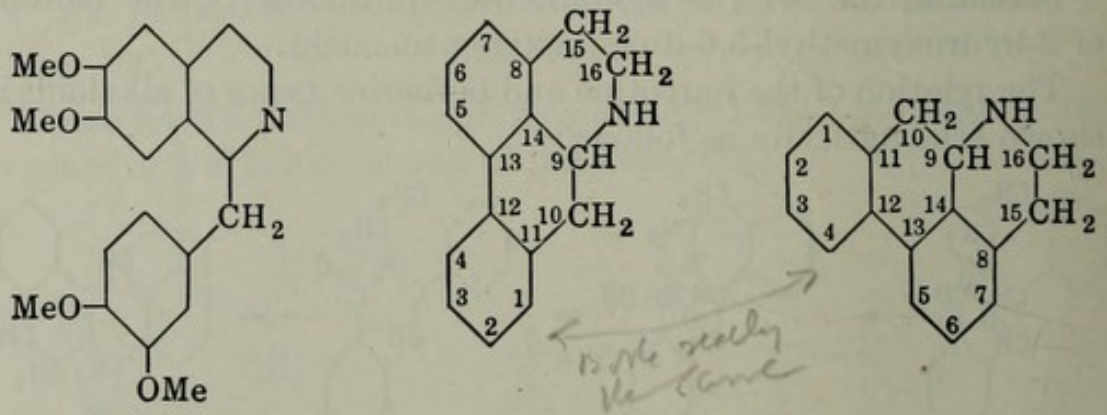

Narceine Aponarceine

**Hydrastine,** $C_{21}H_{21}NO_6$, m. 132°, differs structurally from narcotine only in not having the 8-MeO group. It is not found in opium and differs from narcotine in having no narcotic properties. Its oxidation gives opianic acid and *hydrastinine*, m. 117°, which is cotarnine without the 8-MeO group (Rep. 1931, 166).

Other phthalide isoquinoline alkaloids related to narcotine are *adlumine* and *bicuculline* and the free hydroxy acid of the latter, *bicucine* (Manske 1933).

## *Q.* Aporphine Alkaloids

The parent substance, aporphine, a phenanthrene isoquinoline type, is closely related to tetrahydropapaverine (Rep. 1924, 136; 1927, 173).

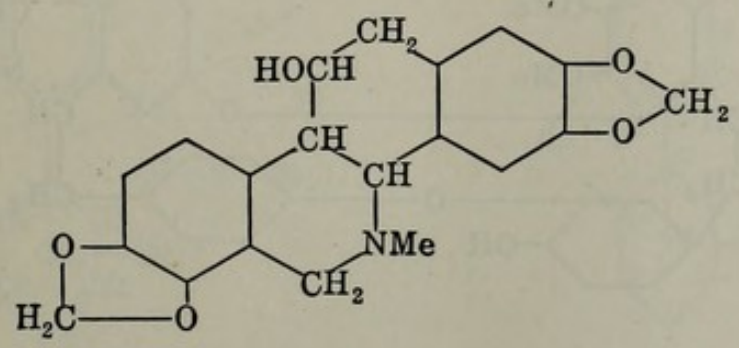



Papaverine Aporphine

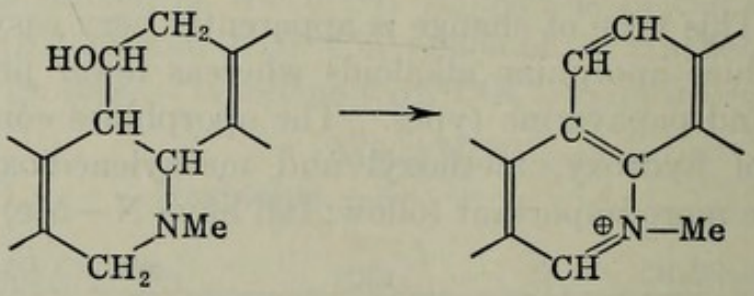
The relation to morphine is also close, $C_{15}$ being attached to $C_{13}$ in the latter substance. The relation is shown by the ready conversion of morphine to apomorphine on boiling with dilute HCl (p. 952). This type of change is apparently very easy as many plants produce aporphine alkaloids whereas fewer produce the morphine and papaverine types. The aporphines contain combinations of hydroxy, methoxyl and methylenedioxy groups. Some of the more important follow: (all have N—Me)

| Aporphine alkaloid | Position of groups | | |
|---|---|---|---|
| | —OH | —OMe | —$OCH_2O$— |
| Apomorphine | 3,4- | | |
| Morphothebaine | 4,6- | 3- | |
| Isothebaine | 4- | 3,5- | 5,6- |
| Pukateine | 4- | | |
| Laureline | | 3- | 5,6- |
| Boldine | 2,6- | 3,5- | |
| Corytuberine | 4,5- | 3,6- | |
| Laurepukine (?) | 5,6 | | 3,4- |
| Actinodaphnine (Domesticine) | 2- | 3- | 5,6 |
| Dicentrine (Isodomesticine) | 3- | 2- | 5,6 |
| Epidicentrine | | 5,6- | 2,3- |
| Bulbocapnine | 4- | 3- | 5,6- |
| Isocorydine | 4- | 3,5,6- | |
| Corydine | 5- | 3,4,6- | |
| Glaucine | | 2,3,5,6- | |

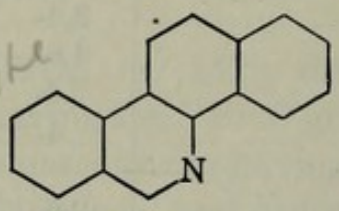
**Laurotetanine** has a free NH group, being 2-OH-3,5,6-$(OMe)_3$-aporphine. A variation in the aporphine ring structure is found in *chelidonine* (Rep. 1931, 168).



**Sanguinarine** is the quarternary base related to it. The change in the central portion of the molecule is as follows:



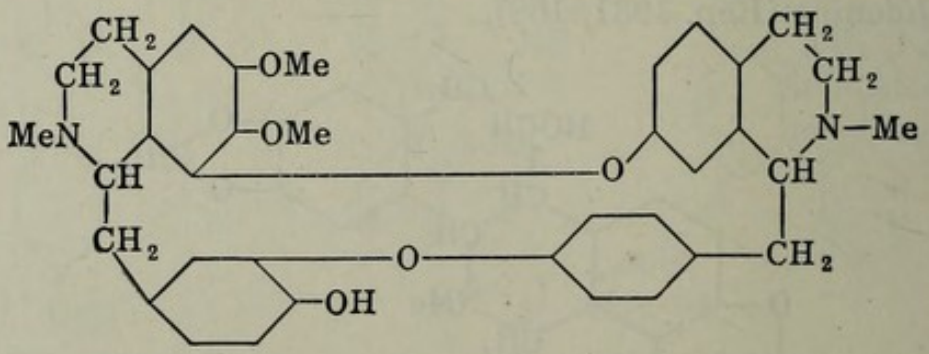

Distillation with Zn dust converts them to $\alpha$-naphthaphenanthridine



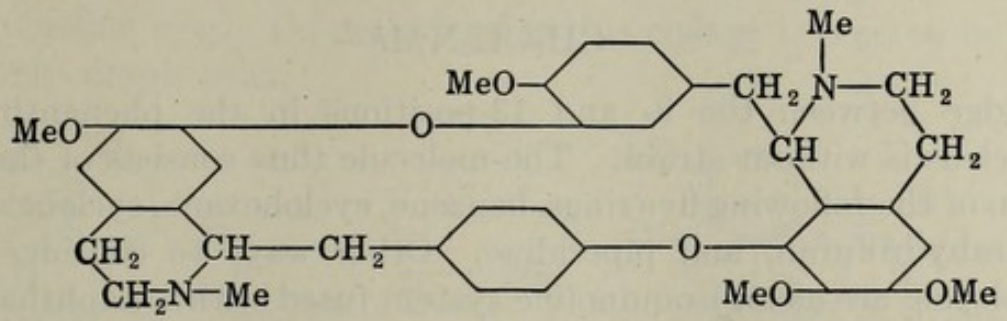

**Homochelidonine** and **chelerythrine** are a similarly related pair having two OMe groups in the isoquinoline ring in place of the $O_2CH_2$ group.

### *R.* Bis-benzylisoquinoline Alkaloids

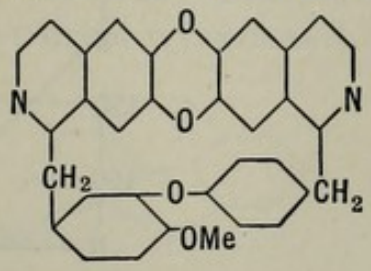
These involve combinations of two molecules of the papaverine type by means of ether linkages in large strainless rings (Rep. 1933, 242–50). *Oxycanthine* is an example (R. Robinson, Rev. Bio. 1935, 509).



**Bebeerine** ($\alpha$-chondodendrine, curine) has each phenyl group linked by O to an isoquinoline group.

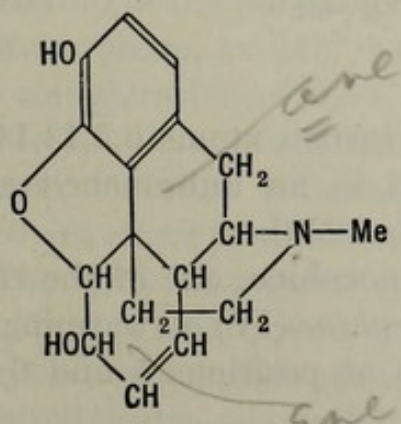


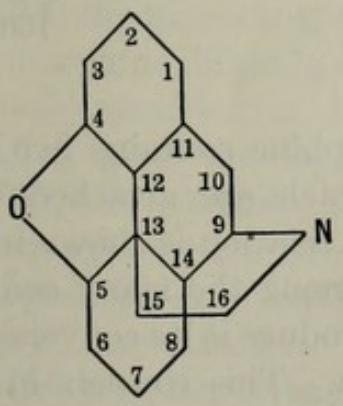

**Berbamine, tetrandine, oxycanthine, isochondodendrine** and probably **menisarine,** and **trilobamine** belong to these types. *Dauricine* probably has only one ether linkage instead of the two forming the large ring (Rep. 1933, 250). *Trilobine, isotrilobine* and probably *phaeanthine* contain three instead of two ether linkages possibly giving a combination such as




## *S.* Morphine and Related Alkaloids

**Morphine,** $C_{17}H_{19}NO_3$, m. 253°, is the most important of about 25 alkaloids found in opium. The relation of the N to the rest of the molecule is less simple than in the other alkaloids. The accepted structure (R. Robinson, 1925, Rep. 1926, 173) as ordinarily written emphasizes its relation to a partially hydrogenated phenanthrene

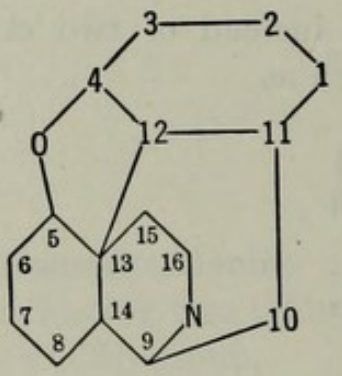


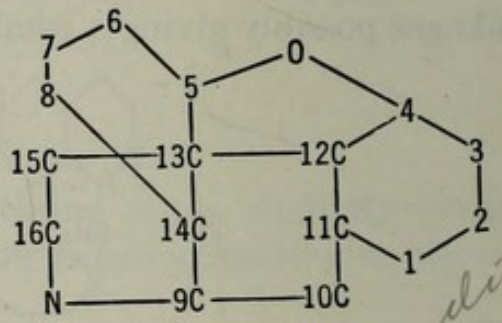
While such a formula appears awkward in two dimensions, scale models (Organospheres, Steiger) show that the

$$-CH_2CH_2NMe-$$

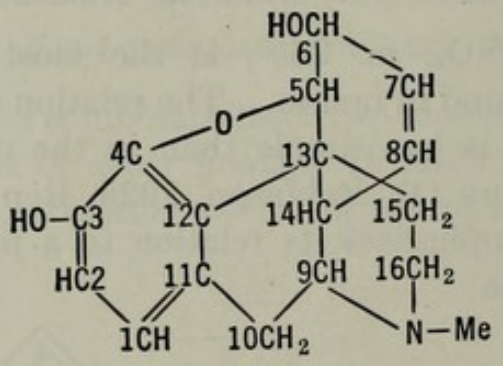
bridge between the 9- and 13-positions in the phenanthrene nucleus is without strain. The molecule thus consists of the fusion of the following five rings, benzene, cyclohexane, cyclohexene, tetrahydrofuran, and piperidine. Other ways to consider the molecule are as an isoquinoline system fused with a naphthalene system across positions 9 and 13 (I) or as a mornuclidine system fused with two benzene rings in the 11,12- and 13,14-positions (II). The carbons of the supplementary rings are represented by their numbers.




(I)




(II)

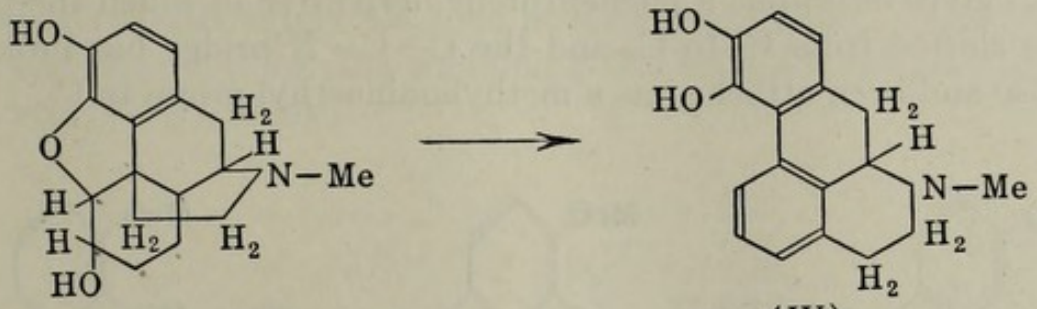



(III)

Morphine contains five asymmetric carbon atoms 6,5,13,14 and 9 which are attached in succession in an unbranched chain. This relation is shown in (III) (Emde 1930).

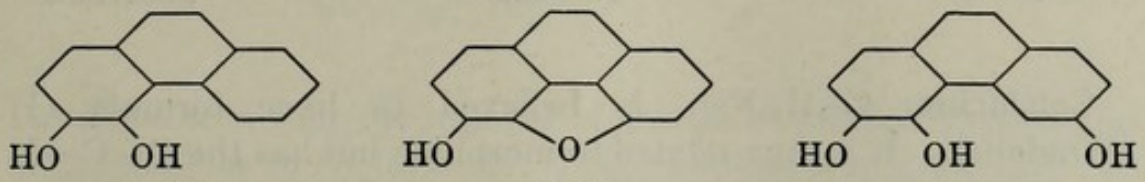
Among the many conversions of morphine, one of the easiest to produce is its conversion to *apomorphine* (IV) on warming with acids. This consists in dehydration at positions 5 and 6 with

formation of a new benzene ring and the consequent shift of the N bridge from the quarternary $C_{13}$ to $C_8$ thus forming a different isoquinoline ring. On scale models this change is seen to be an entirely simple shift.




(IV)

Distillation of morphine with Zn dust gives phenanthrene. The position of the oxygen atoms is shown by conversion to the phenanthrene derivatives, the 3-Me ethers of morphol (V), morphenol (VI), and 3,4,6-trihydroxyphenanthrene (VII)




(V) (VI) (VII)

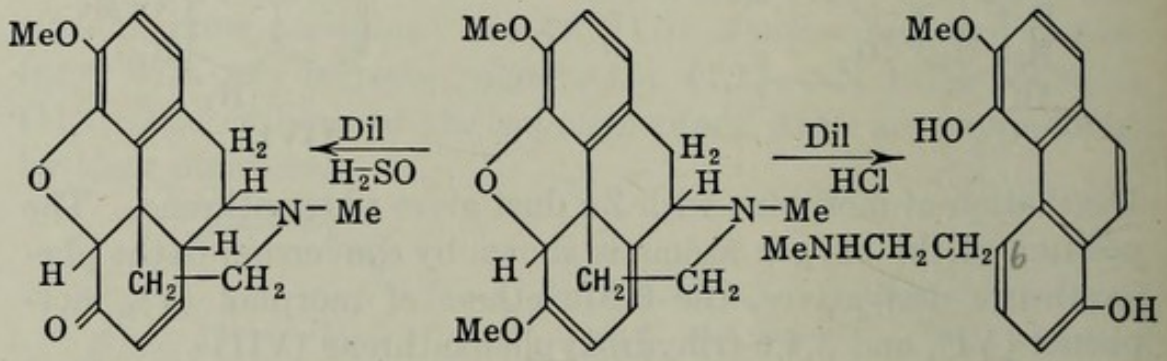
The C—C—N bridge is readily removed by any change which makes the middle ring aromatic. As shown by models the mornuclidine system can exist only because of the polyplanar nature of the cyclohexane ring. As soon as the latter is flattened by becoming aromatic, the meta bridge from $C_9$ to $C_{13}$ becomes impossible.

**Codeine,** m. 155°, is the 3-methyl ether of morphine. The methylation of the phenolic hydroxyl reduces the narcotic action.

**α-Isomorphine,** m. 247° is an epimer of morphine differing only in the configuration of the CHOH. It gives *isocodeine,* m. 172°. Both codeine and isocodeine on oxidation give the ketone, *codeinone,* m. 187°. **β-Isomorphine,** m. 183°, and **γ-isomorphine,** m. 278° are epimers with the alcoholic hydroxyl on $C_8$ instead of $C_6$. They give *allopseudo-codeine,* liq. and *pseudocodeine,* m. 181° both of which form *pseudocodeinone,* m. 174°, on oxidation.

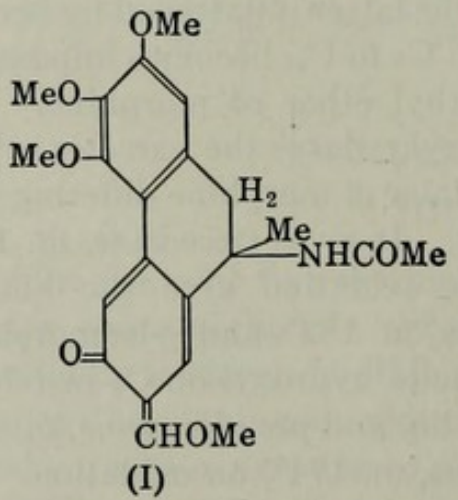
Ethyl morphine, Dionine, is next to codeine in importance in the United States as a morphine derivative. Diacetyl morphine, Heroin, is prohibited in the United States but is still produced elsewhere.

**Thebaine,** $C_{19}H_{21}NO_3$, m. 193°, is the methyl ether of the enol form of codeinone as shown by its conversion to that substance and MeOH by action of dilute sulfuric acid. In general, its conversions correspond to those of morphine except that dilute HCl gives *thebenine*, a phenanthrene derivative in which the OH has shifted from $C_6$ to $C_8$ and the C—C—N bridge has broken loose and been attached as a methylaminoethyl group to $C_6$.

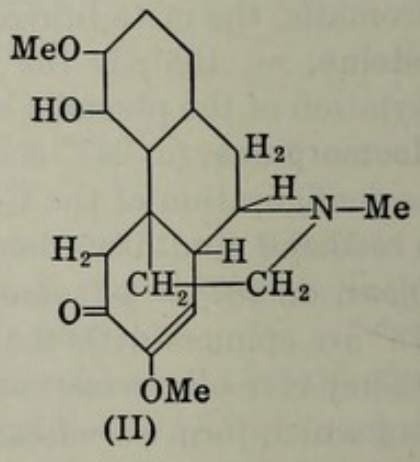



**Colchicine,** $C_{22}H_{25}NO_6$, is believed to have formula (I) (Windaus). It is thus related to morphine but has the C—C—N grouping as an acetylamino group in the 9-position instead of as a 9,13-bridge. It can be converted to 9-Me-phenanthrene.

**Sinomenine** is related to morphine and thebaine and probably has formula (II)



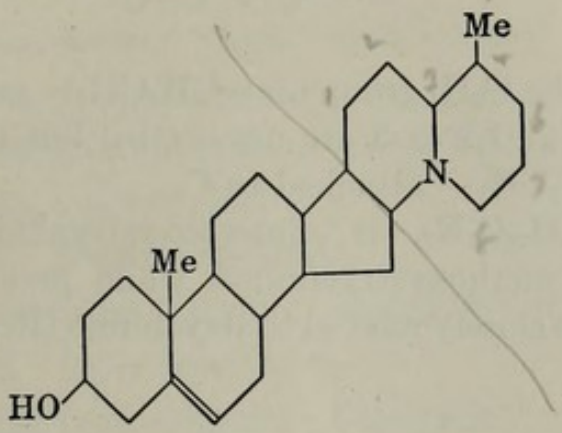

(I)



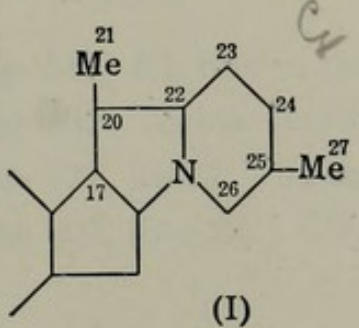

(II)

## *T.* Other Alkaloids

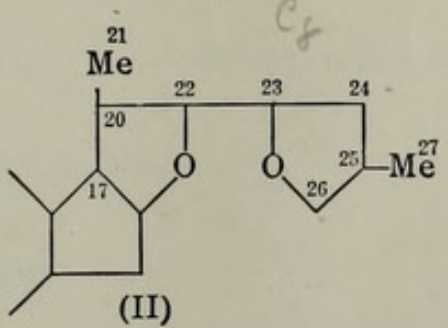
**Solanidine,** $C_{23}H_{43}ON$, contains the cyclopentanohydrophenanthrene nucleus which is characteristic of so many biologically important substances such as the sterols, bile acids, sex hormones, heart aglucones, toad poisons and the like. For it has been suggested a formula combining this nucleus and a lupinane system (Soltys 1936)




It will be seen that the number of carbon atoms attached at $C_{17}$ is the same as in cholesterol. The following arrangement (I) of the nitrogenous part of the molecule would retain the cholesterol chain much as it is retained in *tigogenine* (II).




(I)

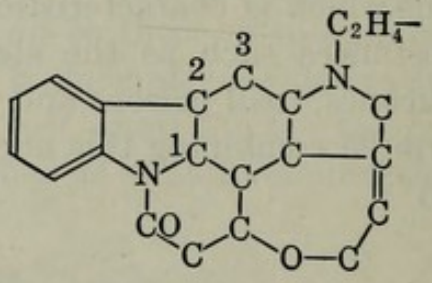



(II)

Grouping (I) involves a fusion of pyrrolidine and piperidine rings as found in δ-coniceine.

**Strychnine,** $C_{21}H_{22}O_2N_2$, contains groupings not found in other classes of alkaloids. In spite of an enormous amount of study, its constitution is not definitely settled (Rep. 1926, 173; 1932,

201, Rev. Bio. 1935, 512). Agreement has been reached on the main portion of the skeleton




The nature of the $C_2H_4$ group as $-CH_2CH_2-$ or $-CHMe-$ and its attachment at 1,2 or 3 are not settled but the probability is that it is $-CH_2CH_2-$ attached to $C_2$.

*Brucine*, $C_{23}H_{26}O_4N_2$, is dimethoxystrychnine. *α-* and *β-Colubrines* are methoxystrychnines while *pseudostrychnine* and *vomicine* are less closely related to strychnine (Rep. 1932, 205).

## ERRATA

Page 33, line 13. dihalides

Page 132. **3-Me-pentanol-1,** b. 154° (Norris 1925)

Page 164, line 4. Shriner

Page 169, line 4. vinyl sulfonic

Page 188, 2nd line from bottom. quarternary

Page 249, bottom. $Cl_3$-butanal,

Page 276, 7th line from bottom. (Rep. 1911, 106).

Page 320, line 23. tariric acid

Page 354, line 4. acetic anhydride

Page 372, 3rd line from bottom. monoethyl ether,

Page 405, line 5. inner hemi-acetal,

Page 437, 8th line from bottom. **Glyoxylic**

Page 465, 9th line from bottom. *cyclo*-butane

Page 466, 15th line from bottom. malic acid

Page 508, 5th line from bottom.

pentene-2, 2,4-$Me_2$-pentene-2, nonene-4

Page 513, (*b*). H : O : H

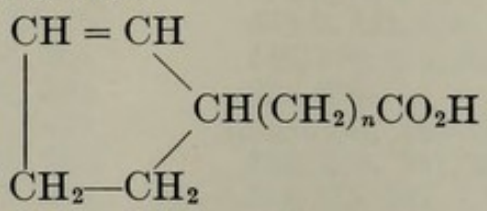
Page 525, 4th line in table. Ortal Ethyl, *n*-hexyl

Page 552. delete line 5

Page 571, line 7. methylphenylhydrazine,

Page 607, line 22. $CO_2H$ groups.

Page 643, last formula.



Page 667. delete H on $C_1$ in first two formulas

Page 681, lines 2 to 3. hydroxysapotaline,

Page 732, 2nd formula in 4th equation. $NH_2$ on $C_2$



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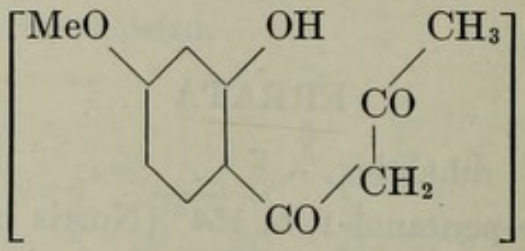
Page 800, 2nd formula in 1st equation.




Page 819, side chain in first formula. $(EtO_2CO)_3C_6H_2CO_2$-

Page 822. middle formula in first equation should have two $CH_2$ groups

Page 836, line 12. *read* former *instead of* latter

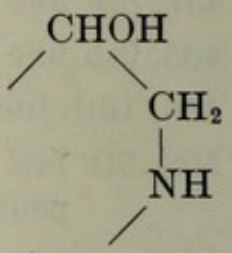
Page 886, bottom. L. Pseudoisatin

Page 887, 5th line from bottom. *change to* indoxyl, which is readily

Page 897, middle. H missing from 3-position

Page 912. all three formulas in first equation have OH missing at top of benzene ring

Page 945. lower left formula should contain




Page 947. top left formula should have $CH_2$ attached to 3-position of benzene ring.

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a-, Ana-position
α-, Alpha position or angle of rotation of plane polarized light
[α], Specific rotation
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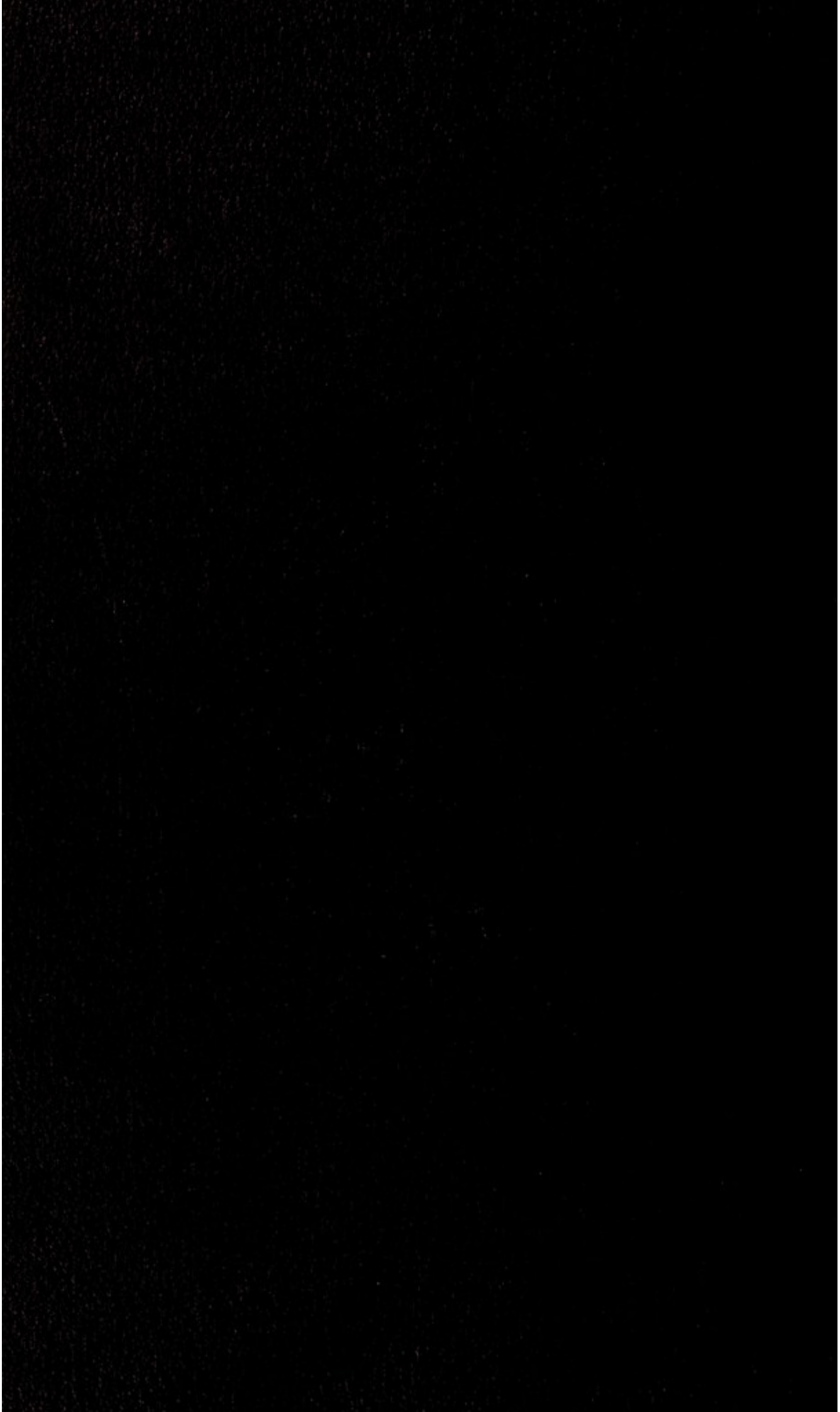
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