Organic compounds of arsenic & antimony / by Gilbert T. Morgan.

Monographs on Industrial Chemistry

ORGANIC COMPOUNDS OF ARSENIC AND ANTIMONY

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ARSENIC & ANTIMONY

BY

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PREFACE

ORGANIC derivatives of arsenic appeal to the scientific public for two widely different reasons. From the historical standpoint these substances are of considerable interest because they have been under investigation throughout a period of time coeval with the birth and development of modern chemistry. Successive generations of chemists have examined these compounds from points of view which varied with the gradual evolution of chemical science, and the results of their researches have played an important part in the establishment of current theories of the molecular constitution of matter.

Additional importance is conferred on the subject by the circumstance that very early in the study of organic arsenical compounds it was realised that, in these synthetic products, the physician has at his disposal substances of great physiological potency. It is chiefly this medicinal attribute of organic arsenicals which has evoked the more recent activities in the synthesis of organo-metalloidal compounds. These utilitarian investigations have not been restricted to organic arsenicals, but have extended to the corresponding derivatives of antimony, and accordingly these related products are also discussed in the present monograph.

Both series of organo-metalloidal compounds are already so extensive that a detailed description of every individual member would render this treatise unduly bulky, but a liberal selection has been made comprising those substances having either a practical application or some aspect of theoretical interest. A bibliography of the most important researches and treatises down to the end of 1917 has been included, and these references to original memoirs supply the necessary clue to further information regarding any known organic arsenical or antimonial which may in the future acquire increased prominence.

It is my pleasant duty to express my grateful thanks for assistance received in the compilation of this monograph from the following firms:—Les Établissements Poulenc Frères, Messrs. Burroughs Wellcome & Co., and Messrs. May and Baker.

I also desire to acknowledge the friendly help received from Dr. W. H. Martindale, from Mr. E. Scholl, formerly of the Farbwerke vormals Meister, Lucius, und Brüning; from Mr. F. W. Clifford, Librarian of the Chemical Society; and from Messrs. E. D. Evens, B.Sc., and W. R. Grist, who have assisted me in reading the proofs and in arranging the index and bibliographic data.

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CONTENTS

CHAPTER VII.

CHAPTER VIII.

CHAPTER IX.

CHAPTER X.

INTRODUCTION

I.—*Chemical.*

ARSENIC and antimony belong to the nitrogen group of chemical elements, one of a pair of related families constituting the fifth series of elements in the periodic system of classification. The relative positions of the members of these two natural families of elements are shown in the following table.

Inasmuch as the physical and chemical properties of arsenic and antimony bridge over the differences between the non-metals nitrogen and phosphorus and the metal bismuth, these two intervening elements are frequently termed *metalloids*, this expression signifying that certain of their attributes are metallic, whereas others are non-metallic.

Periodic Classification :—Fifth Vertical Series.

Typical oxide, R_2O_5. Typical fluoride, RF_5.

Family A :—Nitrogen group.			*Family B :—Vanadium group.*		
Typical hydride, RH_3.			Hydrides and organic derivatives—unknown.		
Typical alkyl derivative, $R(CH_3)_3$.					
	Element.	*At. Wt.*		*Element.*	*At. Wt.*
non-metals	nitrogen	14			
	phosphorus	31			
metalloids	ARSENIC	75	metals	vanadium	51
	ANTIMONY	120		columbium	93·5
metal	bismuth	208		tantalum	181

The members of the two families A and B show occasional points of resemblance. Phosphorus, vanadium, and arsenic form an isomorphous series as illustrated by the following mineral species :—

Pyromorphite	$3Pb_3(PO_4)_2,PbCl_2$.
Vanadinite	$3Pb_3(VO_4)_2,PbCl_2$.
Mimetite	$3Pb_3(AsO_4)_2,PbCl_2$.

Antimony, columbium, and tantalum show a certain similarity in their oxy-salts, as, for example, in the series

$KSbO_3$, $KCbO_3$, and $KTaO_3$.

These points of resemblance between the two families are, however, much less conspicuous than their dissimilarities. Two of the most striking differences are in regard to the respective affinities of the members of the two families for organic radicals and for hydrogen.

The members of the nitrogen family without exception furnish organic derivatives, but on the contrary vanadium and the other two metals of its family have not so far been induced to combine directly with hydrocarbon radicals.[1]

The organic compounds of arsenic and antimony are not found in nature; they are invariably obtained as products of chemical synthesis.

Arsenic and antimony usually occur in the mineral kingdom in combination with sulphur, forming either simple or complex sulphides. Arsenic furnishes two simple sulphides, *realgar*, As_2S_2, and *orpiment*, As_2S_3, whilst antimony is commonly obtained from the crystalline *stibnite*, Sb_2S_3.

In combination with cobalt, arsenic gives rise to the mineral *smaltite*, and with sulphur and cobalt it occurs as *cobaltite*. These two mineral species were often confounded by the earlier French mineralogists and chemists, who applied the name "Cobolt" to these two naturally occurring arsenical cobalt compounds.

II.—*Historical.*

In the earlier half of the eighteenth century the French chemist Hellot obtained private information from a German artist that the mineral cobolt from Schneeberg when extracted with aquafortis yielded a solution which could be employed in the preparation of sympathetic inks. He was thus led to examine specimens of cobolt from various sources with the object of testing their suitability for the production of inks to be used in writing secret despatches. His results, which were published in the form of two memoirs to the Académie Royale des Sciences in 1737, described the action of mineral acids and especially of aquafortis on the cobolt from Schneeberg, Anneberg, and other German sources and also on French specimens from Sainte-Marie-aux-Mines (Vosges) and the Dauphiné. Judging from the origin of these specimens it seems likely that they were

[1] This difference between the combining powers of the two families of this series towards hydrocarbon radicals is noticeable in other vertical series of the periodic arrangement. (Morgan, *Science Progress*, 1914, **8**, 695.)

samples of smaltite, this mineral species being known to occur in the foregoing localities. Hellot refers to the fact that the blue ceramic pigment, smalt, is made from cobolt and that this mineral is a source of white arsenic.[1] These experiments on the production of sympathetic ink containing cobalt salts were resumed about twenty years later by Louis Claude Cadet de Gassicourt, a military apothecary stationed in Paris.[2] His memoir published in 1760 is chiefly concerned with the extraction of cobalt solutions suitable for the production of sympathetic inks by the action of various acids—including organic acids—on the mineral "cobolt." As a side issue he refers to experiments made on the white arsenic also derived from cobolt. This investigation, described in his own words in the opening chapter of this monograph, led in a singularly fortuitous manner to the production of the earliest known organo-arsenical compounds. The product, a liquid with an intolerable stench, had the remarkable property of taking fire on exposure to the atmosphere. On this account it was known for many years as "Cadet's fuming arsenical liquid." A few years later this liquid was again prepared by Guyton de Morveau, Hugues Maret, and Jean François Durande, three French chemists working in Dijon, who placed on record the disagreeable odour of the product and its spontaneous inflammability in air at the ordinary temperature.[3]

For a third time this uninviting material was examined by a French chemist, Louis Jacques Thénard, who made repeated distillations of the mixture of white arsenic and potassium acetate by means of which Cadet had obtained his original result. A more detailed study led Thénard to the conclusion that the liquid was a complex acetate containing arsenic. He also investigated its chemical reactions and identified some of the volatile by-products set free during its preparation.

The next investigator to undertake the difficult and disagreeable task of elucidating the chemical nature of this re-

[1] "Sur une nouvelle encre sympathique." Histoire de l'Académie Royale des Sciences, 1737, **1**, 101 and 228.

[2] "Suite d'Expériences nouvelles sur l'encre sympathique de M. Hellot qui peuvent servir à l'analyse du cobolt ; et Histoire d'une liqueur fumante tirée de l'arsenic." Par M. Cadet, apothicaire-major de l'Hôtel Royal des Invalides. Mémoires de Mathématique et de Physique. Présentés à l'Académie Royale des Sciences par divers Savans et lûs dans ses Assemblées, 1760, **3**, 623.

[3] Elémens de chimie théorique et pratique, 1778, **3**, 39.

markable substance was Robert Wilhelm Bunsen, who occupied himself with the problem during the period 1837–1843.

Bunsen prepared large quantities of Cadet's arsenical liquid and separated from this solution the predominant organic constituent. His investigations, published in several memoirs, showed that the chief organic constituent of Cadet's liquid is a compound consisting of arsenic, carbon, hydrogen, and oxygen. The last of these elements could be replaced by the halogens, cyanogen and sulphur, without altering the relative proportions of carbon, hydrogen, and arsenic, so that it appeared as if these three elements had coalesced to form a complex which remained unchanged during the foregoing substitutions. Later Bunsen isolated the complex itself.

The significance of this remarkable discovery was at once appreciated by the Swedish chemist Berzelius, who recognised in Bunsen's oxygenated arsenical compound an analogue of the alkali oxides in which the elementary alkali radical is replaced by a compound organic radical. To this compound radical isolated by Bunsen, Berzelius gave the name "*cacodyl*" on account of the disagreeable stench of its compounds. The isolation of cacodyl afforded substantial experimental support for the compound radical theory of the constitution of organic compounds, of which important generalisation the Swedish philosopher was the most eminent protagonist.

Bunsen never attempted any dissection of the cacodyl complex, but the inner constitution of this compound radical was explained by E. Frankland in 1849 as the result of his brilliant investigations on zinc alkyls and other compounds of the hydrocarbon radicals. This promising intervention did not, however, inspire many other English chemists to study the organic derivatives of arsenic and antimony. The few who embarked on these researches were as *rari nantes in gurgite vasto*, so that the British contribution to this section of synthetic chemistry is of very modest dimensions.

To France belongs the honour of the first pioneering efforts both as regards the earliest known aliphatic arsenicated compounds and the more useful discovery of an aromatic arsenical drug. The latter advance was made by Béchamp during the years 1860–63, but the significance of this research was not appreciated at the time in France, where it has needed the painful and costly stimulus of two sanguinary wars with the neighbours across the Rhine in order to demonstrate that these chemical

tours de force are worthy of support by co-ordinated effort. At present this effort is being supplied, and academic and industrial chemists are collaborating in the work of making and improving arsenicated drugs. Already Les Établissements Poulenc Frères have developed the manufacture of 3:3′-diamino-4:4′-dihydroxy-arsenobenzene (Salvarsan) and its methylenesulphinate (Neo-salvarsan) on an industrial scale, whilst Oechslin, Mouneyrat, and Danysz have introduced improvements into the chemio-therapy of these aromatic arsenicals.

In England the above-mentioned drugs are being manufactured by Messrs. Burroughs Wellcome & Co. and by Messrs. May and Baker, the latter firm working in association with Poulenc Frères. The chemists of the former firm have also carried through a considerable amount of research on atoxyl and its derivatives. Similar steps are now being taken in America and other industrialised countries where a home production of arsenical medicaments is urgently needed to replace the excluded German supply. These developments, however, all arise from the necessities imposed on society by the world-war, and in order to maintain a chronological sequence it is necessary to return to the decade immediately following on Bunsen's researches on cacodyl.

The experimental verification of Frankland and Kolbe's views on this substance was initiated in the Swiss Federal Polytechnic at Zurich, where Löwig and Schweitzer synthesised the first organic derivative of antimony in 1850. The method they employed was sufficiently general to be applied to the arsenical series, with the result that Cahours and Riche employed it in synthesising cacodyl in 1853.

Bunsen's work on cacodyl was revised, substantiated, and greatly extended by Baeyer in 1858, who first prepared primary methyl arsenicals by partially demethylating cacodyl trichloride, in this way arriving at methylarsinic acid, the soluble salts of which have been employed medicinally as "new cacodyl" and "arrhenal."

In so far as organic arsenicals are concerned Bunsen and Baeyer's researches were individual efforts carried out with little help from assistants and collaborators. The next stage in advance illustrates the growth of co-ordinated efforts in German scientific research. Twelve years after Béchamp's discovery of the first aromatic arsenical, Michaelis began a systematic study of the aromatic derivatives of phosphorus, arsenic, and antimony,

establishing first at Karlsruhe and Aachen and then at Rostock a school of chemistry in this particular branch of organic synthesis. The chapters on aromatic arsenicals and antimonials indicate the extent to which this field of inquiry was developed with the assistance of many collaborators. Michaelis with the aid of La Coste, Reese, and others devised general methods of preparation for the compounds of both series and prepared the first aromatic antimony derivatives. At first these laborious contributions to our knowledge of organic derivatives of arsenic and antimony were entirely of academic interest, but subsequently the technical skill acquired in these researches has been utilised in the synthesis of arsenical drugs and certain allied toxic chemicals.

Béchamp's compound, then supposed to be an anilide of arsenic acid, began to be tried in therapeutics in or about the year 1902. Thomas and Breinl at this stage employed the compound in the treatment of sleeping sickness. Owing to the comparatively non-toxic nature of the drug, to which circumstance it owes its name of "*atoxyl*," a certain degree of success attended these pioneering efforts in the chemiotherapy of aromatic arsenicals, with the result that the compound was subjected to systematic investigation by Ehrlich and many collaborators. It was speedily shown in 1907 by Ehrlich and Bertheim that atoxyl is truly an organo-arsenical, being the sodium salt of *p*-arsanilic acid. Comprehensive researches were started in special laboratories, notably at the Georg Speyer Hospital in Frankfort and at the Höchst Farbwerke vormals Meister, Lucius, und Brüning. The Béchamp reaction was extended from aniline to other similarly constituted bases and even to phenol. A very active exploitation of aromatic arsenicals now commenced, which continues at the present time. Atoxyl and its homologues are organic derivatives of quinquevalent arsenic, in which condition the metalloid is fully saturated in regard to principal valency and exhibits residual affinity to a minimum extent. Ehrlich noticed that aromatic compounds of tervalent arsenic were much more efficacious in combating trypanosomiasis, relapsing fever, and other diseases of protozoal origin. After many trials, in the course of which it is stated that 605 compounds were examined, Ehrlich arrived in 1909 at *Salvarsan* or "606." This substance, introduced into pharmacy in the form of its dihydrochloride, exhibits a remarkably specific action on the protozoal parasite to which the varied manifestations of syphilis are attributed. In this application the drug carefully neutralised

with aqueous sodium hydroxide is injected intravenously. Although when skilfully administered the drug produces favourable results in the great majority of cases, yet the preliminary chemical treatment is a matter which needs careful adjustment. On this account search was made for a drug which would combine the valuable germicidal action of salvarsan with the property of dissolving in water or physiological salt solution with a neutral reaction. Ehrlich's solution of this problem resulted in the production of another drug, *Neosalvarsan*, introduced into therapeutics in 1911. This compound is the sodium methylene-sulphinate of salvarsan. At the present time these two drugs, salvarsan and neosalvarsan, sold as such or under various synonyms, are the substances chiefly relied on in the arsenical treatment of syphilis.

Research has not, however, halted at the production of these two medicaments, excellent though they have proved to be. At the International Medical Congress held in London in 1913 Ehrlich announced a further significant development in the chemistry and chemiotherapy of aromatic arsenicals. Salvarsan and other derivatives of arsenobenzene possess the singular property of coupling with the salts of copper, silver, gold, and the metals of the platinum group in such a way that the ordinary analytical properties of these metals are not apparent in the resulting combinations which can be administered intravenously just like salvarsan itself. The intervention of the heavy metal is beneficial, for, in these circumstances, it exerts a germicidal action reinforcing that of the aromatic arsenical, while the toxic effect on the patient is less than that of salvarsan. Already one substance of this type has been employed clinically in the form of the drug "*Luargol*," first prepared by Danysz in 1913, and since used with considerable success in the French Army. An alternative drug to neosalvarsan has been recommended in the product "*Galyl*," a complex phosphamate of salvarsan, synthesised by Mouneyrat in 1912.

Another development in progress at the present time is the production of organic arsenicals containing also other metalloids, such as antimony, selenium, tellurium, etc. The preparation of these complex substances is greatly facilitated by the discovery of a general reaction for which the United States deserve the credit.

The chemists of the Old World had settled down to the belief that primary and secondary arsines are incapable of existence

when Palmer and Dehn, two American chemists, exploded this ill-founded prejudice by preparing dimethylarsine in 1894 and methylarsine and phenylarsine in 1901, and by devising a general method for obtaining other more complicated primary arsines. Dehn also generalised the process for producing monoalkyl-arsinic acids.

The primary aromatic arsines are of the greatest value in the preparation of certain physiologically active organic arsenicals possessing a dissymmetric configuration.

The synthesis of aromatic organo-metalloidal compounds has been further facilitated by the discovery that these substances are obtainable through the well-known diazo-reaction. This process has been applied to aromatic arsenicals by H. Bart and to aromatic antimonials by the Chemische Fabrik von Heyden of Dresden. The latter development has been very prolific, so that antimony analogues of the principal aromatic arsenicals have already been prepared by this means.

Meanwhile new derivatives of arsenobenzene are being investigated by Karrer and by the firms of Meister, Lucius, und Brüning and of C. F. Boehringer und Söhne. Attention is being directed specially to certain partly methylated hexaminoarseno-benzenes which have the noteworthy property of forming stable solutions with soluble bicarbonates. The latter salts have the same degree of alkalinity as that of normal blood serum, so that the foregoing property may acquire important physiological significance when the arsenical hexamine is injected into the circulatory system.

ABBREVIATED TITLES OF JOURNALS TO WHICH REFERENCES ARE MADE.

Abbreviated Title.	Journal.
Amer. Chem. J.	American Chemical Journal.
Amer. J. Pharm.	American Journal of Pharmacy.
Amer. J. Physiol.	American Journal of Physiology.
Amer. J. Sci.	American Journal of Science.
Analyst	The Analyst.
Annalen.	Justus Liebig's Annalen der Chemie.
Ann. Chim. anal.	Annales de Chimie analytique appliquée à l'Industrie, à l'Agriculture, à la Pharmacie et à la Biologie.
Ann. Chim. Applicata	Annali di Chimica Applicata.
Ann. Chim. Phys.	Annales de Chimie et de Physique.
Ann. Inst. Pasteur	Annales de l'Institut Pasteur.
Arch. expt. Path. Pharm.	Archiv für experimentelle Pathologie und Pharmakologie.
Arch. Pharm.	Archiv der Pharmazie.
Ber.	Berichte der Deutschen chemischen Gesellschaft.
Biochem. Bull.	Biochemical Bulletin.
Bio-Chem. J.	The Bio-Chemical Journal.
Biochem. Zeitsch.	Biochemische Zeitschrift.
Boll. chim. farm.	Bollettino chimico farmaceutico.
Chem. Zentr.	Chemisches Zentralblatt.
Chem. News	Chemical News.
Chem. Soc. Proc.	Proceedings of the Chemical Society.
Chem. Soc. Trans.	Transactions of the Chemical Society.
Chem. Zeit.	Chemiker Zeitung.
Compt. rend.	Comptes rendus hebdomadaires des Séances de l'Académie des Sciences.
Gazzetta	Gazzetta chimica italiana.
J. Amer. Chem. Soc.	Journal of the American Chemical Society.
J. Biol. Chem.	Journal of Biological Chemistry, New York.
J. Chem. Soc.	Journal of the Chemical Society (London).
J. Med. Research	Journal of Medical Research.
J. Path. Bact.	Journal of Pathology and Bacteriology.
J. Pharm.	Journal of Pharmacy.
J. Pharm. Chim.	Journal de Pharmacie et de Chimie.
J. Physiol.	Journal of Physiology.
J. pr. Chem.	Journal für praktische Chemie.

JOURNALS TO WHICH REFERENCES ARE MADE

Abbreviated Title.	Journal.
J. Russ. Phys. Chem. Soc.	Journal of the Physical and Chemical Society of Russia.
J. Soc. Chem. Ind.	Journal of the Society of Chemical Industry.
Monatsh.	Monatshefte für Chemie und verwandte Theile anderer Wissenschaften.
Pflüger's Archiv	Archiv für die gesammte Physiologie des Menschen und der Thiere.
Pharm. J.	Pharmaceutical Journal.
Pharm. Weekblad	Pharmaceutisch Weekblad.
Pharm. Zeit.	Pharmazeutische Zeitung.
Pharm. Zentr-h.	Pharmazeutische Zentralhalle.
Phil. Trans.	Philosophical Transactions of the Royal Society of London.
Proc. Amer. Physiol. Soc.	Proceedings of the American Physiological Society.
Proc. Roy. Soc.	Proceedings of the Royal Society.
Quart. J. exp. Physiol.	Quarterly Journal of experimental Physiology.
Rec. trav. chim.	Receuil des travaux chimiques des Pays-Bas et de la Belgique.
Trans. Path. Soc.	Transactions of the Pathological Society.
Zeitsch. anal. Chem.	Zeitschrift für analytische Chemie.
Zeitsch. angew. Chem.	Zeitschrift für angewandte Chemie.
Zeitsch. anorg. Chem.	Zeitschrift für anorganische Chemie.
Zeitsch. Biol	Zeitschrift für Biologie.
Zeitsch. Nahr. Genussm.	Zeitschrift für Untersuchung der Nahrungs- und Genussmitte.
Zeitsch. physikal. Chem.	Zeitschrift für physikalische Chemie, Stöchiometrie und Verwandtschaftslehre.
Zeitsch. physiol. Chem.	Hoppe-Seyler's Zeitschrift für physiologische Chemie.
Zeitsch. für Chem.	Zeitschrift für Chemie.

Abbreviated Titles	Patent Literature.
Eng. P.	English Patent.
Fr. P.	French Patent.
D.R.-P.	German Patent.
U.S.P.	United States Patent.
M. L. and B.	Farbwerke vormals Meister, Lucius und Bruning.
Fabr. Heyden,	Chemische Fabrik von Heyden.
Poulenc	Les Établissements Poulenc Frères.

ORGANIC COMPOUNDS OF ARSENIC AND ANTIMONY

CHAPTER I

CACODYL

Earliest Researches on Organic Arsenicals.

THE large number and diverse types of organo-arsenical compounds isolated and described during the last 150 years furnish ample evidence that the metalloid arsenic is endowed with a great capacity for combining with hydrocarbon radicals. Nevertheless this affinity has not manifested itself by the production of these compounds either in the mineral kingdom or as a result of the vital activities of living organisms. The special conditions under which this chemical attraction becomes effective have been, without exception, established by the art of the chemist. All the organo-arsenicals are synthetic products.[1]

Section I.—Cadet's Fuming Arsenical Liquid.

The earliest of these syntheses was brought about in a remarkably unpremeditated manner. In 1760 the mineral "cobolt" or smaltite, cobalt arsenide, became the subject of an inquiry by L. C. Cadet de Gassicourt, who was chiefly interested in extracting therefrom by the action of various acids cobalt

[1] A possible exception to this generalisation is noted on p. 54, in reference to the production of diethylarsine by the growth of moulds on carpets and wall-papers containing arsenical pigments. It is conceivable that this phenomenon might be realised with naturally occurring arseniferous materials altogether apart from the intervention of human activities, but hitherto this likely formation of organic arsenicals has not been recorded.

salts suitable as a basis for 'sympathetic' ink. The circumstance that smaltite is also a source of white arsenic led Cadet to examine the latter substance, although, apart from the common origin of the materials, there is no obvious connection between the latter experiment and those on cobalt preparations. The greater part of Cadet's memoir is devoted to the work on cobalt inks, but his "Histoire d'une liqueur fumante, tirée de l'arsenic" has led in the hands of subsequent workers to such important theoretical and practical results that it is of interest to record his procedure in his own words.

"Je prends deux onces d'arsenic, je le mets en poudre très fine dans un mortier de marbre; j'y ajoute deux onces de terre foliée de tartre bien préparé, j'enferme aussitôt ce mélange dans une cornue de verre lutée, que je place à nu dans un petit fourneau de réverbère. J'adapte à la cornue un récipient que je lutte, je la chauffe par degré, il en sort quelque temps après une liqueur un peu colorée, qui répand l'odeur d'ail la plus pénétrante, il passe ensuite une liqueur d'un rouge brun, qui remplit le ballon d'un nuage épais.

En continuant la distillation, il se sublime au col de la cornue une poudre noire, qui paroît être de la nature de celle que les Allemands appellent *Musken gifft* [Mücken Gift]; en françois, poison des mouches: on y trouve aussi du régule d'arsenic et une matière qui brûle comme le soufre lorsqu'on la présente à la flamme d'une bougie. Indépendamment de tous ces produits, on retire encore du col de la cornue un peu d'arsenic en forme de petits crystaux, et le résidu de la distillation est une matière charbonneuse qui répand une odeur d'ail sur les charbons ardens.

La première liqueur qui passe dans la distillation fait une vive effervescence avec l'alkali fixe; elle répand en même temps une si forte odeur d'ail, qu'il est impossible de la supporter: le vinaigre, les odeurs les plus fortes ne peuvent pas détruire celle qui reste aux vaisseaux lorsqu'ils en ont été impregnés, elle ne se dissipe qu'en la laissant plusieurs mois à l'air libre.

La dernière liqueur qui est d'un rouge brun, dépose au bout d'un certain temps une matière d'un beau jaune, que je soupçonne être une substance métallique qu'elle entraîne dans la distillation, et qui par son propre poids, l'oblige de se précipiter au fond de la première liqueur. Ce qui m'autorise à le croire, c'est que quand elle a déposé cette matière, que je nomme métallique, elle prend une couleur limpide et devient d'une si grande légéreté, qu'elle surnage la première liqueur comme feroit une huile essentielle sur l'eau.

Ces deux liqueurs ont une petite couleur ambrée et sont très-claires: agitées ensemble, elles forment comme une espèce de

nutritum ; mais si on les laisse réposer, elles reprennent leur première limpidité : si on les expose au contact de l'air, elles fument d'abord comme le phosphore, en répandant une très-forte odeur d'ail. Ces vapeurs ne s'enflamment pas à l'approche d'une bougie allumée ; mais en versant les deux liqueurs du récipient, elles ont enflammé avec une promptitude singulière le lut gras de ce premier vaisseau, ce qui me surprit beaucoup. Il est vrai que ce lut s'étoit si fort desséché par l'action du feu, que l'huile étoit devenue dans un état de résine. Quelques gouttes de la liqueur surnageante, mises dans un flacon rempli d'une once d'eau, ont paru s'y dissoudre en partie et ont communiqué à l'eau la qualité de fumer continuellement lorqu'elle éprouve l'action de l'air."

After summarising the results of his experiments on "cobolt" and sympathetic inks, Cadet reverts to his researches on the arsenical liquid in the following words :—

"Qu'enfin par l'intermède de la terre foliée du tartre,[1] on tire de l'arsenic une liqueur fumante très singulière qui prouve bien la grande volatilité de cette substance minérale que nous fournit le cobolt."

Cadet's account of his experiment is an accurate description of the appearances observed during the distillation of equal parts by weight of arsenious oxide and potassium acetate in a glass retort luted to a receiver of the same material. The proportions in which the reagents were employed were maintained by later investigators.

Two liquids passed over of which the more volatile exhibited acid properties, whereas the less volatile and reddish-brown liquid was specifically heavier and filled the receiver with thick fumes.

[1] The origin of the term "terre foliée de tartre bien preparé" and its German equivalent "gute blättrige Weinsteinerde" for potassium acetate (Crell's *Neuestes Chemisches Archiv.*, Erstes Band, Weimar, 1798, p. 212) is as follows.

At the time Cadet's experiment was performed the most esteemed form of vegetal alkali was potassium carbonate, or as it was then termed "sel de tartre" or "sel alkali fixe de tartre," the product of the calcination of cream of tartar (potassium hydrogen tartrate). A superior quality of potassium acetate was prepared by adding distilled vinegar to pure white "sel de tartre," the product which crystallised on concentrating the solution being then called "terre foliée de tartre." These terms were in common use by contemporaries of Cadet (*v.* "*Éleméns de Chymie théorique et pratique*," 1778, Vol. III, p. 39, by Guyton de Morveau, H. Maret, et Jean François Durande), and a current determination of the solubilities in water of "crème de tartre, sel de tartre," and "terre foliée de tartre" leaves no doubt as to the identity of these salts (*loc. cit.*, Vol. I, p. 356).

Both liquids had an intensely disagreeable and persistent odour resembling that of garlic. The heavier oily liquid deposited a yellow solid impurity and then assumed an amber colour; it was slightly soluble in water, to which it imparted the property of fuming in the air. When poured from the receiver it took fire spontaneously in air at the ordinary temperature. Cadet identified metallic arsenic and arsenious oxide as sublimation products and detected arsenic in the carbonaceous residue.

This experiment was repeated in Dijon by Guyton de Morveau, Maret, and Durande, who separated the two liquids and showed that the heavier oily one had the more intolerable stench and the property of inflammation in the air at the ordinary temperature.

"La liqueur rouge conserve même après le refroidissement la propriété de fumer toutes les fois que l'on débouche le flacon qui la contient et répand la même odeur atroce que rien ne peut détruire. . . .

Nous voulions examiner cette partie de la liqueur rouge qui se rassemble au fond du flacon. . . . Pour cela nous avions commencé à décanter le plus exactement qu'il étoit possible la liqueur surnageante; nous versâmes le reste sur un filtre de papier, à peine passa-t-il quelques gouttes, il s'éleva tout-à-coup une fumée infecte très épaisse qui formoit une colonne depuis le vase jusqu' au plafond, la matière fait vers les bords un petit mouvement d'ébullition, il en partit alors une belle flamme de couleur de rose, qui dura quelques instans; il n'y eut qu'un des côtés du papier du filtre de brûlé."

Following on this graphic account of the spontaneous inflammation of Cadet's fuming liquid, the authors conclude that this inflammability cannot be attributed merely to the concentration of vinegar by white arsenic, but rather to the union of these two substances to form a new compound. This supposition is confirmed by the red colour of the flame, by the formation of a sublimate on burning, and by the absence of any inflammable product (methane) on decomposing the liquid with caustic alkali. In view of the physiological activities of organic arsenicals, it is of interest to note the statement of these workers that although subjected for some time to the abominable and penetrating stench of this fuming liquid they experienced no personal inconvenience beyond a very disagreeable irritation of the throat.

The next investigation of Cadet's fuming arsenical liquid was undertaken by Louis Jacques Thénard,[1] who found that carbon

[1] *Annales de chimie*, 30 Vendémiaire An XIII [1804], **52**, 54.

dioxide and hydrocarbons were evolved during the distillation ; potassium carbonate remained in the retort and crystals of arsenious oxide were obtained by sublimation. Of the two liquids, the upper one was a solution of the lower in water and acetic acid. The horribly fetid odour and spontaneous inflammability noticed by Cadet and by the chemists of Dijon were due to the denser oily liquid. The spontaneous inflammation of this substance in air was regarded as being due to oxidation and hydration, the former reaction being the more important. After oxidation with chlorine the oily liquid gave the reactions of carbonic and acetic acids and inorganic arsenic. Thénard concluded that the fuming liquid was a complex arsenical acetate containing partially deoxidised arsenious oxide produced by the combination in the receiver of arsenious oxide, acetic acid, and an oily substance not further specified.

"Cette liqueur est un composé d'huile, d'acide acéteux et d'arsenic, que celui-ci y est probablement voisin de l'état metallique, et qu'elle doit être regardée comme une espèce de savon à base d'acide et d'arsenic ou comme une sorte d'acetite oleo-arsenical."

Section II.—Cacodyl and its Derivatives.

Although the qualitative results obtained by the early French chemists showed that Cadet's liquid was a product of considerable chemical interest, yet no further information regarding its constitution was forthcoming until Robert Wilhelm Bunsen undertook the dangerous and unpleasant task of making a quantitative examination of this malodorous and nauseating material. These investigations, carried out during a period of six years, 1837–43, are regarded as a classical model of organic research both on account of the very great experimental difficulties which were successfully overcome and because of the theoretical importance of the results.

Bunsen published his researches in two treatises. The first of these was a preliminary communication divided into two parts on "A series of Organic Compounds containing Arsenic as a Constituent,"[1] in which he described Cadet's fuming liquid as "Alkarsin," ascribing to it the composition $As(CH_3)_2$. This name was chosen from the circumstance that the compound was regarded as containing the elements of alcohol with the oxygen

[1] *Pogg. Ann.*, 1837, **40**, 219, **42**, 145 ; v. *Annalen*, 1837, **24**, 271 ; 1839, **31**, 175.

present in this substance replaced by arsenic. The initial letters of the words " alkohol " and arsenic were taken to form the name " alk-arsin " for the supposed arsenical analogue of alcohol.

Cadet's preparation was repeated on a considerable scale, a kilogram of the mixture containing equal parts by weight of arsenious oxide and potassium acetate being distilled from a glass retort in one operation. The temperature of the retort was gradually raised to redness; the two liquids distilled over accompanied by an appreciable amount of reduced arsenic. The gases evolved consisted principally of carbon dioxide, methane, and olefiant gas. Contrary to Thénard's statement, Bunsen could not detect hydrogen arsenide. The upper liquid was a solution of alkarsin and arsenious acid in acetone, acetic acid and water; the lower brown oily layer was crude alkarsin, of which more than 150 grams were obtained from a kilogram of the heated mixture.

Berzelius, who had followed the course of these difficult researches with the liveliest interest, suggested that alkarsin contained oxygen. This anticipation was confirmed by Bunsen,[1] who subsequently estimated the arsenic as well as the carbon and hydrogen in carefully purified samples of the fuming liquid, and arrived at the molecular formula $C_4H_{12}As_2O$ for the substance. Berzelius, from the viewpoint of the theory of radicals, regarded this compound as the oxide of a compound radical, $C_4H_{12}As_2$, for which he suggested the name " kakodyl " in reference to the disagreeable odour of its derivatives.[2]

Shortly after the publication of Bunsen's first treatise on alkarsin, J. B. Dumas intervened with an analysis of this material which appeared to confirm Bunsen's original view of the composition of the substance. The French chemist obtained the following percentages: C = 23·60, H = 5·66, As = 69·0; total, 98·26.[3] In his *Traité de Chimie*, 1844, **5**, 182, Dumas gives similar numbers, but states that he does not regard these analytical data as decisive owing to the experimental difficulties attending the purification and analysis of the arsenical constituent of Cadet's

[1] Bunsen, *Annalen*, 1839, **31**, 175.

[2] Kakodyl or cacodyl from κακὸς and ὕζη.

Following the modern usage it is preferable to consider C_2H_6As as the radical, cacodyl (symbol Kd), and $C_4H_{12}As_2$ as free cacodyl (Kd_2). A similar notation is employed for the cyanogen radical (CN = or Cy), whereas free cyanogen is C_2N_2 or Cy_2.

[3] *Annalen*, 1838, **27**, 148.

liquid. Dumas also states (*Traité de Chimie*, **7**, 273) that this liquid contains cacodyl mixed with cacodyl oxide and may sometimes consist of almost pure cacodyl. Although this view is scarcely confirmed by other workers, yet it is certain that the relative proportions of the two constituents would be modified by distillation. Fractionation would lead to separation of cacodyl oxide (b.p. 120°) from cacodyl (b.p. 170°). Possibly Bunsen's earlier analyses and Dumas's determinations were made on the less volatile fractions.

Bunsen's second treatise on the arsenical liquid, which is entitled " Researches in the Cacodyl Series," is divided into three sections.[1] In the first he deals with cacodyl oxide and its derivatives, in the second with free cacodyl, and in the third with cacodylic acid, the oxidation product of cacodyl oxide. These investigations, which were long afterwards extended by Baeyer, have completely elucidated the nature of Cadet's liquid.

A systematic examination of this material showed that its pungent constituents were two substances containing arsenic. The main constituent was cacodyl oxide containing the metalloid associated with carbon, hydrogen, and oxygen ; it has the composition and vapour density indicated by the formula $As_2C_4H_{12}O$. The second compound, which was present only in small amount, is free cacodyl consisting of the three elements arsenic, carbon, and hydrogen ; its empirical formula is AsC_2H_6, but the vapour density corresponds with the molecular formula $As_2C_4H_{12}$.

It is obvious from the observations of all the experimentalists from Cadet downwards that the following equation does not represent quantitatively the course of the distillation :

$$As_2O_3 + 4CH_3{\cdot}CO_2K = [As(CH_3)_2]_2O + 2K_2CO_3 + CO_2$$
Cacodyl oxide.

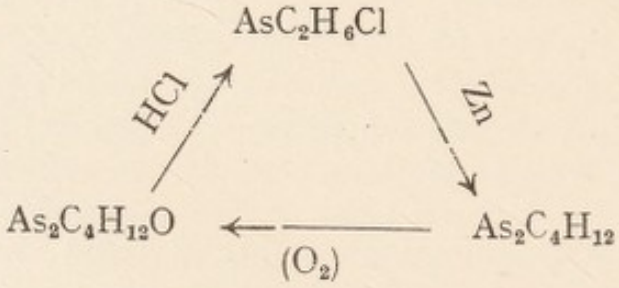
Reduction of arsenious oxide to metallic arsenic invariably occurs, and the charring of the acetate is accompanied by an evolution of methane and unsaturated hydrocarbons. A portion of the cacodyl oxide also undergoes reduction with the formation of a certain amount of free cacodyl, $[As(CH_3)_2]_2$. It is to the presence of this constituent that the fuming and inflammability of Cadet's liquid are due. Pure cacodyl oxide (Bunsen's " paracacodyl oxide ") obtained by hydrolysing cacodyl chloride with potassium hydroxide neither fumes nor takes fire in air.[2]

[1] *Annalen*, 1841, **37**, 1–57 ; 1842, **42**, 14–46 ; 1843, **46**, 1–48.
[2] Baeyer, *ibid*, 1858, **107**, 282.

Free cacodyl was most conveniently obtained by the following series of reactions. Mercuric chloride added to crude cacodyl oxide (Cadet's liquid) yielded the sparingly soluble mercurichloride, $[As(CH_3)_2]_2O,2HgCl_2$.

This product, when distilled with fuming hydrochloric acid, yielded a volatile oil having the molecular formula AsC_2H_6Cl, and this chloride when heated with zinc in an inert atmosphere lost its chlorine and became converted into free cacodyl, $As_2C_4H_{12}$.

The following diagram illustrates the relationship between the three arsenical substances :—



These compounds contain the cacodyl group $[AsC_2H_6]$ in common, and groups such as this arsenical complex, which pass without change in composition from one compound to another in the course of chemical change, are called compound radicals. This particular group is of special interest as being one of the first compound radicals to be definitely recognised.

The recognition by Bunsen of the cacodyl complex, possessing many properties comparable with those of the elementary radicals, afforded striking experimental confirmation of the theory of compound radicals which had then been recently advocated by Berzelius.[1] The close analogy subsisting between the cacodyl radical and the metallic elements potassium and thallium is illustrated in the following series :—

CACODYL.	CACODYL OXIDE.
$As_2C_4H_{12} = [AsC_2H_6]_2$	$[AsC_2H_6]_2O$
Kd_2	Kd_2O

[1] Berzelius's estimate of the cacodyl research was expressed in the following words :—

"Bunsen hat durch diese Untersuchung seinen Namen in der Wissenschaft unvergesslich gemacht. Die Mitwelt ist es schuldig, ihm ihre Erkenntlichkeit für die Ausmittelung eines so wichtigen und so gefährlich zu bearbeitenden Gegenstandes auszudrücken, eine Forschung, von der wohl mit Recht gesagt werden kann, dass sie wenig zu wünschen übrig lässt."—(*Berzelius' Jahresber.*, 1842, **21**, 503.)

METAL.	METALLIC OXIDE.
$2K$	K_2O
Tl_2	Tl_2O
CACODYL CHLORIDE.	CACODYL TRICHLORIDE.
$[AsC_2H_6]Cl$	$[AsC_2H_6]Cl_3$
$KdCl$	$KdCl_3$
METALLIC CHLORIDE.	METALLIC TRICHLORIDE.
KCl	$TlCl_3$
$TlCl$	

In an examination of Cadet's reaction, Dehn[1] distilled 250 grams of arsenious oxide and 250 grams of anhydrous potassium acetate in a short-necked hard glass half-litre flask placed in a hemispherical iron sand-bath, which was gradually heated to redness over a period of 8–10 hours. The flask was connected in series with a Liebig condenser, a filter flask receiver, and several wash-bottles containing mercuric oxide. By the most careful and long-continued heating the largest yield of cacodyl oxide was 25 per cent., increased by the amount of cacodylic acid present in the solutions to more than 30 per cent. of crude cacodyl oxide, cacodyl, and cacodylic acid. This mixture was utilised in the production of dimethylarsine (p. 37).

The distillate in the receiver separated as usual into three layers, the two liquid layers and the lowest solid layer composed of arsenic and polymerised products of arsenomethane (p. 40).

Although spontaneously inflammable in air, cacodyl can be oxidised without decomposition by the addition of a moderate amount of oxygen, or preferably by the action of moist mercuric oxide. Under these conditions it changes first to cacodyl oxide, and then to an extremely soluble substance, which, having acidic properties, is appropriately termed cacodylic acid. In his preliminary treatise, Bunsen gave to this acid the name "Alkargen," as being produced by addition of oxygen to alkarsin.

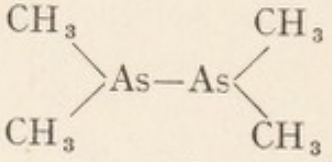
$$Kd_2 + O = Kd_2O. \quad Kd_2O + O_2 + H_2O = 2KdO{\cdot}OH.$$

Bunsen examined the physiological action of cacodyl and its derivatives, and made the remarkable discovery that although cacodyl and its oxide are both extremely poisonous, yet cacodylic

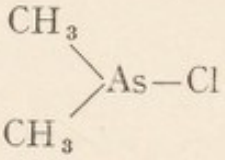
[1] *Amer. Chem. J.*, 1906, **35**, 2.

acid, containing 54 per cent. of soluble arsenic, is nevertheless practically non-poisonous. In the form of its sodium salt, cacodylic acid has been employed medicinally, although at present it is largely superseded by arsenical preparations containing aromatic groups.

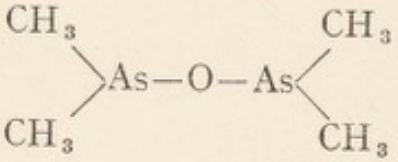
Bunsen did not investigate further the constitution of the cacodyl radical, and it should be remembered that at the time his researches were carried out the hydrocarbon radicals had not been recognised. Subsequent investigations by Frankland, Kolbe, Cahours, Landolt, von Baeyer, and others elucidated the inner constitution of cacodyl, so that it is now known to consist of tervalent arsenic associated with two methyl radicals :—



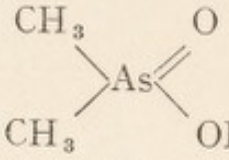
CACODYL, b.p. 170°.



CACODYL CHLORIDE, b.p. 109°.



CACODYL OXIDE, b.p. 120°.



CACODYLIC ACID.

In all these compounds but the last arsenic is tervalent ; in cacodylic acid it is quinquevalent.

In addition to the foregoing cacodyl oxide and chloride Bunsen described the bromide, iodide, cyanide, and mono- and di-sulphides of cacodyl. The existence of these compounds emphasises still further the metallic character of the cacodyl radical.

Cacodyl,[1] $[As(CH_3)_2]_2$, heavy oil with repulsive odour, sparingly soluble in water ; b.p. 170° ; solidifying at − 6° to square plates ; vapour density 7·1 corresponding with double formula. Obtained as a by-product in Cadet's reaction. Prepared by heating cacodyl chloride with zinc in carbon dioxide at 100°. It is immediately inflammable in air or chlorine. By regulated oxidation with moist air or preferably mercuric oxide it yields successively cacodyl oxide and cacodylic acid. It behaves as a univalent or tervalent radical combining with sulphur and

[1] Bunsen, *Annalen*, 1842, **42**, 14.

the halogens. Methyl iodide[1] interacts with cacodyl to yield tetramethylarsonium iodide and cacodyl iodide, $[As(CH_3)_2]_2 + 2CH_3I = As(CH_3)_4I + As(CH_3)_2I$. Methyl bromide reacts similarly with cacodyl. At 400–500° cacodyl decomposes, yielding arsenic and hydrocarbons but no free carbon.

Owing to the very inflammable nature of cacodyl, its isolation from cacodyl chloride by the action of metals (zinc, iron, and tin) and other reducing agents presents considerable experimental difficulties.

The chloride, which must be perfectly dry and free from cacodyl oxide, was first digested with fuming hydrochloric acid

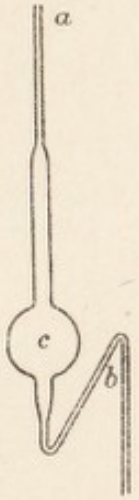


FIG. 1.

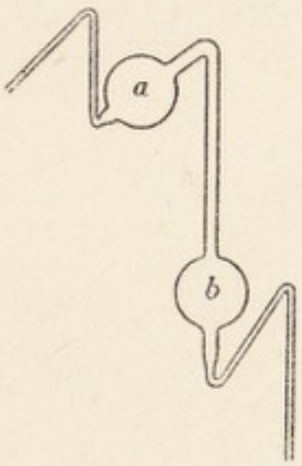


FIG. 2.

and dried over calcium chloride and quicklime in the bulb *c* of the drying tube (Fig. 1). This tube was filled with dry carbon dioxide and sealed up until required, when the upper end *a* was opened and connected with an air pump; the lower end *b* was opened under the hydrochloric acid covering the cacodyl chloride so that this liquid was drawn into the drying bulb, the ends of which were again sealed.

The upper bulb *a* of the reduction apparatus Fig. 2 was charged with carefully-cleaned zinc foil cut into small shavings (this being the best reducing agent). The tube was filled with carbon dioxide, dried cacodyl chloride drawn into bulb *a*, the ends sealed off and the apparatus heated to 100° until the bulb *a* on cooling showed a solid mass of zinc chloride. The

[1] Cahours, *Annalen*, 1862, **122**, 209.

heated tube was opened under cold boiled out water, the upper bulb heated to drive out carbon dioxide and cooled to suck in water which was tilted into the reduction bulb. Zinc chloride dissolved and cacodyl formed a heavy layer which was drawn off into drying bulb (Fig. 1). The reduction was repeated with fresh zinc in bulb *a* until no more action was observed, then the cacodyl was distilled in carbon dioxide from the upper bulb *a* to the lower. When pure it was a colourless oil crystallising at $-6°$.[1]

The constitution of cacodyl was first determined by Cahours and Riche,[2] who obtained this compound together with trimethylarsine and tetramethylarsonium iodide by the action of methyl iodide on the alloy of arsenic and sodium.[3] Frankland had already suggested this structure for cacodyl based on the analogies subsisting between the substance and the organo-metallic compounds.

Cacodyl oxide, $[As(CH_3)_2]_2O$, heavy oil, sp. gr. 1·462/15°, not fuming in air and non-inflammable when free from cacodyl; b.p. 120°, crystallising at −25°. Sparingly soluble in water, intolerable tear-exciting odour. Vapour density = 7·55, corresponding with the foregoing formula. Obtained as the main constituent of Cadet's liquid; prepared by distilling cacodyl chloride with aqueous potassium hydroxide and subsequently rectifying the dried oil in an atmosphere of carbon dioxide.[4]

Cacodyl oxide mercuri-chloride, $[As(CH_3)_2]_2O,2HgCl_2$, rhombic

[1] Bunsen, *Annalen*, 1842, **42**, 28-30.

[2] *Compt. rend.*, 1854, **39**, 541.

[3] The simultaneous formation of cacodyl (tetramethyldiarsine) and trimethylarsine from sodium-arsenic alloy suggests the presence in this material of two compounds, $As–Na_2$ and $As–Na_3$. The latter has been obtained in a crystalline condition by heating arsenic with excess of sodium and removing the unchanged alkali metal with liquid ammonia. An alloy approximating to this composition was utilised by Landolt in the synthesis of ethylcacodyl and triethylarsine. An alloy with excess of arsenic (3 parts As, 1 part Na) has been prepared, so that it is probably from some compound of this type that cacodyl derivatives are formed by the action of alkyl iodides.

Arsenical alloys of sodium and potassium, *v.* Gmelin-Kraut, *Handbuch der Anorganischen Chemie*, 1908, III, 2 pp., 514, 531.

Saunders, *Chem. News*, 1899, **79**, 66; Soubeiran, *J. Pharm.*, 1830, **16**, 353.

Roscoe and Schorlemmer, *Treatise on Chemistry*, 1913, 2, pp. 219, 353; Meyer, *Zeitsch. anorg. Chem.*, 1905, **18**, 1382.

[4] Baeyer, *Annalen*, 1858, **107**, 282.

plates, by the direct combination of its generators in alcoholic solution. Soluble in 28·8 parts of boiling water. Yields cacodyl chloride on distillation with fuming hydrochloric acid.

The production of this mercurichloride[1] occurs quantitatively in the presence of concentrated hydrochloric acid, and affords the most practicable method of obtaining successively pure cacodyl chloride and cacodyl oxide.

The crude Cadet's arsenical liquid is mixed with excess of concentrated hydrochloric acid and treated with excess of powdered mercuric chloride. The mixture sets to a thick, crystalline magma which when rendered liquid by addition of more hydrochloric acid is distilled. Cacodyl chloride passes over and is dried with calcium chloride, and freed from excess of hydrochloric acid with powdered calcium carbonate and rectified. This purified cacodyl chloride when distilled with aqueous potassium or sodium hydroxide yields cacodyl oxide, which passes over in steam. The oily distillate, when dried and rectified, consists of pure cacodyl oxide.

It is noteworthy that cacodyl chloride on treatment with alkalis yields the oxide and not the hydroxide, $As(CH_3)_2 \cdot OH$; the latter product has not hitherto been isolated.

Cacodyl chloride, $As(CH_3)_2Cl$, colourless ethereal non-fuming liquid heavier than water and insoluble therein; b.p. slightly above 100°; very penetrating and stupefying odour, and an intensely irritating action on the eyes and nose; vapour density 4·56, corresponding with empirical formula. *Cacodyl bromide* and *iodide* yellow oils, the latter boils at 160°.[2] These cacodyl halides show a great tendency to form compounds with cacodyl oxide. The three compounds corresponding with the general formula $6As(CH_3)_2Hal,As_2(CH_3)_4 \cdot O$ were described by Bunsen, but their existence is questioned by Baeyer.[3]

Co-ordinated Compounds with Metallic Salts.

With platinic chloride, cacodyl chloride yields a noteworthy series of co-ordinated compounds, compared by Bunsen with Reiset's platinammines.[4]

[1] *Amer. Chem. J.*, 1908, **40**, 127. Dehn suggests that this mercurichloride is in reality a double compound of cacodyl chloride and mercuric chloride.

[2] Cahours and Riche, *Compt. rend.*, 1854, **39**, 541.

[3] Ostwald's *Klassiker der exakten Wissenschaften*, 1891, **27**, 145.

[4] *Berz. Jahresber.*, 1842, **21**, 500.

Cacodyl platinichloride, $2As(CH_3)_2Cl,PtCl_4$, brick-red precipitate soluble in hot water to a colourless solution from which the co-ordinated compound, $As_2(CH_3)_4O,PtCl_2,H_2O$ separates in colourless needles, becoming dehydrated and yellow at 160°. Double decomposition with KBr, KI, and silver oxy-salts yields respectively $As_2(CH_3)_4O,PtBr_2,H_2O$ (colourless) ; $As_2(CH_3)_4O,PtI_2,H_2O$ (yellow) ; $Kd_2O,Pt(NO_3)_2,H_2O$ and $Kd_2O,PtSO_4,H_2O$. $2KdCl,Cu_2Cl_2$, white ppt.

Cacodyl cyanide, $As(CH_3)_2{\cdot}CN$.[1]

Lustrous colourless prisms ; m.p. 33° ; b.p. 140°. This remarkable substance, the most poisonous of the cacodyl series, is of theoretical interest as being composed of the first two organic radicals to be recognised and isolated. It is produced by double decomposition from cacodyl oxide and hydrocyanic acid, but prepared more conveniently by the interaction of cacodyl and mercuric cyanide.

$$[As(CH_3)_2]_2O + 2HCN = H_2O + 2As(CH_3)_2{\cdot}CN.$$
$$[As(CH_3)_2]_2 + Hg(CN)_2 = Hg + 2As(CH_3)_2{\cdot}CN.$$

The cyanide has a remarkable capacity for crystallising and it sublimes readily at the ordinary temperature. Sparingly soluble in water, it dissolves readily in alcohol or ether. A few grains subliming into the atmosphere of a room produce rapidly numbness of hands and feet, giddiness and stupor leading to complete unconsciousness. These symptoms are nevertheless only of short duration and without after effect providing that exposure to this poisonous substance is not unduly prolonged.

Cacodyl sulphide, $[As(CH_3)_2]_2S$, colourless oil with repulsive odour of mercaptan and cacodyl oxide, b.p. well above 100°, distillable in steam, insoluble in water, miscible with ether or alcohol : vapour density at 215° corresponding with foregoing formula. Prepared by distilling barium hydrosulphide with cacodyl chloride, or with the acid aqueous upper layer obtained in Cadet's distillation.[2]

$$2KdCl+Ba(SH)_2=Kd_2S+H_2S+BaCl_2.$$
$$Kd_2O+2CH_3CO_2H+Ba(SH)_2 = Kd_2S+H_2S+H_2O+(CH_3CO_2)_2Ba.$$

[1] Bunsen, *Annalen*, 1841, **37**, 23.
[2] Dumas, *Traité de Chimie*, 1844, **7**, 273.

Cacodyl disulphide,[1] $[As(CH_3)_2]_2S_2$, white, rhombic plates; m.p. 50°; odour of asafœtida produced by the direct combination of the foregoing sulphide with sulphur and crystallised from dilute alcohol below 40°. Sulphuretted hydrogen passed through aqueous and alcoholic solutions of cacodylic acid yields respectively cacodyl sulphide and disulphide.

Cacodyl cupri-sulphide,[2] $Kd_2S,3CuS$, crystallises from alcoholic solutions of cacodyl sulphide and copper nitrate in well-defined, lustrous octahedra.

Cacodylic acid.[3] *Dimethylarsinic acid,* $As(CH_3)_2O{\cdot}OH$; inodorous, colourless, obliquely truncated prisms; m.p. 200°. Solubility :—1 in $0{\cdot}5H_2O$, 1 in 4 alcohol 90 %. Obtained in almost quantitative yield (95 %) by the oxidation of cacodyl oxide (76 grams) with mercuric oxide (218 grams) under water. Remarkably stable; not decomposed by the most powerful oxidising agents (HNO_3, CrO_3, $KMnO_4$, or aqua regia). Reduced by phosphorous acid to cacodyl oxide; this reducing agent acts specifically on analogues of arsenic acid. Cacodylic acid is also reduced by stannous chloride.

Experiments by Bunsen[4] on frogs and by Kürschner on rabbits showed that cacodylic acid is not acutely poisonous even in large doses. Six grains introduced into the stomach of a rabbit had no ill effect; 7 grains injected into the jugular vein of this animal and 4 grains introduced into the lungs were similarly innocuous.[5] The acid and its salts pass through the system principally without change, being excreted in the urine, but a portion undergoes reduction to cacodyl oxide which is exhaled.

Cacodylic acid is monobasic; its salts are soluble in water and generally non-crystalline: it has a slightly acid taste and reaction, being neutral to methyl orange and acid to phenolphthalein, and it exhibits amphoteric properties yielding the following unstable compounds with hydrogen halides: $As(CH_3)_2O_2H,HCl(HBr)$; the composition of the hydrofluoride is doubtful. Prolonged treatment with hydrogen chloride converts dry cacodylic acid into methylarsenious chloride, $As(CH_3)_2O_2H + 3HCl = As(CH_3)Cl_2 + CH_3Cl + 2H_2O$.

[1] Dumas, *loc. cit.*, 282.
[2] Bunsen, *Annalen*, 1841, **37**, 18; 1843, **46**, 18.
[3] Bunsen, *ibid.*, 1843, **46**, 2.
[4] Bunsen, *ibid.*, 1843, **46**, 11.
[5] *Cf.* Marshall and Green, *Amer. Chem. J.*, 1886, **8**, 128; *Zeit. physiol. Chem.*, 1905, **49**, 410.

The *silver* salts are crystallisable, $As(CH_3)_2O{\cdot}OAg$, needles; $As(CH_3)_2O{\cdot}OAg,2As(CH_3)_2O_2H$, needles; $As(CH_3)_2O{\cdot}OAg,AgNO_3$, scales. Cacodylates of the rare earths,[1] $[As(CH_3)_2O_2]_3R,xH_2O$.

The following cacodylates[2] have been used in medicine :—

Sodium Cacodylate (Ph. Helv.), $As(CH_3)_2O_2Na,3H_2O$. Arsenic and water contents 35 and 18–25% respectively. Solubility, 1 in $0{\cdot}5H_2O$.

Magnesium Cacodylate, $[As(CH_3)_2O_2]_2Mg,?H_2O$. Solubility, 1 in $3H_2O$.

Ferric Cacodylate, $[As(CH_3)_2O_2]_3Fe$, yellowish powder. Solubility, 1 in $15H_2O$.

Strychnine Cacodylate, $C_{21}H_{22}O_2N_2,As(CH_3)_2O_2H$. White, crystalline powder.

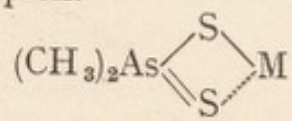
Guaiacol Cacodylate, $As(CH_3)_2O_2H,HO{\cdot}C_6H_4{\cdot}OCH_3$.

[3] *Antipyrine Cacodylate*, $As(CH_3)_2O_2H,C_{11}H_{12}ON_2$, crystallising from alcoholic solution of its generators. Soluble in water or alcohol; m.p. below 100°.

In the presence of one molecular proportion of caustic soda, cacodylic acid behaves as a monobasic acid, but with excess of this alkali it functions in the tribasic form, $(CH_3)_2As(OH)_3$, but only in strongly alkaline solutions.[4]

Although free cacodylic acid is converted into cacodyl sulphides by sulphuretted hydrogen in aqueous or alcoholic solution (*v. supra*), its salts on similar treatment are transformed into *thiocacodylates* which can also be prepared from cacodyl disulphide and metallic salts. The thiocacodylates of the heavy metals are remarkably crystalline and insoluble, the *lead* salt, $(KdS_2)_2Pb$, is colourless; the *cuprous*, $(KdS_2)_2Cu_2$, *bismuth*, $(KdS_2)_3Bi$, *antimony* $(KdS_2)_3Sb$, and *aurous*, $(KdS_2)Au$, are yellow.

The properties of these thiocacodylates suggest the presence of a co-ordination complex.



Cacodyl trichloride, $(CH_3)_2AsCl_3$, prisms or leaflets from ether; fumes in air, hydrolysed by water and decomposed even at 40–50° into methylarsenious chloride, $AsMeCl_2$, and methyl chloride. Obtained either by passing chlorine into cacodyl chloride in carbon bisulphide solution or by adding powdered

[1] Whittemore and James, *J. Amer. Chem. Soc.*, 1913, **35**, 127

[2] Martindale, *Congress of Applied Chemistry*, 1909.

[3] Barthe, *Pharm. J.*, 1915, **94**, 99.

[4] Hantzsch, *Ber*, 1904, **37**, 1076.

cacodylic acid slowly to phosphorus pentachloride covered with a layer of dry ether.[1]

Bunsen described a complex product of the action of hydrochloric acid on cacodylic acid as " basic cacodyl superchloride." It is probably the additive compound $As(CH_3)_2O_2H,HCl$ (*v. supra*) which on distillation yields a mixture of methylarsenious chloride and cacodyl oxide. This mixture when redistilled with phosphoric anhydride furnishes pure methylarsenious chloride.[2]

Section III.—Homologues of Cacodyl.

An important step in advance was made in 1853 when Landolt showed that a homologue of cacodyl could be synthesised by treating the alloy of arsenic and sodium with ethyl iodide.[3] This process was afterwards applied by Cahours and Riche to the synthesis of cacodyl itself and by other workers to cacodyl homologues containing propyl, butyl, and amyl groups.

Ethylcacodyl. Tetraethyldiarsine, $[As(C_2H_5)_2]_2$.

Metallic arsenic in powder was heated in a furnace till it began to fume; small pieces of sodium were added slowly till the mixture assumed a liquid consistence which occurred when the weight of metal added was equal to that of the metalloid ($As - Na_3 = 75 : 69$). The product on cooling was a silver-white alloy with crystalline fracture. Being very oxidisable, the alloy was kept in closely-stoppered bottles filled with quartz sand; it was decomposed by water with evolution of arsine.

This sodium arsenide, powdered up with 4 to 5 times its weight of quartz sand, was introduced into short-necked flasks, ethyl iodide was added, and the flasks were filled with carbon dioxide and fitted to a reflux apparatus. The reaction was so vigorous that ethyl iodide distilled away and was replaced so long as reaction ensued. About 2 oz. of mixed volatile ethyl arsenides were obtained from a pound of ethyl iodide. This volatile product on fractional distillation in an atmosphere of carbon dioxide yielded ethylcacodyl boiling at 185–190° and triethylarsine boiling at 140°/736 mm. The former is also obtained by extracting with ether the product of the reaction between excess of ethyl iodide and sodium arsenide. The ethereal extract is mixed with

[1] Baeyer, *Annalen*, 1858, **107**, 263.

[2] Baeyer, *loc. cit.*, p. 273.

[3] Hans Landolt, *Inaug. Diss.*, Breslau, 1853; *Annalen*, 1854, **89**, 316; 1854, **92**, 365.

absolute alcohol, ether removed and the alcoholic residue diluted with water, when ethylcacodyl is precipitated, whilst tetraethylarsonium iodide (formed by the action of ethyl iodide on triethylarsine) remains dissolved.

Ethylcacodyl is a pale yellow very refractive oil, heavier than water, with disagreeable alliaceous odour. It rapidly absorbs oxygen from the air, bursting into a dull flame which gives off arsenious oxide. By concentrated nitric acid it is oxidised completely with generation of light and heat. Dilute nitric acid gives rise to a light red powder slowly turning brown, which on exposure to the atmosphere finally becomes white. This product is apparently analogous to Bunsen's "erytarsin," $C_4H_{12}As_6O_3$,[1] a red amorphous substance arising as a by-product in the preparation of cacodyl chloride or as a phase in the partial oxidation of cacodyl or its oxide.

Unlike triethylarsine, ethylcacodyl has a powerful reducing action on salts of silver, mercury, and the noble metals. It combines directly with oxygen, sulphur, and the halogens. The additive compounds $[As(C_2H_5)_2]_2O$, $[As(C_2H_5)_2]_2S$, and $As(C_2H_5)_2Cl$ are oily liquids with repulsive and tear-exciting odours. The iodide, $As(C_2H_5)_2I$, an oil insoluble in water and boiling at 228–232°, regenerates ethylcacodyl with zinc amalgam.

Diethylarsinic acid, Ethylcacodylic acid,[2] $As(C_2H_5)_2O{\cdot}OH$, lustrous leaflets; m.p. 190°; very soluble in water, and resembling cacodylic acid in chemical properties. *Acid barium* salt, $[As(C_2H_5)_2O]_2Ba,As(C_2H_5)_2O_2H,2H_2O$, crystalline, very soluble in water, less so in alcohol. This acid is prepared either by the regulated oxidation of ethylcacodyl in alcoholic solution by atmospheric oxygen, or according to Bunsen's process by shaking ethylcacodyl under water with finely-divided mercuric oxide. The solution of mercuric diethylarsinate treated with excess of baryta water precipitates mercuric oxide; the filtrate is treated with carbon dioxide to precipitate excess of barium hydroxide, and the solution of barium diethylarsinate carefully acidified with sulphuric acid. On concentrating the filtrate from barium sulphate, pure diethylarsinic acid separates.

Higher Aliphatic Homologues of Cacodyl.

The far-reaching results of Cadet's experiment as systematically investigated by Bunsen led naturally to other researches

[1] Bunsen, *Annalen*, 1842, **42**, 42; *cf.* page 41.

[2] Landolt, *J. pr. Chem.*, 1854, **63**, 283; *Annalen*, 1854, **92**, 365.

in which potassium acetate was replaced in this condensation by the corresponding salts of homologous acids of the acetic series. There is, however, very little definite evidence derivable from the published results of these inquiries.

Wöhler,[1] on distilling a mixture of equal parts by weight of potassium butyrate and arsenious oxide, obtained, as in Cadet's distillation, a mixture of two liquids together with a considerable proportion of reduced arsenic and some malodorous gas. The heavier oily liquid, although not spontaneously inflammable, burnt with a white, smoky flame giving off an arsenical odour ; it yielded a crystalline, white precipitate with mercuric chloride, recalling the double compound of cacodyl and the mercury salt. This inodorous product when boiled with hydrochloric acid and zinc shavings evolved an odour resembling that of free cacodyl. When boiled with concentrated hydrochloric acid the oily distillate gave off a pungent odour affecting the mucous membranes of the nose and eyes. These reactions are all highly suggestive of cacodyl derivatives, but whether they are to be attributed to cacodyl oxide itself, either alone or mixed with free cacodyl, or whether they are due to homologues of these compounds, has not been determined.

Similar inconclusive results were obtained by Gibbs[2] on distilling equal parts by weight of white arsenic and potassium valerate. An oily, malodorous liquid was obtained yielding a copious white precipitate with mercuric chloride, but no definite chemical substances were isolated.

In the absence of further evidence on the formation of homologous compounds, the production of cacodyl oxide and cacodyl from potassium acetate and arsenious oxide is still to be regarded as a unique reaction.

Mixed Cacodyl Derivatives.—The discovery of secondary aliphatic arsines has now furnished a synthetic method for producing simple and mixed cacodyls. For instance, dimethylarsine and di*iso*amylarsenious chloride give rise to *dimethyldi*iso*amylcacodyl.*[3]

$$(CH_3)_2AsH + (C_5H_{11})_2AsCl = (CH_3)_2{\cdot}As{\cdot}As(C_5H_{11})_2 + HCl.$$

[1] *Annalen*, 1848, **68**, 127.
[2] *Sillimann's Amer. J.*, [ii], **15**, 118 ; *Annalen*, 1853, **86**, 222.
[3] Dehn, *Amer. Chem. J.*, 1908, **40**, 123.

CHAPTER II

Aliphatic Arsenicals and Antimonials

Syntheses of Alkyl Organo-metalloidal Compounds containing Arsenic and Antimony

After Bunsen's illuminating researches, the next advance in the study of organic derivatives of arsenic and antimony was made on the theoretical side by E. Frankland, who in 1849, as the result of his researches on hydrocarbon radicals, put forward the view that cacodyl is a compound of arsenic and the radical methyl. Frankland was led to this conclusion by his discovery that the organo-metallic derivatives of zinc are obtained by the action of this metal on alkyl iodides. Whereupon he suggested that a similar reaction between arsenic and methyl and ethyl iodides would probably lead to cacodyl and its next homologue respectively.[1]

Kolbe, who had previously collaborated with Frankland in a study of the action of potassium on ethyl cyanide,[2] came subsequently to a similar conclusion, and in 1850[3] gave in the notation of that epoch the correct interpretation of the cacodyl reaction

$$2KO(C_2H_3)C_2O_3 + AsO_3 = (C_2H_3)_2AsO + 2KOCO_2 + 2CO_2,$$

which corresponds with the modern equation given on page 7. His views on the cacodyl radical itself were expressed as follows: "Ich trage kein Bedenken diese Frage bejahend zu beantworten und glaube vor Allem das Kakodyl als ein solches gepaartes Radical ausprechen zu müssen, worin 2 Aeq. Methyl den Paarling von 1 Aeg. Arsenik ausmachen: Kakodyl = $(C_2H_3)_2As$."

[1] Frankland, *Annalen*, 1849, **71**, 215.
[2] Frankland and Kolbe, *Annalen*, 1848, **65**, 269.
[3] Kolbe, *Annalen*, 1850, **75**, 218; **76**, 30.

Interpreted by modern notation this formulation gives $(CH_3)_2As$ as the formula for cacodyl.

This hypothesis was confirmed in 1853 by the synthesis of cacodyl by Cahours and Riche, but the initial step towards the realisation of this prediction was taken by Löwig and Schweitzer,[1] who in 1850 prepared the first organic derivative containing antimony.

Section I.—General Reactions. 1. *Interaction of Alkyl Halides and Alloys of Arsenic and Antimony.*

An alloy of antimony and potassium was prepared by igniting at white heat in a covered crucible an intimate mixture of five parts of crude potassium hydrogen tartrate (cream of tartar) and four parts of antimony. After being cooled in the absence of air the product formed a crystalline regulus having a distinctly metallic lustre. The alloy containing 12 per cent. of potassium was decomposed by water liberating hydrogen ; it oxidised on exposure to air, taking fire when in pulverulent form. To avoid this inflammation the alloy was ground up with two to three parts of fine quartz sand and treated in small 2 to 3 oz. flasks with sufficient ethyl iodide to moisten the solid mixture. The experiment was conducted in an inert atmosphere ; a violent reaction set in so that the excess of ethyl iodide boiled away.

The residue, rectified in an atmosphere of carbon dioxide, yielded triethylstibine as a colourless, highly refractive liquid having an unpleasant odour resembling that of onions. The oil took fire in air at the ordinary temperature, burning with a highly luminous white flame, and when projected in a fine stream into oxygen gave a dazzling light.

The production of triethylstibine from the antimony-potassium alloy was also effected with ethyl chloride and ethyl bromide, but the iodide was preferred. It is probable that the crystalline by-product noticed by Löwig and Schweitzer when ethyl iodide was employed was tetraethylstibonium iodide.

This initial discovery in the antimony series was speedily followed by a similar investigation by Landolt in 1851,[2] who treated the antimony–potassium alloy with methyl iodide, thus obtaining trimethylstibine and tetramethylstibonium iodide.

[1] *Mitth. d. Zürch. Naturforsch. Gesellschaft*, 1850, **45**, 1 ; *Annalen*, 1850, **75**, 315, 327.

[2] *Annalen*, 1851, **78**, 91.

The interaction of alkyl halides on antimony-potassium alloy is a simpler chemical change than that arising from the corresponding experiment in the arsenical series. In the latter condensation,[1] Landolt discovered three substances, triethylarsine, tetraethylarsonium iodide, and ethylcacodyl.[2] Cahours and Riche subsequently obtained a similar result using methyl iodide, when they isolated tetramethylarsonium iodide, trimethylarsine, and cacodyl.

In these syntheses of organic arsenicals the alloy of arsenic and sodium or potassium was employed. Other arsenical alloys have been utilised giving similar results. Methyl iodide[3] acting on zinc and cadmium alloys of arsenic at 180° leads to the double salts $2As(CH_3)_4I,ZnI_2$ and $2As(CH_3)_4I,CdI_2$ respectively. Ethyl iodide[4] and these alloys yield the corresponding complex iodides $2As(C_2H_5)_4I,ZnI_2$ and $2As(C_2H_5)_4I,CdI_2$. From these double salts the quaternary iodide is obtained by treatment with caustic alkali.

2. *Interaction of Alkyl Halides and Arsenic or Antimony.*

A further variant of this experiment is to employ free arsenic with the alkyl iodide in sealed tubes at 160–200°, when methyl iodide[5] gives rise to the double salt $As(CH_3)_4I,AsI_3$, and ethyl iodide[6] yields $As(C_2H_5)_4I,AsI_3$. Treatment of these complex iodides with caustic alkali decomposes the arsenious iodide into potassium arsenite and iodide liberating the quaternary iodide.

Amorphous arsenic has since been recommended for this purpose. It is prepared by reducing a solution of arsenious oxide in hydrochloric acid with stannous chloride or sodium hypophosphite. In the latter case concentrated solutions should be employed and the solid hypophosphite added to the warm liquid

$$As_4O_6 + 3NaH_2PO_2 = 4As + 3NaH_2PO_4.$$

This form of arsenic reacts with methyl iodide at the ordinary temperature.[7]

The action of alkyl iodides on antimony has been much less

[1] *Annalen*, 1854, **89**, 321 ; *v. Quart. J. Chem. Soc.*, 1854, **7**, 258.
[2] *Annalen*, 1854, **92**, 361 ; *Compt. rend.*, 1854, **39**, 541.
[3] Cahours, *Compt. rend.*, 1859, **49**, 87.
[4] Cahours, *Annalen*, 1862, **122**, 200.
[5] Cahours, *ibid.*, 198.
[6] Cahours and Riche, *Compt. rend.*, 1854, **39**, 541.
[7] Martindale, *Congress Applied Chemistry*, 1909.

extensively examined, but Buckton found that methyl iodide and this metalloid at 140° yielded trimethylstibine iodide, $Sb(CH_3)_3I_2$.[1]

The production of tetra-alkyl quaternary arsonium iodides was extended by Mannheim[2] who, after experiencing the considerable experimental difficulties arising from the inflammable and poisonous character of sodium arsenide, employed the general method discovered by Cahours of heating finely divided arsenic and alkyl iodides in sealed tubes at temperatures ranging from 160° to 235°. The double iodide, R_4AsI,AsI_3, thus produced was decomposed by aqueous caustic alkali to remove arsenious iodide. The tetra-alkylarsonium iodides thus isolated were compared very carefully with the products obtained by the action of alkyl iodides on mercuric arsenide, Hg_3As_2, produced in the wet way by passing hydrogen arsenide (arsine) into an alcoholic solution of mercuric chloride (27·1 grams $HgCl_2$ in 2,000 c.c.).[3] The result of this systematic comparison was to show that the supposed hexa-alkyldiarsonium halides and double halides recorded by Partheil, Amort, and Gronover are in reality tetra-alkylarsonium halides and double halides. These hexa-alkyldiarsonium halides should accordingly be deleted from the list of organic arsenical compounds.[4]

$$\overset{V}{I}R_3As—\overset{V}{A}sR_3I \quad \text{[non-existent]}.$$

This correction brings arsenic into line with phosphorus and antimony. Mercuric phosphide, Hg_3P_2, on treatment with alkyl iodides[5] gave only tetra-alkylphosphonium iodides. Under similar conditions mercuric antimonide yielded tetra-alkylstibonium iodides.[6]

Although this monograph furnishes many examples of organic arsenicals containing pairs of arsenic atoms, doubly and singly linked, yet it will be observed that in all these instances the

[1] *Journ. Chem. Soc.*, 1860, **13**, 120; *Jahresber.*, 1860, 374.

[2] *Annalen*, 1905, **341**, 196.

[3] Partheil and Amort, *Arch. Pharm.*, 1899, **237**, 126.

[4] *Arch. Pharm.*, 1899, **237**, 121; Amort, *Inaug. Dissert.*, Heidelberg, 1898; Gronover, *Inaug. Dissert.*, Heidelberg, 1899.

[5] Partheil and van Haaren, *Arch. Pharm.*, 1900, **238**, 28; Van Haaren, *Inaug. Dissert.*, Bonn, 1900.

[6] *Arch. Pharm.*, 1900, **238**, 166; Mannheim, *Inaug. Dissert.*, Bonn, 1900.

composition of the compounds is consistent with the view that the arsenic is tervalent in these substances.

Singly-linked arsenic atoms.

Cacodyl, $\begin{matrix} CH_3\cdot As\cdot CH_3 \\ | \\ CH_3\cdot As\cdot CH_3 \end{matrix}$

Doubly-linked arsenic atoms.

Arsenobenzene, $C_6H_5\cdot As{:}As\cdot C_6H_5$. (p. 87)

Single and doubly-linked arsenic atoms.

$\begin{matrix} As{:}As\cdot C_6H_5 \\ | \\ As{:}As\cdot C_6H_5 \end{matrix}$ (p. 270).

This tendency for arsenic to combine with itself in its organic derivatives is undoubtedly to be correlated with the behaviour of the free element which even in vaporous condition possesses a tetratomic molecule, As_4.[1]

$$\begin{matrix} As{:}As \\ | \quad | \\ As{:}As \end{matrix}.$$

The absence of antimonial analogues of cacodyl is a noteworthy difference in the chemical deportment of the two metalloids which may be correlated with their behaviour in their inorganic compounds.

In the mineral kingdom arsenic frequently replaces sulphur isomorphously, as for instance in the well-known pair of minerals pyrite, FeS_2, and cobaltite, CoAsS, which both crystallise in the cubic system. Many varieties of pyrites are highly arseniferous, showing a partial displacement of sulphur by arsenic. Moreover, the two elements combine in atomic proportions in the mineral realgar, As_2S_2. The close relationship between arsenic and sulphur exhibited in these minerals is not shown between the latter element and antimony. This apparent bivalency of arsenic in realgar and cacodyl is probably due, however, to a tendency for this metalloid to unite with itself when in this state of combination.

$\begin{matrix} As{:}S \\ | \\ As{:}S \end{matrix}$	$\begin{matrix} As(CH_3)_2 \\ | \\ As(CH_3)_2 \end{matrix}$
Realgar.	Cacodyl.

[1] The active yellow modification of elemental arsenic obtained by suddenly cooling arsenic vapour is soluble in carbon bisulphide and gives a molecular weight corresponding with As_4. Grey and brown arsenic are respectively As_2 and As_8, whereas metallic arsenic is regarded as being the monoatomic form As. (Erdmann and others, *Zeitsch. anorg. Chem.*, 1902, **32**, 437; *Annalen*, 1908, **361**, 1; *cf.* Jolibois, *Compt. rend.*, 1911, **152**, 1767.)

In this respect arsenic resembles phosphorus and nitrogen, which give rise respectively to the hydrides P_2H_4 and N_2H_4 and their organic derivatives.

The groups PH_2, NH_2, and $As(CH_3)_2$ are univalent like the hydrocarbon radicals methyl, CH_3, ethyl, C_2H_5, etc. All these univalent radicals exist in a state of freedom only as the double (dimeric) molecules P_2H_4, N_2H_4, $As_2(CH_3)_4$, $CH_3{\cdot}CH_3$, and $C_2H_5{\cdot}C_2H_5$.

The trialkylstibines (and trialkylarsines) behave as bivalent radicals comparable with ethylene, and like the latter they are capable of existing in the free state as simple monomeric molecules. Löwig and Schweitzer demonstrated this fact by determining the vapour density of triethylstibine, which showed that this compound has in the gaseous state a molecular complexity corresponding with the simplest formula, $Sb(C_2H_5)_3$.

The condensation between potassium-antimony alloy and amyl iodide as studied by Berlé[1] led to triamylstibine, and this author supposed that on distilling the crude product of reaction a diamylstibine was obtained. This substance did not, however, yield any crystalline derivatives, and it can scarcely be conceded that the evidence for the existence of this antimony analogue of amylcacodyl is conclusive.

Similar uncertainty still exists in regard to aliphatic antimonides containing more than three alkyl groups. Buckton by the action of zinc ethyl on tetraethylstibonium iodide obtained an oily liquid distilling in coal gas at 160–170°, and giving on analysis higher percentage amounts of carbon and hydrogen than are present in triethylstibine ; the antimony in the product was not estimated. Buckton, who supposed that this liquid contained tetraethylstibine, made a similar experiment with zinc methyl and tetramethylstibonium iodide. The liquid obtained in this instance was rectified when the fraction boiling at 86–96° gave carbon and hydrogen values corresponding with the formula $Sb(CH_3)_4$; the fraction boiling at 96–100° gave numbers on combustion approximating to the formula $Sb(CH_3)_5$. The antimony was not estimated. If these results could be substantiated the existence of tetra-alkyl and penta-alkyl derivatives of antimony would be a fact of the highest theoretical importance. Tetramethylstibine would be the only organic derivative of the phosphorus–antimony family of elements capable of existence in the free state in which one atom of the element is attached

[1] *Annalen*, 1856, **97**, 316.

solely to four hydrocarbon radicals without a fifth electronegative group as in the following examples :—

$N(CH_3)_4I$, $P(C_2H_5)_4OH$,
$As(CH_3)_2(C_2H_5)_2Br$, and $Sb(C_2H_5)_4OH$.

Pentamethylstibine would be unique among organo-metallic and organo-metalloidal compounds in containing one atomic proportion of the metalloidal element attached to more than four hydrocarbon radicals.[1]

An impartial survey of the existing evidence shows, however, that the case for bi-alkyl, tetra-alkyl-, and penta-alkyl-antimonides has not been substantiated.

The analogous experiment with tetramethylarsonium iodide and zinc methyl was made by Cahours.[2] There was a violent reaction; zinc iodide was produced and gas evolved. Four-fifths of the volatile product consisted of trimethylarsine; the remaining less volatile oily product gave on analysis numbers for carbon and hydrogen approximating to the formula for pentamethylarsine, $As(CH_3)_5$. Further evidence was obtained from the decomposition of the substance by iodine when it yielded methyl iodide and tetramethylarsonium iodide. With hydrochloric acid the supposed pentamethylarsine gave methane and tetramethylarsonium chloride.

3. *Interaction of Metallic Alkyls and Halides of Arsenic and Antimony.*

A third general method of synthesising aliphatic arsenicals and antimonials depends on the employment of zinc alkyls and the halides of arsenic and antimony.

[1] *Compounds of nitrogen with five hydrocarbon residues.*—That substances containing five hydrocarbon groups associated with one non-metallic atom are capable of existence is shown by the synthesis of *triphenylmethyltetramethylammonium*,

$$(C_6H_5)_3C{\cdot}Na + Cl{\cdot}N(CH_3)_4 = (C_6H_5)_3C{\cdot}N(CH_3)_4 + NaCl,$$

and an even simpler member of this new group of nitrogen penta-alphyls, namely, *benzyltetramethylammonium*,

$$C_6H_5{\cdot}CH_2{\cdot}Na + Cl{\cdot}N(CH_3)_4 = (C_6H_5){\cdot}CH_2{\cdot}N(CH_3)_4 + NaCl.$$

These remarkable compounds are intensely red, crystalline substances with metallic reflex; they are very sensitive to moisture and are decomposed by water into tetramethylammonium hydroxide and the corresponding hydrocarbon (triphenylmethyl and toluene respectively) with considerable generation of heat (*Ber.*, 1916, **49**, 605; 1917, **50**, 275).

[2] *Annalen*, 1862, **122**, 338.

Zinc dimethyl and zinc diethyl acting on arsenious chloride give rise respectively to trimethylarsine and triethylarsine.[1] These reagents are specially useful for producing mixed arsines, thus dimethylethylarsine is obtained from dimethylarsenious iodide, $As(CH_3)_2I$, and zinc diethyl, whereas methyldiethylarsine results from the interaction of this zinc compound and methylarsenious iodide.[2]

These reactions are available for preparing the organic stibines. Zinc dimethyl[3] and antimony trichloride give rise to trimethylstibine, which also results from the action of mercury dimethyl[4] on the same chloride.

Mercury dimethyl has also been employed in synthesising organic arsenicals containing only one alkyl radical. Ethylarsenious chloride is produced by the interaction of arsenious chloride and mercury diethyl.[5]

$$AsCl_3 + Hg(C_2H_5)_2 = C_2H_5 \cdot AsCl_2 + C_2H_5 \cdot HgCl.$$

4. *Grignard Reaction applied to the Synthesis of Aliphatic Arsenicals and Antimonials.*

The Grignard reaction, which comes under the category of the foregoing general synthetic method, has so greatly facilitated the process of producing organo-metallic and organo-metalloidal derivatives that it merits a separate section.

Arsenious[6] bromide and magnesium methyl iodide interact to yield trimethylarsine, providing that the Grignard reagent is maintained in excess. The arsenious halide (50 grams) dissolved in 100 c.c. of ether is added slowly at −20° to the Grignard reagent (magnesium, 12·2 grams, methyl iodide, 71 grams, in 200–300 c.c. of pure ether). A yellow precipitate is formed at first which subsequently dissolves. The product is distilled from the water-bath, and the trimethylarsine collected in the form of its dibromide, $(CH_3)_3AsBr_2$; the yield is over 70 per cent. of the calculated amount.

Antimony trichloride (18·9 grams) in 80–100 c.c. of ether is added slowly to the well-cooled Grignard reagent (magnesium,

[1] Hofmann, *Jahresber.*, 1855, 538; *Annalen*, 1857, **103**, 357.
[2] Cahours, *ibid.*, 1862, **122**, 220.
[3] Hofmann, *ibid.*, 1857, **103**, 357.
[4] Buckton, *Quart. J. Chem. Soc.*, 1863, **16**, 22.
[5] La Coste, *Annalen*, 1881, **208**, 33.
[6] Hibbert, *Ber.*, 1906, **39**, 160.

6·1 grams, methyl iodide, 35·5 grams, in 200–300 c.c. of pure ether). The yellow intermediate product is precipitated and redissolved when the solution forms two layers, an upper ethereal layer and a lower oily layer which ultimately solidifies. The mixture is distilled up to 170° in a current of carbon dioxide. The yield of trimethylstibine weighed as crystalline dibromide is 60–70 per cent. of the calculated amount.

The method gives rise to primary and secondary organic derivatives of arsenic and primary compounds of antimony when the Grignard reagent is employed in suitable proportions (one mol. to one mol. of arsenic or antimony halide). In these circumstances arsenious chloride and magnesium ethyl bromide yield small amounts of ethylarsenious chloride, $C_2H_5 \cdot AsCl_2$, and diethylarsenious chloride, $(C_2H_5)_2AsCl$, which are obtained together with arsenious chloride and bromide by distilling the product of the Grignard reaction *in vacuo* after removing the ether. These chlorides are identified as their corresponding arsenic acids, $C_2H_5 \cdot AsO_3H_2$ and $(C_2H_5)_2AsO_2H$. The principal product is triethylarsine oxide, $As(C_2H_5)_3O$, isolated in the form of sulphide by passing sulphuretted hydrogen through concentrated aqueous solution of the residue left after the foregoing fractionation.

An ethereal solution of magnesium ethyl bromide (from 75 grams of ethyl bromide) is added at −18° to antimony trichloride (200 grams) in 200 c.c. of ether. The product, after removing ether, is distilled under 12 mm. pressure, when antimony trichloride and tribromide are obtained together with ethylantimonious chloride and bromide, $C_2H_5 \cdot SbCl_2$ and $C_2H_5 \cdot SbBr_2$. Excess of potassium iodide converts these four compounds into antimony tri-iodide and ethylantimonious iodide. After removing the former iodide by solution in dilute hydrochloric acid, the latter, $C_2H_5 \cdot SbI_2$, is obtained in golden-yellow leaflets, m. p. 43°.[1]

5. *Alkylation of Arsenical Oxy-compounds.*

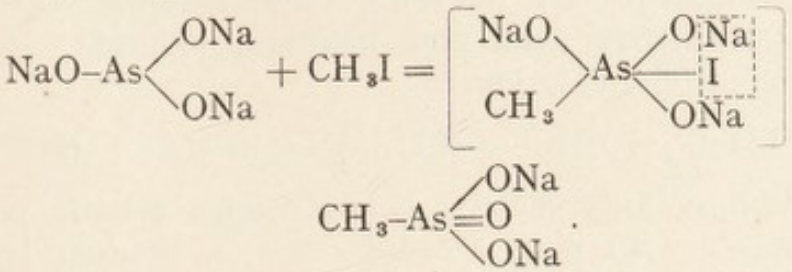
The synthetic methods described in the foregoing section suffer from one grave disadvantage ; they require to be carried out in the absence of moisture, and in some instances in an inert atmosphere. These are serious defects when the manufacture of organic arsenicals on an industrial basis is attempted. These difficulties can, however, be avoided by an ingenious process of alkylation due to G. Meyer.[2]

[1] Auger and Billy, *Compt. rend.*, 1904, **139**, 597. [2] *Ber.*, 1883, **16**, 1440.

Sodium arsenite and methyl iodide are heated together in alkaline solution, when sodium methylarsinate is produced.[1]

III V

$$As(OH)(ONa)_2+CH_3I+NaOH=CH_3\cdot AsO(ONa)_2+NaI+H_2O.$$



The process has been generalised by Dehn and McGrath so that ethyl-, *n*-propyl-, *iso*amyl- and benzyl-arsinic acids have been synthesised.[2]

Moreover, it has been found that this alkylation can be carried further after reducing methylarsinic acid to methylarsenious oxide, $CH_3\cdot AsO$, the sodium derivative, $CH_3As(ONa)_2$, of which is similarly methylated to cacodylic acid. This compound on reduction gives cacodyl oxide, the sodium derivative of which is then methylated to trimethylarsine oxide. Trimethylarsine obtained by the reduction of this oxide combines additively with methyl iodide to form tetramethylarsonium iodide. By this series of reactions we can obtain from sodium arsenite by progressive methylation, organic arsenic derivatives containing one, two, three, or four methyl groups.[3]

6. *Dealkylation of Tertiary Arsines and their Derivatives.*

Excluding the Grignard reaction, the foregoing general syntheses have led to organic antimony derivatives containing three or four alkyl groups. In the arsenic series these synthetic processes have in certain instances yielded tertiary arsines and quaternary arsonium salts with cacodyl and its homologues as by-products. It is now necessary to consider methods whereby primary alkyl derivatives of arsenic have been produced by processes of dealkylation from dialkyl compounds.

Among the earlier researches on organic arsenic derivatives should be mentioned specially the work of Baeyer, whose investigations were an extension of Bunsen's study of cacodyl.[4]

[1] *Cf.* Klinger and Kreutz, *Annalen*, 1888, **249**, 147.

[2] *Cf.* Dehn, *Amer. Chem. J.*, 1905, **33**, 138; Dehn and McGrath, *J. Amer. Chem. Soc.*, 1906, **28**, 351.

[3] V. Auger, *Compt. rend.*, 1903, **137**, 925.

[4] *Annalen*, 1858, **107**, 282.

Bunsen's preparations of cacodyl oxide (alkarsin) probably contained varying proportions of free cacodyl, for when the latter was allowed to become oxidised purer non-inflammable specimens of the oxide were obtained which he designated "paracacodyl oxide." By distilling Cadet's liquid with concentrated hydrochloric acid and mercuric chloride, Baeyer obtained pure cacodyl chloride

$$(CH_3)_2AsO,HgCl_2 + 2HCl = (CH_3)_2AsCl_2 + H_2O + HgCl_2.$$

The distillation of this cacodyl chloride with caustic potash furnished Baeyer with pure cacodyl oxide, a product having properties identical with those of Bunsen's "paracacodyl oxide."

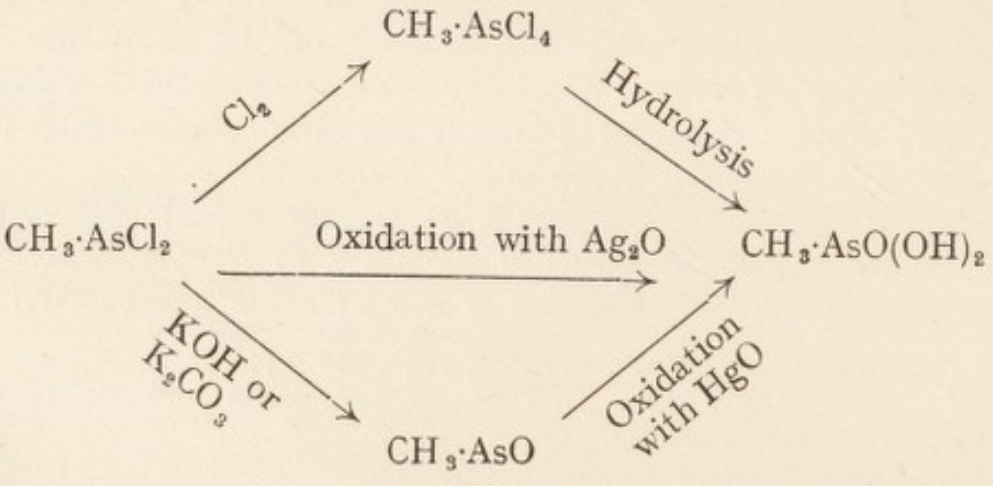
Cacodyl chloride was shown to be an unsaturated compound combining with chlorine to form a trichloride, $(CH_3)_2AsCl_3$, which on hydrolysis yielded cacodylic acid, and on warming decomposed into methyl chloride and methylarsenious chloride (IV.) :—

$$(CH_3)_2AsCl_3 \xrightarrow{2H_2O} (CH_3)_2AsO\cdot OH$$

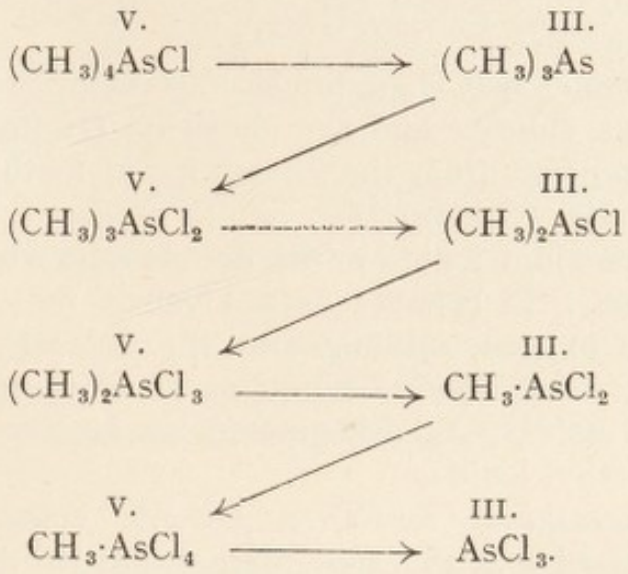
$$(CH_3)_2AsCl_3 \xrightarrow{\text{distillation}} CH_3AsCl_2 + CH_3Cl$$

IV

Methylarsenious chloride belongs to the series of organic arsenic compounds containing only one alkyl group attached to the metalloidal atom. With alkali it yields the corresponding methylarsenious oxide, $CH_3\cdot AsO$, and with chlorine it combines, forming the very unstable methylarsenic tetrachloride, $CH_3\cdot AsCl_4$. Hydrolysis of the tetrachloride or oxidation of the dichloride or oxide leads to methylarsinic acid $CH_3\,AsO(OH)_2$:—



Dealkylation in the arsenical series can be brought about by the distillation of the alkyl-arsenic chlorides in accordance with the following scheme in which all the steps indicated by unbroken lines have been realised.



Dealkylation is also effected through the agency of iodine derivatives. The periodides of the quaternary arsonium bases decompose on heating to yield cacodyl derivatives. The following reactions were first investigated by Cahours.[1]

$$As(CH_3)_4I_3 = As(CH_3)_2I + 2CH_3I.$$
$$As(C_2H_5)_4I_3 = As(C_2H_5)_2I + 2C_2H_5I.$$
$$As(CH_3)_2I + 2I = As(CH_3)I_2 + CH_3I.$$
$$As(C_2H_5)_2I + 2I = As(C_2H_5)I_2 + C_2H_5I.$$

Cacodyl itself undergoes partial or complete demethylation on distillation with iodine :—

$$As_2(CH_3)_4 + 3I_2 = 2As(CH_3)I_2 + 2CH_3I.$$
$$As_2(CH_3)_4 + 5I_2 = 2AsI_3 + 4CH_3I.$$

Trimethylarsine undergoes similar changes.

$$As(CH_3)_3 + 2I = As(CH_3)_2I + CH_3I.$$
$$As(CH_3)_3 + 4I = As(CH_3)I_2 + 2CH_3I.$$
$$As(CH_3)_3 + 6I = AsI_3 + 3CH_3I.$$

These reactions can be reversed by the action of zinc dimethyl on the arsenical products on the right-hand side of the foregoing equations.[2]

[1] Cahours, *Compt. rend.*, 1860, **50**, 1023.
[2] Cahours, *Annalen*, 1862, **122**, 218.

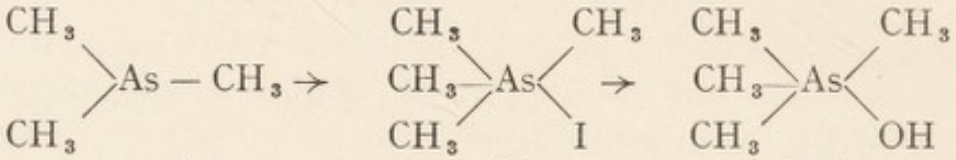
Section II.—Aliphatic Arsenic Compounds.

1. *Methyl Series.*

(For Cacodyl Group, *v.* p. 10.)

Trimethylarsine, $As(CH_3)_3$, liquid, b.p. below 100°, obtained from arsenious chloride and zinc dimethyl (Hofmann, *loc. cit.*) and as a by-product from the interaction of methyl iodide and sodium arsenide (Cahours, *loc. cit.*); prepared by distilling tetramethylarsonium iodide or its double salts with dry potassium hydroxide. It behaves as a bivalent radical combining directly with oxygen, sulphur, and the halogens. *Trimethylarsine oxide*, $As(CH_3)_3O$, deliquescent crystals. *Trimethylarsine iodide*, $As(CH_3)_3I_2$, decomposed on heating into cacodyl iodide and methyl iodide.

Tetramethylarsonium iodide, $As(CH_3)_4I$, colourless leaflets, readily decomposing at 170–180°, produced by the direct addition of its generators, trimethylarsine and methyl iodide. Obtained as chief product by treating sodium arsenide with excess of methyl iodide (Cahours and Riche).[1] This compound, which Cahours also prepared in the form of the double iodide, $As(CH_3)_4I,AsI_3$, by the action of methyl iodide on elemental arsenic at 160–200°, has the properties of a soluble metallic iodide, such as potassium iodide :—



I. II. III.

Although not decomposed by aqueous caustic potash, tetramethylarsonium iodide (II.) reacts with moist silver oxide, yielding silver iodide and a very soluble compound, *tetramethylarsonium hydroxide* (III.). This complex hydroxide is a strongly caustic substance resembling sodium or potassium hydroxide; it combines readily with acids, even carbonic acid, to form salts; it turns red litmus blue, precipitates hydroxides of heavy metals from their soluble salts, and saponifies fats. Tetramethylarsonium hydroxide behaves precisely as if it were the hydroxide of an alkali metal, but its alkali radical or ion is complex and

[1] *Annalen*, 1854, **92**, 361.

consists of an arsenic atom combined with four alkyl or aliphatic groups.

Tetramethylarsonium iodide combines with iodine to form a *periodide*, $As(CH_3)_4I_3$, brown needles with metallic lustre. On heating, the periodide decomposes into methyl iodide (2 mols.) and cacodyl iodide. The quaternary *bromide*, $As(CH_3)_4Br$, is a highly deliquescent salt produced by the interaction of methyl bromide on cacodyl.

$$As_2(CH_3)_4 + 2CH_3Br = As(CH_3)_4Br + As(CH_3)_2Br.$$

Tetramethylarsonium mercuri-iodide,[1] $As(CH_3)_4I,HgI_2$, yellow needles, m.p. 184°, produced by combining its components in alcoholic solution: the *mercuri-chloride*, colourless needles, melts at 175–176°. The *platinichloride*, yellow crystals, and the *aurichloride*, yellow needles, are obtained through the quaternary hydroxide.

Methylarsenious chloride,[2] $As(CH_3)Cl_2$, liquid, b.p. 133°, resulting from the decomposition of cacodyl trichloride even at 40–50°, or, preferably, by the prolonged action of hydrogen chloride on dry cacodylic acid. It neither fumes in air nor is decomposed by water. The vapour has a terribly irritating action on the mucous membrane. When inhaled, the eyes, nose, and face become swollen, and a peculiar gnawing pain is felt extending into the throat. It absorbs chlorine at −10° to yield the crystalline *methylarsenic tetrachloride*, $As(CH_3)Cl_4$, which decomposes even at 0° into methyl chloride and arsenious chloride.

Methylarsenious sulphide, $As(CH_3)$:S, leaflets, m.p. 110°; insoluble in water, soluble in ether, alcohol, or carbon bisulphide; produced by the action of sulphuretted hydrogen either on the chloride or on the following iodide. *Methylarsenious iodide*, lustrous, yellow needles, m.p. 25°, volatilises unchanged above 200°. Sparingly soluble in water and more so in alcohol, ether, or carbon bisulphide; prepared by adding hydriodic acid to an alcoholic solution of methylarsenious oxide.

Methylarsenious oxide, $As(CH_3)$:O, cubical crystals sometimes changing into a white, porcellanous variety, m.p. 95°, odour of asafœtida, slightly volatile in steam or alcohol vapour, but decomposed on heating; prepared by decomposing methylarsenious chloride with saturated aqueous potassium carbonate, the oxide being extracted with alcohol or carbon bisulphide.

[1] Mannheim, *Annalen*, 1905, **341**, 196.
[2] Baeyer, *ibid.*, 1858, **107**, 272.

Methylarsinic acid, $CH_3 \cdot AsO(OH)_2$, anhydrous, colourless, tabular aggregates of dendritic needles, m.p. 161°, from alcohol, very soluble in water. A strong acid decomposing carbonates and forming an ammonium salt. Prepared from methylarsenious chloride by the action of excess of moist silver oxide or from the oxide by oxidation with mercuric oxide and warm water; purified through the barium salt. With sulphuretted hydrogen this acid yields the yellow, viscid disulphide, $CH_3 \cdot As \cdot S_2$, and with concentrated hydriodic acid the tetra-iodide, $As(CH_3)I_4$.

Sodium methylarsinate[1] (Arrhenal, New cacodyl),

$$CH_3AsO(ONa)_2,H_2O,$$

very soluble in water (1 : 1), only sparingly so in alcohol (90 per cent.). Prepared by heating an aqueous solution of sodium arsenite with methyl iodide and alcohol.

This salt was first recommended in therapeutics by Gautier, who stated that it had a specific action on malaria;[2] it is, however, without effect on trypanosomes.

Distinctive Reactions of Sodium Cacodylate and Sodium Methylarsinate (Arrhenal).[3]

Reagent.	$(CH_3)_2AsO \cdot ONa,3H_2O$.	$CH_3 \cdot AsO(ONa)_2,H_2O$.
Silver nitrate	No ppt.	White, silky ppt.
Mercuric chloride... ...	White ppt.... ...	Reddish-yellow ppt.
Baryta-water...	White ppt.... ...	No ppt.

Potassium methylarsinate, $CH_3 \cdot AsO(OK)_2,xH_2O$, is readily prepared by the action of methyl chloride on aqueous potassium arsenite.[4]

Calcium methylarsinate, $CH_3AsO \cdot O_2Ca,H_2O$, soluble in dilute acetic acid, crystallising from this solution after neutralising with ammonia. The *barium* salt, $CH_3AsO \cdot O_2Ba,5H_2O$, and the *silver* salt are crystalline.

The mercurous, mercuric, and iron salts have been employed therapeutically. The methylarsinates of many alkaloids have been prepared, and of these the two anhydrous *quinine* salts, $CH_3 \cdot AsO(OH)_2(C_{20}H_{24}O_2N_2)_2$, and $CH_3 \cdot AsO(OH)_2,C_{20}H_{24}O_2N_2$, and

[1] Auger, *Compt. rend.*, 1903, **137**, 925; Auger and Billy, *Compt. rend.*, 1904, **139**, 599; G. Meyer, *loc. cit.*; Klinger and Kreutz, *loc. cit.*

[2] *Presse médicale*, 1902, 791 and 824; *Compt. rend.*, 1902, **134**, 329; Moore, Nierenstein and Todd, *Ann. trop. medicine*, 1908, **2**, 269; *cf.* Mouneyrat, *Compt. rend.*, 1903, **136**, 696.

[3] *Cf.* Vitali, *Chem. Centr.*, 1903, II, 1416.

[4] Dehn and McGrath, *J. Amer. Chem. Soc.*, 1906, **28**, 347.

the two *strychnine* salts, $CH_3{\cdot}AsO(OH)_2,(C_{21}H_{22}O_2N_2)_2$, and $CH_3{\cdot}AsO(OH)_2,C_{21}H_{22}O_2N_2$, are of therapeutic interest.[1]

Pyrobismethylarsinic acid,[2] $CH_3{\cdot}AsO(OH){\cdot}O{\cdot}As(CH_3)O{\cdot}OH$, is produced by heating methylarsinic acid at 130°. At higher temperatures (170–180°) this product decomposes into methyl alcohol and arsenious oxide.

Magnesium methylarsinate,[3] $CH_3{\cdot}AsO{\cdot}O_2Mg,5H_2O$, small, white crystals. Solubility in 1 litre of water :—2·118 grams at 22° and 3·085 grams at 99°. Arsenious oxide (318 grams) and caustic potash (540 grams) are dissolved in water, the solution of potassium arsenite, diluted to 3 litres, is treated with a molecular proportion of methyl iodide ($1CH_3I$ to $1K_3AsO_3$) and sufficient alcohol to produce a homogeneous solution. The mixture is left in stoppered bottles for several days, and the solution, which has a powerful odour of some arsine derivative, is distilled to remove alcohol and acidified with dilute hydrochloric acid, when a white precipitate of the compound, $2As_2O_3,KI$, is produced. The filtrate is treated with chlorine until the dark colour due to precipitation of iodine begins to clear. The filtrate from iodine is rendered ammoniacal and treated with magnesia mixture, when magnesium ammonium arsenate separates ; the solution on warming gives magnesium methylarsinate. A better yield is obtained by using potassium arsenite instead of the corresponding sodium salt. A portion of the magnesium methylarsinate is liable to be co-precipitated with magnesium ammonium arsenate even in cold solutions.[4]

Iodine Derivatives of Methyl- and Dimethyl-arsinic Acid.

Amorphous arsenic prepared by reducing a hydrochloric acid solution of arsenious oxide with stannous chloride or hypophosphorous acid is a very active chemical agent, combining with methyl iodide at the ordinary temperature instead of at 160°, as was found by Cahours to be the temperature required for ordinary powdered arsenic.[5] In preparing this amorphous arsenic with hypophosphorous acid it is preferable to work in

[1] Meyer's *Jahresber.*, 1904, **14**, 269; Leprince, *J. Pharm. Chem.*, 1903, [vi], **17**, 22 ; *Chem. Centr.*, 1903, I., 280.

[2] Vitali, *Bull. chim. Farm*, 1905, **44**, 229. *Chem. Centr.*, 1905, I, 1699.

[3] Dehn, *Amer. Chem. J.*, 1905, **33**, 136.

[4] *Cf.* Klinger and Kreutz, *Annalen*, 1888, **249**, 149.

[5] Auger, *Compt. rend.*, 1907, **145**, 808.

warm concentrated solutions, adding solid sodium hypophosphite little by little.[1]

Amorphous arsenic reacts in a remarkable manner on iodoform. The two reagents warmed together without a diluent interact explosively. When diluted with benzene or toluene at the temperature of the water-bath the reaction goes more smoothly and is completed after several hours. On distilling off the solvent a dense black, oily, crystalline magma is left which is oxidised to definite crystalline products by cold nitric acid.

$3CHI_3 + 2As = CHI_2{\cdot}AsI_2 + (CHI_2)_2AsI.$
$CHI_2{\cdot}AsI_2 + 4HNO_3 = CHI_2{\cdot}AsO(OH)_2 + 4NO_2 + H_2O + I_2.$
$(CHI_2)_2AsI + 3HNO_3 = (CHI_2)_2{\cdot}AsO{\cdot}OH + 3NO_2 + H_2O_2 + I$

The oxidised product is extracted with cold water. The aqueous solution on concentration at 40–50° deposits yellow tabular crystals of *di-iodomethylarsinic acid*, $CHI_2{\cdot}AsO(OH)_2,H_2O$; the *sodium* salt, $CH_2I{\cdot}AsO(OH){\cdot}ONa,H_2O$, colourless crystals, is very soluble in water ; the *silver* salt is a white precipitate.

The insoluble oxidised product freed from iodine with boiling benzene or toluene is dissolved in ammonia and reprecipitated by acid. This *tetraiodocacodylic acid*, $(CHI_2)_2AsO{\cdot}OH$, forms small, yellow crystals, soluble in hot acetic or nitric acid. Its *sodium* salt, $(CHI_2)_2AsO{\cdot}ONa,6H_2O$, is obtained from water-alcohol solution in well-defined pale yellow crystals.

Reduction Products of the Methyl Series of Aliphatic Arsenicals.

Recent improvements in the technique of organic reductions have rendered possible the isolation of the hitherto missing primary and secondary alkyl arsines, $AsH_2{\cdot}Alk$ and $AsH(Alk)_2$, and of highly reduced products containing arsenic combined only with one alkyl group, $[Alk.As]x$.

Dimethylarsine,[2] $(CH_3)_2AsH$, colourless liquid, with characteristic odour of cacodyl, b.p. 35·6°/747 mm. and 55°/1·74 atmos. D1·213/29° ; vapour density corresponding with the foregoing formula. Spontaneously inflammable in air ; precipitates silver from aqueous silver nitrate. Prepared by adding cacodyl chloride to a mixture of platinised zinc, alcohol and hydrochloric acid. By the treatment of cacodyl oxide with these reagents a mixture of dimethylarsine and cacodyl is obtained. Dimethyl-

[1] Martindale, *Congress of Applied Chemistry*, 1909.

[2] Palmer, *Ber.*, 1894, **27**, 1378 ; Dehn and Wilcox, *Amer. Chem. J.*, 1906, **35**, 3.

arsine is of great theoretical interest as being the parent hydride of the cacodyl series.

Preparation of Dimethylarsine.

This secondary arsine can be conveniently prepared from crude cacodyl oxide (Cadet's fuming arsenical liquid). A reduction flask containing amalgamated zinc dust (250 grams), cacodyl oxide (50 grams), and alcohol (200 c.c.) is joined in series with a water wash-bottle, a U-tube filled with soda-lime, a condenser for dimethylarsine, a sulphuric acid wash-bottle and a nitric acid wash-bottle, the connections throughout being of glass and cork, because the arsines attack indiarubber. The bulb condenser being surrounded with ice and salt, strong hydrochloric acid is slowly added to the reduction flask through a dropping funnel. A bright yellow substance forms indicating partial reduction; this colour disappears as reduction proceeds. When air is present in the apparatus a red substance always makes its appearance; this product contains a polymeride of arsenobenzene and is identical with Bunsen's "erytarsin."

Dimethylarsine inflames in air above 10° but not below 0°, burning with a bluish-white arsenical flame giving rise to white fumes and a black, solid deposit. It is soluble in the ordinary organic solvents. The oxidation products are very numerous and are formed in accordance with the following equations:

1. $4(CH_3)_2AsH + O_2 = 4(CH_3{\cdot}As)x + 2C_2H_6 + 2H_2O.$
2. $4(CH_3)_2AsH + O_2 = As_4 + 4C_2H_6 + 2H_2O.$
3. $2(CH_3)_2AsH + 9O_2 = As_2O_3 + 4CO_2 + 7H_2O.$
4. $6(CH_3)_2AsH + 3O_2 = (CH_3{\cdot}As)_4, As_2O_3 + 4C_2H_6 + 2H_2O.$
5. $4(CH_3)_2AsH + O_2 = (CH_3)_2{\cdot}As{\cdot}As(CH_3)_2 + 2H_2O.$
6. $2(CH_3)_2AsH + O_2 = [(CH_3)_3As]_2O + H_2O.$
7. $(CH_3)_2AsH + O_2 = (CH_3)_2AsO{\cdot}OH{\cdot}$

The halogens combine additively [1] with dimethylarsine, these additive compounds being dissociated by water or at high temperatures into the corresponding cacodyl halide and the hydrogen halide. The following equations illustrate the chemical changes in the case of bromine.

$$(CH_3)_2AsH + Br_2 = (CH_3)_2AsBr,HBr = (CH_3)_2AsBr + HBr.$$

Aqueous iodine solution oxidises dimethylarsine to cacodylic acid. This secondary arsine possesses feebly basic properties combining with the mineral acids to yield unstable salts.

[1] Dehn, *Amer. Chem. J.*, 1908, **40**, 121.

Dimethylarsonium sulphate, $[(CH_3)_2AsH]_2H_2SO_4$, colourless, prismatic crystals, is produced with generation of heat on mixing dimethylarsine and concentrated sulphuric acid; it decomposes slowly in air and rapidly in water into its generators.

Dimethylarsine and cacodyl chloride interact at 100° in molecular proportions to produce cacodyl and hydrogen chloride.

$$(CH_3)_2AsH + (CH_3)_2AsCl = (CH_3)_2As{\cdot}As(CH_3)_2 + HCl.$$

Oxidising agents convert dimethylarsine into cacodylic acid with cacodyl as an intermediate stage in the oxidation. Sulphur and this arsine give rise to cacodyl mono- and di-sulphides, sulphur dioxide converts the arsine into methylarsenious sulphide, cacodyl disulphide, trimethylarsine sulphide and cacodylic acid. Stannic chloride and dimethylarsine yield *dimethylarsine trichlorostannide*, $(CH_3)_2As{\cdot}SnCl_3$, volatile colourless needles with penetrating odour.

Methylarsine,[1] $CH_3{\cdot}AsH_2$, a very volatile, colourless liquid, of high refractive power, b.p. $+2°/755°$ and $17°/1\frac{1}{2}$ atmos.; odour of cacodyl; very poisonous and fuming, but not spontaneously inflammable in air. Almost devoid of basic properties, forming salts with acids either with great difficulty or not at all. Produced by the reduction of methylarsinic acid with amalgamated zinc dust and alcoholic hydrochloric acid.

Methylarsine[2] is soluble in alcohol, ether, or carbon bisulphide in all proportions, but in water it dissolves only to the extent of 85 parts in 1,000,000. Iodine and water oxidise it to methylarsinic acid; aqueous silver nitrate behaves similarly, giving methylarsinic and nitric acids with a deposit of silver. Methylarsine and hydrogen chloride combine very slightly, if at all, even when mixed for a period of two weeks. With methyl iodide at 110°, methylarsine interacts to form tetramethylarsonium iodide and hydrogen iodide.

The oxidation of methylarsine by nitric acid is a somewhat complex reaction, methylarsinic, formic, and arsenic acids being among the products of this chemical change. When passed into aqueous mercuric chloride, methylarsine is oxidised to mercuric methylarsinate, while mercurous chloride is precipitated. Bromine dissolved in carbon bisulphide decomposes methylarsine completely into arsenious bromide, methyl bromide, and hydrogen bromide.

[1] Palmer and Dehn, *Ber.*, 1901, **34**, 3594.
[2] Dehn, *Amer. Chem. J.*, 1905, **33**, 101.

Preparation of Methylarsine.

Amalgamated[1] zinc dust and sodium methylarsinate mixed together in a large flask are treated with the necessary amount of hydrochloric acid diluted with an equal quantity of alcohol. The generator is connected in series with a wash-bottle containing water, a drying tube filled with soda-lime, and a condensation apparatus *A B C* (shown in the figure,[2] fixed in a wooden vessel charged with solid carbon dioxide. The whole apparatus is filled with hydrogen in order to exclude atmospheric oxygen from the methylarsine which collects in the bulb *B* and is drawn off from time to time into the intermediate receiver *C*. On closing the upper and opening the lower tap of this intermediate vessel, a portion of the liquefied methylarsine is forced into the capillary end of the tube *D* which has previously been filled with dry hydrogen.

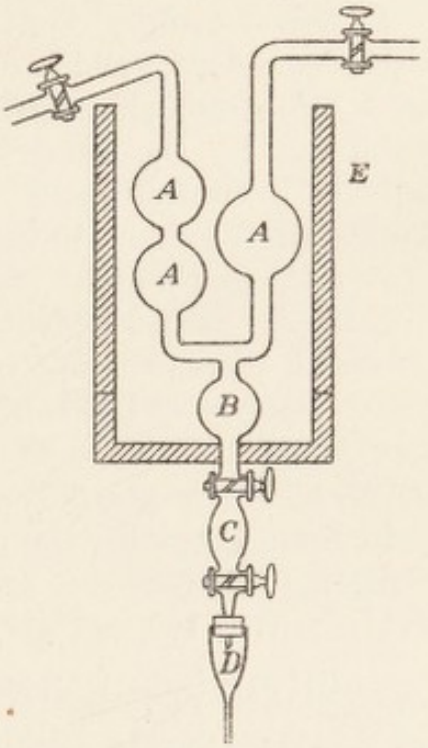


FIG. 3.

The vapour density of methylarsine corresponds with the simple formula $CH_3 \cdot AsH_2$. One volume of the gas over mercury absorbs an equal volume of oxygen producing white solid methylarsine oxide (m.p. 95°). After two weeks' exposure one volume of the methylarsine absorbed 1·414 volumes of oxygen, but if the water produced in the first phase of the process was absorbed by fused calcium chloride no second absorption of oxygen occurred.

i. $CH_3 \cdot AsH_2 + O_2 = CH_3 \cdot AsO + H_2O$.

ii. $2CH_3 \cdot AsH_2 + 3O_2 = 2CH_3 \cdot AsO(OH)_2$.

The second product was distinctly acid and was identified as methylarsinic acid (m.p. 161°). This acid was also produced by oxidising the primary arsine with strong nitric acid. Alcoholic iodine gave with the arsine yellow needles of methylarsine iodide.

[1] Dehn, *Amer. Chem. J.*, 1905, **33**, 120.

[2] Palmer and Dehn, *Ber.*, 1901, **34**, 3595.

Arsenomethane[1] (Methylarsenic), $(CH_3{\cdot}As{:}As{\cdot}CH_3)_2$, light yellow heavy oil with intense garlic odour, b.p. 190°/13 mm. Prepared by reducing sodium methylarsinate with sodium hypophosphite and sulphuric acid. Arsenomethane resembles methylarsine in its behaviour towards oxidising agents, but differs from the primary arsine in the ease with which it polymerises to a dark brown insoluble powder, $[CH_3{\cdot}As]x$. This product when distilled in hydrogen decomposes quantitatively into trimethylarsine and elemental arsenic.

$$3CH_3{\cdot}As = As(CH_3)_3 + 2As.$$

In this decomposition the substance resembles arsenobenzene, $C_6H_5{\cdot}As{:}As{\cdot}C_6H_5$, which on heating breaks down quantitatively into triphenylarsine and free arsenic. A further analogy is exhibited by the behaviour of arsenomethane on heating at 100° with methyl iodide, when it yields tetramethylarsonium iodide and methylarsenious iodide (*cf.* p. 88).

A molecular weight determination of arsenomethane by the cryoscopic method gives a molecular formula of $(CH_3{\cdot}As)_4$, probably corresponding with the above configuration in which the substance is represented as a polymerised form of arsenomethane. This view of its constitution is supported by its colour and other physical properties and by its chemical reactions.

In connexion with the reduction of methylarsinic acid to the foregoing substances it appears probable from the experimental evidence that this operation takes place in two distinct phases,

$$2CH_3{\cdot}HSO(OH)_2 + 8H = CH_3{\cdot}As{:}As{\cdot}CH_3 + 6H_2O.$$
$$CH_3{\cdot}As{:}As{\cdot}CH_3 + 4H = 2CH_3{\cdot}AsH_2.$$

In aqueous solutions as in the preceding reduction the oily arsenomethane separates and polymerises to red and brown solid compounds. When alcohol is present the oily arsenomethane remains dissolved and subjected to further action of the reducing agent. This circumstance explains the utility of alcohol in the preparation of primary arsines.[2]

Erythrarsine.—Cadet noticed that the fuming arsenical liquid had at first a reddish-brown colour and contained a yellow substance, but with the deposition of these coloured materials it slowly became clear and assumed a light amber colour.

Bunsen isolated the red substance, to which he gave the name

[1] Auger, *Compt. rend.*, 1904, **138**, 1705.
[2] Dehn, *Amer. Chem. J.*, 1905, **33**, 120.

"Erytrarsin,"[1] from among the decomposition products of cacodyl or impure cacodyl oxide and chloride. He subjected it to analysis, obtaining numbers corresponding with the formula $(CH_3 \cdot As)_4, As_2O_3$. This composition of the red substance was confirmed by Dehn and Wilcox, who identified the two components. These investigators also observed the formation of a yellow substance as the first stage in the reduction of cacodyl oxide to dimethylarsine. These differently coloured materials, including the black polymeride[2] obtained as above, and also by the action of heat on dimethylarsine,[3] represent successive stages in the polymerisation of arsenomethane.

2. *Ethyl Series.*

(Ethylcacodyl Group, *v.* p. 17.)

Triethylarsine, $As(C_2H_5)_3$, liquid with unpleasant odour; fuming in the air and taking fire on warming, b.p. 140°/736 mm. with slight decomposition, D1·151/16·7°. Insoluble in water; no reducing action on aqueous silver solutions (difference from ethylcacodyl). Combines additively with sulphur and the halogens. Obtained, together with ethylcacodyl and tetraethylarsonium iodide, by the action of ethyl iodide on sodium-arsenic alloy.[4] Pure triethylarsine is prepared by distilling tetraethylarsonium iodide with solid caustic potash.[5] Also obtained by the interaction of arsenious chloride and zinc diethyl.[6] Vapour density of triethylarsine, 5·2783 corresponding with above formula.

Triethylarsine di-iodide,[7] $As(C_2H_5)_3I_2$, yellow, flocculent precipitate, m.p. 160°, b.p. 190°; produced by direct addition and by the distillation of the double iodide, $As(C_2H_5)_4I, AsI_3$.

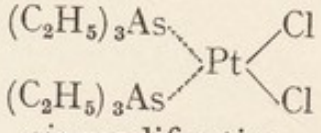
Triethylarsine sulphide,[8] $As(C_2H_5)_3S$, large prismatic crystals, m.p. 119·5°. Prepared by digesting triethylarsine in ethereal solution with flowers of sulphur or by boiling triethylarsine oxide with aqueous potassium pentasulphide. Also obtained by heating ethylarsine disulphide at 195° and formed by the interaction of ethylarsine and carbon bisulphide at 120° in alcoholic solution.[9]

[1] *Annalen*, 1842, **42**, 41.
[2] Auger, *loc. cit.*
[3] Dehn, *loc. cit.*
[4] Landolt, *Annalen*, 1854, **89**, 332.
[5] Cahours, *Annalen*, 1862, **112**, 202.
[6] Hofmann, *Annalen*, 1857, **103**, 357.
[7] [8] Cahours, *Compt. rend.*, 1859, **49**, 87; 1860, **50**, 1023.
[9] Dehn, *Amer. Chem. J.*, 1905, **33**, 135; Landolt, *loc. cit.*

Triethylarsine oxide,[1] $As(C_2H_5)_3O$, oily liquid insoluble in water, produced by aerial oxidation of triethylarsine in ethereal solution. Insoluble in dilute hydrochloric or sulphuric acid, combining with nitric acid to form a nitrate which is also produced from triethylarsine and concentrated nitric acid (D1·42).

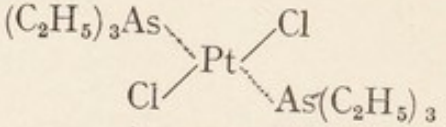
Co-ordination Compounds of Triethylarsine.[2]

On adding triethylarsine drop by drop to platinic chloride solution reduction to the platinous condition occurs and two isomeric compounds (*cis*- and *trans*-bistriethylarsine dichloroplatinum), $PtCl_2,2As(C_2H_5)_3$, are formed. These products, which in all probability are stereoisomerides,



cis-modification.

and

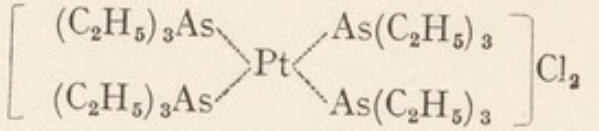


trans-modification.

are separated by extracting the mixture with ether. The isomeride soluble in this medium separates in amber-yellow crystals and from alcohol in sulphur-yellow prisms. The isomeride, insoluble in ether, crystallises from alcohol in long pale yellow prisms.

It has not yet been established which of these isomerides has the *cis*- and which the *trans*-configuration.

The foregoing isomeric compounds of triethylarsine and platinous chloride are analogues of the isomerides obtained by the interaction of triethylphosphine and platinic chloride. By the action of excess of triethylarsine on these isomerides tetrakis-triethylarsine platinous chloride, $[Pt,4As(C_2H_5)_3]Cl_2$, is produced, to which, in accordance with Werner's co-ordination theory, the following configuration is ascribed :



Palladium dichloride and triethylarsine react to yield bis-triethylarsine dichloropalladium, $PdCl_2,2As(C_2H_5)_3$, transparent, reddish-yellow prisms.

The aurous compound, $AuCl,As(C_2H_5)_3$, is unstable and deposits gold on raising the temperature.

[1] Cahours, *Compt. rend.*, 1859, **49**, 87; 1860, **50**, 1023.

[2] Cahours and Gal, *Compt. rend.*, 1870, **70**, 897, 1380. **71**, 208; *Zeitsch. für Chem.*, 1870, **6**, 662.

Quaternary Arsonium Compounds containing Ethyl.

Tetraethylarsonium iodide,[1] $As(C_2H_5)_4I$, colourless crystals darkened on exposure; readily soluble in water and alcohol, insoluble in ether. Prepared by the direct combination of triethylarsine and ethyl iodide and obtained as a rapidly crystallising oil by boiling with aqueous caustic potash the double iodides,[2] $As(C_2H_5)_4I,AsI_3$; $2As(C_2H_5)_4I, ZnI_2$; $2As(C_2H_5)_4I, CdI_2$, produced by the synthetic processes from arsenic and the zinc-arsenic and cadmium-arsenic alloys respectively (*v.* p. 22).[3]

Tetraethylarsonium mercuri-iodide,[4] $As(C_2H_5)_4I,HgI_2$, yellow needles, m.p. 112°, from alcoholic solutions of its components; *mercurichloride*, white needles, m.p. 139°; *platinichloride* and *aurichloride* are yellow crystalline compounds, melting respectively at 224° and 171°.

Tetraethylarsonium hydroxide, $As(C_2H_5)_4{\cdot}OH$, highly caustic white deliquescent mass, absorbing carbon dioxide from the air, liberating ammonia from ammonium salts and precipitating hydroxides of heavy metals from their soluble salts. Prepared by the action of moist silver oxide on the preceding iodide.

Tetraethylarsonium chloride, $As(C_2H_5)_4Cl,4H_2O$, very deliquescent crystals obtained by evaporating down the solution of the quaternary hydroxide in hydrochloric acid; *platinichloride*, sparingly soluble orange-yellow crystals; $3As(C_2H_5)_4Cl,2BiCl_3$, colourless. *Bromide*, $As(C_2H_5)_4Br$, deliquescent crystals; $3As(C_2H_5)_4Br,2BiBr_3$, lemon yellow[5]; $3As(C_2H_5)_4I,2BiI_3$, lustrous, brick-red, hexagonal plates; *periodide*, $As(C_2H_5)_4I_3$, brown needles; *hydrogen sulphate*, $As(C_2H_5)_4{\cdot}HSO_4$, granular crystals easily soluble in water or alcohol.

Methyldiethylarsine, $As(C_2H_5)_2{\cdot}CH_3$, liquid; *Dimethylethylarsine*, $As(CH_3)_2{\cdot}C_2H_5$, liquid. These mixed bases are obtained by the action of zinc diethyl on methylarsenious di-iodide, $As(CH_3)I_2$, and dimethylarsenious iodide, $As(CH_3)_2I$, respectively.

Dimethyldiethylarsonium iodide, $(CH_3)_2As(C_2H_5)_2I$, colourless prisms, obtained readily by the action of ethyl iodide on cacodyl.[6]

$$As_2(CH_3)_4 + 2C_2H_5I = (CH_3)2_2As(C_2H_5)_2I + As(CH_3)_2I.$$

[1] Landolt, *Annalen*, 1854, **89**, 331; **92**, 364.
[2] Cahours and Riche, *Compt. rend.*, 1854, **39**, 541.
[3] Cahours, *Compt. rend.*, 1859, **49**, 87.
[4] Mannheim, *Annalen*, 1905, **341**, 198.
[5] Jörgensen, *J. pr. Chem.*, 1871, [ii], **3**, 336.
[6] Cahours and Riche, *Compt. rend.*, 1854, **39**, 541.

Ethyl bromide reacts similarly but more slowly.

Dimethyldiethylarsonium bromide[1] and *chloride*, very deliquescent needles; *periodide*, $(CH_3)_2As(C_2H_5)_2I_3$, brown needles, metallic lustre; *sulphate*, $[(CH_3)_2As(C_2H_5)_2]_2SO_4$, octahedra, soluble in water or alcohol; *nitrate*, deliquescent granules; *platinichloride*, orange-red needles.

Triethylbromoethylarsonium bromide,[2] $CH_2Br{\cdot}CH_2{\cdot}As(C_2H_5)_3Br$, rhombic dodecahedra, extremely soluble in water, sparingly so in cold alcohol. This bromide is produced by the interaction of triethylarsine and a large excess of ethylene bromide in sealed tubes below 50°. When treated successively with silver chloride and platinic chloride it furnishes the *platinichloride*,

$$(C_2H_4Br{\cdot}As(C_2H_5)_3Cl)_2PtCl_4;$$

sparingly soluble needles.

Vinyltriethylarsonium hydroxide, $CH_2{:}CH{\cdot}As(C_2H_5)_3{\cdot}OH$, obtained readily from the preceding bromide by the action of excess of moist silver oxide; *platinichloride*, $(C_8H_{18}AsCl)_2PtCl_4$, moderately soluble octahedra; *aurichloride*, $C_8H_{18}AsCl,AuCl_3$, sparingly soluble, yellow crystals.

Trimethylethylarsonium iodide, well-defined, glistening needles, softens at 300° and sinters at 320°, soluble in water, chloroform, or hot alcohol; prepared by mixing ethylarsine and methyl iodide,

$$C_2H_5{\cdot}AsH_2 + 3CH_3I = C_2H_5As(CH_3)_3I + 2HI.$$

Primary and Secondary Ethylarsenicals.

Ethylarsenious dichloride, $As(C_2H_5)Cl_2$, liquid with faint fruity odour; b.p. 156°. Prepared by the interaction of arsenious chloride and mercury diethyl,

$$AsCl_3 + Hg(C_2H_5)_2 = As(C_2H_5)Cl_2 + C_2H_5{\cdot}HgCl.$$

Miscible in all proportions with ether, alcohol, or benzene, very soluble in water. Extremely irritating action on the mucous membrane of eyes and nose, leaving painful blisters on the skin.[3]

Ethylarsenious di-iodide, $As(C_2H_5)I_2$, obtained by the interaction of diethylarsenious iodide and iodine,[4]

$$As(C_2H_5)_2I + I_2 = As(C_2H_5){\cdot}I_2 + C_2H_5I.$$

Ethylarsinic acid, $C_2H_5{\cdot}AsO(OH)_2$, crystals from alcohol. Prepared by treating the preceding iodide with excess of silver

[1] Cahours and Riche, *loc. cit.* [2] Hofmann, *Annalen*, 1861, Spl. 1, 313.
[3] La Coste, *Annalen*, 1881, **208**, 33.
[4] Cahours, *Compt. rend.*, 1860, **50**, 1023.

oxide or by warming ethylarsenious chloride with moderately concentrated nitric acid.[1]

Also isolated in the form of its magnesium salt,

$$CH_3 \cdot AsO_3Mg,H_2O,$$[2]

by the interaction of ethyl iodide and aqueous potassium arsenite. Arsenious oxide (318 grams), caustic potash (540 grams), dissolved in water made up to 3 litres and mixed with ethyl iodide (500 grams) and sufficient alcohol to render the solution homogeneous when the reaction is complete after a few hours. The spirit is distilled off, the residual aqueous solution acidified with hydrochloric acid when the compound As_4O_6,KI [3] is precipitated. The filtrate is treated with chlorine in sufficient amount to set free the remaining iodine and the final filtrate rendered ammoniacal and treated with magnesia mixture in excess. After 24 hours the precipitate of magnesium ammonium arsenate is collected and the filtrate boiled. As the ammonia evaporates small, globular masses of magnesium ethylarsinate separate, the yield being about 40–50 per cent.

Potassium ethylarsinate, soluble in alcohol; *magnesium* salt, sparingly soluble in water or alkaline solutions, readily so in acids; *silver* salt, yellowish-white, nacreous scales.

Ethylarsinic disulphide, $C_2H_5 \cdot AsS_2$,[4] light yellow, viscid oil with disagreeable odour; D1·836/24°; insoluble in water, alcohol, or ether. Soluble in chloroform, benzene, or carbon bisulphide, very soluble in alkalis or alkali sulphides, precipitated therefrom by acids.

Diethylarsine, $(C_2H_5)_2AsH$, not definitely isolated.

Diethylarsine appears to result from the action of certain moulds, and it is probably owing to the formation of this arsine that poisoning cases have been noticed in rooms furnished with carpets or wall papers containing arsenic. This reaction is of special interest as being the nearest approach to a natural synthesis of an organic arsenical compound which has hitherto been noticed.

Production of Volatile Arsenical Compounds by Moulds.

Various species of moulds (*mucor* and *penicillium*), and especially the so-called arsenical mould, *Penicillium brevicaule*, when cultivated in a medium containing sodium arsenite evolve a gas containing volatile poisonous arsenical compounds. In

[1] La Coste, *Annalen*, 1881, **208**, 34.

[2] Dehn, *Amer. Chem. J.*, 1905, **33**, 132; *J. Amer. Chem. Soc.*, 1906, **28**, 347.

[3] Rüdorff, *Ber.*, 1886, **19**, 2668.

[4] Dehn, *loc. cit.*

this way small quantities of the inorganic arsenic compound become completely volatilised so that the non-volatile residue is completely free from arsenic.

This phenomenon has been noted by several observers, who have not, however, identified the volatile arsenic compound.[1]

This gas has been more closely examined by P. Biginelli, who passed it into a hydrochloric solution of mercuric chloride when colourless, tabular, triclinic crystals separated, having the composition $AsH(C_2H_5)_2,2HgCl_2$, or possibly the double formula $AsH(C_2H_5)_2{:}AsH(C_2H_5)_2,4HgCl_2$. This substance sinters at 239–240° and decomposes at 255–256°. With boiling water this crystalline product dissolves and the solution on cooling deposits (1) a small quantity of a compound decomposing at 250–251°, (2) a substance of the composition

$$O\begin{<}\begin{matrix}AsH(C_2H_5)_2\\|\\AsH(C_2H_5)_2\end{matrix}\end{>},4HgCl_2,$$

which separates in shining scales, sintering at 270°, but not completely fused at 290°. When treated successively with concentrated aqueous caustic potash and with an ethereal solution of iodine the mercurichloride furnishes the *iodide*,

$O\begin{<}\begin{matrix}AsH(C_2H_5)_2I\\|\\AsH(C_2H_5)_2I\end{matrix}\end{>}$, m. p. 102°, which with silver sulphate gives the *sulphate*, $(C_4H_{11}OAs)_2SO_4$, m. p. 210°. Moist silver oxide on the iodide gives deliquescent needles of the *dioxide*,

$$AsH(C_2H_5)_2\begin{<}\begin{matrix}O\\O\end{matrix}\end{>}AsH(C_2H_5)_2.$$

Nitric acid and alkaline permanganate lead successively to the compound, $O[AsH(C_2H_5)_2{\cdot}OH]_2$, KNO_3,

hygroscopic, acicular prisms, m.p. 129–131°, exploding at higher temperatures.

When the arsenical gas evolved by *P. brevicaule* is passed into mercuric nitrate solution, an insoluble, infusible, yellow powder, $AsH(C_2H_5)_2,2Hg{\cdot}NO_3$, is precipitated.

Although in these experiments the arsenical gas itself was not isolated and identified, Biginelli concludes that the production of the foregoing solid compounds is evidence

[1] Maspmann, *Pharm. Zentr.-h.*, **41**, 666, and *Chem. Centr.*, 1900, ii, 1187. Valerio and Strzyzowski, *Pharm. Post.*, **33**, 637 and 649; *Chem. Centr.*, 1901, i, 63. Emmerling, *Ber.*, 1896, **29**, 2728; 1897, **30**, 1026. Gorio, *Ber.*, 1897, **30**, 1024.

that the gas developed by wall papers to which poisoning is due is diethylarsine.[1] The question would be settled by the preparation and isolation of diethylarsine from diethylarsinic acid or some other derivative of the ethylcacodyl series, an operation which is quite practicable by Palmer and Dehn's general method (pp. 37 and 39).

Ethylarsine,[2] $C_2H_5 \cdot AsH_2$, liquid, b.p. 36°, D1·217/22°, obtained by the reduction of ethylarsinic acid and its salts with amalgamated zinc dust and alcoholic hydrochloric acid; odour resembling cacodyl, very poisonous, almost devoid of basic properties.[3] A freezing mixture of salt and ice can be employed in the condensation of this arsine. The yield is quantitative, although the amount condensed is only about 60 per cent. Its solubility in water is 126 parts in 1,000,000 at 19°. This arsine is very poisonous; a rat breathing a little of the vapour died almost immediately. Its slow oxidation product with air is light yellow. When the vapour of ethylarsine absorbs dry air the reaction is mainly as follows:—

$$C_2H_5AsH_2 + O_2 = C_2H_5AsO + H_2O.$$

Silver nitrate oxidises this arsine to ethylarsinic acid; concentrated nitric acid produces this acid together with acetic and arsenic acids.

Arsenoethane[4] (Ethylarsenic), $(C_2H_5 \cdot As{:}As \cdot C_2H_5)_2$, yellow oil easily polymerising into solid forms.

Bromine and iodine interact with ethylarsine in accordance with the following equation:

$$C_2H_5AsH_2 + X_2 = C_2H_5AsX_2 + H_2.$$

Sulphur reacts to form the monosulphide,

$$C_2H_5AsH_2 + 2S = C_2H_5AsS + H_2S.$$

Mercuric chloride and iodide and stannic chloride convert ethylarsine into ethylarsenious chloride, $C_2H_5 \cdot AsCl_2$, the other products being mercury, mercurous iodide, and stannous chloride.

Arsenious chloride produces a more complex change, for in addition to ethylarsenious chloride a yellow solid is produced which changes to a curdy, brick-red solid which may contain $(C_2H_5 \cdot As)_4$ and arsenic, or, conceivably, a more complex condensation product, $C_2H_5 \cdot As(As{:}As \cdot C_2H_5)_2$.

[1] P. Biginelli, *Atti. R. Accad. Lincei*, 1900, [v], **9**, ii, 210, 242.
[2] Palmer and Dehn, *Ber.*, 1901, **34**, 3594.
[3] Dehn, *Amer. Chem. J.*, 1905, **33**, 143.
[4] Auger, *Compt. rend.*, 1904, **138**, 1705.

Antimony trichloride reacts similarly with ethylarsine, giving a reddish-brown solid which slowly assumes a jet black colour. On drying, this black product takes fire spontaneously.

3. *Propyl Series.*

Tetra-n-*propylarsonium iodide,*[1] $As(C_3H_7)_4I$, is obtained in the form of the double iodide, $As(C_3H_7)_4I,AsI_3$, on heating arsenic and *n*-propyl iodide together at 180°; the quaternary iodide forms colourless needles decomposing at 150°.

Tri-n-*propylarsine,*[2] $As(C_3H_7)_3$, is prepared by distilling the foregoing double iodide with dry caustic potash.

This tertiary arsine, oil, b.p. 167°/90 mm. and 158°/73 mm. is obtained together with primary and secondary *n*-propyl arsenious chlorides, by condensing *n*-propyl chloride and arsenious chloride with sodium in ether.

Tetra-n-*propylarsonium mercuri-iodide,*[3] $As(C_3H_7)_4I,HgI_2$, needles, m.p. 120°. The *mercurichloride* forms colourless needles, m.p. 169°, the *platinichloride,* m.p. 189°, and *aurichloride,* m.p. 127°, are all obtained from tetra-*n*-propylarsonium hydroxide.

*Tetra*iso*propylarsonium iodide,* $As(C_3H_7)_4I$, colourless needles darkening at 150°, prepared by heating finely powdered arsenic with *iso*propyl iodide at 100–180° for 24–30 hours. The double arseno-iodide is decomposed by caustic alkali leaving the quaternary salt. The *mercuri-iodide,* yellow needles, m.p. 114° is obtained from its components in alcoholic solution. From aqueous solutions of tetra*iso*propylarsonium hydroxide the following characteristic salts are obtainable: *mercurichloride,* m.p. 171°, *platinichloride,* decomposing at 211°, and *aurichloride,* m.p. 186–188°.

Tri-n-*propylethylarsonium iodide,*[4] $(C_3H_7)_3As(C_2H_5)I$, m.p. 230–237°, results from the action of *n*-propyl iodide on ethylarsine at 110°.

Tri*iso*propylethylarsonium iodide is similarly prepared; it decomposes at its melting point.

n-*Propylarsine,* $C_3H_7{\cdot}AsH_2$, volatile liquid produced by reducing *n*-propylarsinic acid with amalgamated zinc dust and hydrochloric acid according to Palmer and Dehn's method.

n-*Propylarsinic acid,*[5] $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}AsO_3H_2$, colourless,

[1] Cahours, *Jahresber.*, 1873, 519. [2] Dehn, *Amer. Chem. J.*, **40**, 119.
[3] Mannheim, *Annalen*, 1905, **341**, 200. [4] *Amer. Chem. J.*, 1908, **40**, 113.
[5] Dehn and McGrath, *J. Amer. Chem. Soc.*, 1906, **28**, 352.

acicular crystals, is obtained by adding sulphuric acid in the cold to its magnesium salt and then extracting with alcohol. It is insoluble in ether, but very soluble in water ; a saturated solution (100 parts) at 26° contains 43 parts of the acid. The *disulphide*, $C_3H_7AsS_2$, a viscid oil, is precipitated from acid solutions of the acid by sulphuretted hydrogen.

Magnesium n-*propylarsinate*, $C_3H_7{\cdot}AsO_3Mg,\frac{1}{2}H_2O$ or

$$[C_3H_7{\cdot}As(OH)(O_2Mg)]_2O,$$

in the form of pearly white, soapy crystals, is the product of the following reaction. Arsenious oxide (275 grams, 1 mol.) and caustic potash (460 grams, 6 mols.) are dissolved together in concentrated aqueous solution. Alcohol and propyl iodide (460 grams, 2 mols.) are added, and the mixture shaken, after adding sufficient water or alcohol or both of the solvents to produce a homogeneous solution. The following reactions take place:

$$As(OK)_3 + C_3H_7I = C_3H_7{\cdot}AsO(OK)_2 + KI$$
$$C_2H_5OK + C_3H_7I = C_2H_5{\cdot}O{\cdot}C_3H_7 + KI.$$

After several days the alcohol and ether are distilled off, hydrochloric acid is added till a precipitate appears, chlorine is introduced until all the iodine is precipitated, and the filtrate treated with magnesia mixture to remove arsenate. The filtrate from magnesium ammonium arsenate, when boiled with more magnesia mixture, forms magnesium *n*-propylarsinate, the yield being 42 per cent.

Di-n-*propylarsinic acid*, lustrous leaflets or needles ; m.p. 120°.[1]

4. *Allyl Series.*

Tetrallylarsonium mercuri-iodide,[2] $As(C_3H_5)_4I,HgI_2$, m.p. 74°, is produced by warming allyl iodide and mercuric arsenide on the water-bath.

Dimethylallylarsine, $(CH_3)_2{\cdot}As{\cdot}C_3H_5$; b.p. 160°, obtained from dimethylarsine and allyl iodide.[3]

5. *Butyl Series.*

Tetra-n-*butylarsonium iodide*,[4] colourless needles decomposing at 145–150°. The quaternary hydroxide yields the characteristic salts : *mercuri-iodide*, yellow needles, m.p. 109° ; *platini-*

[1] Partheil, *Arch. Pharm.*, 1899, **237**, 134.
[2] Mannheim, *Annalen*, 1905, **341**, 223.
[3] Dehn and Wilcox *Amer. Chem. J.*, 1906. **35**, 20.
[4] Mannheim, *Annalen*, 1905, **341**, 204.

chloride, yellowish-red crystals darkening at 145°, decomposing at 220°; *aurichloride*, sparingly soluble needles, m.p. 131°.

6. *Amyl Series.*

Dimethyldiisoamylarsonium iodide, $As(CH_3)_2(C_5H_{11})_2I$, leaflets, obtained by the interaction of cacodyl and *iso*amyl iodide at 180°.[1]

$$As_2(CH_3)_4 + 2C_5H_{11}I = A(CH_3)_2(C_5H_{11})_2I + As(CH_3)_2I.$$

Ethyltriisoamylarsonium iodide,[2] $C_2H_5As(C_5H_{11})_3I$, compact crystals not melting below 250°, prepared by mixing ethylarsine with excess of *iso*amyl iodide and heating for eight hours at 140°.

Synthesis of Secondary Aliphatic Derivatives of Arsenic.

An important extension in the synthesis of aliphatic arsenicals was first made in this series by Dehn and Wilcox[3] in 1906.

Before this date there was no ready means of obtaining secondary aliphatic arsenic compounds.

Cadet's reaction still remains unique and restricted to the methyl series. The action of alkyl iodides on sodium arsenide is a more general reaction, but it gives rise to a mixture of products which are separated only with difficulty. A more promising process was discovered by Michaelis and Paetow (p. 114), who found that when benzyl chloride (2 mols.) and arsenious chloride (1 mol.) are condensed by means of sodium the secondary arsine derivative was the predominant product. Dehn and Wilcox applied this reaction to the aliphatic series and found that in the case of *iso*amyl chloride the main product was *diisoamylarsine chloride*, or its basic chloride,

$$6(C_5H_{11})_2AsCl,[(C_5H_{11})_2As]O.$$

Other alkyl halides, such as ethyl bromide and propyl iodide, behave similarly.

Basic Diisoamylarsine chloride, $6(C_5H_{11})_2AsCl,[(C_5H_{11})_2As]_2O$, colourless oil, b.p. 263°/750 mm. and 148°/33 mm., is produced by adding slowly a mixture of *iso*amyl chloride (148 grams = 2 mols.) and arsenious chloride (124 grams = 1 mol.) to 60 grams of sodium wire (4 atoms) in 400–500 c.c. of dry ether in an atmosphere of carbon dioxide. The reaction, which is very violent, is complete in two hours. The filtered solution is fractionated. A white, soapy solid, which separates during fractionation, is probably di*iso*amylarsenious oxide. The red by-

[1] Cahours and Riche, *Compt. rend.*, 1854, **39**, 541.

[2] *Amer. Chem. J.*, 1905, **33**, 146. [3] *Amer. Chem. J.*, 1906, **35**, 48.

product, which is invariably formed during the condensation in quantities varying from 20 to 40 grams, is probably similar to Bunsen's erythrarsine, for when treated with bromine followed by ammonia it dissolves to form the ammonium salts of arsenious, *iso*amylarsinic, and di*iso*amylarsinic acids. The chloride is insoluble in water but soluble in the ordinary organic media.

*Di*iso*amylarsine chlorodibromide*, $(C_5H_{11})_2AsClBr_2$, white, crystalline solid, m.p. 124–125°, with an odour of chloral hydrate, is produced by adding bromine to an ethereal solution of the foregoing chloride.

*Di*iso*amylarsine sulphide*, $[(C_5H_{11})_2As]_2S$, white needles, m.p. 29–30°, insoluble in water but dissolving in ether, carbon bisulphide, or alcohol, is prepared by passing sulphuretted hydrogen into the chloride suspended in water.

*Di*iso*amylarsinic acid*, $(C_5H_{11})_2AsO{\cdot}OH$, large, flaky crystals, m.p. 153–154°. It is easily soluble in alcohol, less so in water, but insoluble in ether. It is prepared in accordance with the following equation :—

$$(C_5H_{11})_2AsCl + Br_2 + 2H_2O = (C_5H_{11})_2AsO{\cdot}OH + HCl + 2HBr.$$

The oily chloride changes to a yellow, crystalline solid, soluble in ammonia. Magnesia mixture added to this solution precipitates arsenious acid, the filtrate on boiling deposits magnesium *iso*amylarsinate (formed from *iso*amylarsenious dichloride, $C_5H_{11}AsCl_2$), and the final mother liquor made slightly acid yields di*iso*amylarsinic acid.

*Di*iso*amylarsine*, $(C_5H_{11})_2AsH$, oil, b.p. 150°/99 mm., is prepared by reducing di*iso*amylarsinic acid with amalgamated zinc dust and concentrated hydrochloric acid in the presence of ether. This arsine has a characteristic odour more suggestive of *iso*amyl alcohol than of arsine.

*iso*Amylarsinic acid,[1] $C_5H_{11}AsO(OH)_2$, pearly white crystals, m.p. 194° : 100 c.c. of saturated aqueous solution at 28° contains 0·82 gram ; the same volume of saturated alcohol contains 2·2 grams ; it is insoluble in ether. The preparation is quite similar to that of propylarsinic acid, potassium arsenite, K_3AsO_3, and *iso*amyl iodide being used in molecular proportions. After two or three days, the alcohol is removed by distillation, the solution carefully neutralised with hydrochloric acid, the double compound, $As_2O_3,2KI$, collected, and the filtrate acidified, when *iso*amylarsinic acid separates slowly as a mass of scaly crystals.

iso*Amylarsine disulphide*, $C_5H_{11}{\cdot}AsS_2$, is a viscid, light yellow oil.

[1] Dehn and McGrath, *J. Amer. Chem. Soc.*, 1906, **28**, 354.

7. *Polyarsines.*[1]

The tertiary alkylarsines behave as unsaturated compounds towards ethylene dibromide, one or two molecular proportions of the arsine combining additively with this alkylene halide. Hofmann, who discovered this reaction, was thus led to isolate complex arsenical bromides containing one or two atoms of arsenic. (Triethylbromoethylarsonium bromide I, *v.* p. 44.)

$$C_2H_4Br_2 \xrightarrow{As(C_2H_5)_3} CH_2Br\cdot CH_2\cdot As(C_2H_5)_3Br \quad \text{I.}$$

$$C_2H_4Br_2 \xrightarrow{2As(C_2H_5)_3} \begin{matrix} CH_2\cdot As(C_5H_5)_3\cdot Br \\ | \\ CH_2\cdot As(C_5H_5)_3\cdot Br \end{matrix} \quad \text{II.}$$

Ethylenehexaethyldiarsonium dibromide,[2] produced by the second of the preceding reactions at 150°, yields on debromination with moist silver oxide a highly caustic solution of the diarsonium hydroxide, $C_2H_4[As(C_2H_5)_3\cdot OH]_2$. The salts of this diacidic base, especially the iodide, are remarkably crystalline, the *platinichloride,* $C_2H_4[As(C_2H_5)_3\cdot Cl]_2PtCl_4$, pale yellow, crystalline precipitate; the *aurichloride,* $C_2H_4[As(C_2H_5)_3Cl]_2.2AuCl_3$, lustrous yellow leaflets from boiling hydrochloric acid.

8. *Mixed Arsenical Bases.*[1]

Ethylenetriethylarsammonium dibromide,

$$\begin{matrix} CH_2\cdot As(C_2H_5)_3Br \\ | \\ CH_2\cdot NH_2HBr \end{matrix},$$

is produced by the action of ammonia on bromoethyltriethylarsonium bromide; it forms a sparingly soluble *platinichloride,* $C_8H_{22}AsNPtCl_6$,[3] and an *aurichloride* $C_8H_{22}AsNAu_2Cl_8$, lustrous yellow leaflets; these salts crystallise from boiling hydrochloric acid.

Ethylenehexaethylphospharsonium dibromide,

$$\begin{matrix} CH_2\cdot P(C_2H_5)_3Br \\ | \\ CH_2\cdot As(C_2H_5)_3Br \end{matrix},$$

obtained by the action of triethylarsine on bromoethyltriethylphosphonium bromide, yields a *platinichloride* crystallising in

[1] *Cf.* Hofmann, *Phil. Trans.*, 1860, **150**, 518.
[2] Hofmann, *Annalen*, 1861, Spl. 1, 316. [3] Hofmann, *loc. cit.*, 306.

orange-red triclinic prisms.[1] The diquaternary base is decomposed by boiling water,

$$HO\cdot(C_2H_5)_3As\cdot C_2H_4\cdot P(C_2H_5)_3\cdot OH = As(C_2H_5)_3 + C_2H_5\cdot O\cdot P(C_2H_5)_3\cdot OH.$$

Section III.—Aliphatic Antimony Compounds.

1. *Methyl Series.*

Trimethylstibine,[2] $Sb(CH_3)_3$, colourless liquid with odour of onions, b.p. 80·6°, D1·523/15°; slightly soluble in water or alcohol, more soluble in ether. Takes fire in chlorine, oxidised easily in the air, spontaneously inflammable when in large quantities. Combines additively with sulphur and the halogens and reduces gold, mercury, and silver from aqueous solutions of their salts. An alloy of antimony and sodium (1 part Na + 4 parts Sb) mixed with an equal volume of sand to reduce its inflammability is moistened with methyl iodide. After the vigorous reaction has subsided the product is distilled, and trimethylstibine and methyl iodide pass over and recombine in the receiver forming tetramethylstibonium iodide. The dried quaternary iodide is distilled with an alloy of antimony and potassium in a current of carbon dioxide, when pure trimethylstibine is obtained.

Trimethylstibine oxide, $Sb(CH_3)_3O$, obtained from the sulphate $Sb(CH_3)_3SO_4$ by the action of barium hydroxide; crystalline mass easily soluble in water, reacts with hydrogen sulphide and acids, but not with carbon dioxide.

Trimethylstibine dichloride, $Sb(CH_3)_3Cl_2$, hexagonal crystals, sparingly soluble in cold water; made by direct addition of chlorine to trimethylarsine and by the interaction of antimony trichloride and mercury dimethyl.

$$SbCl_3 + 2Hg(CH_3)_2 = Sb(CH_3)_3Cl_2 + Hg(CH_3)\cdot Cl + Hg.$$

Trimethylstibine di-iodide,[3] $Sb(CH_3)_3I_2$, hexagonal prisms produced by heating antimony with methyl iodide at 140°. The *dibromide,* $Sb(CH_3)_3Br_2$, is produced by direct addition of bromine to trimethylstibine. The three dihalides each combine with the oxide, giving compounds $Sb(CH_3)_3Hal_2$, $Sb(CH_3)_3O$, crystallising in octahedra; the oxy-iodide has a yellow tint.

[1] Hofmann, *loc. cit.*, 318.

[2] Landolt, *Annalen*, 1851, **78**, 91; *Jahresber.*, 1861, 569.

[3] Buckton, *Quart. J. Chem. Soc.*, 1860, **13**, 120.

The *nitrate*, $Sb(CH_3)_3(NO_2)_2$ and *sulphate*, $Sb(CH_3)_3SO_4$, are crystalline and readily soluble in water.

The *sulphides*, $Sb(CH_3)_3S$, scales, sparingly soluble in water, and $SSb(CH_3)_2{\cdot}S{\cdot}Sb(CH_3)_2{\cdot}S$, yellow, insoluble in water, are produced on passing hydrogen sulphide through an ethereal solution of trimethylstibine.

Tetramethylstibonium iodide,[1] $Sb(CH_3)_4I$, hexagonal plates, soluble in 3·3 parts of water at 23° : produced by direct combination of trimethylstibine and methyl iodide, easily soluble in alcohol, less so in ether ; saline taste, bitter after-taste.

Tetramethylstibonium hydroxide, $Sb(CH_3)_4{\cdot}OH$, prepared by the action of moist silver oxide on the foregoing iodide. A deliquescent, crystalline mass, slippery to the touch, closely resembling caustic potash. It withdraws moisture and carbon dioxide from the atmosphere, fumes with hydrochloric acid, sublimes to a partial extent without decomposition, neutralises the strongest acids ; it precipitates the metallic hydroxides, including barium hydroxide, from aqueous solutions of their salts. Tetramethylstibonium salts are crystalline and devoid of emetic action.

Zinc hydroxide, when precipitated from solutions of zinc salts by tetramethylstibonium hydroxide, is redissolved by excess of the antimonial base. Copper hydroxide is insoluble in excess of this precipitant.

Tetramethylstibonium chloride, $Sb(CH_3)_4Cl$, prepared by evaporating down the iodide with hydrochloric acid or by treating the hydroxide with this acid ; also from the iodide by double decomposition with mercuric chloride ; white, deliquescent, hexagonal crystals easily soluble in water or alcohol, insoluble in ether : *platinichloride*, $[Sb(CH_3)_4]_2PtCl_6$, orange-yellow crystals, very slightly soluble in water. The *nitrate*, $Sb(CH_3)_4NO_2$, the *sulphate*, $[Sb(CH_3)_4]_2SO_4{,}5H_2O$, m.p. 150°, and the *hydrogen sulphate*, $Sb(CH_3)_4{\cdot}HSO_4$, are all crystalline and very soluble in water. The *hydrogen carbonate*, $Sb(CH_3)_4{\cdot}HCO_3$, forms stellate aggregates of needles, and gives no precipitate with neutral magnesium salts.

2. *Ethyl Series.*

Triethylstibine, $Sb(C_2H_5)_3$, colourless liquid with odour of onions ; b.p. below 75°/16–18 mm., 158·5/730 mm. ; D

[1] Landolt, *Annalen*, 1852, **84**, 44.

1·3244/16°. Takes fire in air and burns with a white flame. The liquid is insoluble in water, but miscible with ether and alcohol; its vapour density corresponds with the simple molecular formula. Obtained by the action of ethyl iodide on an alloy of antimony and potassium,[1] or by the interaction of antimony trichloride and zinc diethyl [2] or mercury diethyl.[3]

Triethylstibine is conveniently prepared by distilling triethylstibine di-iodide with zinc.[4] With fuming hydrochloric acid the converse change occurs; triethylstibine decomposing this acid to form triethylstibine dichloride and free hydrogen.

Triethylstibine oxide, $Sb(C_2H_5)_3O$, is not easily obtained pure by the aerial oxidation of triethylstibine because of the simultaneous formation of ethylstibinic acid. It is preferably prepared by shaking an alcoholic solution of triethylstibine with finely divided mercuric oxide; mercury is set free and the organic oxide results. The latter can be purified through its sulphate or nitrate. The former salt (*v. infra*) dissolved in water is treated with barium hydroxide, the barium sulphate removed, and the filtrate evaporated to dryness on the water-bath. The residue is taken up with alcohol and saturated with carbon dioxide to remove barium as barium carbonate, and the final alcoholic filtrate evaporated.

Triethylstibine oxide is thus obtained as a colourless, transparent, viscid, non-volatile mass devoid of crystalline character. After several days over concentrated sulphuric acid it becomes moderately hard, but softens again on the water-bath. It is easily soluble in water or alcohol, less so in ether. Its taste is bitter, like quinine, and when taken internally it has no emetic action and is not markedly poisonous. It couples directly with mineral acids forming salts and precipitates metallic hydroxides from solutions of their salts. Triethylstibine, which possesses to a remarkable degree the chemical properties of a bivalent metallic radical; it combines directly with oxygen, sulphur, and the halogens.

Triethylstibine dichloride, $Sb(C_2H_5)_3Cl_2$, a colourless, highly refractive liquid, not solidified at −12°. D1·540/17°; insoluble in water, soluble in alcohol or ether. It has a terpenoid odour and bitter taste. Prepared by (1) direct combination of

[1] Löwig and Schweitzer, *Annalen*, 1850, **75**, 315.
[2] Hofmann, *Annalen*, 1857, **103**, 357.
[3] Buckton, *Quart. J. Chem. Soc.*, 1863, **13**, 118.
[4] Buckton, *loc. cit.*, 116.

triethylstibine and chlorine : this reaction is very violent and, unless controlled, leads to inflammation ; (2) triethylstibine and hydrochloric acid ; (3), the preferable method, by evaporating down the crystalline nitrate, $Sb(C_2H_5)_3(NO_3)_2$, with strong hydrochloric acid.

Triethylstibine dibromide, $Sb(C_2H_5)_3Br_2$; the foregoing methods are available, the preferable process being to mix cooled alcoholic solutions of triethylstibine and bromine. A colourless, transparent, highly refractive liquid, solidifying at — 10° to snow-white crystals. Insoluble in water, easily soluble in ether or alcohol. Unpleasant terpenoid odour ; on warming the liquid, it becomes increasingly tear-exciting and causes vigorous sneezing.

Triethylstibine di-iodide, $Sb(C_2H_5)_3I_2$, colourless, acicular crystals, m.p. 70·5°, subliming at 100°. Prepared (1) by adding iodine to an alcoholic solution of triethylstibine and purified by successive crystallisation from alcohol and ether ; (2) by heating antimony with ethyl iodide at 140°.[1]

These foregoing triethylstibine halides present many analogies with the metallic halides. They are decomposed by strong sulphuric acid with liberation of the corresponding halogen hydride and formation of triethylstibine sulphate. The iodide when treated with ammonia or with a molecular proportion of triethylstibine oxide furnishes an *oxyiodide*, $Sb(C_2H_5)_3I_2,Sb(C_2H_5)_3O$, tetrahedral or octahedral crystals ; with mercuric chloride and silver nitrate and sulphate this oxysalt gives rise respectively to an oxychloride, oxynitrate, and oxysulphate.[2]

Triethylstibine sulphide, $Sb(C_2H_5)_3S$, white, crystalline mass with silvery lustre and faintly unpleasant odour recalling mercaptan ; bitter taste ; soluble in water, alcohol, or hot ether, melts at 100° to a colourless liquid. Preparation (1) action of hydrogen sulphide on triethystibine oxide ; (2) direct combination of sulphur and triethylstibine under water or preferably with ethereal solution of latter reagent, heat is evolved, and on cooling a mass of crystalline sulphide results. This compound resembles the sulphides of alkali metals ; and it precipitates the sulphides of the heavy metals and is decomposed by dilute mineral acids evolving hydrogen sulphide. Its selenium analogue is soon oxidised in the air.

Triethylstibine sulphate, $Sb(C_2H_5)_3SO_4$, white, crystalline mass, m.p. 100° ; bitter taste ; extremely soluble in water, less so in

[1] Buckton, *Quart. J. Chem. Soc.*, 1860, **13**, 116.
[2] Merck, *Annalen*, 1856, **97**, 329.

alcohol. Preparation (1) by the action of sulphuric acid on triethylstibine oxide and halides; (2) best obtained by double decomposition between triethylstibine sulphide and copper sulphate.

Triethylstibine nitrate, well-defined rhomboidal crystals, m.p. 62·5°, setting point 57°, readily soluble in water, less so in nitric acid, alcohol, or ether; bitter taste; not affected by hydrogen sulphide. Easily purified and serves for the preparation of pure triethylstibine oxide and its derivatives. Preparation (1) action of nitric acid on triethylstibine oxide and halides; (2) action of triethylstibine on dilute nitric acid; nitric oxide is evolved and the nitrate crystallises from the acid solution.

Tetraethylstibonium iodide, $Sb(C_2H_5)_4I,1\frac{1}{2}H_2O$, well-defined hexagonal prisms; bitter taste; 19·02 parts soluble in 100 parts of water at 20°, more soluble in alcohol, less so in ether.

Tetraethylstibonium hydroxide, $Sb(C_2H_5)_4{\cdot}OH$, obtained as an extremely alkaline, viscid oil by the action of moist silver oxide on the preceding iodide. It is miscible in all proportions in water or alcohol, but insoluble in ether. It sets free ammonia from ammonium salts, precipitates the hydroxides of the metals excepting those of the alkaline earths; the hydroxides of aluminium and tin are redissolved by excess of this quaternary hydroxide. Its salts with the mineral and organic acids are crystalline but generally hygroscopic.

Tetraethylstibonium chloride, bromide, and *nitrate* form deliquescent needles. The bromide and iodide form with bismuth halides, yellow to red double halides of the general formula $3Sb(C_2H_5)_4X,2BiY_3$.[1]

The *platinichloride*, yellow crystals moderately soluble in water or alcohol, has the normal constitution $[Sb(C_2H_5)_4]_2PtCl_6$.[2] The double *mercuri-iodide*, $2Sb(C_2H_5)_4I,3HgI_2$, formed by adding mercuric chloride to a solution of the quaternary iodide, is a white, crystalline precipitate, insoluble in water or ether, sparingly soluble in boiling alcohol, from which it separates in colourless, hexagonal prisms. When melted under water at 70° red spots appear in the molten mass which changes to a red modification crystallising in the regular system. When dissolved in boiling alcohol the red modification changes into the colourless one, which separates again in hexagonal crystals.[3]

[1] Jörgensen, *J. pr. Chem.*, 1871, [ii], **3**, 342.
[2] Buckton, *Quart. J. Chem. Soc.*, 1860, **13**, 119.
[3] R. Löwig, *J. pr. Chem.*, 1855, **64**, 423; *Annalen*, 1856, **97**, 326.

The hydrosulphide, a yellow oil, is produced by the action of hydrogen sulphide on aqueous solutions of tetraethylstibonium hydroxide.

Methyltriethylstibonium iodide, $CH_3 \cdot Sb(C_2H_5)_3I$, prepared by the action of methyl iodide on triethylstibine, rhombic prisms, soluble in 2 parts of water at 20°. Silver oxide gives the free quaternary hydroxide, $CH_3 \cdot Sb(C_2H_5)_3 \cdot OH$, as a viscid, highly alkaline oil yielding crystallisable salts. The chloride, oxalate and acid oxalate are acicular; the sulphate (m.p. 100°) is extremely hygroscopic.[1]

3. *Amyl Series.*

Triamylstibine, $Sb(C_5H_{11})_3$, produced by the action of amyl iodide on potassium-antimony alloy, a fuming but not spontaneously inflammable liquid, heavier than water. Oxidised to *triamylstibine oxide*, $Sb(C_5H_{11})_3 \cdot O$, a brownish-yellow very viscid mass, insoluble in water but dissolving in alcohol. Its salts are oily with the exception of *triamylstibine dinitrate*, $Sb(C_5H_{11})_3(NO_3)_2$. Stellate clusters of crystals, insoluble in water, soluble in alcohol; peculiar metallic taste.[2]

Summary of the Results attained by the Study of Aliphatic Arsenicals and Antimonials.

The foregoing chapters contain references to all the more important organic derivatives of arsenic and antimony containing aliphatic or open chain radicals, and before passing on to consider the aromatic and other closed chain derivatives of these metalloids it is advisable, by way of summary, to indicate briefly the salient features of interest revealed by these researches which have now been carried on for more than 150 years.

The work of the earliest French chemists need not be recapitulated because, although it was invaluable as a pioneering effort, it led directly to no results of theoretical or practical importance. The chemical significance of the cacodyl investigation began to be apparent as the result of Bunsen's classical researches. At that time chemists were engaged in the endeavour to establish a theory of chemical affinity which should be applicable to organic as well as to inorganic compounds. Lavoisier in 1789

[1] Friedländer, *Jahresber.*, 1857, 423.

[2] Berlé, *J. pr. Chem.*, 1855, **65**, 385; Cramer, *Jahresber.*, 1855, 590.

had already contrasted the properties of inorganic and organic acids in the following words.

"I have already remarked that in the mineral kingdom nearly all the oxidisable and acidifiable radicals were simple; that in the vegetable kingdom on the contrary and above all in the animal kingdom there exist scarcely any which were composed of less than two substances, hydrogen and carbon; that often nitrogen and phosphorus were united with them, and that there resulted radicals with four bases."[1]

The existence of these compound radicals being postulated, the chemical instinct of the chemists of the early years of the nineteenth century led these workers to search for more definite evidence of the presence of these hypothetical complexes either by tracing them through a series of chemical changes or more decisively by isolating the radicals themselves. Both forms of evidence were speedily forthcoming in the case of cyanogen, a compound radical of organic origin which was identified by Gay-Lussac[2] in prussic acid and the cyanides and was also shown by him to be capable of existence in the free state. The remarkably close analogy between this compound organic radical and the simple inorganic halogen radicals is shown by the following table, in which chlorine is selected as the typical halogen.

Compound radical CN or Cy.	*Simple radical* Cl.
Free cyanogen, C_2N_2 or Cy_2.	Free chlorine, Cl_2.
Cyanogen iodide, CNCl or CyI.	Iodine monochloride, ICl.
Hydrogen cyanide, HCN or HCy.	Hydrogen chloride, HCl.
Silver cyanide, AgCN or AgCy.	Silver chloride, AgCl.
Mercuric cyanide, $Hg(CN)_2$ or $HgCy_2$.	Mercuric chloride, $HgCl_2$.
$C_2N_2 + 2KOH = KCN + KCNO + H_2O$.	$Cl_2 + 2KOH = KCl + KClO + H_2O$.

Theory of Compound Radicals.

The researches by Berzelius and Hisinger and by Davy on the effect of the electric current on inorganic compounds had shown that very frequently this agent brought about the decomposition of these complex substances into their component elements. Water was decomposed into hydrogen and oxygen, dissolved salts into acid and base, and the alkali hydroxides into metal,

[1] Lavoisier, *Traité élémentaire de chimie*, 1789, I., 209.

[2] *Ann. de chim.*, 1815, **95**, 161.

hydrogen and oxygen. Inasmuch as the electric current proved to be a specially suitable agent for decomposing compounds it was inferred that the force of chemical affinity which promoted the combination of elements to form compounds was electrical in character. It was regarded as in the highest degree probable "that substances on the point of combining exhibit opposite electric charges," and "that in all chemical combinations there is a neutralisation of opposite electric charges." The generation of heat and light, which often accompanies chemical combination, was compared to similar phenomena accompanying electric discharges. One characteristic of this electro-chemical theory due to Berzelius is the combination of elements or compounds in pairs, and for this reason it is frequently termed the "*dualistic theory*." For example, potassium (electropositive) and oxygen (electronegative) combine to form potassium oxide, K_2O. Sulphur (electropositive) and oxygen (electronegative) combine similarly to form sulphur trioxide, SO_3.

The potassium oxide (electropositive) and sulphur trioxide (electronegative)—compounds of the first order—couple similarly to produce potassium sulphate, a compound of the second order. This salt (electropositive) can now pair with aluminium sulphate (electronegative), another compound of the second order, to yield dry alum or anhydrous potassium aluminium sulphate, a compound of the third order. This double salt may finally unite with water to produce ordinary alum, hydrated potassium aluminium sulphate. At each of the successive steps in this inorganic synthesis a combination between pairs of compounds is observable.

Berzelius's dualistic electro-chemical theory could readily be applied to mineral substances—salts, acids, and bases—because these compounds were amenable to the action of the electric current. But it could not be tested on organic compounds, which were often non-conductors and not decomposed by the electric current. Accordingly Berzelius assumed that the difference was due to the presence in the organic materials of compound radicals.

"In inorganic nature all oxidised bodies contain a simple radical while all organic substances are oxides of compound radicals. The radicals of vegetable substances consist generally of carbon and hydrogen, and those of animal substances of carbon, hydrogen and nitrogen" (Berzelius, *Text-book*, 1817, **1**, 544).

At first Berzelius was indisposed to admit that oxygen could be

a component of an electropositive organic radical, although he waived this reservation in the case of the compound radical benzoyl identified by Wöhler and Liebig (1832) in oil of bitter almonds (benzaldehyde). Although this radical was not isolated, it was traced through a series of chemical changes resulting in the formation of the following group of organic compounds.

Benzoyl radical	$= C_7H_5O$.
Benzaldehyde (benzoyl hydride)	$= C_7H_5O{\cdot}H$.
Benzoic acid (benzoyl hydroxide)	$= C_7H_5O{\cdot}OH$.
Benzoyl chloride (bromide or iodide)	$= C_7H_5O{\cdot}Cl$ (or Br or I).
Benzoyl cyanide	$= C_7H_5O{\cdot}CN$.
Benzamide	$= C_7H_5O{\cdot}NH_2$.

The search for compound radicals was in full progress when Bunsen took up the study of Cadet's fuming arsenical liquid, and the identification and subsequent isolation of the compound radical, cacodyl, was acclaimed with the utmost enthusiasm and delight by Berzelius in terms which have already been cited (p. 8).

Cacodyl had all the characteristics of a compound radical as defined by Lavoisier and afterwards by Berzelius; it contained the two elements, carbon and hydrogen, common to nearly all organic radicals, and associated with them a third element, arsenic. This radical had a further significance in the eyes of Berzelius in that it was not oxygenated. Moreover, its isolation in an uncombined condition proved conclusively that the complex had a real existence.

The three complexes which were regarded by Berzelius as affording the main support for his theory of compound radicals were the following :—

Compound radical.	*Discoverers.*	*Molecular complexity in free state.*	*Elementary or inorganic analogues.*
Cyanogen, CN.	Gay-Lussac.	C_2N_2.	Halogens, Cl_2, etc.
Benzoyl, $CO{\cdot}C_6H_5$.	Liebig and Wöhler.	Not isolated.	Acidic groups, SO_3, NO_2.
Cacodyl, $As(CH_3)_2$.	Bunsen.	$[As(CH_3)_2]_2$.	K, Na, or preferably Tl.

Of these three compound radicals, cacodyl undoubtedly exhibits the most intimate relationship to its elementary analogues.

Further noteworthy examples of organic radicals of the type recognised by Berzelius were subsequently forthcoming in the tertiary stibines. The first of these, triethylstibine, discovered by Löwig and Schweitzer (p. 55), presented very close analogies

with bivalent metals, such as zinc, as shown in the following table :—

Triethylstibine radical.	*Triethylstibine-oxide.*	*-sulphide.*	*-chloride.*
$(C_2H_5)_3Sb$, existing also in the free state.	$[(C_2H_5)_3Sb]O$.	$[(C_2H_5)_3Sb]S$.	$[(C_2H_5)_3Sb]Cl_2$.

Metal.	*Metallic-oxide.*	*-sulphide.*	*-chloride.*
Zn (monatomic).	ZnO.	ZnS.	$ZnCl_2$.

Analogous reactions
$$\begin{cases} (C_2H_5)_3Sb + 2HCl = (C_2H_5)_3SbCl_2 + H_2. \\ Zn + 2HCl = ZnCl_2 + H_2. \end{cases}$$

The great upholder of the radical theory scarcely lived long enough to recognise the important bearing of the tertiary alkylstibines on his generalisation, inasmuch as his death occurred in the year in which Löwig and Schweitzer's results were published.

The next stage in the history of the aliphatic arsenicals was the explanation of the inner constitution of cacodyl by Frankland. This theoretical advance was speedily followed by the synthesis of cacodyl and the preparation of many alkyl derivatives of arsenic and antimony.

The dealkylation of these aliphatic arsenicals was first accomplished by Baeyer, who was thus led to methylarsinic acid and its derivatives. Progressive alkylation of arsenious acid to mono-, di-, and tri-alkyl derivatives was the joint contribution of G. Meyer, of Klinger and Kreutz, of Auger and of Dehn. The isolation of primary arsines was first accomplished by Palmer and Dehn. As the result of all these researches on aliphatic arsenicals this series has been very considerably extended and completed. The available synthetic methods are now so generalised that almost any required aliphatic arsenical should be capable of preparation.

In the antimonial series progress has been much slower. The experimental difficulties are considerably greater chiefly owing to the fact that antimony differs from arsenic in possessing much less affinity for the hydrocarbon radicals. Only the more drastic synthetic processes are available, and these lead most readily to tertiary stibines and quaternary stibonium halides. The series of aliphatic antimonials is still very incomplete.

Bunsen's discovery that cacodylic acid was a comparatively innocuous substance, has led to the use of its salts in medicine. Therapeutic use has also been made of the salts of methylarsinic acid, notably of sodium methylarsinate employed under the names " arrhenal " and " new cacodyl." The pro-

cesses devised by G. Meyer and by Dehn for preparing methylarsinic and other alkylarsinic acids render the production of these drugs easily practicable.

In the main, however, these alkylarsenical drugs have been superseded by more potent substances containing aromatic groups.

The alkylantimonials have not hitherto been employed in medicine.

CHAPTER III

Aromatic Arsenicals

Arylarsines and their Immediate Derivatives

We owe to France the original discovery of organic arsenical compounds by Cadet de Gassicourt, and it was a French chemist who, about one hundred years later, made the second pioneering effort in this field of scientific inquiry which led to the isolation of the first arsenic derivative containing an aromatic radical.

The second period in the history of organic arsenic and antimony compounds is characterised by the discovery of derivatives of these elements containing aromatic groups. Although these researches attracted very little attention for many years, it can now be seen that they led to great advances in our knowledge of organo-metalloidal compounds and in the laboratory processes for producing these substances.

The discovery of mauveine and magenta, which occurred about the middle of last century, led chemists to study the action of various oxidising agents on aniline and its homologues. Arsenic acid, one of these oxidising agents, was employed for many years in the manufacture of magenta from aniline containing ortho- and para-toluidines. The conditions under which magenta or fuchsine is produced from aniline and its homologues were studied by Béchamp in 1860,[1] who in one of his two publications of that year noted that aniline arsenate heated with excess of aniline did not give rise to coloured products until a fairly high temperature (190–200°) was reached. At lower temperatures aniline was eliminated from the normal arsenate so that the acid salt, $C_6H_5 \cdot NH_2, H_3AsO_2$, became an intermediate product which at higher temperatures underwent decomposition with the elimination of water and the formation of a certain amount of

[1] *Compt. rend.*, 1860, **50**, 870; **51**, 356.

magenta and other coloured substances together with arsenious acid. The development of colour was less pronounced than might have been expected, and the investigation of the colourless products was carried further.[1]

In 1863 Béchamp found that arsenic acid could react with aniline without oxidising this base. By heating aniline arsenate with excess of aniline at 190–200° he obtained, besides colouring matters, a colourless product which he supposed was an acidic anilide, or anilic acid (VI.), comparable with oxanilic acid (V.).

$C_6H_5{\cdot}NH{\cdot}CO{\cdot}CO{\cdot}OH$ V.

$C_6H_5{\cdot}NH{\cdot}AsO(OH)_2$ VI.

The sodium, potassium, silver, and barium salts of the compound described by Béchamp showed that it was a monobasic acid, and until 1907 it was regarded as having the constitution (VI.) indicated by its discoverer. The sodium salt was introduced into therapeutics under the name of atoxyl. The earliest trials of the drug are associated with the names of Schild, Kionka, Blumenthal, and Henius, whose experiments were initiated in the year 1902. The employment of the drug in sleeping sickness is due to Thomas and Breinl, of the Liverpool School of Tropical Medicine, whose pioneering inquiry was a forerunner of Ehrlich's systematic investigations on the treatment of diseases of protozoal origin with atoxyl and other more efficacious arsenicals.

The practical importance of atoxyl and its homologues and derivatives justifies the special consideration of these substances in a separate chapter (page 153). The present chapter is devoted to the aromatic arsines and their immediate derivatives.

Twelve years after Béchamp's observation, Michaelis began his comprehensive studies of aromatic arsenic derivatives, discovering two general methods of preparation.

In one of these processes advantage was taken of the fact that mercury diaryl derivatives are readily obtained by the interaction of sodium amalgam, and the bromo-derivatives of aromatic hydrocarbons.

$$[Hg - 2Na] + 2C_6H_5{\cdot}Br = Hg(C_6H_5)_2 + 2NaBr.$$

Similar results were obtained with bromotoluenes, bromoxylenes, and bromonaphthalenes, the condensation being usually facilitated by the addition of a small proportion of ethyl acetate.

[1] *Compt. rend.*, 1863, **56**, 1172.

With arsenious chloride the mercury diaryls react, giving rise to primary and secondary aromatic derivatives of arsenic.

$$Hg(C_6H_5)_2 + 2AsCl_3 = HgCl_2 + 2C_6H_5AsCl_2.$$

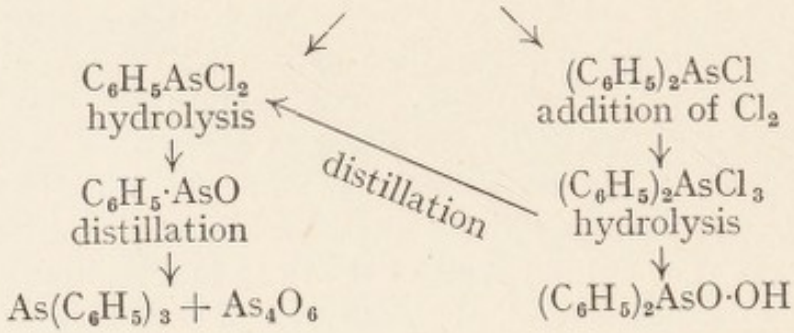
Prolonged action leads to the further change:

$$Hg(C_6H_5)_2 + 2C_6H_5{\cdot}AsCl_2 = HgCl_2 + 2(C_6H_5)_2AsCl,$$

the products being phenylarsenious dichloride and diphenylarsenious chloride.

I.—Mercury Diaryl Method.

$Hg(C_6H_5)_2$ and $AsCl_3$



These reactions were generalised by Michaelis, La Coste, and other workers, with the result that a very large number of primary and secondary aromatic derivatives of arsenic became available for further research.

In a recent modification of the mercury aryl synthesis, arylmercurichlorides are employed. These substances are readily obtained by treating benzene and its homologues and derivatives with mercuric acetate in acetic acid solution. The resulting arylmercuri-acetate is converted by double decomposition with calcium chloride (or other suitable metallic chloride) into arylmercurichloride, and the latter when heated at 100° with arsenious chloride gives rise to the corresponding arylarsenious chloride. Carboxyl, hydroxyl, and amino groups, if present, must be protected by alkylation or acylation to prevent interaction with arsenious chloride. With this precaution the reaction is general for para-substituted arylmercurichlorides.[1] The ortho-substituted isomerides are less effective.

The second general method discovered by Michaelis and his collaborators may be regarded as an adaptation of Fittig's

[1] Roeder and Blasé, *Ber.*, 1914, **47**, 2748.

synthesis of hydrocarbons. It led to the production of tertiary aromatic arsines, the simplest example being triphenylarsine, which was prepared by adding sodium to an ethereal solution of arsenious chloride and chlorobenzene.

$$AsCl_3 + 3C_6H_5Cl + 6Na = 6NaCl + As(C_6H_5)_3.$$

This reaction was extended to other aromatic chloro- and bromo-compounds, giving rise to homologues and derivatives of triphenylarsine. These tertiary aromatic arsines take up chlorine or bromine, forming dihalides, which, on heating, furnish secondary arsenious halides.

$$(C_6H_5)_3AsCl_2 = C_6H_5Cl + (C_6H_5)_2AsCl.$$

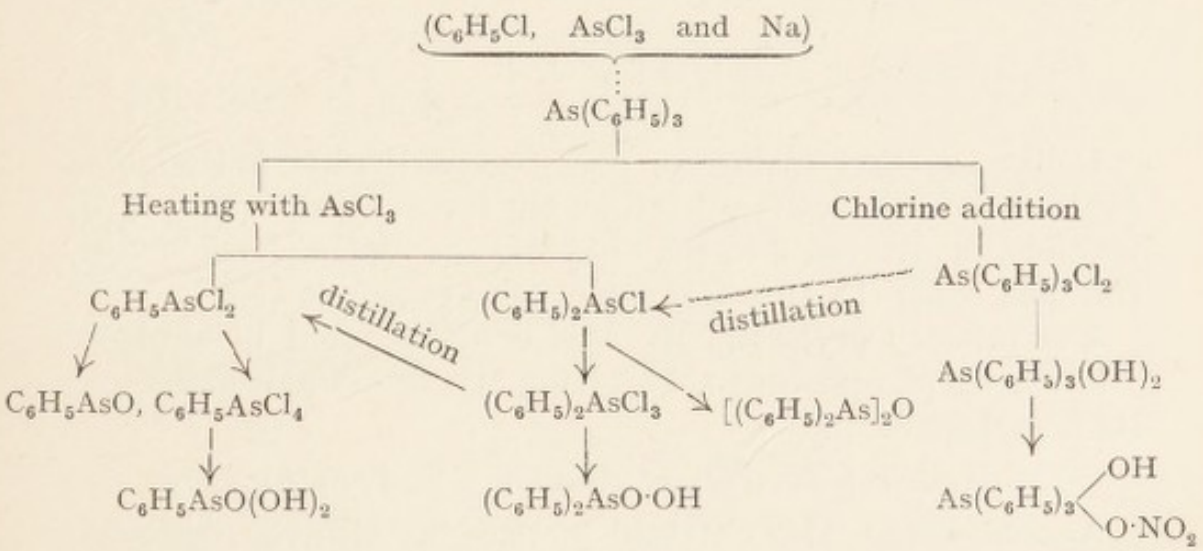
Diphenylarsenious chloride.

The foregoing process constitutes a second method of obtaining members of the secondary series.

The tertiary aromatic arsines can also be employed in preparing primary derivatives, this result being attained by heating them under pressure at 250° with arsenious chloride. A certain amount of the secondary chloride is formed as a by-product.

$$(C_6H_5)_3As + 2AsCl_3 = 3C_6H_5AsCl_2 \text{ (main product)}.$$
$$2(C_6H_5)_3As + AsCl_3 = 3(C_6H_5)_2AsCl \text{ (by-product)}.$$

II:—Sodium Method.



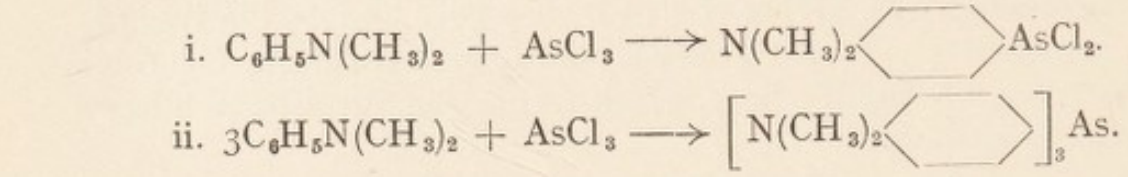
It will be seen from the diagrams that each synthetic method can be utilised for the production of primary, secondary, and tertiary arsenic derivatives.

In certain instances Michaelis found that arsenic could be

introduced into the aromatic nucleus without the intervention of mercury diaryls or sodium.

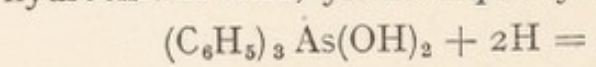
Phenylarsenious dichloride and diphenyl were produced by passing the vapours of benzene and arsenious chloride through a red-hot tube, but the separation of the products was difficult.

Dimethylaniline contains a reactive hydrogen atom which is readily replaced by an arsenic radical.

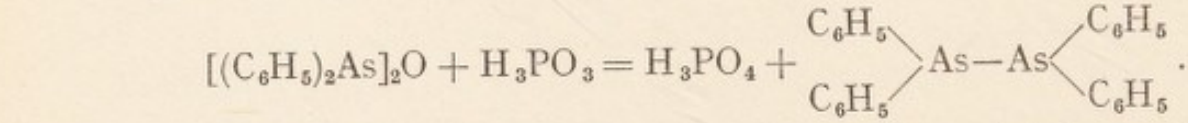


These reactions are not, however, general, and primary and secondary aromatic amines do not invariably react smoothly with arsenious chloride. The diagrams of the two synthetic methods indicate the production of oxygenated aromatic derivatives of arsenic. The reduction products of these derivatives, examined by Michaelis, La Coste, and others are of great interest as foreshadowing some of the more recent developments in the production of arsenical drugs.

Triphenylarsine dihydroxide, when reduced with tin and hydrochloric acid, yields triphenylarsine.

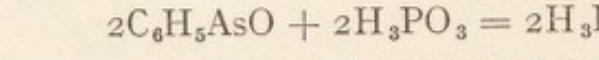


The secondary diarylarsenious oxides are reduced by phosphorous acid to arylcacodyl derivatives.



Unlike its alkyl analogues, phenylcacodyl is not inflammable in air at the ordinary temperature, but it readily absorbs oxygen, becoming converted into the anhydride of diphenylarsinic acid, this acid being the aromatic analogue of cacodylic acid.

The primary arylarsenious oxides are reduced in alcoholic solution by phosphorous acid, giving rise to arsenobenzene and its homologues.



Arsenobenzene, also obtained by reducing phenylarsinic acid, is a substance of great theoretical interest ; it is the analogue of the colour principle, azobenzene, $C_6H_5{\cdot}N{:}N{\cdot}C_6H_5$, moreover it is the parent substance of salvarsan. It crystallises in yellowish needles, readily resinifies in solution, combines

additively with chlorine and sulphur, and is readily oxidised to phenylarsinic acid. The aliphatic analogues of arsenobenzene have already been described (*v.* pp. 40, 47).

In his second detailed memoir on aromatic arsenic compounds Michaelis[1] shows that the foregoing general methods are applicable to the production of substances containing the principal aromatic hydrocarbon groups. He also describes the outstanding characteristics of the products.

Tertiary Aromatic Arsines.

The sodium method of synthesis is the most generally useful. The simple tertiary arsines are readily and quantitatively obtained by the action of this metal on ethereal solutions of arsenious chloride and the aryl halide,

$$3R{\cdot}Cl + AsCl_3 + 6Na = AsR_3 + 6NaCl.$$

The mixed tertiary aromatic arsines are produced in a similar way by the action of sodium on ethereal solutions of monoarylarsenious chloride and an aryl halide,

$$2R'Cl + AsRCl_2 + 4Na = AsRR'_2 + 4NaCl.$$

These tertiary aromatic arsines are also obtainable by two other processes :

i. The action of aromatic mercury compounds on the arylarsenious dichlorides, $HgR'_2 + RAsCl_2 = HgCl_2 + AsRR_2'$.

ii. The heating of arylarsenious oxides in sealed tubes,

$$3RAsO = AsR_3 + As_2O_3.$$

The second of these processes was the method whereby the tertiary arylarsines were originally produced.

It is noteworthy that the method with sodium, which is so generally available to the preparation of aromatic arsines and stibines, gives only poor yields or fails entirely in the production of the corresponding phosphines.

The following arsines have been obtained by the sodium method.

Simple Tertiary Arsines.

Triphenylarsine, $(C_6H_5)_3As$, m.p. 59°.
Tri-*p*-anisylarsine, $(CH_3{\cdot}O{\cdot}C_6H_4)_3As$, m.p. 156°.
Tri-*p*-phenetylarsine, $(C_2H_5{\cdot}O{\cdot}C_6H_4)_3As$, m.p. 98°.
Tribenzylarsine, $(C_6H_5{\cdot}CH_2)_3As$, m.p. 104°.

[1] Michaelis, *Annalen*, 1902, **320**, 271 ; **321**, 141

Tri-*p*-tolylarsine, $(CH_3 \cdot C_6H_4)_3As$, m.p. 146°.
Tri-*m*-tolylarsine, $(CH_3 \cdot C_6H_4)_3As$, m.p. 96°.
Tri-*m*-xylylarsine, $[(CH_3)_2 \cdot C_6H_3]_3As$, m.p. 166°.
Tri-*p*-ethylphenylarsine, $(C_2H_5 \cdot C_6H_4)_3As$, m.p. 78°.
Tripseudocumylarsine, $[(CH_3)_3 \cdot C_6H_2]_3As$, m.p. 223°.
Trimesitylarsine, $[(CH_3)_3C_6H_2]_3As$, m.p. 170°.
Tri-*p*-cumylarsine, $(C_3H_7 \cdot C_6H_4)_3As$, m.p. 140°.
Tritertiarybutylphenylarsine, $(C_4H_9 \cdot C_6H_4)_3As$, m.p. 235°.
Tri-α-naphthylarsine, $(C_{10}H_7)_3As$, m.p. 252°.
Tri-β-naphthylarsine, $(C_{10}H_7)_3As$, m.p. 165°.

Mixed Tertiary Arsines.

Diphenyl-*p*-tolylarsine, $(C_6H_5)_2AsC_6H_4 \cdot CH_3$, m.p. 50°.
Phenyldi-*p*-tolylarsine, $C_6H_5 \cdot As(C_6H_4 \cdot CH_3)_2$, m.p. 101°.
Phenyldi-*m*-xylylarsine, $C_6H_5 \cdot As[C_6H_3(CH_3)_2]_2$, m.p. 99°.
Phenyldipseudocumylarsine, $C_6H_5 \cdot As[C_6H_2(CH_3)_3]_2$, m.p. 138·5°.

The tertiary arsines are well-defined, crystalline, inodorous substances having no irritating effect on the skin. They are insoluble in concentrated hydrochloric acid, but combine with chloroplatinic acid in alcoholic solutions to give sparingly soluble *platinichlorides*, $(AsR_3)_2,H_2PtCl_6$. They combine with mercuric chloride to form the *mercurichlorides*, $AsR_3,HgCl_2$, white crystalline substances sparingly soluble in alcohol, dissolving more readily in glacial acetic acid.

When treated with chlorine or bromine in carbon tetrachloride solution these arsines combine additively with the halogen to yield the corresponding dichloride, R_3AsCl_2, or dibromide, R_3AsBr_2, the product being precipitated by ether. Alcohol converts certain dihalides into hydroxyhalides, $R_3As(OH) \cdot Cl$ or $R_3As(OH) \cdot Br$, but in some cases the dihalides are stable in this reagent.

By the interaction of alkalis on the dihalides or hydroxyhalides the hydroxides or oxides of the arsines are obtained. Some of these hydroxides crystallise with water, as, for example, tripseudocumylarsine hydroxide, $(C_9H_{11})_3As(OH)_2,4H_2O$.

Trinitro-compounds of the arsine oxides are produced by the action of nitric–sulphuric acids on the arsines or their oxides. These trinitro-compounds are reduced by phosphorous acid to trinitroarsines, and by tin and hydrochloric acid to triamino-arsines: triaminotriphenylarsine is very unstable, whereas triaminotri-*p*-tolylarsine is quite stable.

The *sulphides*, R_3AsS, are obtained by three different methods : (i) direct combination of the arsine and sulphur in carbon bisulphide ; (ii) interaction of the arsine and alcoholic ammonium polysulphide ; (iii) introduction of hydrogen sulphide into an alcoholic solution of the oxide.

Triarylalkylarsonium iodides, $R_3As(alkyl)I$.—Contrary to the earlier experiments, it has been found that the tertiary arylarsines combine with methyl and ethyl iodides when warmed with excess of these halides on the water-bath. The triarylarsines do not as a rule combine with the higher alkyl iodides, but tri-*m*-tolylarsine behaves exceptionally in giving quaternary iodides with great facility ; it combines with methyl iodide in the cold and with propyl iodide or benzyl chloride on warming gently.

Triarylmethylarsonium hydroxides, $R_3As(CH_3)\cdot OH$, differ from their phosphorus and nitrogen analogues in crystallising from concentrated aqueous solutions. When evaporated in the open air these solutions yield crystallisable bicarbonates, $R_3As(CH_3)\cdot HCO_3$. When gently heated the triarylmethylarsonium hydroxides lose methyl alcohol and regenerate the tertiary arsine, differing in this respect from the corresponding phosphonium compounds which lose a portion of the aromatic constituent and leave a substituted phosphine oxide,

$$R_3As(CH_3)\cdot OH = AsR_3 + CH_3OH$$
$$R_3P(CH_3)OH = R_2P(CH_3){:}O + R\cdot H.$$

Arylarsine oxide carboxylates are produced by the oxidation of arylarsines containing aliphatic side chains with dilute nitric acid under pressure. The three tolyl derivatives, for example, furnish the following oxidation products :—

$$(C_6H_5)_2As\cdot C_6H_4\cdot CH_3 \longrightarrow (C_6H_5)_2AsO\cdot C_6H_4\cdot CO_2H.$$

Triphenylarsine oxide carboxylic acid.

$$C_6H_5\cdot As(C_6H_4\cdot CH_3)_2 \longrightarrow C_6H_5\cdot AsO\begin{cases} C_6H_4\cdot CH_3 \\ C_6H_4\cdot CO_2H \end{cases} \longrightarrow$$

Tolyldiphenylarsine oxide carboxylic acid.

$$C_6H_5\cdot AsO(C_6H_4\cdot CO_2H)_2.$$

Triphenylarsine oxide dicarboxylic acid.

$$As(C_6H_4\cdot CH_3)_3 \longrightarrow (HO)_2As(C_6H_4\cdot CO_2H)_3.$$

Triphenylarsine dihydroxide tricarboxylic acid.

When these acids are esterified with alcoholic hydrochloric

acid the oxygen attached to arsenic is replaced by chlorine. For instance, the third of the foregoing carboxylic acids furnishes the chloro-ester, $Cl_2As\begin{matrix}C_6H_5\\ \diagdown\!\!\diagdown\\ (C_6H_4\cdot CO_2\cdot C_2H_5)_2\end{matrix}$.

Arylarsenious Chlorides (*Primary Chloroarsines*), $R\cdot AsCl_2$.

As already indicated, these chlorides are obtainable by three general methods :

1. The mercury diaryl method (*v.* p. 78).

2. The arylmercurichloride method (*v.* p. 79). This process is convenient because of the ease with which arylmercuriacetates can be produced.

3. Heating the corresponding tertiary arsine with excess of arsenious chloride in sealed tubes at 150–300°.

Owing to the ease with which tertiary arsines are prepared, the third method is much to be preferred.

It is noteworthy that Friedel and Crafts' method of synthesis with aluminium chloride, although rendering good service in the preparation of aromatic phosphorous chlorides, is useless in the case of the aromatic arsenious chlorides. In the latter series only tarry products are obtained.

The lower homologues of the arylarsenious chlorides are liquids, the higher members are colourless well-defined crystalline solids. They can be boiled without decomposition under the ordinary pressure, but it is preferable to distil them under reduced pressure. They are very poisonous and when dropped on the skin produce painful and slowly healing wounds. Faintly odorous in the cold, they evolve a penetrating and irritant odour on warming. Insoluble in water, these arsenious chlorides are readily soluble in alcohol, ether, or benzene.

The following arylarsenious chlorides have been prepared :—

Phenylarsenious chloride, $C_6H_5\cdot AsCl_2$, b.p. 254°, liquid.

Nitrophenylarsenious chloride, $NO_2\cdot C_6H_4\cdot AsCl_2$, m.p. 47°.

p-Anisylarsenious chloride, $CH_3\cdot O\cdot C_6H_4\cdot AsCl_2$, b.p. 160°, and m.p. 48°.

p-Phenetylarsenious chloride, $C_2H_5\cdot O\cdot C_6H_4\cdot AsCl_2$, b.p. 198°.

Benzylarsenious chloride, $C_6H_5\cdot CH_2\cdot AsCl_2$, b.p. 175°/100 mm.

p-Tolylarsenious chloride, $CH_3\cdot C_6H_4\cdot AsCl_2$, b.p. 267°, m.p. 31°.

m-Tolylarsenious chloride, $CH_3\cdot C_6H_4\cdot AsCl_2$, b.p. 270°.

o-Tolylarsenious chloride, $CH_3 \cdot C_6H_4 \cdot AsCl_2$, b.p. 264°.

1 : 3-Xylyl-4-arsenious chloride, $(CH_3)_2C_6H_3 \cdot AsCl_2$, b.p. 278°, m.p. 41°.

1 : 4-Xylyl-2-arsenious chloride, b.p. 285°, m.p. 63°.

Pseudocumylarsenious chloride, b.p. 190°/30 mm., m.p. 82·5°.

p-Cumylarsenious chloride, b.p. 170°/30 mm.

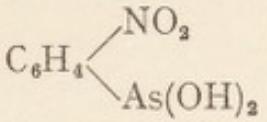
Tertiarybutylphenylarsenious chloride, b.p. 177°/20 mm.

α-Naphthylarsenious chloride, m.p. 63°.

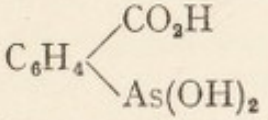
β-Naphthylarsenious chloride, m.p. 69°.

Arylarsenious Oxides, R·AsO.—The foregoing arylarsenious chlorides are only slightly attacked by water even on heating, but with aqueous sodium carbonate they are converted into oxides. These arylarsenious oxides are somewhat devoid of crystalline habit. By hydrochloric acid they are reconverted into arylarsenious chlorides. Hydrobromic and hydriodic acids lead to arylarsenious bromides and iodides respectively. On heating, these oxides give rise to triarylarsines and arsenious oxide (*v.* p. 80).

Arylarsenious Acids, $R \cdot As(OH)_2$.—These compounds are capable of existence only when the aromatic nucleus contains acidic constituents, which confer on the AsO group a greater affinity for hydroxyl. There are no arylarsenious acids containing simple aromatic nuclei.



Nitrophenylarsenious acid (*v.* p. 145).



Benzarsenious acid (*v.* p. 131).

This conferred power of hydration is very remarkable, inasmuch as arsenious oxide does not form a stable hydroxide.

The *esters* of arylarsenious acids,

$$C_6H_5As(O \cdot CH_3)_2 \text{ and } C_6H_5As(O \cdot C_6H_5)_2,$$

produced by the action of sodium alkoxide or phenoxide on arylarsenious chlorides, even when no acidic substituents are present in the aromatic ring, are very sensitive to moisture, which decomposes them into the arylarsenious oxide and alcohol or phenol.

Arylarsenic chlorides, $R \cdot AsCl_4$, are for the most part crystalline substances, though some, like *m*-tolylarsenic chloride, are liquid. They are produced by the direct addition of chlorine to primary arylarsenious chlorides. When the aromatic nucleus contains

an acidic constituent, as in the nitroarsenious chlorides, this addition of chlorine occurs less readily, and in this respect these nitro-derivatives resemble arsenious chloride. *Arylarsenic oxychlorides*, $RAsOCl_2$, are obtained similarly by the addition of chlorine to the arylarsenious oxides.

Arylarsinic acids, $R{\cdot}AsO(OH)_2$, are well-crystallised, very stable compounds, obtained by the action of water on the foregoing tetrachlorides or oxychlorides. They are prepared more easily when the arylarsenious chloride is suspended in water and treated with chlorine until it is completely dissolved,

$$RAsCl_2 + Cl_2 + 3H_2O = RAsO(OH)_2 + 4HCl.$$

An alternative method, which leads to products free from chlorine, consists in dissolving the arylarsenious chloride in glacial acetic acid and adding gradually hydrogen peroxide,

$$RAsCl_2 + H_2O_2 + H_2O = RAsO(OH)_2 + 2HCl.$$

The composition of the metallic arylarsinates indicates that the acids are dibasic. The corresponding esters are liquid and rapidly hydrolysed by moisture into alcohol and arylarsinic acids.

Arylarsinic anhydrides, $R{\cdot}AsO_2$, corresponding in composition with aromatic nitro-compounds, are obtained on heating the arylarsinic acids; the reverse change occurs on adding warm water to these anhydrides. If electronegative (acidic) substituents are present in the nucleus of arylarsinic acids the dehydration occurs much less readily (*v.* arylarsenious acids, p. 73).

The arylarsinic acids are not affected by chlorine or bromine, but undergo nitration with concentrated nitric acid (100 per cent. HNO_3) or with a mixture of concentrated nitric and sulphuric acids. The nitroarylarsinic acids are well-defined crystalline compounds, either with high melting points or infusible until they intumesce over the direct flame. In Michaelis's researches these nitro-compounds were not reduced to the primary aminoarylarsinic acids. The *N*-alkylated aminoarylarsinic acids are producible directly from alkylamino-arylarsenious oxides. For instance, dimethylaminophenylarsinic acid is obtained from dimethylaminoarsenious oxide by oxidation with mercuric oxide and water,

Oxidation of the methylated homologues of phenylarsinic acid with alkaline permanganate or with dilute nitric acid (D 1·2) in sealed tubes leads to benzarsinic acid and its homologues.

Thio-derivatives of Arylarsinic Acids.

Saturation of ammoniacal solutions of arylarsinic acids with hydrogen sulphide leads to the formation of ammonium arylthioarsinates, $R{\cdot}AsS(SNH_4)_2$. These salts are decomposed by mineral acids with the formation of arylarsenic sulphides,

$$R{\cdot}AsS(SNH_4)_2 + 2HCl = RAsS_2 + 2NH_4Cl + H_2S.$$

In some instances the disulphide is unstable and loses sulphur with the production of a sesquisulphide, $R_2As_2S_3$; these substances are the organic analogues of P_2S_4 and the hypothetical As_2S_4.

Phenylarsinic acid, its nitro-derivative, and *p*-tolylarsinic acid furnish the following sesquisulphides :—

$$(C_6H_5)_2As_2S_3,\ (NO_2{\cdot}C_6H_4)_2As_2S_3,\ \text{and}\ (C_7H_7)_2As_2S_3,$$

whereas nitro-*p*-tolylarsinic acid and *p*-xylylarsinic acid give the disulphides, $NO_2{\cdot}C_7H_6{\cdot}AsS_2$ and $C_8H_9{\cdot}AsS_2$.

When the disulphides are not obtainable by the foregoing process they may frequently be prepared by the direct addition of sulphur to arylarseno-compounds.

Arylarsenious sulphides, R·AsS, are white, crystallisable compounds prepared either by passing hydrogen sulphide into alcoholic solutions of arylarsenious chlorides or oxides or by the addition of sulphur to arylarseno-compounds.

Arylarseno-derivatives, R·As:As·R, result from the reduction of arylarsenious oxides with phosphorous acid. They are also prepared by the reduction of arylarsinic acids with aqueous phosphorous acid in sealed tubes or by the action of sodium amalgam or sodium and alcohol on the arylarsenious oxides or chlorides.

These arylarseno-compounds, the analogues of the aromatic azo-compounds, are yellowish-white to yellow compounds; their nitro-derivatives are yellowish-brown. They combine additively with chlorine and bromine to form respectively di- and tetrachlorides, $RAsCl_2$ and $RAsCl_4$, and the dibromides, $RAsBr_2$. With sulphur they give the disulphides, $RAsS_2$, and with oxidising agents (*e.g.* nitric acid) the arylarsinic acids. Iodoarseno-derivatives are characteristic yellowish-red unstable compounds

obtained either by adding iodine to the arseno-derivatives or by reducing the arylarsenious iodides; they correspond with arsenious di-iodide,

$$\begin{matrix} C_6H_5\cdot AsI \\ | \\ C_6H_5\cdot AsI \end{matrix} \qquad \begin{matrix} AsI_2 \\ | \\ AsI_2 \end{matrix}.$$

Primary aromatic arsines, $RAsH_2$, were not isolated in Michaelis's investigations, his reduction experiments leading to arseno-compounds. Yet frequently in these researches a characteristic pungent odour was distinguishable, and this was attributed to the formation of a small amount of primary arsine. The conditions necessary for the preparation of aromatic arsines were discovered by Palmer and Dehn, who isolated phenylarsine, the first member of this series.

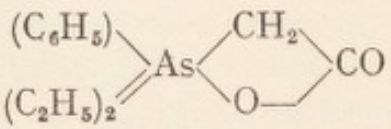
Synthesis of Mixed Aromatic-aliphatic Arsines (*v.* p. 90).

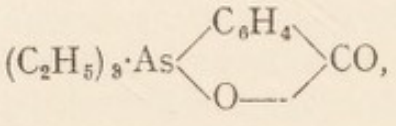
The arylarsenious chlorides subjected to the Grignard reaction with magnesium alkyl iodides furnish mixed tertiary arsines containing two aliphatic groups. These tertiary arsines give dibromides which on heating evolve an alkyl bromide and leave an arylalkylarsenious chloride. This secondary arsenic compound yields with a second magnesium alkyl iodide a mixed tertiary arsine containing dissimilar groups. This very elastic method of synthesis may be indicated by the following equations, where R and R′ are aryl radicals :—

1. $C_6H_5\cdot AsCl_2 + 2MgRI = C_6H_5\cdot AsR_2 + MgCl_2 + MgI_2$.
2. $C_6H_5\cdot AsR_2Br_2 = C_6H_5\cdot AsRBr + RBr$.
3. $C_6H_5\cdot AsRBr + MgR'I = C_6H_5\cdot AsRR' + MgBrI$.

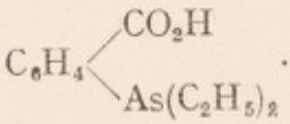
In these syntheses the Grignard reagents may be replaced by zinc dialkyls.

The products are colourless liquids of high boiling point; they possess a faint unpleasant odour. From these arylaliphatic tertiary arsines can be obtained quaternary arsonium derivatives, betaines of various types,





and also dialkylarsinobenzoic acids,



Secondary diarylarsenious chlorides, R_2AsCl, are obtained by several methods of formation, but a process giving a good yield of these substances remains to be found.

(1) The heating of the tertiary arsine with a moderate excess of arsenious chloride gives the diarylarsenious chloride, but only in small yield.

For example, 50 grams of triphenylarsine and 25 grams of arsenious chloride at 250° (not higher) for ten hours gives only 10–12 grams of diphenylarsenious chloride.

(2) The heating of the tertiary arsine dichloride under reduced pressure gives only a small yield of diarylarsenious chloride,

$$(C_6H_5)_3AsCl_2 = (C_6H_5)_2AsCl + C_6H_5Cl,$$

because a portion of the dichloride decomposes into chlorine and tertiary arsine.

(3) The most preferable method is to heat the primary arylarsenious chloride with the corresponding mercury diaryl,

$$2RAsCl_2 + HgR_2 = 2R_2AsCl + HgCl_2.$$

(4) Another process, which has only been tried for di-*p*-anisylarsenious chloride, consists in heating the tertiary arsine with hydriodic acid. The resulting secondary iodide is converted into its oxide by alkalis and the oxide treated with hydrochloric acid to furnish the diarylarsenious chloride,

$$R_3As + HI = R_2AsI + RH.$$
$$2R_2AsI + 2NaOH = (R_2As)_2O + 2NaI + H_2O.$$
$$(R_2As)_2O + 2HCl = 2R_2AsCl + H_2O.$$

Probably this process is capable of further extension.

The diarylarsenious chlorides are, like the arylarsenious chlorides, poisonous and very irritating to the skin. They are not affected by water and only slowly by aqueous caustic alkalis. Alcoholic alkalis convert them at once into the oxides, $(R_2As)_2O$. These oxides are not soluble in aqueous alkalis, but are reconverted into the chlorides, R_2AsCl, by hydrochloric acid. Hydrogen sulphide converts the oxides in alcoholic solution into crystallisable diarylarsenious sulphides, $(R_2As)_2S$.

Although the hydroxides, $R_2As{\cdot}OH$, are not known, sodium phenoxide and the diarylarsenious chlorides give rise to esters, *e.g.* $(C_6H_5)_2As{\cdot}O{\cdot}C_6H_5$, corresponding with these hypothetical hydroxy-derivatives.

The *arylcacodyls*, $R_2As{\cdot}AsR_2$, are obtained by warming alcoholic solutions of the diarylarsenious oxides with phosphorous acid.

Their derivatives are readily oxidised and take up chlorine or bromine to regenerate the diarylarsenious chloride, R_2AsCl, or bromide, R_2AsBr.

The *diarylarsenic trichlorides*, R_2AsCl_3, which result from the addition of chlorine to the diarylarsenious chlorides, are hydrolysed by water into the corresponding *diarylarsinic acids*, $R_2AsO{\cdot}OH$. These crystallisable products are amphoteric, behaving as monobasic acids towards strong bases and as weak bases towards strong acids, nitric acid, for instance, giving the nitrate, $(C_6H_5)_2AsO{\cdot}O{\cdot}NO_2$.

Dinitrodiarylarsinic acids, obtained from the diarylarsinic acids by the action of nitric and sulphuric acids, yield nitro-arylcacodyl compounds on reduction with phosphorous acid. Reduction with hydrogen sulphide and subsequent acidification gives rise to diaminodiarylarsenious sulphides,

$$[(NH_2{\cdot}C_6H_4)_2As]_2S.$$

Section I.—Benzene Derivatives with One Aromatic Nucleus attached to One Arsenic Atom.

Phenylarsenious chloride, $C_6H_5{\cdot}AsCl_2$, colourless, highly refractive, somewhat viscid liquid, b.p. 252–254°. Its odour, which is faintly unpleasant in the cold, becomes very pungent on warming. It fumes only slightly in the air and is not decomposed by water. It has a powerfully irritating action on the skin. Aqueous caustic alkalis dissolve the dichloride, eliminating chlorine and giving rise to unstable compounds of the type $C_6H_5{\cdot}As(OK)_2$; these substances regenerate phenylarsenious chloride on warming with concentrated hydrochloric acid. The dichloride combines additively with chlorine but not with bromine.

Preparation.—Phenylarsenious chloride, the starting point for many monophenyl arsenicals, was first obtained by the repeated passage of the vapours of benzene and arsenious chloride through a heated tube. The reaction goes much less readily than in the case of phosphorous chloride, and the products are diphenyl and phenylarsenious chloride which are not readily separated by distillation or crystallisation.[1] Phenylarsenious chloride can, however, be prepared by either of the three general methods described on page 72.

(i) Mercury diphenyl (70 grams) is added with stirring to 800 grams of carefully-purified arsenious chloride and the

[1] La Coste and Michaelis, *Ber.*, 1878, **11**, 1883.

mixture rapidly heated to 254°. The mercury is converted completely into the dichloride,[1]

$$2AsCl_3 + Hg(C_6H_5)_2 = 2C_6H_5{\cdot}AsCl_2 + HgCl_2.$$

At lower temperatures some phenylmercuric chloride is obtained.

(ii) Triphenylarsine,[2] when heated with arsenious chloride in sealed tubes at 250° is converted readily into phenylarsenious chloride,

$$(C_6H_5)_3As + 2AsCl_3 = 3C_6H_5{\cdot}AsCl_2.$$

(iii) A third more recent synthesis[3] leads from arylmercurichlorides to phenylarsenious chloride and its homologues. Benzene (100 c.c.) is heated for five hours at 100° with mercuric acetate in acetic acid solution. The filtrate is concentrated and treated with alcoholic calcium chloride, when phenylmercurichloride separates. This compound (30 grams) heated with arsenious chloride (100 grams) at 100° for four to five hours yields phenylarsenious chloride,

$$C_6H_5HgCl + AsCl_3 = HgCl_2 + C_6H_5AsCl_2.$$

The reaction is a general one, but carboxyl and hydroxyl groups must be protected by alkylation to prevent their hydrogen atoms interacting with arsenious chloride to form hydrogen chloride.

Phenylarsenic chloride,[4] $C_6H_5{\cdot}AsCl_4$. — Although arsenious chloride does not combine with chlorine, this halogen is absorbed by phenylarsenious chloride with considerable generation of heat. The product solidifies at 0° to yellow flattened needles melting at 45°. When added to water the tetrachloride is decomposed violently with a hissing sound, considerable heat being generated. In this respect phenylarsenic chloride resembles phosphenyl tetrachloride, $C_6H_5{\cdot}PCl_4$; but towards organic acids it behaves differently, acting as a chlorinating agent, whilst the phosphorus compound forms acid chlorides by replacing hydroxyl by chlorine,

$$CH_3{\cdot}CO_2H + C_6H_5AsCl_4 = C_6H_5AsCl_2 + CH_2Cl{\cdot}CO_2H + HCl.$$

The foregoing reaction takes place on warming; in the cold the tetrachloride dissolves in the acid without interaction.

On warming, the tetrachloride dissociates into the dichloride and free chlorine; this change is facilitated by heating in a

[1] La Coste and Michaelis, *Annalen*, 1880, **201**, 1

[2] Michaelis and Reese, *Ber.*, 1882, **15**, 2873.

[3] Roeder and Blasé, *Ber.*, 1914, **47**, 2748.

[4] Michaelis, *Ber.*, 1877, **10**, 622.

stream of dry carbon dioxide. At 150° the tetrachloride is decomposed completely into chlorobenzene and arsenious chloride, a reaction recalling the behaviour of methylarsenic chloride (*v.* p. 33),

$$C_6H_5AsCl_4 = C_6H_5Cl + AsCl_3.$$

Phenylarsenic oxychloride,[1] $C_6H_5AsOCl_2$, a white, crystalline substance melting at 100° and hydrolysed by water or moist air to phenylarsinic acid, is obtained by adding the requisite amount of water to the foregoing tetrachloride, but is prepared more readily by the addition of chlorine to phenylarsenious oxide. At 150° it is decomposed into chlorobenzene and arsenious oxychloride. The corresponding oxybromide is produced, together with bromobenzene, by the action of bromine on phenylarsenious oxide.

Phenylarsenious bromide,[2] $C_6H_5{\cdot}AsBr_2$, a colourless or faintly yellow liquid, D = 2·0983/15°, b.p. 285° (with slight decomposition), is prepared by warming phenylarsenious oxide with concentrated hydrobromic acid. Bromine decomposes the bromide into bromobenzene and arsenious bromide.

Phenylarsenious iodide, $C_6H_5{\cdot}AsI_2$,[3] a red oil obtained by treating phenylarsenious oxide with highly concentrated hydriodic acid (D = 1·7), is reduced to di-iodoarsenobenzene, $C_6H_5{\cdot}AsI{\cdot}AsI{\cdot}C_6H_5$, by phosphorous acid.

Phenylarsenious oxide,[4] $C_6H_5{\cdot}AsO$, colourless, crystalline crusts from alcohol, m.p. 119–120°, is obtained by adding sodium carbonate to a suspension of phenylarsenious chloride in warm water. In the cold the oxide has a characteristic odour resembling anise; on warming it becomes very irritant to the mucous membrane of the nose. It is slightly volatile in steam, insoluble in water, easily soluble in hot alcohol or cold benzene. Treatment with hydrochloric acid regenerates phenylarsenious chloride. It is scarcely soluble in ammonia, but dissolves readily in aqueous sodium hydroxide to a saline substance, $C_6H_5As(ONa)_2$, from which the oxide is reprecipitated by acids.

Heated above its melting point it is decomposed into triphenylarsine and arsenious oxide,

$$3C_6H_5AsO = (C_6H_5)_3As + As_2O_3.$$

[1] La Coste and Michaelis, *Annalen*, 1880, **201**, 191.
[2] *Loc. cit.* Michaelis, *Ber.*, 1877, **10**, 625.
[3] Michaelis and Schulte, *Ber.*, 1881, **14**, 913.
[4] Michaelis, *Ber.*, 1877, **10**, 623.

When reduced with phosphorous acid the oxide is converted into arsenobenzene; other reducing agents, such as sodium amalgam and zinc and hydrochloric acid, bring about the same change.

Esters of Phenylarsenious Acid,[1]

Although phenylarsenious acid, $C_6H_5 \cdot As(OH)_2$, has not been isolated except as its anhydride, phenylarsenious oxide, $C_6H_5 \cdot AsO$, yet its alkyl and aryl esters have been prepared by the action of alkali, alkyl- and aryl-oxides on phenylarsenious chloride.[2]

Methyl phenylarsenite, $C_6H_5 \cdot As(O \cdot CH_3)_2$, colourless liquid with characteristic odour, b.p. 220°, with partial decomposition under atmospheric pressure, 116°/18 mm.; D = 1·343/20°. Immediately hydrolysed into phenylarsenious oxide by water or alkalis. It absorbs dry chlorine, forming the additive compound, $C_6H_5AsCl_2(O \cdot CH_3)_2$, colourless crystals, m.p. 90°, hydrolysed by water or alcohol to phenylarsinic acid

$$C_6H_5 \cdot AsCl_2(O \cdot CH_3)_2 + 3H_2O = C_6H_5 \cdot AsO(OH)_2 + 2CH_3 \cdot OH + 2HCl.$$

Ethyl phenylarsenite, $C_6H_5 \cdot As(O \cdot C_2H_5)_2$, colourless liquid with unpleasant odour, b.p. 122°/15 mm. This compound and the preceding ester are prepared by adding phenylarsenious chloride to sodium ethoxide and methoxide respectively suspended in dry ether. Additive compound, $C_6H_5AsCl_2(O \cdot C_2H_5)_2$, cubical crystals, m.p. 95°.

Phenyl phenylarsenite, $C_6H_5 \cdot As(O \cdot C_6H_5)_2$, colourless liquid, b.p. 245°/15 mm. D = 1·32/20°. Prepared by adding phenylarsenious chloride to sodium phenoxide in dry ether. No chlorine additive compound is obtainable since this halogen decomposes the ester into phenylarsenic chloride and trichlorophenol,

$$C_6H_5 \cdot As(O \cdot C_6H_5)_2 + 8Cl_2 = C_6H_5 \cdot AsCl_4 + 2C_6H_2Cl_3 \cdot OH + 6HCl.$$

Bromine reacts similarly.

p-Cresyl phenylarsenite, $C_6H_5 \cdot As(O \cdot C_6H_4 \cdot CH_3)_2$, pale yellow oil, b.p. 285°/12 mm. D = 1·2989/13°. Prepared by adding phenylarsenious chloride to sodium *p*-tolyloxide suspended in xylene, the condensation being completed by boiling.

Benzyl phenylarsenite, $C_6H_5 \cdot As(O \cdot CH_2 \cdot C_6H_4)_2$, light yellow oil,

[1] Michaelis, *Annalen*, 1902, **320**, 286.

[2] Fromm, *Inaug. Dissert.*, Rostock, 1896.

odour of benzyl alcohol, b.p. 296°/30mm. D = 1·2853/13°. Obtained as in the preceding preparation.

β-Naphthyl phenylarsenite, $C_6H_5{\cdot}As(O{\cdot}C_{10}H_7)_2$, colourless needles from benzene–petroleum, m.p. 113–114°, readily hydrolysed by water. In this preparation phenylarsenious chloride is added to an ethereal solution of sodium β-naphthoxide.

Catechyl phenylarsenite, $C_6H_5{\cdot}As\langle{}^{O}_{O}\rangle C_6H_4$, colourless, crystalline mass, m.p. 83°; b.p. 197–198°/15mm.; easily hydrolysed by water. Prepared by adding phenylarsenious chloride to the dry lead (not sodium) salt of catechol suspended in anhydrous xylene.

Phenylarsenimide,[1] $C_6H_5{\cdot}As{:}NH$, colourless, crystalline mass from benzene–ether, sintering at 265°, m.p. 270°. Prepared by passing dry ammonia into phenylarsenious chloride in benzene solution; considerable heat is generated, the benzene boiling during the separation of ammonium chloride. The imide is readily soluble in benzene or xylene, dissolving sparingly in ether or absolute alcohol. From the last solvent it separates in well-defined leaflets. Hydrolysed by water or dilute acids,

$$C_6H_5{\cdot}AsCl_2 + 3NH_3 = C_6H_5{\cdot}As{:}NH + 2NH_4Cl.$$
$$C_6H_5{\cdot}As{:}NH + H_2O = C_6H_5{\cdot}AsO + NH_3.$$

Organic amines also interact with phenylarsenious chloride. Butylamine and dibutylamine give $C_6H_5{\cdot}AsCl{\cdot}NHC_4H_9$ and $C_6H_5{\cdot}AsCl{\cdot}N(C_4H_9)_2$. Aniline yields $C_6H_5{\cdot}AsCl{\cdot}NH{\cdot}C_6H_5$, whilst tertiary amines furnish additive compounds such as

$$C_6H_5AsCl_2{:}N(C_2H_5)_3.$$

Phenylarsenious sulphide,[2] $C_6H_5{\cdot}AsS$, white needles from benzene, m.p. 152°. Obtained by passing hydrogen sulphide into an alcoholic solution of phenylarsenious oxide or phenylarsenious chloride. Sparingly soluble in alcohol, ether, or cold benzene, dissolving readily in hot benzene or carbon bisulphide. Not attacked by hydrochloric acid, but oxidised by nitric acid, yielding phenylarsinic acid; sparingly soluble in ammonia or colourless ammonium sulphide. It dissolves readily in yellow ammonium sulphide, from which solution acids precipitate *phenylarsenic sesquisulphide,* $(C_6H_5{\cdot}As)_2S_3$. This higher sulphide

[1] Michaelis, *Annalen,* 1902, **320**, 291.
[2] Schulte, *Ber.,* 1882, **15**, 1955.

is also prepared by saturating with hydrogen sulphide an ammoniacal solution of phenylarsinic acid and precipitating with mineral acid,

$$C_6H_5\cdot AsO(ONH_4)_2 + 3H_2S = C_6H_5\cdot AsS(SNH_4)_2 + 3H_2O.$$
$$2C_6H_5\cdot AsS(SNH_4)_2 + 4HCl = (C_6H_5\cdot As)_2S_3 + S + 2H_2S + 4NH_4Cl.$$

The sesquisulphide crystallises from benzene in light yellow prisms and from glacial acetic acid in leaflets, m.p. 130°. It is easily soluble in carbon bisulphide, sparingly so in alcohol or ether ; insoluble in ammonia, dissolving sparingly in aqueous sodium hydroxide, and readily in sodium polysulphide to yield *sodium phenyltrithioarsinate,* $C_6H_5\cdot AsS(SNa)_2,6H_2O$; well-defined needles, which are easily soluble in water and precipitated by alcohol. The free phenylthioarsinic acid does not exist.

Phenylarsinic acid,[1] $C_6H_5\cdot AsO(OH)_2$, elongated, colourless prisms from water. D = 1·840. Softening at 158°, and passing into *phenylarsinic anhydride,* $C_6H_5\cdot AsO_2$, a white, amorphous powder regenerating the acid in water and decomposed on heating without melting. The acid is soluble in absolute alcohol and is extracted by ether from aqueous solutions containing excess of mineral acid. It is very stable towards oxidising agents, and is not affected by hot concentrated nitric acid or by chromic acid. When treated with ordinary zinc in acid or alkaline solution there is no very marked change, although the development of a garlic odour suggests the formation of an arsine. It has recently been shown by Palmer and Dehn (*v.* p. 89) that phenylarsine can be produced by the reduction of phenylarsinic acid.

Phosphorous acid at 180° reduces phenylarsinic acid to arsenobenzene, and potash fusion leads to phenol and potassium arsenite. This acid is distinctly poisonous, and the period between the commencement of poisonous symptoms and the death of the experimental animal is less than with arsenious acid but similar to that of arsenic acid.

Phenylarsinic acid results from the interaction of phenylarsenic chloride and water, but in this preparation it is quite unnecessary to isolate the higher chloride.

Phenylarsenious chloride (25 grams) is suspended in water (100 c.c.) and chlorine passed in until the oily drops of lower chloride entirely disappear. With a rapid stream of the gas the

[1] La Coste and Michaelis, *loc. cit.* ; Michaelis, *Ber.*, 1877, **10**, 626.

liquid becomes sufficiently heated to dissolve the product. The solution of phenylarsinic acid is evaporated to dryness and crystallised from alcohol.

This acid is also obtainable by Bart's reaction on adding potassium arsenite to an aqueous solution of potassium benzene-*iso*diazo-oxide, the mixture being stirred and heated till nitrogen is evolved. The excess of alkali is then neutralised with acid, the filtered solution evaporated to dryness, and potassium phenylarsinate extracted from the residue with alcohol. From this salt the free acid is precipitated with hydrochloric acid.[1] It is also obtained from benzenediazonium chloride, sodium arsenite, sodium hydroxide, and cuprous oxide.[2]

Phenylarsinic acid is prepared from *p*-arsanilic acid by treating the diazo-compound of the latter by Mai's method[3] with sodium hypophosphite and dilute hydrochloric acid. In this process the product is purified successively through its barium, zinc, and sodium salts.[4]

Salts of Phenylarsinic Acid.[5]—*Alkali* salts amorphous. *Acid barium salt,* $(C_6H_5\cdot AsO_3H)_2Ba$, needles, less soluble in hot than in cold water. *Acid calcium salt,* $(C_6H_5\cdot AsO_3H)_2Ca$, prepared by adding ammonia to a boiling solution of calcium chloride and phenylarsinic acid; nacreous leaflets with a greasy texture. *Normal calcium salt,* $C_6H_5\cdot AsO_3Ca,2H_2O$, acicular aggregates. *Copper* salt, $C_6H_5\cdot AsO_3Cu$, and *lead* salt are green and white precipitates respectively. *Silver phenylarsinate,* $C_6H_5\cdot AsO(OAg)_2$, colourless, microcrystalline powder from ammonium salt and silver nitrate.

Esters of Phenylarsinic Acid.[6]

Preparation : (i) By the action of sodium alkyloxide on phenylarsenic oxychloride,

$$C_6H_5\cdot AsOCl_2 + 2NaOR = C_6H_5\cdot AsO(OR)_2 + 2NaCl.$$

(ii) Double decomposition between alkyl iodides and silver phenylarsinate,

$$C_6H_5\cdot AsO(OAg)_2 + 2RI = C_6H_5\cdot As(OR)_2 + 2AgI.$$

The reaction sets in even at the ordinary temperature and

[1] Bart, D.R.-P., 250264.
[2] Chem. Fabrick von Heyden, D.R-P., 264924.
[3] *Ber.*, 1902, **35**, 162. [4] Bertheim, *Ber.*, 1908, **41**, 1854.
[5] Michaelis and Loesner, *Ber.*, 1894, **27**, 265.
[6] Michaelis, *Annalen*, 1902, **320**, 294.

is completed at 100° in a reflux apparatus. The calculated amount of alkyl iodide must be used, because excess leads to liberation of iodine and formation of alkyl phenylarsenites,

$$C_6H_5\cdot AsO(OAg)_2 + 4CH_3I = C_6H_5\cdot As(OCH_3)_2 + 2AgI + I_2 + (CH_3)_2O.$$

Methyl phenylarsinate, $C_6H_5\cdot AsO(OCH_3)_2$, colourless liquid of unpleasant odour, b.p. 188°/95 mm. D = 1·3946/23°. *Ethyl* ester, b.p. 168–170°/15 mm. D = 1·318/15°.

Halogen Derivatives of Phenylarsinic Acid.

p-*Chlorophenylarsinic acid,*[1] $C_6H_4Cl\cdot AsO(OH)_2$, colourless crystals obtained from *p*-arsanilic acid by the Gattermann diazo-reaction (hydrochloric acid and copper powder); it is characterised by its *barium* salt, $(C_6H_4Cl\cdot AsO_3H)_2Ba$, which separates in white needles.

p-*Bromophenylarsinic acid,*[2] $C_6H_4Br\cdot AsO(OH)_2$, white needles, sparingly soluble in water, is prepared by adding successively sodium arsenite and caustic alkali to a solution of *p*-bromobenzenediazonium chloride obtained by the ordinary diazotisation of *p*-bromoaniline hydrochloride. The mixture is heated until nitrogen is all evolved and the product isolated by acidifying the filtered solution.

p-*Iodophenylarsinic acid,*[3] $C_6H_4\cdot IAsO_3H_2$, needles, slightly soluble in water or cold alcohol, dissolving in caustic and carbonated alkalis, is prepared together with *p-iodophenylarsenious iodide,* $C_6H_4I\cdot AsI_2$, by treating diazotised atoxyl with a hydrochloric acid solution containing potassium iodide, copper sulphate, and sodium thiosulphate. p-*Iodophenylarsenious oxide* is produced by the action of alkalis on the preceding iodide. Reduction with phosphorous acid at 120° for twelve hours leads to 4 : 4′-*di-iodoarsenobenzene,* $I\cdot C_6H_4\cdot As{:}As\cdot C_6H_4\cdot I$, yellow powder, m.p. 145–150°, insoluble in all organic media.

Phenylarsinic acid p-*iodochloride,*[4] $ICl_2\cdot C_6H_4\cdot AsO(OH)_2$, is precipitated as a yellow, crystalline powder on saturating with chlorine a cold solution of *p*-iodophenylarsinic acid in glacial acetic acid. p-*Iodosophenylarsinic acid,* $IO\cdot C_6H_4\cdot AsO(OH)_2$, is obtained as a white, microcrystalline precipitate by adding

[1] Bertheim, *Ber.*, 1908, **41**, 1854. [2] H. Bart, D.R.-P., 250264.

[3] Mameli and Patta, *Giorn. Farm. Chim.*, 1909, **58**, 97; *Arch. Farmacol. sperim.*, 1909, **8**, 395.

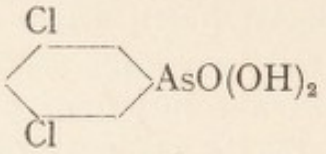
[4] Karrer, *Ber.*, 1914, **47**, 96.

dilute hydrochloric acid to a solution of the preceding chloride in aqueous sodium hydroxide. It is a powerful oxidising agent setting free iodine from acidified potassium iodide, decomposing litmus and bleaching indigo. It explodes on heating and is sparingly soluble in alcohol, acetic acid, or water, but dissolves readily in alkalis or in sodium acetate.

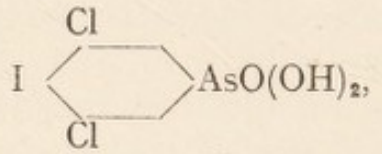
p-*Iodoxyphenylarsinic acid*, $IO_2 \cdot C_6H_4AsO(OH)_2$, a white, granular substance obtained by oxidising *p*-iodophenylarsinic acid or the preceding compound with chlorine and cold *N*-sodium hydroxide. It is extremely insoluble in the ordinary solvents, its oxidising action is more pronounced than that of the iodoso-compound, and it explodes sharply on heating.

Polyhalogenated Phenylarsinic Acids.[1]

3 : 5-*Dichlorophenylarsinic acid* (I),



I.



II.

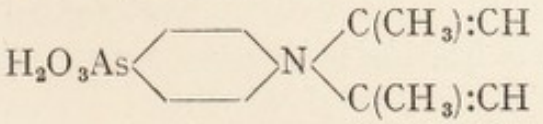
is obtained in well-defined snow-white leaflets by diazotising 3 : 5-dichloro-*p*-arsanilic acid by Witt's method,[2] which consists in mixing this acid with potassium pyrosulphite and adding the mixture slowly to ice-cold nitric acid (D = 1·49). On adding ice a clear solution is produced from which the diazo-derivative subsequently crystallises. The clear solution of the diazo-compound is mixed with alcohol and a small amount of finely divided copper is added. Effervescence sets in at the ordinary temperature and is completed by warming. When all the copper has dissolved the solution is cooled, when 3 : 5-dichlorophenylarsinic acid separates.

3 : 5-*Dichloro-4-iodophenylarsinic Acid* (II).—The foregoing crystalline diazo-derivative is dissolved in water and treated with 10% potassium iodide solution. A vigorous effervescence results and the product separates. When crystallised from 50% acetic acid it takes the form of white, felted needles, sparingly soluble in water.

The two foregoing polyhalogenated phenylarsinic acids when injected into mice produce extremely acute jaundice, the

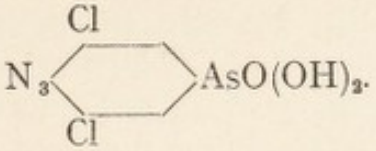
[1] Karrer, *Ber.*, 1914, **47**, 1781. [2] Witt, *Ber.*, 1909, **42**, 2953.

intensity of which exceeds that produced either by 4-iodophenylarsinic acid or by the so-called "icterogen." [1]



The toxicity of these halogenated compounds as shown towards mice is of interest. 3 : 5-Dichlorophenylarsinic acid is much less lethal than 3 : 5-dichloro-4-iodophenylarsinic acid or 4-iodophenylarsinic acid, which have the same degree of toxicity. The presence of halogen in the para-position with respect to arsenic has a marked effect on the physiological action of these substances.

4-*Triazo*-3 : 5-*dichlorophenylarsinic Acid*,



—The crystalline diazo-derivative of 3 : 5-dichloro-*p*-arsanilic acid is treated with sodium azide in aqueous solution, when the colourless triazo-compound results at the ordinary temperature.

Arsenobenzene,[2] $C_6H_5{\cdot}As{:}As{\cdot}C_6H_5$, light yellow needles, m.p. 196° ; insoluble in water or ether ; very sparingly soluble in alcohol, dissolving readily in benzene, chloroform, or carbon bisulphide to solutions which readily resinify. It is prepared by adding crystallised phosphorous acid in excess to a moderately concentrated alcoholic solution of phenylarsenious oxide,

$$2C_6H_5AsO + 2H_3PO_3 = 2H_3PO_4 + C_6H_5{\cdot}As{:}As{\cdot}C_6H_5.$$

It can also be obtained by reducing phenylarsinic acid with phosphorous acid, but this reaction goes more slowly and requires a higher temperature (180°).

On boiling the solution the arsenobenzene separates until the liquid becomes pasty. It separates in well-defined crystals from boiling xylene, but the mother liquor yields only tarry products.

Arsenobenzene combines directly with chlorine or sulphur,

[1] This dimethylpyrrole derivative of *p*-arsanilic acid is referred to by Ehrlich (*Ber.*, 1909, **42**, 39) as having been prepared by Schmitz from acetonylacetone and *p*-arsanilic acid. It is 20–30 times as toxic as the latter compound and is lacking in curative value. On the other hand, it induces fatal jaundice (icterus) in mice, rats, and guinea pigs.

[2] Michaelis and Schulte, *Ber.*, 1881, **14**, 912 ; 1882, **15**, 1952.

yielding phenylarsenious chloride and phenylarsenious sulphide respectively. With oxidising agents it gives rise to phenylarsinic acid and with mercury diethyl at 150° it furnishes phenyldiethylarsine. On heating it changes completely into triphenylarsine and arsenic (compare p. 40).

$$3(C_6H_5As)_2 = 2(C_6H_5)_3As + As.$$

Co-ordination Compound with Cupric Chloride.[1]—Phenylarsinic acid (4 grams) and hydrated cupric chloride (1·7 grams) are heated to boiling with 50 c.c. of 35 per cent. hypophosphorous acid ; the product separates as a yellowish-brown precipitate, readily soluble in pyridine.

Fission of Arsenobenzene and its Derivatives by Alkyl Iodides.[2]

Arsenobenzene when heated with methyl iodide in a sealed tube at 100° undergoes fission into two aromatic compounds, each containing one atomic proportion of arsenic. The reaction is a general one for methyl iodide and occurs also with the aliphatic arseno-compounds—arseno-methane and -ethane. The reactions with the homologous alkyl iodides are more complicated. The following equations indicate the analogies between this fission process and other reactions of arsenic and its organic derivatives,

$$\begin{matrix} As \\ 3CH_3 \end{matrix}\!\!\equiv\!\!\begin{matrix} As \\ I \end{matrix} + CH_3I = As(CH_3)_4I,AsI_3 \quad \text{(page 22)}$$

$$\begin{matrix} CH_3\cdot As \\ 2CH_3 \end{matrix}\!\!=\!\!\begin{matrix} AsCH_3 \\ I \end{matrix} + CH_3I = As(CH_3)_4I + CH_3AsI_2 \quad \text{(page 40)}$$

$$\begin{matrix} (CH_3)_2As \\ CH_3 \end{matrix}\!\!-\!\!\begin{matrix} As(CH_3)_2 \\ I \end{matrix} + CH_3I = As(CH_3)_4I + (CH_3)_2AsI \quad \text{(page 11)}$$

$$\begin{matrix} C_6H_5\cdot As \\ 2CH_3 \end{matrix}\!\!=\!\!\begin{matrix} As\cdot C_6H_5 \\ I \end{matrix} + CH_3I = C_6H_5As(CH_3)_3I + C_6H_5AsI_2$$

Arsenobenzene yields phenyltrimethylarsonium iodide and phenylarsenious iodide, the latter being identified by conversion into phenylarsenious oxide and phenylarsinic acid.

Arseno-*p*-toluene behaves similarly, yielding *p*-tolyltrimethylarsonium iodide and *p*-tolylarsenious iodide.

Di-iodo arsenobenzene,[3] $C_6H_5\cdot AsI\cdot AsI\cdot C_6H_5$, bright yellow needles, by reducing with phosphorous acid an alcoholic solution of phenylarsenious iodide. A very unstable compound, oxidised

[1] M. L. and B., D.R.-P., 270258. [2] Bertheim, *Ber.*, 1914, **47**, 271.
[3] Mameli and Patta, *loc. cit.*, 1909.

in the air: $As_2(C_6H_5)_2I_2 + O_2 + H_2O = C_6H_5AsI_2 + C_6H_5{\cdot}AsO_3H$. Oxidised by nitric acid to phenylarsinic acid; combining with iodine to form phenylarsenious iodide; decomposed on heating as follows: $3As_2(C_6H_5)_2I_2 = 2As(C_6H_5)_3 + 2AsI_3 + 2As$. When heated with methyl iodide at 100°, di-iodoarsenobenzene undergoes fission into p-*iodophenyltrimethylarsonium iodide*, iridescent leaflets melting above 300°, and *p*-iodophenylarsenious iodide identified as p-*iodophenylarsinic acid*.[1]

p-*Phenylenediarsinic acid*,[2]

colourless crystals from water, is prepared from atoxyl (p. 158) by Bart's reaction. Sodium *p*-arsanilate is diazotised in dilute hydrochloric acid and warmed gently with alkaline sodium arsenite. The solution is then neutralised, filtered, and evaporated to dryness with a slight excess of hydrochloric acid, and the residue extracted with methyl alcohol. The alkali salts of this acid are readily soluble in water but dissolve only sparingly in alcohol.

Phenylarsine,[3] $C_6H_5{\cdot}AsH_2$, colourless, highly refractive oil, b.p. 148°/760 mm., 93°/70 mm., 84°/55 mm., and 77°/33 mm.; odour resembling that of phenyl *iso*cyanide, but on dilution like that of hyacinths. Soluble in alcohol or ether. Vapour density normal.

Phenylarsine is prepared by mixing in a reflux apparatus purified calcium phenylarsinate[4] (*v.* p. 84) with excess of amalgamated zinc dust; this mixture is covered with water and a layer of ether. Hydrochloric acid is added at the rate of 5–10 drops per minute. The ethereal layer which contains the phenylarsine is dried over calcium chloride and distilled; the product passing over at 93°/70 mm. is collected in an atmosphere of carbon dioxide.

Phenylarsine oxidises in the air to a mixture of phenylarsenious oxide, phenylarsinic acid, and arsenobenzene, and in ethereal solution to the last of these products, which separates in well-defined, yellow crystals melting at 195–196°. Oxidation with nitric acid yields phenylarsinic acid and a yellow oil contain-

[1] Bertheim, *Ber.*, 1914, **47**, 276. [2] H. Bart, D.R.-P., 250264.

[3] Palmer and Dehn, *Ber.*, 1901, **34**, 3598; *Amer. Chem. J.*, 1905, **33**, 147.

[4] La Coste and Michaelis, *Annalen*, **201**, 203, 209; Michaelis and Loesner, *Ber.*, 1894, **27**, 264.

ing nitrobenzene and arsenobenzene. Iodine in potassium iodide solution oxidises phenylarsine partly to phenylarsinic acid and partly to phenylarsenious iodide. Methyl and ethyl iodides and phenylarsine at 120° give rise to hydrogen iodide and to phenyltrimethylarsonium and phenyltriethylarsonium iodides respectively.

Phenyldimethylarsine,[1] $C_6H_5 \cdot As(CH_3)_2$, colourless, refractive, moderately limpid liquid with repulsive odour, b.p. 200°. Insoluble in water, completely miscible with alcohol or benzene. Prepared by the action of zinc dimethyl on phenylarsenious chloride.

Phenyltrimethylarsonium iodide, $C_6H_5As(CH_3)_3 \cdot I$, white needles, m.p. 244°, readily soluble in water or alcohol, insoluble in ether. Prepared by the addition of methyl iodide to the foregoing compound,[2] and by the interaction of phenylarsine and methyl iodide ; the iodide dissociates into its generators when heated in a current of carbon dioxide : *platinichloride*, red lamellæ, m.p. 219°.

Phenyldiethylarsine,[3] $C_6H_5 \cdot As(C_2H_5)_2$, colourless, highly refractive liquid with faint unpleasant odour, b.p. 240°. Prepared by adding zinc diethyl slowly to phenylarsenious chloride diluted with benzene or ether. The reaction is very vigorous and the tertiary arsine is obtained after removing the solvent and treating the residue with caustic alkali. This compound is not affected by hydrochloric acid, but absorbs chlorine readily, to yield the crystalline *phenyldiethylarsinic chloride*,

$$C_6H_5 \cdot As(C_2H_5)_2Cl_2.$$

Phenyltriethylarsonium iodide,[4] $C_6H_5 \cdot As(C_2H_5)_3I$.—Ethyl iodide and the preceding base do not interact at the ordinary temperature, but only at 100°. The product forms colourless, prismatic crystals of intensely bitter taste, m.p. 112–113° ; it dissociates into its generators on heating in carbon dioxide. This quaternary iodide is also obtained by the interaction of phenylarsine and ethyl iodide at 120°.[5] Moist silver oxide liberates the highly caustic *phenyltriethylarsonium hydroxide* obtained as a syrupy mass absorbing carbon dioxide from the atmosphere. The corre-

[1] Michaelis and Link, *Annalen*, 1881, **207**, 205.
[2] Dehn, *Amer. Chem. J.*, 1905, **33**, 152.
[3] Michaelis and La Coste, *Annalen*, 1880, **201**, 212.
[4] La Coste and Michaelis, *Ber.*, 1878, **11**, 1884.
[5] Dehn, *Amer. Chem. J.*, 1905, **33**, 151.

sponding chloride is uncrystallisable; the *platinichloride* forms golden-yellow leaflets.

Phenylmethyldiethylarsonium iodide, $C_6H_5 \cdot As(C_2H_5)_2(CH_3) \cdot I$, well-defined prisms, m.p. 122°; *chloride* oily, *platinichloride*, m.p. 190°.

Phenyltriethylarsonium dichloro-iodide, $C_6H_5 \cdot As(C_2H_5)_3 \cdot ICl_2$, lustrous dark yellow crystals, m.p. 79°. Obtained by passing chlorine into a glacial acetic acid solution of phenyltriethylarsonium iodide.

Phenyliodomethyldiethylarsonium iodide,

$$C_6H_5As(C_2H_5)_2\begin{cases}CH_2I \\ I\end{cases},$$

crystallises in needles from dilute alcohol, m.p. 173°. Sparingly soluble in hot alcohol, acetone, or water, more so in methyl alcohol; prepared by warming on the water-bath phenyldiethylarsine and methylene iodide.

*Phenyltri*iso*amylarsonium iodide*,[1] pearly white crystals, m.p. 163°. Very soluble in chloroform or alcohol, but insoluble in benzene, light petroleum, ether, or cold water. It is prepared by heating phenylarsine and *iso*amyl iodide at 140–150°.

The Asymmetric Arsenic Atom.[2]

The following arsines and arsonium iodides were prepared in the hope that the latter would be resolvable into optically active components. This anticipation has not, however, been realised.

Phenyldimethylarsine[3] is conveniently made by the interaction of phenylarsenious chloride and magnesium methyl iodide in ether, or preferably petroleum (b.p. 30–40°); in the former medium the yield is 40 and in the latter 75 per cent.

Phenyldimethylarsine dibromide, $C_6H_5 \cdot As(CH_3)_2Br_2$, crystalline, white solid, m.p. 128°, is formed from the preceding base and bromine, keeping the former in excess. If the bromine is in excess, *phenyldimethylarsine tetrabromide*, a compound of exceptional composition, $C_6H_5 \cdot As(CH_3)_2Br_4$, is produced, forming dark red crystals melting at 65° and yielding at 160° phenylarsenious dibromide and methyl bromide (2 mols.).

Phenylmethylarsenious bromide, $C_6H_5 \cdot As(CH_3) \cdot Br$, prepared by heating the dibromide at 180°, is a colourless liquid, b.p. 250°.

[1] *Amer. Chem. J.*, 1905, **33**, 152.

[2] Winmill, *Chem. Soc. Trans.*, 1912, **101**, 722; *c.f.* Michaelis and Predari, p. 109.

[3] Michaelis and Link, *Annalen*, 1881, **207**, 205.

Phenylmethylallylarsine, $C_6H_5 \cdot As(CH_3) \cdot C_3H_5$, colourless liquid, b.p. 192°, is preferably obtained by adding magnesium powder to a mixture of phenylmethylarsenious bromide and allyl iodide (mol. proportions) in dry ether; when very little diallyl is thus produced,

Phenylbenzylmethylallylarsonium iodide,

$$C_6H_5CH_2 \cdot As(C_6H_5)(CH_3)(C_3H_5)I,$$

is made by mixing the foregoing tertiary base and benzyl iodide. On crystallising from acetone, it is obtained in colourless crystals, m.p. 100°.

Phenylethyl-n-*propylarsine*, $C_6H_5As(C_2H_5) \cdot C_3H_7$, colourless liquid, b.p. 245°, a very feeble base, characteristic odour, insoluble in concentrated hydrochloric acid. Prepared by the following series of reactions:—

1. $(C_6H_5)_3As + 2AsCl_3$ (at 290–300°) $= 3C_6H_5AsCl_2$.
2. $C_6H_5AsCl_2 + Zn(C_2H_5)_2 = C_6H_5As(C_2H_5)_2 + ZnCl_2$.

These reactions proceed smoothly, using light petroleum (b.p. 40–50°) instead of ether.

3. *Phenylethylarsenious bromide*, $C_6H_5As(C_2H_5) \cdot Br$, is obtained by heating the dibromide of the preceding tertiary base; the corresponding chloride is similarly prepared from the dichloride.

Phenylethyl-n-*propylarsine* is produced by the action of zinc dipropyl on the preceding bromide. When heated with benzyl iodide (1 mol.) at 40–50° it combines additively with this compound, giving *phenylbenzylmethyl*-n-*propylarsonium iodide*,

$$C_6H_5 \cdot As(C_7H_7)(CH_3)(C_3H_7)I,$$

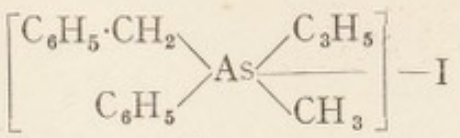
colourless crystals, m.p. 128°. The d-*camphor-β-sulphonate* from this quaternary iodide is readily soluble in water and organic media; it showed no signs of resolution into optically active components during crystallisation.

Phenylethyl-n-*propylallylarsonium iodide*, produced by the combination of phenylethyl-*n*-propylarsine and allyl iodide, crystallises in colourless plates, and gives a d-*α-bromocamphor-π-sulphonate* which crystallises from alcohol-acetone in colourless prisms, m.p. 189°, and is not resolvable by fractional crystallisation from this solvent.[1] The *d*-camphor-*β*-sulphonate is syrupy and non-resolvable.

These experiments indicate that arsonium compounds of the type I. are not resolvable into optically active components under experimental conditions comparable with those in which this

[1] Winmill, *Chem. Soc. Trans.*, 1912, **101**, 720.

resolution was effected in the case of the analogously constituted quaternary ammonium compounds II.[1]



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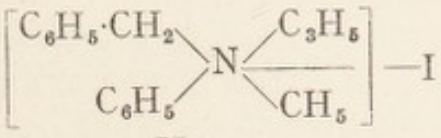


II.

Alkoxyarylarsenious Chlorides and their Derivatives.

p-*Anisylarsenious chloride*,[2] $CH_3 \cdot O \cdot C_6H_4 \cdot AsCl_2$, colourless, crystalline mass, m.p. 48°, b.p. 160°/30 mm., 230°/117 mm. In the *p*-anisyl series Michaelis selected the second general synthetic method with sodium and *p*-bromoanisole (made by the direct bromination of anisole in 2½ parts of carbon bisulphide). The resulting tri-*p*-anisylarsine is heated with excess of arsenious chloride for 24 hours at 200°. The latter reagent is distilled off and the residue fractionated *in vacuo*. *p*-Anisylarsenious chloride when distilled under the ordinary pressure is partially decomposed. With caustic and carbonated alkalis it yields *p*-anisylarsenious oxide, $CH_3 \cdot O \cdot C_6H_4 \cdot AsO$, a colourless, crystalline mass. It absorbs chlorine in the cold to form p-*anisylarsenic chloride*, $CH_3 \cdot O \cdot C_6H_4 \cdot AsCl_4$, a viscid, yellow liquid decomposed by water, yielding p-*anisylarsinic acid*, $CH_3 \cdot O \cdot C_6H_4 \cdot AsO(OH)_2$, colourless, hard, crystalline mass, m.p. 179–180°, sparingly soluble in cold water, dissolving more readily in alcohol or warm water. Prepared free from chlorine by adding hydrogen peroxide to a solution of *p*-anisylarsenious chloride in glacial acetic acid.[3]

p-Anisylarsinic acid[4] is more conveniently prepared by methylating sodium phenol-4-arsinate with methyl sulphate in aqueous caustic soda. When maintained for several hours at 190–200° this acid furnishes the p-*anisylarsinic anhydride* (*arsino*-p-*anisole*), $CH_3 \cdot O \cdot C_6H_4 \cdot AsO_2$. *Silver* p-*anisylarsinate*, $CH_3 \cdot O \cdot C_6H_4 \cdot AsO(OAg)_2$, forms a white precipitate from neutral solutions.

Arseno-p-*anisole*, $CH_3 \cdot O \cdot C_6H_4 \cdot As{:}As \cdot C_6H_4 \cdot O \cdot CH_3$, yellow, amorphous powder, m.p. 200° (with decomposition), obtained by heating *p*-anisylarsinic acid with ten parts of aqueous phosphorous acid in sealed tubes at 100°. When heated at this temperature with methyl iodide the arseno-derivative undergoes

[1] Pope and Peachey, *Chem. Soc. Trans.*, 1899, **75**, 1127.

[2] Michaelis and Feitz, *Ber.*, 1887, **20**, 51; Michaelis, *Annalen*, 1902, **320**, 298.

[3] Michaelis, *Annalen*, 1902, **320**, 299.

[4] Bertheim, *Ber.*, 1914, **47**, 276.

fission into p-*anisyl-trimethylarsonium iodide* (colourless, acicular prisms, m.p. 213°) and *p*-anisylarsenious iodide, characterised as *p*-anisylarsinic acid.[1]

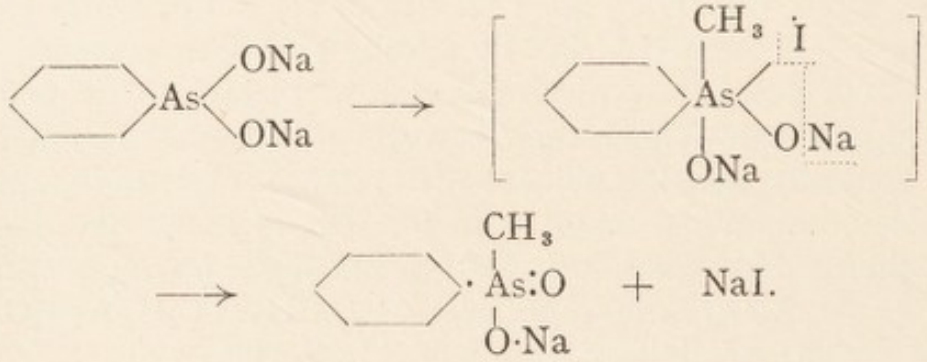
p-*Phenetylarsenious chloride*,[2] $C_2H_5\cdot O\cdot C_6H_4\cdot AsCl_2$, colourless liquid, b.p. 198°/28 mm., obtained by heating tri-*p*-phenetylarsine with eight parts of arsenious chloride at 220° for 24 hours. The *oxide*, $C_2H_5\cdot O\cdot C_6H_4\cdot AsO$, m.p. 105°, from the preceding chloride and aqueous sodium carbonate.

Arseno-p-*phenetole*, $C_2H_5\cdot O\cdot C_6H_4\cdot As{:}As\cdot C_6H_4\cdot O\cdot C_2H_5$, yellow powder readily becoming resinous.

p-*Phenetylarsinic acid*, $C_2H_5\cdot O\cdot C_6H_4\cdot AsO(OH)_2$, colourless crystals from water, m.p. 209–210°, by passing chlorine into water containing *p*-phenetylarsenious chloride. *Calcium*, *copper*, and *silver* salts are insoluble in water. This acid is also prepared from *p*-arsanilic acid by diazotising the latter with ethyl nitrite in absolute alcohol. The diazo-compound, which is deposited as a white precipitate, is decomposed into the ethoxy-derivative on gently warming.[3]

Mixed Aromatic-Aliphatic Arsinic Acids.[4]

The secondary arsinic acids containing one aromatic and one aliphatic group are conveniently prepared by an extension of G. Meyer's reaction described by Ehrlich and Bertheim.



Phenylmethylarsinic Acid, $C_6H_5\cdot As(CH_3)O\cdot OH$.—Methyl iodide (8 grams) added to an alcoholic solution (80 c.c.) of phenylarsenious oxide (16·8 grams) and 20 c.c. of 10*N*-sodium hydroxide produces a vigorous action, and the mixture after twelve hours is mixed with 300 c.c of water and treated with silver nitrate (25 grams) in 50 c.c. of water and 50 c.c. of nitric acid (D = 1·12).

[1] Bertheim, *loc. cit.*
[2] Michaelis, *Annalen*, 1902, **320**, 299.
[3] Bertheim, *Ber.*, 1908, **41**, 1854.
[4] Bertheim, *Ber.*, 1915, **48**, 350.

The filtrate from silver iodide is decolorised by animal charcoal and the silver salt of phenylmethylarsinic acid precipitated by further addition of 25 grams of silver nitrate and 17 c.c. of concentrated ammonia. The yield of silver salt is 22 grams. This compound is decomposed with 2*N*-hydrochloric acid, the filtrate from silver chloride evaporated to the crystallising point, 20·8 grams of salt yielding 12·6 grams of free acid. Phenylmethylarsinic acid when dissolved in two parts of water crystallises in silky needles (m.p. 179·5°) on the addition of ten parts of acetone. It is very soluble in alcohol, water, or glacial acetic acid, but less so in acetone or ether; its aqueous solution is neutral to methyl orange, but can be titrated with barium hydroxide in presence of litmus. The acid is amphoteric, forming salts both with metallic bases and with mineral acids. The *nitrate*, $C_7H_8O_2As,HNO_3$, is crystalline.

Phenylethylarsinic acid, $C_6H_5As(C_2H_5)O{\cdot}OH$, prepared from phenylarsenious oxide and ethyl iodide, separates from the concentrated slightly acidified solution after removing iodine with freshly prepared silver chloride and is crystallised from ethyl acetate (8·4 grams of phenylarsenious oxide yield 7·8 grams of the acid). It is very soluble in water, ethyl and methyl alcohols, chloroform, or acetic acid, dissolves less readily in acetone, benzene or ether, and melts at 108°.

Phenylisoamylarsinic acid, $C_6H_5As(C_5H_{11})\cdot AsO{\cdot}OH$, prepared by the general method, resembles the foregoing compound in solubility and melts at 108°.

Phenylbenzylarsinic acid, $C_6H_5As(CH_2{\cdot}C_6H_5)\cdot AsO{\cdot}OH$, prepared by adding freshly distilled benzyl chloride to an alcoholic alkaline solution of phenylarsenious oxide (8·4 grams). After three days the filtrate from sodium chloride is diluted with water, freed from benzyl chloride by ether-extraction, and carefully acidified with 2*N*-hydrochloric acid. The arsinic acid (11 grams) separates and is crystallised from alcohol in colourless, lustrous needles, m.p. 206–207°. Hot concentrated hydrochloric acid decomposes this arsinic acid into benzyl chloride and phenylarsenious chloride.

Section II.—Benzene Derivatives with Two Aromatic Nuclei Attached to One Arsenic Atom.

Diphenylarsenious chloride, $(C_6H_5)_2AsCl$, yellow, faintly odorous oil, not fuming in air and less irritating to the skin than phenylarsenious chloride; b.p. 333° in a current of carbon dioxide;

$D = 1{\cdot}42231/15°$. Insoluble in water, dissolving readily in ether, benzene, or absolute alcohol. It is insoluble in aqueous ammonia or alkali carbonates and only slightly soluble in caustic alkalis. It is formed as a by-product, together with a small proportion of triphenylarsine, in the preparation of phenylarsenious chloride from arsenious chloride and mercury diphenyl[1]; also prepared by adding mercury diphenyl (50 grams) to phenylarsenious chloride (230 grams) heated to its boiling point. The dark liquid decanted from a precipitate of mercuric chloride is fractionated and the recovered phenylarsenious chloride again treated as before with mercury diphenyl (50 grams). Fractionation of the total product yielded 96 grams of diphenylarsenious chloride. The main reaction is as follows :—

$$2C_6H_5AsCl_2 + Hg(C_6H_5)_2 = 2(C_6H_5)_2AsCl + HgCl_2,$$

although there is a certain amount (10–20 per cent.) of mercury phenylchloride produced together with an appreciable quantity of triphenylarsine. The addition of mercury diphenyl to excess of phenylarsenious chloride maintained at its boiling point minimises the formation of mercury phenylchloride.[2]

Diphenylarsenious chloride is also obtainable by distilling triphenylarsine chloride under 13–14 mm. pressure.

$$(C_6H_5)_3AsCl_2 = (C_6H_5)_2AsCl + C_6H_5Cl.$$

In this way 2·5 grams of the monochloride (b.p. 230°/13–14 mm.) were obtained from 8 grams of triphenylarsine.

Diphenylarsenic chloride, $(C_6H_5)_2AsCl_3$, colourless plates from benzene, m.p. 174°, is produced with generation of heat by the addition of dry chlorine to diphenylarsenious chloride. This substance readily dissociates in a current of carbon dioxide, regenerating diphenylarsenious chloride and liberating chlorine. When heated at 200° it decomposes into phenylarsenious chloride and chlorobenzene.

$$(C_6H_5)_2AsCl_3 \rightleftharpoons (C_6H_5)_2AsCl + Cl_2$$
$$(C_6H_5)_2AsCl_3 = C_6H_5{\cdot}AsCl_2 + C_6H_5{\cdot}Cl.$$

Diphenylarsenious chloride absorbs bromine to form an easily decomposable chlorobromide, $(C_6H_5)_2AsClBr_2$, a flesh-coloured solid. *Diphenylarsenious bromide*, a viscid, yellow liquid; b.p. 356° (with partial decomposition); obtained by heating

[1] La Coste and Michaelis. *Ber.*, 1878, **11**, 1885; *Annalen*, 1880, **201**, 215.

[2] Michaelis and Link, *Annalen*, 1881, **207**, 195.

diphenylarsenious oxide with fuming hydrobromic acid in sealed tubes.

Diphenylarsenious oxide, $[(C_6H_5)_2As]_2O$, crystalline aggregates from ether; m.p. 91–92°. Prepared by heating diphenylarsenious chloride with alcoholic potash. Also obtained by the Grignard reaction from powdered arsenious oxide and magnesium phenylbromide in ethereal solution.[1] Combines with chlorine to form *diphenylarsenic oxychloride*, $[(C_6H_5)_2AsCl_2]_2O$, white powder, m.p. 117°. Soluble in benzene.

Diphenylarsinic acid, $(C_6H_5)_2AsO{\cdot}OH$, colourless needles, m.p. 174°; D = 1·545; produced by the action of water on the preceding oxychloride or on diphenylarsenious chloride. Sparingly soluble in cold water, ether, or benzene, dissolving more readily in hot water or alcohol. No anhydride formed at 190–200°, but the acid shows a slight tendency to sublime. Not attacked by hot nitric acid or by chromic acid.

Diphenylarsinic acid and its salts are poisonous, the toxic action being somewhat more rapid than that of phenylarsinic acid.[2] This circumstance has led to a revision of the often quoted statement that cacodylic acid is not poisonous. A few decigrams of sodium cacodylate injected subcutaneously into rabbits and frogs caused within one to two days the death of these animals with symptoms of arsenical poisoning.

Diphenylarsinates.—The acid is comparatively weak and its *ammonium* salt is completely dissociated over sulphuric acid. *Sodium* salt, $(C_6H_5)_2AsO_2Na$, hygroscopic powder. *Barium* salt, $[(C_6H_5)_2AsO_2]_2Ba$, very soluble mass, scarcely crystalline.

The *copper* salt is a light blue precipitate. The *lead* and *silver* salts are white precipitates, the former slightly soluble in hot water and crystallising therefrom in lustrous needles.

Phenylcacodyl[3] (*Tetraphenyldiarsine*), $(C_6H_5)_2As{\cdot}As(C_6H_5)_2$, crystalline mass, m.p. 135°; somewhat soluble in alcohol, less so in ether. Prepared by boiling an alcoholic solution of diphenylarsenious oxide with excess of phosphorous acid; the cacodyl derivative separates as an oil which solidifies on washing with ether. It absorbs oxygen to form the anhydride (?) of diphenylarsinic acid; chlorine converts it into diphenylarsenic chloride. On distillation, it decomposes into triphenylarsine and free

[1] Sachs and Kantorowicz, *Ber.*, 1908, **41**, 2767.

[2] Schultz, *Ber.*, 1879, **12**, 21; *Archiv exper. Pathol. u. Pharmak.*, 9, 131 and 147.

[3] Michaelis and Schulte, *Ber.*, 1882, **15**, 1954.

arsenic. It is also obtained by heating diphenylarsinic acid in alcoholic solution with excess of phosphorous acid in sealed tubes at 100°.

Phenyl diphenylarsenite,[1] $(C_6H_5)_2As{\cdot}O{\cdot}C_6H_5$, colourless liquid, b.p. 230–231°/15 mm. D = 1·3113/11°. Although diphenylarsenious acid has not been isolated, its phenyl ester is obtainable by the action of sodium phenoxide on diphenylarsenious chloride dissolved in xylene. This substance, which is isomeric with triphenylarsine oxide, is hydrolysable and absorbs chlorine to form the compound $(C_6H_5)_2AsCl_2{\cdot}O{\cdot}C_6H_5$, needles, m.p. 121–122°; the *bromide*, $(C_6H_5)_2AsBr_2O{\cdot}C_6H_5$, yellowish-red crystals, melts at 100° and is readily hydrolysed.

Diphenylmethylarsine,[2] $(C_6H_5)_2As{\cdot}CH_3$, colourless, highly refractive, oily liquid, b.p. 306°, pungent fruity odour; insoluble in water, dissolving readily in alcohol or benzene. Prepared by the action of zinc dimethyl on diphenylarsenious chloride in cold benzene solution in an atmosphere of carbon dioxide. It does not combine with *iso*butyl iodide even at 120°.

Diphenyldimethylarsonium iodide, $(C_6H_5)_2As(CH_3)_2I$, colourless, spicular crystals, m.p. 190°, bitter taste, is produced even in the cold by adding methyl iodide to diphenylmethylarsine. Sparingly soluble in cold water, more so in hot water or alcohol, insoluble in ether. The substance is sensitive to light and is preferably crystallised from faintly alkaline solutions. It dissociates into its generators when heated in a current of carbon dioxide: *platinichloride*, flattened, reddish-yellow needles from hot water.

Diphenylethylarsine,[3] $(C_6H_5)_2As{\cdot}C_2H_5$, colourless liquid, fruity odour, b.p. 320°, prepared by the general method with zinc diethyl on diphenylarsenious chloride. The addition of dry chlorine leads to *diphenylethylarsine dichloride*, needles from benzene, m.p. 137°, decomposed by water with elimination of hydrogen chloride.

Diphenyldiethylarsonium iodide,[4] $(C_6H_5)_2As(C_2H_5)_2I$, colourless, flattened needles, m.p. 184°, prepared from diphenylethylarsine and ethyl iodide at 100°.

Diphenylmethylethylarsonium iodide,[5] $(C_6H_5)_2As(CH_3)(C_2H_5)I$,

[1] Michaelis, *Annalen*, 1902, **321**, 143.

[2] Michaelis and Link, *Annalen*, 1881, **207**, 199.

[3] Michaelis and Link, *loc. cit.*; La Coste and Michaelis, *Annalen*, 1880, **201**, 235.

[4] La Coste and Michaelis, *Ber.*, 1878, **11**, 1886.

[5] Michaelis and Link, *loc. cit.*

rhombic prisms, m.p. 170°, produced either by adding methyl iodide to diphenylethylarsine or ethyl iodide to diphenylmethylarsine, the combination being promoted by warming. The substance is readily soluble in alcohol or hot water; it is sensitive to light, and is preferably crystallised from slightly alkaline solutions. It dissociates on warming in a stream of carbon dioxide into diphenylmethylarsine and ethyl iodide. The free base, *diphenylmethylethylarsonium hydroxide*, produced by the action of moist silver oxide on the iodide, is a very soluble syrupy mass with strongly alkaline reaction and bitter taste: *platinichloride* and *picrate* form yellowish-red and yellow needles respectively.

Diphenylarsenious sulphide, $[(C_6H_5)_2As]_2S$, colourless, silky needles, m.p. 67°, obtained by passing hydrogen sulphide into alcoholic solution of the corresponding oxide and chloride. Insoluble in the alkalis and alkali monosulphides.

Tetraphenylarsenic disulphide, $[(C_6H_5)_2As]_2S_2$, white leaflets from hot alcohol, sinters at 60°; m.p. 100°. Like the monosulphide soluble in the ordinary organic solvents, it dissolves readily in yellow ammonium sulphide, probably to form an ammonium diphenylthioarsinate. It is prepared by successively saturating with hydrogen sulphide an ammoniacal solution of diphenylarsinic acid, acidifying and extracting the precipitate with alcohol. Also obtained by the action of hydrogen sulphide on diphenylarsinic acid in glacial acetic acid.

Di-p-*anisylarsenious chloride*,[1] $(CH_3{\cdot}O{\cdot}C_6H_4)_2AsCl$, slender pale yellow needles from ether, m.p. 79–80°. This substance was not prepared by either of the general methods, but by an experiment which had for its object the demethylation of tri-*p*-anisylarsine. On warming this base with hydriodic acid (D = 1·56) a heavy, red oil was produced which when treated with aqueous caustic soda yielded a solid—di-*p*-anisylarsenious oxide—crystallisable from alcohol or benzene (m.p. 130°), and this compound on mixing with concentrated hydrochloric acid gave the corresponding chloride. The first reaction is represented by the following equation:

$$(CH_3{\cdot}O{\cdot}C_6H_4)_3As + HI = C_6H_5{\cdot}O{\cdot}CH_3 + (CH_3{\cdot}O{\cdot}C_6H_4)_2AsI.$$

More drastic heating with hydriodic acid carries this decomposition to the final stage of arsenious iodide and three molecular proportions of *p*-anisole.

[1] Michaelis and Weitz, *Ber.*, 1887, **20**, 50.

Diphenylarsine,[1] $(C_6H_5)_2AsH_2$, colourless oil, b.p. 174°/25 mm., with an odour recalling that of phenylarsine but less pleasant. It is prepared by adding, with energetic agitation, concentrated hydrochloric acid to diphenylarsinic acid mixed with excess of amalgamated zinc dust and covered with a layer of ether. The ethereal solution is dried over calcium chloride and distilled in an atmosphere of carbon dioxide. The arsine is soluble in ether, alcohol, and other organic solvents, but insoluble in water. The diphenylarsinic acid required for this preparation is most readily obtained in the following manner: triphenylarsine (2 mols.) and arsenious chloride (1 mol.) are heated at 220° for thirty hours, the product is poured into water, and the mixture saturated with chlorine. The filtered solution is treated with excess of magnesia mixture, boiled, and filtered. On adding hydrochloric acid to the final filtrate, diphenylarsinic acid separated as an oil changing to colourless needles. After one crystallisation from water the acid is obtained in a state of purity, the yield being more than 40 per cent.

Diphenylarsine is oxidised in the air to diphenylarsine oxide (phenylcacodyl oxide) and diphenylarsinic acid. With bromine and iodine it yields the corresponding diphenylarsenious halide,

$$(C_6H_5)_2AsH + X_2 = (C_6H_5)_2AsX + HX.$$

Section III.—Benzene Derivatives with Three Aromatic Nuclei attached to One Arsenic Atom.

Triphenylarsine,[2] $(C_6H_5)_3As$, colourless, vitreous, triclinic plates from alcohol, m.p. 58–60°; D = 1·306; b.p. above 360°, without decomposition in carbon dioxide. It is obtainable by both general methods of synthesis, being produced in small amount during the action of mercury diphenyl on phenyl arsenious chloride, and also by prolonged heating of phenylarsenious oxide at 180–200°. $3C_6H_5AsO = (C_6H_5)_3As + As_2O_3$. Preferably it is prepared by adding sodium (80 grams) to a mixture of chlorobenzene (101 grams) or bromobenzene (140 grams), arsenious chloride (54 grams), and ether (4 volumes).[3] After an interval a vigorous reaction sets in so that the mixture requires cooling and stirring. In two hours the process is mainly over; after six to eight hours the filtered solution is distilled and the residual

[1] Dehn and Wilcox, *Amer. Chem. J.*, 1906, **35**, 45.
[2] La Coste and Michaelis, *loc. cit.*; Michaelis, *Annalen*, 1902, **321**, 160.
[3] Philips, *Ber.*, 1886, **19**, 1031.

triphenylarsine allowed to solidify. In some instances the onset of the reaction is unduly delayed and may be induced by the addition of a small amount of dry ethyl acetate; the most favourable results and the best yields are obtained, however, when this chemical change proceeds spontaneously.[1]

Triphenylarsine is readily prepared by the Grignard reaction. Arsenious chloride[2] (10 grams) is added to an ethereal solution of phenylmagnesium bromide (from 4·1 grams Mg and 26 grams C_6H_5Br). The reduction product is mixed with water, extracted with ether, and the ethereal solution dried over calcium chloride and concentrated when 9·5 grams of triphenylarsine are obtainable.

Powdered arsenious oxide (4·9 grams) is added to 2·4 grams of magnesium dissolved in 15·7 grams of bromobenzene and 30 c.c. of dry ether. The mixture is heated for three hours on the water-bath. Triphenylarsine (2·7 grams) is isolated by extraction with ether after removing diphenyl by distillation in steam.[3]

Triphenylarsine is extremely soluble in ether or benzene, sparingly so in cold alcohol; insoluble in water or the halide acids. It forms a *mercurichloride*, $(C_6H_5)_3As,HgCl_2$, nacreous leaflets, easily soluble in absolute alcohol, less so in dilute spirit. This product may be employed in separating triphenylarsine from diphenylarsenious chloride; from the mercurichloride the arsine is regenerated by the action of hydrogen sulphide or of cold alcoholic potash. When warmed with aqueous caustic potash, the mercurichloride yields triphenylarsine hydroxide, $(C_6H_5)_3AsHgCl_2 + 2KOH = (C_6H_5)_3As(OH)_2 + 2KCl + Hg$.

Platinichloride, $(C_6H_5)_3As,H_2PtCl_6$, formed from its generators in alcoholic solution, separates in pale yellow leaflets melting at 285°.

Triphenylarsine dichloride, $(C_6H_5)_3AsCl_2$, colourless plates from benzene, sintering at 158° and melting at 204–205°. Prepared by passing chlorine over triphenylarsine, heat is generated, the base melts, and the dichloride subsequently solidifies. When heated at 280° the dichloride loses chlorobenzene,

$$(C_6H_5)_3AsCl_2 = C_6H_5Cl + (C_6H_5)_2AsCl.$$

Triphenylarsine dihydroxide,[4] $(C_6H_5)_3As(OH)_2$, plates or needles from water, m.p. 115–116°; soluble in alcohol. At 189° it loses one molecular proportion of water. Prepared either by

[1] Michaelis and Loesner, *Ber.*, 1894, **27**, 264.
[2] Pfeiffer, *Ber.*, 1904, **37**, 4621.
[3] Sachs and Kantorowicz, *Ber.*, 1908, **41**, 2767.
[4] Philips, *Ber.*, 1886, **19**, 1032.

boiling the preceding dichloride with dilute ammonia or by successively adding bromine to triphenylarsine dissolved in glacial acetic acid and pouring the solution of triphenylarsine dibromide into concentrated aqueous caustic soda. On cooling the crude dihydroxide is obtained as a brown cake and is purified by dissolving in alcohol, treating again with ammonia and precipitating with water. Reduced to triphenylarsine by tin and alcoholic hydrochloric acid. *Triphenylarsine hydroxynitrate*, $(C_6H_5)_3As(OH)\cdot NO_3$, from the hydroxide and dilute nitric acid; lustrous needles, m.p. 160–161°, easily soluble in alcohol. *Triphenylarsine sulphide*, $(C_6H_5)_3AsS$, lustrous needles, m.p. 162°, insoluble in water, alkali sulphides, acids, or ether; crystallising from hot alcohol. Prepared by melting together sulphur and triphenylarsine, by boiling triphenylarsine dichloride with yellow ammonium sulphide, and by passing hydrogen sulphide into an alcoholic solution of triphenylarsine hydroxide.[1]

The dichloride is converted by atmospheric moisture into the more stable *triphenylarsine hydroxychloride*, m.p. 171°,

$$(C_6H_5)_3As(OH)\cdot Cl,$$

a substance readily obtained by saturating with chlorine a solution of triphenylarsine in commercial chloroform. After removing excess of chlorine with carbon dioxide, addition of dry ether precipitates the hydroxychloride in vitreous crystals (yield 90 per cent.). This substance reacts with platinic chloride in alcoholic solution to give a complex *platinichloride* of exceptional composition, $[(C_6H_5)_3As(OH)Cl]_3PtCl_4$, which crystallises in yellow needles, m.p. 180–182°.

Triphenylarsine dibromide, $(C_6H_5)_3AsBr_2$, colourless crystals, sintering at 165° and melting at 215°; triphenylarsine tetraiodide, $(C_6H_5)_3AsI_4$, steel blue needles, m.p. 142–144°, are obtained by direct addition of the halogen in carbon tetrachloride; the analogous compound, $(C_6H_5)_3AsBr_2I_2$, yellowish-red needles, m.p. 120–121°, separates from chloroform-ether.

Triphenylarsine nitrate, $(C_6H_5)_3As(NO_3)_2$, radiating aggregates, m.p. 99–100°, obtained by evaporating to dryness a solution of triphenylarsine hydroxide or oxide in concentrated nitric acid.

Triphenylarsine hydroxychromate, $(C_6H_5)_3As(OH)O\cdot HCrO_3$, yellowish-red precipitate from the hydroxychloride and potassium chromate.

Triphenylarsine oxide trisulphonic acid,[2] $O{:}As(C_6H_4\cdot SO_3H)_3$.

[1] Philips, *loc. cit.*

[2] Michaelis, *Annalen*, 1902, **321**, 186.

—When triphenylarsine is warmed on the water-bath with concentrated sulphuric acid there is no sulphonation, but the production of triphenylarsine hydroxide,

$$(C_6H_5)_3As + H_2SO_4 = (C_6H_5)_3As(OH)_2 + SO_2.$$

By further heating to the boiling point of sulphuric acid this hydroxide undergoes sulphonation. The barium salt of the resulting trisulphonic acid is a white, crystalline powder easily soluble in water.

Triphenylalkylarsonium derivatives.[1]—Although the first experiments on triphenylarsine had seemed to indicate that this tertiary aromatic arsine did not combine with alkyl iodides even on heating in sealed tubes, yet addition occurs with excess of methyl iodide on prolonged boiling under the ordinary pressure. This reaction also occurs, although with less facility, with ethyl iodide, but not with the higher alkyl iodides.

Triphenylmethylarsonium iodide, $(C_6H_5)_3As(CH_3)\cdot I$, pale yellow leaflets from alcohol or colourless, feathery needles from water, m.p. 176°; it dissolves readily in alcohol or ether, but only sparingly in water. The *iodochloride,* $B\cdot ICl_2$, is a yellow, crystalline mass from alcohol, m.p. 144°.

Triphenylmethylarsonium chloride, colourless needles, m.p. 121°, very soluble in water or alcohol, obtained by neutralising with hydrochloric acid an aqueous solution of the hydroxide or by digesting the iodide with silver chloride; *platinichloride,* yellowish-red needles, m.p. 224–225°.

Triphenylmethylarsonium hydroxide, $(C_6H_5)_3As(CH_3)\cdot OH$, transparent, elongated, prismatic crystals, m.p. 125–126°, is produced by digesting aqueous or preferably alcoholic solutions of the iodide with moist silver oxide when spontaneous evaporation of the filtrate leads to the separation of the crystalline hydroxide. These crystals are extremely soluble in water to an alkaline solution in which the hydroxide decomposes on heating on the water-bath. At 100° the solid hydroxide loses methyl alcohol and leaves pure triphenylarsine. The solution absorbs carbon dioxide from the air and on evaporation deposits colourless, transparent plates of the hydrated *hydrogen carbonate,* $(C_6H_5)_3As\cdot HCO_3,H_2O$; this salt effervesces with acid, gives a white precipitate with baryta water, and reddens phenolphthalein only slightly in the cold and more markedly on boiling.

[1] Michaelis, *Annalen,* 1902, **321**, 166; Gimborn, *Inaug. Dissert.,* Rostock, 1891.

Triphenylmethylarsonium nitrate, $(C_6H_5)_3As(CH_3)\cdot NO_3$, needles from alcohol-ether, is nitrated with considerable difficulty when added to concentrated sulphuric acid (5 parts) containing fuming nitric acid (2 parts). The product poured into water and the precipitate extracted with alcohol leaves a red residue; the alcoholic extract deposits a yellow powder of *trinitrotriphenylmethylarsonium nitrate*, m.p. 195°.

Triphenylethylarsonium iodide, $(C_6H_5)_3As(C_2H_5)I$, lustrous needles, m.p. 158°, produced by prolonged boiling of triphenylarsine with ethyl iodide, is easily soluble in alcohol and sparingly so in water; *platinichloride*, m.p. 221°

Triphenyliodomethylarsonium iodide, $(C_6H_5)_3As(CH_2I)I$, silvery needles from alcohol, m.p. 227°, is preferably obtained by heating triphenylarsine (15 grams) and methylene iodide (17 grams) for thirty minutes at 130°. Insoluble in ether, sparingly soluble in water, dilute alcohol, glacial acetic acid, and chloroform. Chlorine passed into the hot solution of this iodide in acetic acid gives the iodochloride, $(C_6H_5)_3As(CH_2Cl)ICl_2$, forming intensely yellow crystals from alcohol. When heated with aqueous caustic soda this iodochloride is decomposed into triphenylarsine dihydroxide and iododichloromethane.

$$(C_6H_5)_3As(CH_2Cl)ICl_2 + 2NaOH = (C_6H_5)_3As(CH_2Cl)I + NaOCl + NaCl + H_2O.$$

$$(C_6H_5)_3As(CH_2Cl)ICl_2 + NaOCl + NaOH = (C_6H_5)_3As(OH)_2 + CHICl_2 + 2NaCl.$$

Triphenyliodomethylarsonium chloride (*Triphenylarsinomethylcholine chloride*), $(C_6H_5)_3As(CH_2I)Cl$, lustrous needles, m.p. 208°, obtained by treating the iodide with freshly precipitated silver chloride. Decomposition of the iodide with silver oxide leads to the replacement of both iodine atoms by hydroxyl. The hydroxide, $(C_6H_5)_3As(CH_2\cdot OH)\cdot OH$, is a syrup, but the addition of hydrochloric acid gives the crystalline *chloride*,

$$(C_6H_5)_3As(CH_2\cdot OH)Cl,$$

m.p. 112°: *platinichloride*, m.p. 224°; the *iodide*,

$$(C_6H_5)_3As(CH_2\cdot OH)I,$$

yellow, flattened needles, m.p. 171°, very soluble in water or alcohol.

Triphenylhydroxyethylarsonium chloride (*Triphenylarsinocholine chloride*), $(C_6H_5)_3As(CH_2\cdot CH_2\cdot OH)Cl$, colourless needles, m.p. 215°, produced by boiling triphenylarsine with ethylenechlorohydrin.

Tri-p-*anisylarsine*,[1] $(CH_3 \cdot O \cdot C_6H_4)_3As$, colourless, cubical, transparent crystals (from benzene and alcohol), m.p. 156°, prepared by adding sodium parings (20 grams) to *p*-bromoanisole and arsenious chloride (30 grams) in four volumes of ether. After the addition of a little ethyl acetate a vigorous reaction ensues. The precipitate, when freed by water from unattacked sodium, is extracted with hot benzene from which the arsine (15 grams) crystallises on cooling. With this arsine the absorption of chlorine and bromine occurs less readily than with triphenylarsine.

Tri-p-*phenetylarsine*, $(C_2H_5 \cdot O \cdot C_6H_4)_3As$, obtained in very poor yield from *p*-bromophenetole, arsenious chloride, and sodium, m.p. 88–89°, very soluble in ether.

Section IV.—Toluene Derivatives with One Aromatic Nucleus attached to One Arsenic Atom.

o-*Tolylarsenious chloride*,[2] $C_7H_7 \cdot AsCl_2$, colourless liquid, b.p. 264° in a current of carbon dioxide, obtained by boiling mercury di-*o*-tolyl (m.p. 107°) with excess of arsenious chloride. Insoluble in water, dissolving readily in ether, alcohol, or benzene; absorbs chlorine (but not bromine) to yield o-*tolylarsenic chloride*, $C_7H_7AsCl_4$, dark yellow, syrupy liquid decomposed by water into *o*-tolylarsinic and hydrochloric acids.

o-*Tolylarsenious oxide*, $C_7H_7 \cdot AsO$, m.p. 145–146°, obtained by warming *o*-tolylarsenious chloride with aqueous sodium carbonate. Easily soluble in hot water, sparingly so in alkalis. Absorbs chlorine and bromine to yield the corresponding oxyhalide $C_7H_7 \cdot AsOX_2$, and regenerates *o*-tolylarsenious chloride on treatment with concentrated hydrochloric acid.

o-*Tolylarsinic acid*, $CH_3 \cdot C_6H_4 \cdot AsO(OH)_2$, aggregates of colourless needles, m.p. 159–160°. Prepared by the action of water on the preceding oxyhalides, or on *o*-tolylarsenic chloride. When maintained at its melting point, the acid slowly loses water and forms its anhydride, light yellow, crystalline mass.

o-*Tolylarsinates*: *Calcium*, $C_7H_7 \cdot AsO_3Ca$, and *acid barium*, $(C_7H_7AsO_3H)_2Ba$ salts, colourless, crystalline precipitates, less soluble in hot than in cold water; *silver* salt, $C_7H_7 \cdot AsO_3Ag_2$, white amorphous precipitate.

m-*Tolylarsenious chloride*,[3] $CH_3 \cdot C_6H_4 \cdot AsCl_2$, colourless liquid,

[1] Michaelis and Weitz, *Ber.*, 1887, **20**, 49.

[2] La Coste and Michaelis, *Annalen*, 1880, **201**, 246.

[3] Michaelis, *Annalen*, 1902, **321**, 326; Eisenlohr, *Inaug. Dissert.*, Rostock, 1893.

b.p. 270°, prepared by heating tri-*m*-tolylarsine with arsenious chloride (10 parts) at 300° : yield 40%.

m-*Tolylarsenious oxide*, stringy mass produced by the action of aqueous sodium carbonate on the preceding compound, reduced in alcoholic solution by phosphorous acid to *arseno*-m-*toluene*, $CH_3 \cdot C_6H_4 \cdot As{:}As \cdot C_6H_4 \cdot CH_3$, white, amorphous powder, m.p. 106°, insoluble in the ordinary solvents except carbon bisulphide and warm cymene. m-*Tolylarsenic chloride*,

$$CH_3 \cdot C_6H_4 \cdot AsCl_4,$$

crystalline mass, m.p. 38°, hydrolysed by water to m-*tolylarsinic acid*, $C_7H_7AsO(OH)_2$, acicular aggregates from hot water, m.p. 150°, changing to m-*tolylarsinic anhydride*, $C_7H_7 \cdot AsO_2$, at 220–230°.

Salts : *Acid ammonium* salt, $C_7H_7 \cdot AsO(OH) \cdot O \cdot NH_4$, crystalline mass ; *acid phenylhydrazine* salt, $C_7H_7AsO(OH) \cdot O \cdot NH_3 \cdot NH \cdot C_6H_5$, lustrous leaflets ; *calcium* salt, sparingly soluble in hot water ; *silver* salt, $C_7H_7AsO(OAg)_2$, white precipitate ; the other salts of the heavy metals are insoluble.

p-*Tolylarsenious chloride*, $CH_3 \cdot C_6H_4AsCl_2$, colourless highly refractive tablets, pungent aromatic odour, m.p. 31°, b.p. 267° in a current of carbon dioxide, obtained from mercury di-*p*-tolyl (m.p. 235°) and arsenious chloride. Preferably prepared by heating tri-*p*-tolylarsine with 10 parts of arsenious chloride at 230–240° for sixty hours ; the yield is nearly quantitative. Addition of chlorine leads to p-*tolylarsenic chloride*, $C_7H_7AsCl_4$, and treatment with alkali carbonates to p-*tolylarsenious oxide*, m.p. 156°.

p-*Tolylarsinic acid*, $C_7H_7 \cdot AsO(OH)_2$, colourless needles from water, darkens at 300° without melting. Preparation : (i) action of chlorine on *p*-tolylarsenious chloride in water ; (ii) hydrogen peroxide added to the chloride dissolved in glacial acetic acid ; (iii) oxidation of chloride with nitric acid. The first two methods give quantitative yields ; in the third process a portion of the acid undergoes nitration. (iv) [1] *p*-Tolylarsinic acid is obtainable also by Bart's reaction when a solution of *p*-toluenediazonium chloride is neutralised with caustic soda, treated with aqueous sodium arsenite, and warmed till nitrogen is evolved, when the product is precipitated by mineral acid from the filtered solution.

Concentrated nitric acid yields a nitro-*p*-tolylarsinic acid. Permanganate oxidises the methyl substituent with the production of benzarsinic acid (*p*-carboxyphenylarsinic acid).

[1] Bart, D.R.-P., 250264.

p-*Tolylarsinates*: *Potassium* salt, uncrystallisable; *acid calcium*, $(C_7H_7\cdot AsO_3H)_2Ca$, and *acid barium*, $(C_7H_7\cdot AsO_3H)_2Ba$, salts, colourless needles from water; *silver* salt, $C_7H_7\cdot AsO_3Ag_2$, white precipitate, rendered crystalline by boiling with alcohol; *copper* and *lead* salts, $C_7H_7\cdot AsO_3R''$, bluish-green and white precipitates respectively.

Arseno-p-*toluene*,[1] $CH_3\cdot C_6H_4\cdot As{:}As\cdot C_6H_4\cdot CH_3$, lustrous needles from chloroform, m.p. 184°, obtained by heating *p*-tolylarsenious oxide with excess of phosphorous acid at 100°. Chlorine converts the arseno-compound successively to dichloride and tetrachloride. Nitric acid oxidises it to *p*-tolylarsinic acid.

p-*Tolylarsenious sulphide*, $CH_3\cdot C_6H_4As\cdot S$, lustrous, colourless crystals from benzene-ether, m.p. 146°, obtained by passing hydrogen sulphide into alcoholic solutions of *p*-tolylarsenious oxide.

p-*Tolylarsenic sesquisulphide*, $\begin{matrix} CH_3\cdot C_6H_4\cdot AsS \\ | \\ CH_3\cdot C_6H_4\cdot AsS \end{matrix}\!\!>\!S$, white needles from benzene-alcohol, m.p. 119°. Acidification of an ammoniacal solution of *p*-tolylarsinic acid after saturation with hydrogen sulphide,

$$2CH_3\cdot C_6H_4\cdot AsS(SNH_4)_2 + 4HCl = (CH_3\cdot C_6H_4\cdot AsS)_2S + 4NH_4Cl + 2SH_2 + S.$$

Mixed Tertiary Arsines containing a Tolyl Radical.[2]

p-*Tolyldimethylarsine*, $CH_3\cdot C_6H_4\cdot As(CH_3)_2$, colourless liquid, unpleasant odour, b.p. 220° in carbon dioxide. This arsine or the following homologue is prepared by the action of pure zinc dimethyl (or diethyl) in excess on *p*-tolylarsenious chloride diluted with dry ether. p-*Tolyldiethylarsine*, b.p. 250°.

p-*Tolyltrimethylarsonium iodide*, $CH_3\cdot C_6H_4\cdot As(CH_3)_3I$, plates, m.p. 274–275°, dissociating into its generators on heating; *platinichloride*, reddish-yellow needles, m.p. 225°.

p-*Tolylmethyldiethylarsonium iodide*, $CH_3\cdot C_6H_4\cdot As(CH_3)(C_2H_5)_2I$, colourless leaflets, m.p. 220°.

p-*Tolyltriethylarsonium iodide*, colourless, prismatic crystals, m.p. 230°; *chloride*, crystallisable only with difficulty, *platinichloride*, m.p. 210°.

[1] Michaelis, *Annalen*, 1902, **320**, 301.

[2] Michaelis, *Annalen*, 1902, **320**, 304; Klatt, *Inaug. Dissert.*, Rostock, 1893.

Section V.—Toluene Derivatives with Two or Three Aromatic Nuclei attached to One Arsenic Atom.

1. *Diaryl Series.*

Di-p-*tolylarsenious chloride*,[1] $(CH_3 \cdot C_6H_4)_2AsCl$, colourless crystals, m.p. 45°, b.p. 340–345°, prepared by boiling together mercury di-*p*-tolyl and *p*-tolylarsenious chloride (3–4 parts), and also by distilling tri-*p*-tolylarsine dichloride under reduced pressure.[2] Decomposed by repeated distillation

$$2(C_7H_7)_2AsCl = C_7H_7 \cdot AsCl_2 + (C_7H_7)_3As.$$

Not affected by aqueous sodium carbonate, but decomposed by boiling alcoholic potash to yield *di*-p-*tolylarsenious oxide*, $[(C_7H_7)_2As]_2O$, silky needles from ether; m.p. 98°, giving tri-*p*-tolylarsine on heating.

Di-p-*tolylarsenic chloride*, $(C_7H_7)_2AsCl_3$, pale yellow mass obtained by passing dry chlorine into di-*p*-tolylarsenious chloride; when added to water the trichloride is readily decomposed, giving first an oxychloride and then *di*-p-*tolylarsinic acid*, granular crystals from alcohol, m.p. 167°, very sparingly soluble in hot water, and dissolving readily in alcohol; its salts are generally soluble in water. *Silver* salt, white precipitate.

Phenyl-p-*tolylarsenious chloride*,[3] $C_6H_5(C_7H_7)AsCl_2$, colourless oily liquid not affected by moisture, b.p. 215–237°/29 mm. and 215–240°/50 mm.; prepared by adding 30 grams of mercury-*p*-ditolyl (m.p. 238°) to phenylarsenious chloride (180 grams); the mixture, which becomes brown and deposits mercuric chloride, is heated to boiling for five hours, decanted from solid and mixed with dehydrated light petroleum (b.p. 50°), when a dark brown oil separates and subsequently solidifies (mercury-*p*-tolyl chloride). The filtrate is fractionated in carbon dioxide. Unaltered phenylarsenious chloride comes over up to 300°; at 347° the pressure is reduced to 29 mm., and the secondary chloride obtained and redistilled. Yield 41 per cent. on the weight of mercury-*p*-ditolyl.

Phenyl-p-*tolylarsenious oxide*, $[C_6H_5 \cdot (C_7H_7)As]_2O$, an oil obtained

[1] La Coste, *Annalen*, 1881, **208**, 18. [2] Michaelis, *Annalen*, 1902, **321**, 160.

[3] Michaelis, *Annalen*, 1902, **321**, 155; Predari, *Inaug. Dissert.*, Rostock, 1894.

by the action of alcoholic potash on the preceding chloride ; addition of chlorine leads to the *oxychloride*,

$$[C_6H_5(C_7H_7)As]_2OCl_4,$$

colourless, fan-shaped aggregates of needles. *Phenyl*-p-*tolyl-arsenious sulphide*, $[C_6H_5{\cdot}(C_7H_7)As]_2S$, is an oily substance.

Phenyl-p-*tolylarsinic acid*, $C_6H_5(C_7H_7)AsO{\cdot}OH$, colourless,felted needles, m.p. 158–160°. Soluble in hot water, alcohol, benzene, or concentrated nitric acid, dissolving sparingly in cold water or ether. *Silver* salt, white precipitate. For a satisfactory preparation of this acid pure phenyl-*p*-tolylarsenious chloride is necessary, otherwise the product is tarry.

Phenyl-p-*tolylethylarsine*, $C_6H_5(C_7H_7)As{\cdot}C_2H_5$, colourless oil with fruity odour, b.p. 210–225°/50 mm. This mixed tertiary arsine with three dissimilar hydrocarbon groups is prepared by the action of zinc diethyl on phenyl-*p*-tolylarsenious chloride ; the *dichloride*, $C_6H_5(C_7H_7)As(C_2H_5)Cl_2$, colourless needles from benzene, m.p. 148°. The tertiary arsine combines readily with alkyl iodides, in the cold with methyl iodide and with its homologues on the water-bath.

Phenyl-p-*tolylmethylethylarsonium iodide*,

$$C_6H_5(C_7H_7)As(CH_3)(C_2H_5)I,$$

colourless, monoclinic acicular prisms, m.p. 150–151° from water, and 145° from alcohol. This quaternary arsonium iodide is noteworthy because it contains arsenic associated with five different radicals ; it should accordingly exist in two stereo-isomeric forms. Michaelis and Predari state that in alcoholic solution this arsonium iodide exhibits a slight optical activity ; they were not, however, able to resolve the substance into optically active isomerides by means of tartaric or aspartic acid. Moreover, these arsenical iodides are toxic towards moulds, so that these organisms could not be employed in isolating one of the active forms (compare Winmill, p. 92).

The corresponding *chloride* is not crystallisable ; the *platini-chloride* forms yellowish-red, triclinic prisms, m.p. 214°

Phenyl-p-*tolyldiethylarsonium iodide*, $C_6H_5(C_7H_7)As(C_2H_5)_2I$, monoclinic crystals from water, m.p. 148°. The n-*propyl* and iso*propyl* derivatives form monoclinic crystals melting in-definitely ; the *benzyl iodide* forms rhombic crystals, m.p. 150°, and the *benzyl chloride* is uncrystallisable.

2. *Triaryl Series.*

Tri-p-*tolylarsine*,[1] $(CH_3 \cdot C_6H_4)_3As$, large colourless rhombic crystals (from ether), m.p. 145–146°, b.p. above 360° without decomposition. Derived from both general synthetic methods. (i) *p*-Tolylarsenious oxide heated in a sealed tube to 300° and extracted from the product by means of ether,

$$3C_7H_7 \cdot AsO = (C_7H_7)_3As + As_2O_3.$$

(ii) [2] Most conveniently prepared by adding sodium shavings or wire (40 grams) to *p*-bromotoluene (100 grams) and arsenious chloride (45 grams) dissolved in 500 grams of anhydrous ether. The violent reaction, which is regulated by cooling, is completed in 36 hours. The filtered solution is evaporated to dryness, a small amount of yellow impurity removed with alcohol, and the residue dried over sulphuric acid, when 69–70 per cent. of the calculated quantity of colourless tri-*p*-tolylarsine is obtained.

(iii) It is also obtained in the Grignard condensation by the interaction of arsenious oxide and magnesium *p*-tolyl bromide in ethereal solution.[3]

Less soluble in alcohol than in ether, chloroform, or benzene. Oxidised by alkaline permanganate to tribenzarsinic (tri-*p*-carboxyphenylarsinic) acid. Absorbs chlorine in chloroform solution to yield *tri*-p-*tolylarsine chloride*, $(C_7H_7)_3AsCl_2$, m.p. 228–230°, yielding, with hot water, the *hydroxychloride*,

$$(C_7H_7)_3As(OH)Cl,$$

feathery crystals, m.p. 185° from chloroform-ether. Aqueous alkali converts the dichloride or hydroxychloride into *tri*-p-*tolylarsine dihydroxide*, $(C_7H_7)_3As(OH)_2$, flattened needles, m.p. 96°.

The *mercurichloride* $(C_7H_7)_3As,HgCl_2$, is a white, crystalline powder, m.p. 246°, sparingly soluble in hot glacial acetic acid.

Tri-p-*tolylarsine dibromide*, colourless, thick crystals, m.p. 245°, and *tri*-p-*tolylarsine di-iodide*, reddish-yellow needles, m.p. 172°, are obtained by direct addition of the halogen in carbon tetrachloride, an excess of iodine leading to the *tetraiodide*, steel grey needles, m.p. 153°.

Tri-p-*tolylarsine sulphide*, $(CH_3 \cdot C_6H_4)_3AsS$, lustrous leaflets, m.p. 170–171°, is not obtained pure by direct addition of its

[1] La Coste, *Annalen*, 1881, **208**, 26.
[2] Michaelis, *Annalen*, 1902, **321**, 201.
[3] Sachs and Kantorowicz, *Ber.*, 1908, **41**, 2767.

generators in carbon bisulphide, but by passing sulphuretted hydrogen into an alcoholic solution of the oxychloride.

Tri-p-*tolylmethylarsonium iodide*,[1] $(C_7H_7)_3As(CH_3)I$, m.p. 179°, is prepared like its phenyl homologue (*v.* p. 103) and further characterised by the *chloride*, transparent crystals, m.p. 87°, *platinichloride*, reddish-brown, refractive prisms, and *iodochloride*, $(C_7H_7)_3As(CH_3)\cdot ICl_2$, reddish-yellow crystals, m.p. 146°.

Tri-p-*tolyliodomethylarsonium iodide*, $(C_7H_7)_3As(CH_2I)I$ (*v.* p. 104), crystallises from alcohol in transparent, colourless crystals, m.p. 215°.

Tri-p-*tolylallylarsonium bromide*, $(C_7H_7)_3As(C_3H_5)I$, colourless prisms from water, lustrous crystals from dilute alcohol, m.p. 82°, easily soluble in the ordinary solvents except ether. The bromide is prepared by five hours' heating of equal parts of tri-*p*-tolylarsine and allyl bromide in a reflux apparatus; the corresponding *chloride* is oily, the *platinichloride* forms a red powder, m.p. 225°, and the *iodide* crystallises from dilute alcohol in colourless prisms, m.p. 141°. *Tri*-p-*tolyldibromoallylarsonium bromide*,

$$(C_7H_7)_3As(C_3H_5Br_2)Br,$$

snowlike mass, m.p. 112°, obtained by adding bromine to the foregoing bromide in alcoholic solution.

Tri-m-*tolylarsine*,[2] $(CH_3\cdot C_6H_4)_3As$.—For this preparation pure *m*-bromotoluene is required (Wroblewski, *Annalen*, 1870, **156**, 74; Grete, *loc. cit.*, 1875, **177**, 2), 50 grams being mixed with arsenious chloride (18 grams) and sodium (30 grams) in 300 grams of anhydrous ether. Only two-thirds of this sodium is added at first, and the remainder as the reaction slackens. The crude arsine left after distilling off the ether is purified by crystallisation. Colourless leaflets from alcohol, prismatic and tabular crystals of the rhombic system from ether; m.p. 96°, D = 1·31/18°; easily soluble in the ordinary solvents except light petroleum. The following derivatives are obtainable by the general methods:—

Mercurichloride $(C_7H_7)_3As,HgCl_2$, sparingly soluble, m.p. 174°; *hydroxychloride* $(C_7H_7)_3As(OH)Cl$, m.p. 205°; *hydroxybromide*, rhombic crystals, m.p. 190°; *oxide*, $(C_7H_7)_3AsO$, white, crystalline mass, m.p. 170°, by the action of hot caustic soda on hydroxybromide; *sulphide*, $(C_7H_7)_3AsS$, silvery needles, m.p. 186°, by direct addition of sulphur to the arsine.

[1] Michaelis, *Annalen*, 1902, **321**, 204.
[2] Michaelis, *Annalen*, 1902, **321**, 216.

Quaternary alkyl iodides.—Tri-*m*-tolylarsine possesses in a special degree the capacity for combining with alkyl iodides. Unlike the other tertiary aromatic arsines, it combines with methyl iodide even in the cold, and on warming with the higher alkyl halides, including benzyl chloride.

Tri-m-*tolylmethylarsonium iodide*, $(C_7H_7)_3As(CH_3)I$, prisms or plates of the rhombic system, m.p. 181°, from water or alcohol; the *chloride* is oily, the *platinichloride* a pale yellow precipitate.

Tri-m-*tolylethylarsonium iodide*, $(C_7H_7)_3As(C_2H_5)I$, separates from dilute alcohol in distorted rhombohedra of the triclinic system, m.p. 130°; *tri*-m-*tolyl*-n-*propylarsonium iodide*,

$$(C_7H_7)_3As(C_3H_7)I,$$

needles, m.p. 143°, obtained by the prolonged interaction of its generators at the ordinary temperature: *tri*-m-*tolyl*iso*propylarsonium iodide*, m.p. 162°; *tri*-m-*tolylbenzylarsonium chloride*, $(C_7H_7)_3As(CH_2{\cdot}C_6H_5){\cdot}Cl$, obtained, not by boiling, but by allowing its generators to interact at 30–40°; easily soluble in water, dissolving sparingly in water, m.p. 102°.

Diphenyl-p-*tolylarsine*,[1] $(C_6H_5)_2As{\cdot}C_7H_7$, colourless crystals, m.p. 50°, somewhat difficult to obtain in solid condition. *p*-Tolylarsenious chloride (30 grams), bromobenzene (42 grams), and 24 grams of sodium in thin slices are brought together in 500 grams of dehydrated ether. The reaction begins at the ordinary temperature and is completed by warming for about three days. The syrupy residue left after removing the ether separates in oily drops from alcoholic solution unless the liquid is maintained for weeks at low temperatures. The oily arsine suffices, however, for the preparation of derivatives. *Mercurichloride*, $(C_6H_5)_2As{\cdot}C_7H_7,HgCl_2$, crystals from glacial acetic acid, m.p. 147°; *platinichloride*, yellow precipitate, m.p. 233°.

Diphenyl-p-*tolylarsine dihydroxide*, $(C_6H_5)_2As(C_7H_7){\cdot}OH$, m.p. 68°; prepared by successively adding bromine to the foregoing arsine in glacial acetic acid solution, treating the cooled solution of the dibromide with aqueous caustic potash, and finally boiling for 1½ hours. Dissolved in hot dilute nitric acid, the dihydroxide yields the *basic nitrate*, $(C_6H_5)_2As(C_7H_7)(OH){\cdot}NO_3$, yellow needles from water or alcohol-ether, m.p. 125°.

Diphenyl-p-*tolylarsine sulphide*, $(C_6H_5)_2As(C_7H_7)S$, granular crystals, m.p. 135°, from sulphuretted hydrogen and an alcoholic solution of the hydroxide.

[1] Michaelis, *Annalen*, 1902, **321**, 187; F. Lauterwald, *Inaug. Dissert.*, Rostock, 1897.

Diphenyl-p-*tolylmethylarsonium iodide*, $(C_6H_5)_2As(C_7H_7)(CH_3)I$, m.p. 152° (preparation, *v.* p. 103); the *chloride* is oily; *platinichloride*, pale red crystals, m.p. 209°.

Diphenyl-p-*tolylethylarsonium iodide* only obtained as an oil; *platinichloride*, pink crystals, m.p. 220°.

Phenyldi-p-*tolylarsine*,[1] $(C_7H_7)_2As{\cdot}C_6H_5$, colourless, well-defined rhombohedra, m.p. 101°, easily soluble in ether, chloroform, benzene, or hot alcohol, less so in cold spirit or glacial acetic acid. Phenylarsenious chloride (20 grams), *p*-bromotoluene (31 grams), finely-divided sodium (17 grams) in 200 c.c. of dry ether interacts at the ordinary temperature, the condensation being regulated by external cooling. The solid residue, after removing ether, is crystallised from alcohol. *Mercurichloride*, $\bar{A},HgCl_2$, white crystals from hot alcohol, m.p. 210°; *platinichloride*, $\bar{A}_2,H_2PtCl_6$, yellow crystals from alcoholic hydrochloric acid, m.p. 256°.

Phenyldi-p-*tolylarsine dichloride*, $(C_7H_7)_2As(C_6H_5)Cl_2$, preferably obtained by passing dry chlorine through a chloroform solution of the arsine; on evaporating *in vacuo* a transparent, hard mass is left which sinters at 186° and melts at 194°. Very easily hydrolysed by moisture to *hydroxychloride*, $(C_7H_7)_2As(C_6H_5)(OH){\cdot}Cl$, white powder, soluble in alcohol or hot water, but not in ether. The dichloride yields a *platinichloride*, m.p. 201°.

Phenyldi-p-*tolylarsine oxide*, $(C_7H_7)_2AsO(C_6H_5)$, from the chlorides by the action of alkalis, white powder, m.p. 81°, dissolving in dilute nitric acid to form the *basic nitrate*,

$$(C_7H_7)As(C_6H_5)(OH){\cdot}NO_3,$$

rosettes of intertwined needles, m.p. 94°.

Nitration of the oxide has hitherto yielded only tarry products.

Phenyldi-p-*tolylarsine sulphide*, $(C_7H_7)_2AsS(C_6H_5)$, prepared by the general method, m.p. 144°.

Phenyldi-p-*tolylmethylarsonium iodide*, $(C_7H_7)_2As(C_6H_5)(CH_3)I$, colourless needles, m.p. 84°, turning yellow in the light; (preparation, *v.* p. 103); *platinichloride*, golden-yellow needles, m.p. 222°. *Phenyldi*-p-*tolylethylarsonium iodide*,

$$(C_7H_7)_2As(C_6H_5)(C_2H_5)I,$$

oily from hot aqueous solutions, slowly solidifying to yellowish-white crystals, m.p. 125°.

[1] Michaelis, *Annalen*, 1902, **321**, 192.

Section VI.—Benzyl Derivatives.[1]

The starting point in the preparation of benzyl arsenical derivatives is the interaction between benzyl chloride (2 mols.), arsenious chloride (1 mol.), and sodium suspended in dry ether. The addition of a small proportion of pure ethyl acetate determines the onset of a very vigorous reaction, in which tribenzylarsine, tribenzylarsine dichloride, and dibenzylarsine trichloride are produced.

$$3C_6H_5\cdot CH_2Cl + AsCl_3 + 6Na = (C_6H_5\cdot CH_2)_3As + 6NaCl.$$
$$3C_6H_5\cdot CH_2Cl + AsCl_3 + 4Na = (C_6H_5\cdot CH_2)_3AsCl_2 + 4NaCl.$$
$$2C_6H_5\cdot CH_2Cl + AsCl_3 + 2Na = (C_6H_5\cdot CH_2)_2AsCl_3 + 2NaCl.$$

Tribenzylarsine, $As(CH_2\cdot C_6H_5)_3$, colourless, transparent monoclinic prisms from alcohol, m.p. 104°, not distillable without decomposition. Insoluble in water, dissolving sparingly in alcohol and easily in ether, benzene, or glacial acetic acid. Benzyl chloride (100 grams), arsenious chloride (72 grams), diluted with 500 c.c. of dry ether and treated with sodium parings (50 grams) and 5 c.c. of ethyl acetate distilled over sodium. After the first vigorous reaction has subsided, and the mixture has cooled, more ethyl acetate (3 c.c.) is added, and generally the process is completed in eighteen to twenty hours. The yields from the foregoing quantities are tribenzylarsine (15–20 grams), dibenzylarsinic acid (10 grams), and tribenzylarsine oxide (5–7 grams). After distilling off the ether the syrupy residue is mixed with alcohol, when tribenzylarsine and a portion of the dibenzylarsine dihydroxychloride, $(C_6H_5CH_2)_2As(OH)_2Cl$, separate, whilst the remainder of the latter product and tribenzylarsine hydroxychloride, $(C_6H_5\cdot CH_2)_3As(OH)\cdot Cl$, remain dissolved. The precipitate is dissolved in boiling alcohol containing ammonia; on cooling tribenzylarsine crystallises, whilst ammonium dibenzylarsinate remains in solution. Tribenzylarsine combines with the halogens, yielding unstable dihalides decomposed by water into hydroxyhalides; it combines with sulphur and alkyl iodides, but not with hydrochloric acid. With hot dilute nitric acid it is oxidised to arsenic and benzoic acids.

Tribenzylarsine mercurichloride, $(C_6H_5\cdot CH_2)_3As,HgCl_2$, crystalline, white precipitate from ethereal solutions of its generators. White needles melting at 159° from boiling alcohol.

[1] Michaelis and Paetow, *Annalen*, 1886, **233**, 60; Paetow, *Inaug. Dissert.*, Rostock, 1885.

Tribenzylarsine oxide, $(C_6H_5 \cdot CH_2)_3AsO$, colourless prisms from cold dilute alcohol, m.p. 219–220°. Easily soluble in alcohol and glacial acetic acid, sparingly so in cold water, ether, or benzene. Prepared by treating tribenzylarsine chloride with alcohol, also by concentrating the alcoholic mother liquor from the preparation of tribenzylarsine (see above) and adding ether when tribenzylarsine hydroxychloride and dibenzylarsine dihydroxychloride are precipitated. This precipitate, when boiled with aqueous caustic soda and then cooled, gives insoluble tribenzylarsine oxide ; the other product dissolving as sodium dibenzylarsinate, from which solution dibenzylarsinic acid is precipitated by hydrochloric acid.

Tribenzylarsine oxide is reduced to tribenzylarsine by zinc and glacial acetic acid containing hydrochloric acid ; hydriodic acid and red phosphorus convert it into tetrabenzylarsonium iodide.

The following hydroxy-derivatives containing acidic radicals are obtained by adding mineral acids to aqueous solutions of tribenzylarsine oxide : $(C_6H_5 \cdot CH_2)_3As(OH)Cl$, colourless crystals, m.p. 162–163° ; $(C_6H_5 \cdot CH_2)_3As(OH)Br$, colourless, tabular crystals, m.p. 128–129° ; $(C_6H_5 \cdot CH_2)_3As(OH)I,H_2O$, colourless tetragonal plates, m.p. 78° ; $(C_6H_5 \cdot CH_2)_3As(OH) \cdot NO_3$, colourless needles, m.p. 170° with decomposition.

Tribenzylarsine sulphide, $(C_6H_5 \cdot CH_2)_3AsS$, colourless, transparent, rhombic prisms, m.p. 212–214°, sparingly soluble in hot chloroform or glacial acetic acid, insoluble in alcohol, ether, benzene, or carbon bisulphide. It is prepared by addition of sulphur to tribenzylarsine in warm glacial acetic acid or by passing hydrogen sulphide into an alcoholic solution of tribenzylarsine oxide.

Tribenzylalkylarsonium iodides are readily prepared by heating tribenzylarsine with alkyl iodides in sealed tubes at 100°.

Tribenzylmethylarsonium iodide, colourless needles and rhombic crystals, m.p. 143°.

Tribenzylethylarsonium iodide, colourless leaflets, m.p. 148°.

Tribenzylpropylarsonium iodide, colourless, monoclinic plates, m.p. 145–146°.

*Tribenzyliso**propylarsonium iodide***, colourless, tabular crystals, m.p. 143°.

The first of this series treated with moist silver oxide yields a solution of the highly caustic base, *tribenzylmethylarsonium hydroxide*, which rapidly absorbs carbon dioxide, and on heating with concentrated aqueous caustic soda decomposes, with formation of toluene.

Tetrabenzylarsonium chloride, $(C_6H_5\cdot CH_2)_4AsCl,H_2O$, triclinic crystals from dilute hydrochloric acid, m.p. 160°, obtained by heating tribenzylarsine and benzyl chloride in sealed tubes at 170–175°. The corresponding *bromide*, needles, m.p. 173°, *iodide*, transparent needles, m.p. 168°, *periodide*, $(C_7H_7)_4AsI_3$, lustrous red leaflets, m. p. 149–150°.

Tetrabenzylarsonium hydroxide, $(C_6H_5\cdot CH_2)_4As\cdot OH$, obtained from the iodide and moist silver oxide as a syrup with alkaline reaction, rapidly becomes solid by absorbing atmospheric carbon dioxide, and on heating with alkalis it loses toluene and becomes converted into tribenzylarsine oxide,

$$(C_7H_7)_4AsOH = C_7H_8 + (C_7H_7)_3AsO.$$

Tetrabenzylarsonium hydroxide [1] yields the following characteristic salts: *mercuri-iodide*, m.p. 163°; *mercurichloride*, white needles, m.p. 176°; *platinichloride*, m.p. 198°; and *aurichloride*, yellow needles, m.p. 130° (indefinite).

Dibenzylarsinic acid, $(C_6H_5\cdot CH_2)_2AsO\cdot OH$, nacreous leaflets from alcohol, m.p. 210°, very sparingly soluble in cold alcohol, ether, acetone, or benzene. Obtained by treating dibenzylarsinic trichloride with caustic soda (for its preparation see tribenzylarsine and tribenzylarsine oxide). This acid has a saline, bitter taste, it is greasy to the touch, and has a very irritating effect on the mucous membrane. Above 210° it decomposes:

$$2(C_6H_5\cdot CH_2)_2AsO\cdot OH = 2As + 2H_2O + 2C_6H_5\cdot COH + 2C_7H_8,$$

with the formation of benzaldehyde and toluene. Concentrated hydrochloric acid decomposes it completely, forming benzyl chloride, toluene, and arsenious chloride,

$$(C_6H_5\cdot CH_2)_2AsO\cdot OH + 4HCl = C_6H_5\cdot CH_2Cl + C_6H_5\cdot CH_3 + AsCl_3 + 2H_2O.$$

Dibenzylarsinic acid is reduced by zinc and alcoholic hydrochloric acid or by stannous chloride to a white, sparingly soluble powder which on exposure to air regenerates dibenzylarsinic acid. This product may possibly be the cacodyl derivative,

$$(C_7H_7)_2As\cdot As(C_7H_7)_2,$$

but it has not been obtained pure.

The metallic dibenzylarsinates are well defined salts, indicating that the acid is monobasic. The alkali salts are very soluble. The *calcium*, $[(C_7H_7)_2AsO_2]_2Ca,6H_2O$, and *barium*,

$$[(C_7H_7)_2AsO_2]_2Ba,8H_2O,$$

[1] Mannheim, *Annalen*, 1905, **341**, 208.

salts are soluble in water and crystallise from alcohol. *Silver* salt, $(C_7H_7)_2AsO_2Ag$, white, amorphous precipitate.

Dibenzylarsinic acid has a constitution similar to that of cacodylic acid, and, like the latter, it exhibits amphoteric properties, combining with acids as well as with bases. In its basic phase it probably reacts as the ortho-compound,

$$(C_7H_7)_2As(OH)_3,$$

and exchanges one of these three hydroxyl groups for an acid radical.

Dibenzylarsinic acid hydrochloride, $(C_6H_5{\cdot}CH_2)_2As(OH)_2Cl$, white needles, m.p. 128°, prepared by boiling powdered dibenzylarsinic acid with dilute hydrochloric acid. It corresponds with Bunsen's "cacodyl superchloride," $(CH_3)_2AsO{\cdot}OH,HCl$. The *hydrobromide*, $(C_6H_5{\cdot}CH_2)_2As(OH)_2Br$, and the *hydrochloride* both decompose, liberating benzyl bromide and chloride respectively. The *nitrate*, $(C_6H_5{\cdot}CH_2)_2As(OH)_2{\cdot}NO_3$, silky needles, m.p. 128–129°, is more stable than the preceding halide compound.

A compound having the composition $(C_6H_5{\cdot}CH_2)_2As{\cdot}OH,H_2O$, lustrous leaflets, m.p. 215–216°, is produced by applying the Grignard reagent, magnesium benzyl chloride, to arsenious oxide in ethereal solution.[1]

Dibenzylthioarsinic acid, $(C_6H_5{\cdot}CH_2)_2AsO{\cdot}SH$, white, nacreous leaflets from alcohol, m.p. 197–199°. Hydrogen sulphide is passed into an alkaline solution of dibenzylarsinic acid and the liquid then acidified. The precipitate is soluble in benzene or glacial acetic acid.

Benzylarsenious chloride, $C_6H_5{\cdot}CH_2{\cdot}AsCl_2$, liquid, b. p. 175°/50 mm., prepared by heating tribenzylarsine (10 grams) with arsenious chloride (30 grams) for ten to twelve hours at 160–180°. Decomposes in the air,

$$C_6H_5CH_2AsCl_2 + O = C_6H_5CH_2{\cdot}Cl + AsOCl.$$

Water decomposes the chloride into benzaldehyde (benzoic acid) and arsenious oxide. Chlorine also destroys it, giving benzyl chloride and arsenious chloride. Benzylarsenious chloride produces painful blisters on the skin. This chloride is far less stable than purely aliphatic or aromatic arsenious chlorides.

[1] Sachs and Kantorowicz, *Ber.*, 1908, **41**, 2769.

Benzylarsinic acid,[1] $C_6H_5 \cdot CH_2 \cdot AsO(OH)_3$, colourless, glistening needles, m.p. 167°, is readily obtained by dissolving in dilute alcohol the reagents indicated by the following equation :

$$2C_6H_5 \cdot CH_2I + As_2O_3 + 6KOH = 2C_6H_5 \cdot CH_2 \cdot AsO(OK)_2 + 2KI + 3H_2O.$$

The solution, freed from alcohol by distillation, is neutralised, filtered, and then acidified cautiously with hydrochloric acid, when benzylarsinic acid is precipitated to the extent of 60 per cent. The *disulphide*, $C_7H_7 \cdot AsS_2$, a heavy, bright yellow oil, is formed by the action of sulphuretted hydrogen on an aqueous solution of benzylarsinic acid. This acid dissolves only sparingly in cold water ; 100 c.c. of saturated aqueous solution at 22·5°, 27°, and 97° contain respectively 0·34, 0·39, and 3·50 grams ; 100 c.c. of saturated alcohol at 23° and 70° contain 0·87 and 5·91 grams.

Benzylarsinic acid, like the dibenzyl compound (p. 116), is decomposed by strong mineral acids,

$$2C_6H_5 \cdot CH_2 \cdot AsO(OH)_2 + 2HCl = 2C_6H_5 \cdot CH_2 \cdot Cl + As_2O_3 + 3H_2O.$$

Sulphuric acid gives dibenzyl, benzaldehyde, and arsenious oxide. On heating, this arsinic acid decomposes into benzyl alcohol, benzaldehyde, stilbene, arsenious oxide, and water.

Benzylarsine,[2] $C_6H_5CH_2 \cdot AsH_2$, faintly yellow liquid, b.p. 140°/260 mm., is prepared by reducing benzylarsinic acid with amalgamated zinc dust and concentrated hydrochloric acid in the presence of ether,

$$C_6H_5CH_2 \cdot AsO_3H_2 + 6H = C_6H_5 \cdot CH_2 \cdot AsH_2 + 3H_2O.$$

A red condensation product is deposited on the walls of the reduction flask. This substance is probably identical with the red compound obtained by the aerial oxidation of benzylarsine, this reaction giving rise to benzylarsinic acid (m.p. 167°) and *arsenophenylmethane*,

$$(C_6H_5CH_2 \cdot As{:}As \cdot CH_2 \cdot C_6H_5)_2.$$

A black polymeride of the latter product is obtained by heating benzylarsine at 250° *in vacuo*.

[1] Dehn and McGrath, *J. Amer. Chem. Soc.*, 1906, **28**, 354.
[2] Dehn, *Amer. Chem. J.*, 1908, **40**, 113.

Section VII.—Aromatic Arsenicals containing Higher Aryl Groups,

1. *Compounds containing One Aryl Group to One Arsenic Atom.*[1]

m-*Xylylarsenious chloride*, $(CH_3)_2C_6H_3 \cdot AsCl_2$, colourless needles, m.p. 42–43°, b.p. 278°/760 mm. and 215°/320 mm. Obtained by the general methods:

(i) mercury di-*m*-xylyl, added slowly to ten parts of arsenious chloride, and after twenty-four hours the filtrate from mercuric chloride fractionated.

(ii) Tri-*m*-xylylarsine heated at 240° with 40 parts of arsenious chloride and the product fractionated.

m-*Xylylarsenious oxide*, $(CH_3)_2C_6H_3 \cdot AsO$, granules, m.p. 220°, readily obtained from the chloride by alkaline hydrolysis; absorbs chlorine, forming m-*xylylarsenic oxychloride*, colourless, flattened needles, m.p. 150°.

m-*Xylylarsenious sulphide*, $(CH_3)_2C_6H_3 \cdot AsS$, colourless needles from ether or benzene-alcohol, m.p. 169°, by the action of hydrogen sulphide on the preceding oxide or chloride in alcoholic solution.

Arseno-m-*xylene*, $C_8H_9 \cdot As{:}As \cdot C_8H_9$, white needles from chloroform-ether, m.p. 194–196°; addition of iodine in alcoholic solution leads to *iodoarseno*-m-*xylene*, $C_8H_9 \cdot AsI \cdot AsI \cdot C_8H_9$, yellow crystals, m.p. 89°.

m-*Xylylarsenic chloride*, $C_8H_9AsCl_4$, colourless, crystalline mass, hydrolysed to oxychloride and arsinic acid.

m-*Xylylarsinic acid*, $(CH_3)_2C_6H_3 \cdot AsO(OH)_2$, rectangular crystals from dilute alcohol, m.p. 210°, obtained by hydrolysis of the preceding chloride or by adding hydrogen peroxide to *m*-xylylarsenious chloride in glacial acetic acid. *Acid ammonium* salt, soluble crystals, m.p. 136°.

Chloro-m-*xylylarsinic acid*, $(CH_3)_2C_6H_2Cl \cdot AsO(OH)_2$, needles, m.p. 165°, by passing chlorine into *m*-xylylarsenious chloride suspended in water: *dichloro*-m-*xylylarsinic acid*, m.p. 193°, produced by chlorinating the dichloride in glacial acetic acid.

These results show that chloro-derivatives are much more readily obtained in the xylene than in the toluene and benzene series.

m-*Toluarsinic acid*, $CO_2H \cdot C_6H_3(CH_3) \cdot AsO(OH)_2$, is obtained by

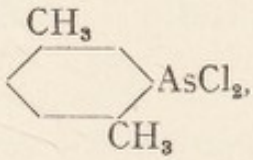
[1] Michaelis, *Annalen*, 1902, **320**, 330; Seemann, *Inaug. Dissert.*, Rostock, 1891.

oxidising *m*-xylylarsinic acid with the calculated amount of permanganate, at 190° it changes into the anhydride,

$$CO_2H{\cdot}C_6H_3(CH_3){\cdot}AsO_2.$$

iso*Phthaloarsinic acid*, $(CO_2H)_2C_6H_3{\cdot}AsO(OH)_2$, colourless crystals, when double the amount of permanganate is employed; this acid decomposes without melting.

p-*Xylylarsenious chloride*,[1]



prepared by the general methods, the process from tri-*p*-xylylarsine and five parts of arsenious chloride at 230° giving the best yield; tufts of colourless needles; m.p. 63°, b.p. 285°/760 mm. The *iodide* obtained by dissolving the oxide in strong hydriodic acid (b.p. 127°), yellow crystals, m.p. 45°; the *oxide*, m.p. 165°; *oxychloride*, needles, m.p. 178°.

Arseno-p-*xylene*, $C_8H_9{\cdot}As{:}As{\cdot}C_8H_9$, white powder, m.p. 208°, takes up iodine to form *iodoarseno*-p-*xylene*, $C_8H_9{\cdot}AsI{\cdot}AsI{\cdot}C_8H_9$, m.p. 97°.

p-*Xylylarsenious sulphide*, $C_8H_9{\cdot}AsS$, yellow needles, m.p. 188°; *disulphide*, $C_8H_9{\cdot}AsS_2$, white precipitate obtained by saturating ammoniacal solution of *p*-xylylarsinic acid with hydrogen sulphide and adding hydrochloric acid.

p-*Xylylarsinic acid*, white needles from hot water, m.p. 223°, prepared from the chloride by the general method, is oxidised to p-*toluarsinic acid*, $CO_2H{\cdot}C_7H_6{\cdot}AsO(OH)_2$, white crystals from alcohol or ether, m.p. 208°. *Silver* salt indicates dibasicity.

Pseudocumylarsenious chloride,[2] $(CH_3)_3C_6H_2{\cdot}AsCl_2$, [$3CH_3 : AsCl_2 = 1:2:4:5$], prepared by heating tri-pseudo-cumylarsine with four parts of arsenious chloride for forty-eight hours at 200°, and fractionating the product under 30 mm. pressure; colourless needles, m.p. 82·5°, b.p. 190°/30 mm.

Pseudocumylarsinic acid, $C_9H_{11}{\cdot}AsO(OH)_2$, colourless needles from alcohol or water, m.p. 224°. *Silver* salt, $C_9H_{11}{\cdot}AsO(OAg)_2$.

p-*Cumylarsenious chloride*, $C_3H_7{\cdot}C_6H_4{\cdot}AsCl_2$, obtained by heating tri-*p*-cumylarsine with four parts of arsenious chloride for forty-eight hours at 170°; oil, b.p. 170°/30 mm.

p-*Cumylarsinic acid*, $C_3H_7{\cdot}C_6H_4AsO(OH)_2$, snow-white, silky needles from warm alcohol or hot water, m.p. 152°, oxidised by

[1] Michaelis, *Annalen*, 1902, **320**, 336. [2] Michaelis, *loc. cit.*, 339.

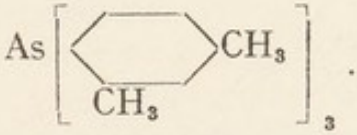
alkaline permanganate to *p*-benzarsinic acid, the propyl group being destroyed.

Tertiary butylphenylarsenious chloride, $(CH_3)_3C\cdot C_6H_4\cdot AsCl_2$, prepared by heating for twenty-four hours at 200° tri-*tert.*-butylphenylarsine with seven parts of arsenious chloride, colourless liquid, b. p. 175–180°/20 mm., converted by aqueous sodium carbonate into the *oxide*, colourless crystals, m.p. 89°, which on reduction with phosphorous acid gives arsenotertiary-butylbenzene, m.p. 198°.

The *arsinic acid*, $(CH_3)_3C\cdot C_6H_4\cdot AsO(OH)_2$, is best prepared by adding hydrogen peroxide to the chloride dissolved in glacial acetic acid; tufts of colourless needles, m.p. 193°.

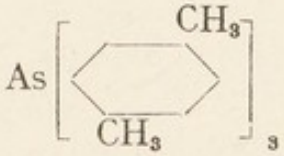
2. *Compounds containing Three Aryl Groups to One Arsenic Atom.*

Tri-m-*xylylarsine*,[1]



This arsine is produced in quantitative yield by the interaction of bromo-*m*-xylene (61 grams), arsenious chloride (20 grams), and sodium (30 grams) in dry ether, the reaction going to completion without external heating; from alcohol-petroleum in colourless, transparent prisms, m.p. 166°; easily soluble in the ordinary organic solvents, although dissolving only sparingly in alcohol. The following derivatives can be employed in characterising this arsine: *mercurichloride*, m.p. 257°; *oxide*, $(C_8H_9)_3AsO$, from the bromide by aqueous alkalis, colourless crystals of hydroxide losing water at 100°; *sulphide*, $(C_8H_9)_3AsS$, silky prisms, m.p. 145°, from the arsine and sulphur; *methiodide*, $(C_8H_9)_3As(CH_3)I$, lustrous crystals, m.p. 179°; *methichloride*, uncrystallisable; *platinichloride*, reddish-brown crystals, m.p. 245°.

Tri-p-*xylylarsine*,

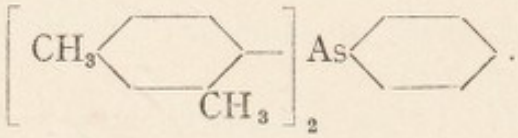


This arsine, prepared like its preceding isomeride from bromo-

[1] Michaelis, *Annalen*, 1902, **331**, 220.

p-xylene, crystallises from the mixture, alcohol–light petroleum–benzene, in lustrous, colourless prisms, m.p. 157°; *mercurichloride*, m.p. 236°; *methiodide*, colourless, tabular crystals, m.p. 175°; *platinichloride*, pale yellow needles, m.p. 250°; no combination with ethyl iodide.

Di-m-*xylylphenylarsine*,[1]



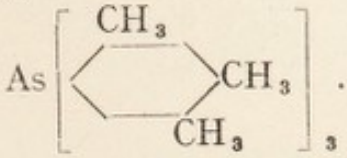
Phenylarsenious chloride (46 grams), bromo-*m*-xylene (77 grams), and sodium (38 grams) in 400 c.c. of ether lead to the production of this dissymmetric arsine (45 grams or 60 per cent. of theory), the product crystallising from ether-alcohol in triclinic crystals, m.p. 99°, dissolving sparingly in alcohol and easily in other organic solvents: *mercurichloride*, $(C_8H_9)_2AsC_6H_5,HgCl_2$, from alcohol-chloroform in lustrous needles, m.p. 224°; *platinichloride*, $(C_8H_9)_2As{\cdot}C_6H_5,H_2PtCl_6$, yellow, felted needles, m.p. above 300°; *dichloride*, m.p. 176°, very easily hydrolysed to *hydroxychloride*, m.p. 186°; *periodide*, $(C_8H_9)_2As(C_6H_5)I_4$, reddish-violet crystals, m.p. 127°; *hydroxide*, m.p. 112°, and passing into *oxide*, m.p. 120°; *hydroxynitrate*, transparent crystals, m.p. 126°, by the action of hot dilute nitric acid on the last two compounds; *methiodide*, lustrous, colourless crystals, m.p. 184°; *di*-m-*xylylphenylarsonium hydroxide*, m.p. 122°; *ethiodide*, m.p. 157°; *trinitrodi*-m-*xylylphenylarsine oxide* from the arsine and nitro-sulphuric acid, separates from alcohol in pale yellow crystals, m.p. 245°.

Tri-p-*ethylphenylarsine*,[2]

is prepared from *p*-bromoethylbenzene (111 grams), arsenious chloride (42 grams), and sodium (50 grams) in 500 grams of dry ether, m.p. 78°, easily soluble in ether, less so in alcohol: *mercurichloride*, m.p. 132°; *dichloride*, m.p. 246°; *dibromide*, m.p. 212°; *hydroxide*, m.p. 180°; *sulphide*, m.p. 123°; *methiodide*, m.p. 126°; *trinitro*-derivative, $[NO_2{\cdot}(CH_3)C_6H_3]_3AsO$, m.p. 232°.

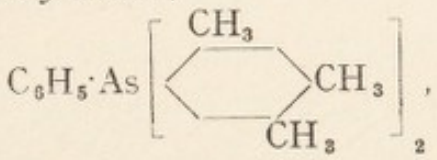
[1] Michaelis, *loc. cit.*, 223. [2] *Ibid.*, 226.

Tripseudocumylarsine,[1]



This arsine is readily prepared by mixing bromopseudocumene (50 grams), arsenious chloride (16 grams), and sodium (21 grams) in 250 c.c. of dry ether, the reaction being completed by prolonged heating on the water-bath; the product is practically insoluble in ether, sparingly soluble in alcohol and light petroleum, and easily so in benzene; snow-white needles, m.p. 223°; *dibromide*, yellow powder, m.p. 224–225°, hydrolysed to *hydroxybromide*, m.p. 108°, and *dihydroxide*, $(C_9H_{11})_3As(OH)_2,4H_2O$, needles from dilute alcohol losing $5H_2O$ at 120°, leaving the *oxide*, m.p. 227–228°.

Dipseudocumylphenylarsine,



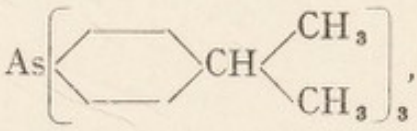
is produced by adding sodium (30 grams) to phenylarsenious chloride (30 grams) and bromopseudocumene (53·5 grams) in 300 c.c. of dry ether. After 45 hours' boiling in a reflux apparatus the reaction is complete (35 grams of arsine—70 per cent. of theory), m.p. 138·5°, soluble in the usual organic solvents; *platinichloride*, $[(C_9H_{11})_2As{\cdot}C_6H_5]_2H_2PtCl_6$, yellow rosettes, m.p. 287°; *aurichloride*, $(C_9H_{11})_2As{\cdot}C_6H_5,HAuCl_4$, colourless aggregates melting at 177° to a golden-yellow mass; *mercurichloride*, $(C_9H_{11})_2AsC_6H_5,HgCl_2$, silvery leaflets from hot glacial acetic acid, m.p. 223°; *dichloride*, m.p. 217°; *hydroxychloride*, transparent crystals, m.p. 173–175°; *hydroxybromide*, m.p. 177°; *di-iodide*, yellowish-red crystals, m.p. 163·5°; *hydroxyiodide*, pale yellow precipitate, m.p. 153°; *dihydroxide*, colourless, transparent prisms, m.p. 113–114°, obtained by the action of alcoholic potash on the preceding halide derivatives, loses water in the desiccator at 100°, giving the *oxide*, m.p. 162·5°; the *sulphide*, $(C_9H_{11})_2AsS{\cdot}C_6H_5$, m.p. 135°, from the arsine and alcoholic yellow ammonium sulphide at 110°; *methiodide*, m.p. 179°; *methochloride*, m.p. 192°; *platinichloride*, m.p. 266·5°; *dipseudocumylphenylmethylarsonium hydroxide*,

$$(C_9H_{11})_2As(C_6H_5)(CH_3){\cdot}OH,$$

[1] *Ibid.*, 227.

from iodide in alcoholic solution with silver oxide, colourless needles, softening at 147°, m.p. 151°; *ethiodide*, colourless crystals, m.p. 189°; *trinitrodipseudocumylphenylarsine oxide*, $\begin{matrix}NO_2\cdot C_6H_4\\(NO_2\cdot C_9H_{11})_2\end{matrix}\!\!>\!\!AsO$, prepared from the arsine or its oxide and nitrosulphuric acid, pale yellow crusts from alcohol, m.p. 163°.

Tri-p-*cumylarsine*,[1]



is prepared by condensing *p*-bromocumene (40 grams), arsenious chloride (12 grams), and sodium (30 grams) in 300 c.c. of dry ether; colourless prisms from ether-alcohol, m.p. 139–140°; *mercurichloride*, $(C_9H_{11})_3As,HgCl_2$, white needles, m.p. 243°; *dichloride*, colourless needles, m.p. 276°; *platinichloride*,

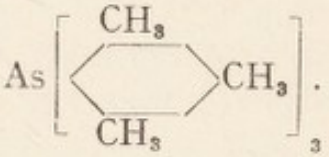
$$[(C_9H_{11})_3AsCl_4]_2PtCl_6,$$

golden-yellow needles from platinichloride and dichloride in alcoholic solution; *dibromide*, m.p. 142°; *oxide*, white needles, m.p. 129°, dissolving in dilute nitric acid to the *hydroxynitrate*, $(C_9H_{11})_3As(OH)\cdot NO_3$, m.p. 147°; *trinitrotricumylarsine oxide*, $(NO_2\cdot C_9H_{10})_3AsO$, yellowish-white needles, m.p. 245°, by dissolving the arsine in nitrosulphuric acid, the *sulphide*, $(C_9H_{11})_3AsS$, silky white crystals, m.p. 149·5°, by leading sulphuretted hydrogen into the alcoholic solution of the oxide; *methiodide*,

$$(C_9H_{11})_3As(CH_3)I,$$

colourless rosettes, m.p. 103°; *ethiodide*, m.p. 138°.

Trimesitylarsine,[2]



The production of this arsine occurs less readily than that of the lower homologues; bromomesitylene (30 grams), arsenious chloride (9 grams), and sodium (20 grams) in dry ether are heated in a reflux apparatus; tufts of colourless prisms from alcohol, m.p. 170°: *hydroxychloride*, colourless prisms, m.p. 100°; *dibromide*, very well defined tabular crystals of the rhombic system from alcohol, m.p. 237°; *oxide*, m.p. 203–204°; *meth-*

[1] *Ibid.*, 235. [2] *Ibid.*, 238.

iodide, $(C_9H_{11})_3As(CH_3)I$, colourless prisms, m.p. 186°, readily obtained from its generators, on the water-bath; *methochloride*, tufts of crystals, m.p. 192°; *platinichloride*, yellowish-red, monoclinic crystals, m.p. 237°.

Tri-tertiary-butylphenylarsine.

The *tert.*-butylbenzene required is obtainable in 60 per cent. yield from benzene, *iso*butyl chloride, and aluminium chloride; bromination with iodine as carrier leads to bromo-*tert.*-butylbenzene (m.p. 13°, b.p. 230°). The bromo-derivative (50 grams) heated in ethereal solution with arsenious chloride and sodium yields 30 grams of arsine crystallising from benzene, m.p. 235°; *oxide*, m.p. above 360°; *methiodide*, m.p. 125°; *tri*-tert.-*butylphenylmethylarsonium hydroxide*,

$$[(CH_3)_3C{\cdot}C_6H_4]_3As(CH_3){\cdot}OH,4H_2O,$$

rhombohedral crystals, m.p. 136°, is exceptionally crystallisable for a quaternary hydroxide; the water of crystallisation cannot be removed without decomposing the compound.

Section VIII.—Arsenical Derivatives of Naphthalene.

α-Naphthylarsenious chloride,[1] $C_{10}H_7{\cdot}AsCl_2$, white, crystalline powder, m.p. 63°, easily soluble in alcohol, benzene, or other organic solvents, is prepared by heating tri-α-naphthylarsine with 20 parts of arsenious chloride at 270° for forty hours; the product, after distilling under reduced pressure to remove excess of this reagent, is extracted with ether. The crude α-naphthylarsenious chloride is purified by repeated crystallisation from alcohol or light petroleum. It is not affected by water, but caustic or carbonated alkalis convert it into *α-naphthylarsenious oxide*, $C_{10}H_7{\cdot}AsO$, white powder, m.p. 245°, insoluble in water, benzene, or ether, dissolving sparingly in boiling alcohol. By dry distillation it yields, not trinaphthylarsine, but naphthalene, elemental arsenic, and carbon.

Arseno-α-naphthalene, $C_{10}H_7{\cdot}As{:}As{\cdot}C_{10}H_7$, yellow needles, m.p. 221°, is insoluble in water or ether and dissolves only sparingly in alcohol, benzene, carbon bisulphide, or chloroform. It is prepared by boiling an alcoholic solution of α-naphthylarsenious oxide with solid phosphorous acid, when the arseno-

[1] Michaelis and Schulte, *Ber.*, 1882, **15**, 1954; *Annalen*, 1902, **302**, 342; Büschler, *Inaug. Dissert.*, Rostock, 1893.

derivative separates as a yellow, crystalline powder. With chlorine, arseno-α-naphthalene combines additively to form α-naphthylarsenious chloride; with sulphur it yields α-naphthylarsenious sulphide; nitric acid oxidises it to α-naphthylarsinic acid.

α-Naphthylarsinic acid,[1] $C_{10}H_7 \cdot AsO(OH)_2$, well defined colourless needles from water, m.p. 197°, prepared by the following series of reactions: mercury di-α-naphthyl dissolved in arsenious chloride leads to a strongly exothermic reaction with separation of mercuric chloride, the condensation being completed in a reflux apparatus. The product diluted with benzene is filtered from this precipitate, the solution evaporated, and the oily residue treated with chlorine so long as the gas is absorbed with generation of heat. Water is then added, when hydrogen chloride is evolved and the arsinic acid separates in a crystalline form,

$$2AsCl_3 + Hg(C_{10}H_7)_2 = HgCl_2 + 2C_{10}H_7 \cdot AsCl_2.$$
$$C_{10}H_7AsCl_2 + 2Cl = C_{10}H_7AsCl_4.$$
$$C_{10}H_7AsCl_4 + 3H_2O = 4HCl + C_{10}H_7AsO(OH)_2.$$

β-Naphthylarsenious chloride,[2] warty aggregates of needles, m.p. 69°, soluble in ether, benzene, or alcohol. As tri-β-naphthylarsine is difficult to obtain, the other general method of preparation is adopted, and mercury di-β-naphthyl is boiled for one hour in a reflux apparatus with seven parts of arsenious chloride. The excess of the latter reagent is removed by distillation, the residue extracted with ether, and the soluble product crystallised repeatedly from light petroleum. This chloride, treated with alcoholic potash, yields the *oxide*, $C_{10}H_7 \cdot AsO$, a white, granular, sparingly soluble powder, m.p. 270°.

Arseno-β-naphthalene, $C_{10}H_7 \cdot As{:}As \cdot C_{10}H_7$, yellow needles from xylene, m.p. 234°, prepared by heating alcoholic solutions of the preceding chloride or oxide with phosphorous acid.

β-Naphthylarsinic acid, $C_{10}H_7 \cdot AsO(OH)_2$, colourless needles from hot water, m.p. 155°, obtained by converting the above dichloride into tetrachloride with chlorine and by hydrolysing the latter chloride with water; this acid closely resembles the α-isomeride; it is easily soluble in alcohol, sparingly so in cold water.

The reaction between the bromonaphthalenes, arsenious chloride (in ether), and sodium takes place far less smoothly than with the chloro- and bromo-derivatives of the benzenoid

[1] Kelbe, *Ber.*, 1878, **11**, 1503. [2] Michaelis, *Annalen*, 1902, **320**, 342.

hydrocarbons; tarry by-products are formed to a considerable extent.[1]

Tri-α-naphthylarsine,

α-Bromonaphthalene (51 grams), arsenious chloride (15 grams), and sodium (20 grams) are mixed in dry ether and after 24 hours the mixture is heated on the water-bath for 15–20 hours. The oily mass left after distilling off the ether is freed from tar by extraction with a little of this solvent, the residual solid is dissolved in hot benzene, and to the solution an equal volume of alcohol is added, when tri-α-naphthylarsine crystallises on cooling in slender prisms (yield 20 %). When recrystallised from benzene the arsine separates in rhombic plates, m.p. 252°; it is easily soluble in carbon bisulphide, sparingly so in chloroform, ether, or alcohol. Unlike the other tertiary aromatic arsines, it does not form a mercurichloride. Addition of bromine to the arsine in benzene leads, not to the dibromide, but to a *tetrabromo*-derivative in which probably two bromine atoms have entered a naphthalene nucleus. When bromine is added to a benzene solution of the arsine rendered turbid by dilute alcohol, the *hydroxybromide* is formed, m.p. 155°, which is changed into the *dihydroxide*, $(C_{10}H_7)_3As(OH)_2,2H_2O$, colourless needles from hot alcohol, melting above 300°; when dried at 110° this compound loses $3H_2O$ and leaves the oxide.

Tri-β-naphthylarsine,

Prepared from β-bromonaphthalene, the procedure being the same as that employed for the α-isomeride. The residue after condensation is extracted successively with alcohol and light petroleum to remove naphthalene and tarry impurity. The crude arsine remaining as a light yellow powder is further purified through its *mercurichloride* (leaflets, m.p. 247°); this derivative, after crystallisation from glacial acetic acid, is decomposed by sulphuretted hydrogen when dissolved in the same solvent;

[1] Michaelis, *Annalen*, 1902, **321**, 242.

mercuric sulphide is precipitated, and tri-β-naphthylarsine separates in colourless crystals, m.p. 165°, readily soluble in benzene, carbon bisulphide, or chloroform, sparingly so in ether; the *dibromide* is tarry and on treatment with alcoholic potash yields the anhydrous *tri-β-naphthylarsine oxide*, $(C_{10}H_7)_3AsO$; the *sulphide*, $(C_{10}H_7)_3AsS$, m.p. 162°, well-defined tablets from dilute alcohol is formed by passing sulphuretted hydrogen through an alcoholic solution of the dibromide. This sulphide is easily soluble in benzene or carbon disulphide, and when its solution in the former is boiled with mercury, the sulphur is removed, and pure tri-β-naphthylarsine is regenerated.

Section IX.—Benzarsinic Acids and their Derivatives.[1]

This section contains a description of a series of arsenical carboxylic acids derived by oxidation from aromatic arsenic derivatives containing methylated benzenoid nuclei.

The arsenical toluene and xylene derivatives contain the metalloid so firmly united to the aromatic nucleus that the methyl group can be oxidised to carboxyl without detaching the arsenic radical. In this way aromatic derivatives of arsenic acid are obtained in which three hydroxyl groups are successively replaced by the univalent radical $-C_6H_4\cdot CO_2H$.

$AsO(OH)_3$

$CO_2H\cdot C_6H_4\cdot AsO(OH)_2$	$(CO_2H\cdot C_6H_4)_2AsO(OH)$	$(CO_2H\cdot C_6H_4)_3AsO$
Benzarsinic acid (carboxyphenyl-arsinic acid).	Dibenzarsinic acid (dicarboxydiphenyl-arsinic acid).	Tribenzarsinic acid (tricarboxy-triphenylarsinic acid).

The *p*-tolyl compounds were selected by La Coste for the study of this reaction. *p*-Tolylarsinic acid remained unchanged after continuous boiling for a week with a large excess of nitric acid in a reflux apparatus. Chromic acid in warm glacial acetic acid solution eliminates arsenic from this organic acid in the form of arsenic acid. The desired oxidation was achieved by the use of alkaline permanganate,

$$CH_3\cdot C_6H_4AsO(OK)_2 + 2KMnO_4 = CO_2K\cdot C_6H_4AsO(OK)_2 + 2MnO_2 + KOH + H_2O.$$

[1] La Coste, *Annalen*, 1881, **208**, 1.

Similar changes can be effected with di-*p*-tolylarsinic acid and tri-*p*-tolylarsine or its dihydroxide.

These benzarsinic acids undergo reduction on treatment with hydriodic acid and phosphorus, giving rise to substituted arsenious iodides, which on successive treatment with aqueous sodium carbonate and dilute mineral acid furnish aromatic arsenious acids, substances of considerable theoretical interest as being derivatives of ortho-arsenious acid, $As(OH)_3$, in which the hydroxyl groups become successively replaced by $C_6H_4 \cdot CO_2H$ groups.

$As(OH)_3$

$CO_2H \cdot C_6H_4 \cdot As(OH)_2$	$(CO_2H \cdot C_6H_4)_2As \cdot OH$	$(CO_2H \cdot C_6H_4)_3As$
Benzarsenious acid (carboxyphenyl-arsenious acid).	Dibenzarsenious acid (dicarboxydiphenyl-arsenious acid).	Tribenzarsenious acid (arsinotribenzoic acid).

The tervalent arsenic of the first two compounds is very exceptional in retaining its hydroxyl group and in not forming the anhydride, $R \cdot AsO$ or $R_2As \cdot O \cdot As \cdot R_2$. This remarkable stability of the hydroxylated compounds is undoubtedly due to the presence of an acidic carboxyl group in the aromatic nucleus. The foregoing property, which is noticeable in certain of the nitro-arylarsenious compounds, corresponds with the stabilising effect produced on *aa*-dihydroxycarbon complexes, $-C(OH)_2-$, by the presence of neighbouring acidic groups as in mesoxalic and dihydroxytartaric acids or in chloral hydrate and its analogues.

1. *Toluene Series.*

p-*Benzarsinic acid* (p-*Carboxyphenylarsinic acid*),

$CO_2H \cdot C_6H_4 \cdot AsO(OH)_2$,

colourless transparent plates, sparingly soluble in water, scarcely so in alcohol or glacial acetic acid.

Preparation: 1. A solution of potassium permanganate (14 grams) in 750 c.c. of water is added slowly to *p*-tolylarsinic acid (10 grams) and potassium hydroxide (6 grams) in 250 c.c. of water. After some days the colourless solution is filtered, concentrated, acidified with acetic acid, evaporated to dryness, and extracted with alcohol to remove potassium acetate. The residual acid potassium *p*-benzarsinate (about 10 grams) is

decomposed by concentrated hydrochloric acid at 60°, when the free acid separates in well defined crystals.

2. A simpler and quicker mode of preparation is afforded by the action of dilute nitric acid (D = 1·2) when *p*-tolylarsinic acid is heated for twelve hours in sealed tubes at 150° with 13–14 parts of this oxidising agent. The residue from the tubes after evaporation to dryness is extracted with dilute alcohol.[1] A practically quantitative yield is obtained by heating *p*-tolylarsinic acid with nitric acid (D = 1·2) for three hours at 170°.[2]

3. A third method of preparation is available through *p*-arsanilic acid. This substance is diazotised in the presence of cuprous cyanide, the intervening *p*-cyanophenylarsinic acid being hydrolysed by concentrated aqueous caustic potash.[3]

At 210° this acid loses water and passes into arsinoxybenzoic acid, $CO_2H \cdot C_6H_4 \cdot AsO_2$, yellowish-white powder, soluble in boiling alcohol and separating in ill-defined crystalline crusts. Alkali fusion of *p*-benzarsinic acid gives rise to phenol. The potassium salt yields with phosphorus pentachloride an unstable chloride, regenerating the acid on treatment with water; phosphorus trichloride furnishes benzarsenious chloride. Benzarsenious iodide is obtained from benzarsinic acid by the action of hydriodic acid.

Salts of p-*benzarsinic acid: Acid potassium* salt,

$$CO_2H \cdot C_6H_4 \cdot AsO(OH)_2, CO_2K \cdot C_6H_4AsO(OH)_2,$$

triclinic plates, produced by dissolving the foregoing oxidation product in hot water and allowing the solution to evaporate at 50–60°; loses $2H_2O$ at 160–170°. Insoluble in absolute alcohol. *Calcium* salt, $CaC_7H_5O_5As,H_2O$, nacreous leaflets, sparingly soluble in cold water. *Silver* salt, $AgCO_2 \cdot C_6H_4AsO(OAg)_2$, white precipitate, soluble in nitric acid or ammonia. *Methyl ester*, $CH_3 \cdot CO_2 \cdot C_6H_4AsO(OH)_2$, colourless, crystalline mass obtained by the action of methyl iodide at 100° on the preceding silver salt; probably the normal ester is first produced, but quickly hydrolysed by moist air to this more stable acid ester.

p-*Benzarsenious iodide* (*carboxyphenylarsenious iodide*),

$$CO_2H \cdot C_6H_4 \cdot AsI_2,$$

yellow, felted needles from chloroform, m.p. 153° (La Coste), 172° (Bertheim), soluble in alcohol or ether, prepared by heating benzarsinic acid with concentrated hydriodic acid containing

[1] Michaelis, *Annalen*, 1902, **320**, 303; *Ber.*, 1915, **48**, 870.
[2] Sieburg, *Arch. Pharm.*, 1916, **254**, 224.
[3] Bertheim, *Ber.*, 1908, **41**, 1854.

red phosphorus. Decomposed by boiling with water into hydriodic acid and benzarsenious acid. This decomposition is facilitated by the presence of sodium carbonate, when the product dissolves and is precipitated by dilute hydrochloric acid.

p-*Benzarsenious acid* (*carboxyphenylarsenious acid*),

$$CO_2H{\cdot}C_6H_4{\cdot}As(OH)_2,$$

colourless needles, changes without melting at 145–146° into its *anhydride*, $CO_2H{\cdot}C_6H_4{\cdot}AsO$. This oxide, which is ten times more toxic than the hydroxide, can be prepared by acidifying a sodium carbonate solution of *p*-benzarsenious iodide; it is only very slowly hydrated by aqueous alkalis.[1] *Calcium salt*,

$$[As(OH)_2{\cdot}C_6H_4CO_2]_2Ca,$$

the free acid is boiled with calcium carbonate, nacreous leaflets, soluble with difficulty in hot water. At 200° it loses water and forms $(AsO{\cdot}C_6H_4CO_2)Ca$. *Silver* salt, $AsO{\cdot}C_6H_4{\cdot}CO_2Ag$, white precipitate dried at 70–80°.

p-*Benzarsenious chloride*, $CO_2H{\cdot}C_6H_4{\cdot}AsCl_2$, colourless needles, m.p. 157–158°, obtained by heating an ethereal solution of the iodide at 100° with freshly precipitated dry silver chloride, or preferably by acting on benzarsinic acid with phosphorus trichloride.

$$CO_2H{\cdot}C_6H_4{\cdot}AsO(OH)_2 + 2PCl_3 = COCl{\cdot}C_6H_4AsCl_2 + POCl_3 + H_3PO_3.$$

The product is distilled at 100° to remove phosphorus trichloride; the residue extracted with benzene, water added to decompose phosphorus oxychloride, the extract dried and concentrated to the crystallising point.

Dichloro-p-*arsinobenzoyl chloride*,[2] $Cl_2As{\cdot}C_6H_4{\cdot}COCl$, mobile liquid fuming in air, b.p. 189–190°/19 mm., is obtained in practically quantitative yield by adding slowly phosphorus trichloride (280 grams) in chloroform (500 c.c.) to benzarsinic acid (250 grams) dissolved in the same solvent (600 c.c.). The reaction is completed on the water-bath, and the solution when decanted from a layer of phosphoric acid deposits on cooling crystals of benzarsenious chloride, to which are added at once 210 grams of phosphorus pentachloride. This second reaction is completed by warming, when chloroform and the volatile

[1] Sieburg, *Arch. Pharm.*, 1916, **254**, 224.

[2] Poulenc, Fr. P., 441, 215.

phosphorus chlorides are removed by distillation and the residue fractionated *in vacuo*. The trichloride is also obtainable by treating benzarsenious acid either with phosphorus tri- and penta-chlorides successively, or with the pentachloride alone; it is also produced by the interaction of benzarsenious chloride and phosphorus pentachloride. This product is soluble in chloroform, ether, or benzene, giving, with water, a white precipitate. It resembles benzoyl chloride in its behaviour towards alcohols, phenols, amino-alcohols, ammonia, and alkaloids like quinine or morphine possessing alcoholic or phenolic functions.

Di-p-*benzarsinic acid* [1] (*Di*-p-*carboxydiphenylarsinic acid*),

$$(CO_2H\cdot C_6H_4)_2\cdot AsO\cdot OH,$$

lustrous, colourless leaflets, decomposed at high temperatures without melting, is practically insoluble in water, slightly soluble in hot concentrated hydrochloric acid or alcohol. The oxidation of di-*p*-tolylarsinic acid requires four molecular proportions of alkaline permanganate and is effected in moderately concentrated solutions at 50–60°. Di-*p*-benzarsinic acid is precipitated from the colourless filtrate by adding dilute hydrochloric acid. The salts of this arsinic acid crystallise badly and vary in composition between normal and acid salts. The mixture of silver salts $(CO_2Ag\cdot C_6H_4)_2AsO\cdot OH$ and $(CO_2Ag\cdot C_6H_4)_2\cdot AsO\cdot OAg$, heated with methyl iodide at 100°, yields the *acid ester*, $HO\cdot OAs(C_6H_4\cdot CO_2\cdot CH_3)_2$, yellowish-white crusts from alcohol.

Di-p-*benzarsenious iodide*, $(CO_2H\cdot C_6H_4)_2AsI$, yellowish-white, ill defined crystals melting above 280°, prepared by heating the preceding acid with concentrated hydriodic acid and red phosphorus.

Di-p-*benzarsenious acid*, $(CO_2H\cdot C_6H_4)_2As\cdot OH$, white, crystalline precipitate, obtained by dissolving the preceding iodide in aqueous sodium carbonate and adding hydrochloric acid. *Calcium* salt, $HO\cdot As(C_6H_4\cdot CO_2)_2Ca,2H_2O$, white, pulverulent precipitate from water on addition of alcohol.

Tri-p-*benzarsinic acid*, $(HO)_2As(C_6H_4\cdot CO_2H)_3$, colourless, granular crystals from ether; loses water without melting; produced by oxidising tri-*p*-tolylarsine with alkaline permanganate. This acid is a derivative of orthoarsenic acid, $As(OH)_5$. The *potassium* salt, $O{:}As(C_6H_4\cdot CO_2K)_3$, easily soluble crystals, and the *calcium* salt, $[O{:}As(C_6H_4)CO_2]_2Ca_3,1\text{–}2H_2O$, soluble in water and precipitated by alcohol, indicate that the

[1] La Coste, *loc. cit.*, p. 23.

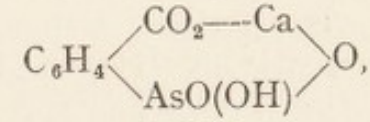
acid is tribasic; the *silver* salt gives numbers approximating to $HO{\cdot}As(OAg)(C_6H_4{\cdot}CO_2Ag)_3$.

Tri-p-*benzarsenious acid* (*Arsinotribenzoic acid*),

$$As(C_6H_4{\cdot}CO_2H)_3,$$

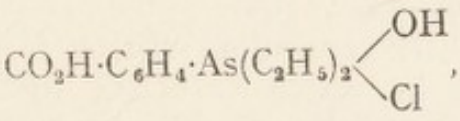
colourless needles from ether, melting with decomposition at high temperatures, is produced by heating the preceding acid with hydriodic acid and red phosphorus, purified by dissolving in aqueous sodium carbonate containing animal charcoal and reprecipitating by hydrochloric acid.

Sodium salt, $As(C_6H_4{\cdot}CO_2Na)_3,2H_2O$, only once obtained in colourless needles; *silver* salt, yellowish-white precipitate.

m-*Benzarsinic acid*,[1] $CO_2H{\cdot}C_6H_4{\cdot}AsO(OH)_2$, colourless, lustrous leaflets, easily soluble in water or alcohol; prepared by the oxidation with alkaline permanganate of *m*-tolylarsinic acid. It passes without melting into the *anhydride*, $CO_2H{\cdot}C_6H_4{\cdot}AsO_2$, yellowish-white powder. *Calcium* salt,  , soluble rectangular plates; *silver* salt, $CO_2Ag{\cdot}C_6H_4{\cdot}AsO(OAg)_2$, white precipitate.

o-*Benzarsinic acid*,[2] colourless needles from water, is obtained by adding aqueous sodium arsenite to a solution of diazotised anthranilic acid. The mixture is neutralised with alkali, warmed and evaporated to dryness. The by-products are extracted with methyl alcohol, the residue acidified, the solution filtered from impurities and evaporated to dryness. From the final residue *o*-benzarsinic acid is extracted with methyl alcohol; its *sodium* and *aniline* salts are readily soluble.

Diethylarsinoxybenzoic acid hydrochloride,



colourless crystals from alcohol-ether, m.p., 162°, very soluble in water. Prepared by shaking *p*-tolyldiethylarsine with aqueous potassium permanganate (2 parts) at first in the cold and then as the oxidation slackens at 30–40°. The *mercurichloride*, $CO_2H{\cdot}C_6H_4{\cdot}AsEt_2(OH){\cdot}Cl,HgCl_2$, colourless crystals from water, m.p. 182°, is produced by mixing aqueous solutions of its generators.

[1] Michaelis, *Annalen*, 1902, **320**, 329. [2] Bart, D.R.-P., 250, 264.

Diethylarsinosulphidobenzoic acid, $CO_2H{\cdot}C_6H_4AsS(C_2H_5)_2$, colourless, transparent needles from hot water, m.p. 184°, produced by passing hydrogen sulphide into an aqueous solution of the preceding hydrochloride.

Diethylarsinebenzoic acid, $(C_2H_5)_2As{\cdot}C_6H_4{\cdot}CO_2H$, colourless needles, m.p. 58°, easily soluble in ether, alcohol, or other volatile solvents, excepting water or light petroleum. Prepared by reducing the foregoing hydrochloride with tin and hydrochloric acid. Removal of the tin by hydrogen sulphide leads to the preceding sulphide, and accordingly the product is isolated as a yellow oil by diluting the acid solution with water. This compound combines the properties of an arsine and an acid. With the exception of the alkali derivatives, its metallic salts are insoluble in water: *barium* salt $[(C_2H_5)_2As{\cdot}C_6H_4CO_2]_2Ba$ and *lead* salt are white precipitates; *ammonium* salt, a soluble crystalline mass.

As a tertiary arsine, diethylarsinebenzoic acid combines with mercuric chloride, the halogens, and methyl iodide: the *mercurichloride*, $CO_2H{\cdot}C_6H_4{\cdot}As(C_2H_5)_2,HgCl_2$, colourless, silky crystals, m.p. 171–172°, insoluble in alcohol, sparingly soluble in water. Addition of the halogens takes place conveniently in chloroform solution, and the dihalogen compounds are obtained in a crystalline form on evaporation. Access of moisture converts them at once into hydroxy-halogen derivatives; the hydrochloride is described above. The *hydrobromide*, $CO_2H{\cdot}C_6H_4{\cdot}As(C_2H_5)_2O,HBr$, colourless needles, m.p. 144–145°; the *hydriodide*, brown leaflets from alcohol, m.p. 84°.

The *methiodide*, $CO_2H{\cdot}C_6H_4{\cdot}As(C_2H_5)_2(CH_3)I$, colourless needles from alcohol, m.p. 131°, obtained by heating the arsine with excess of methyl iodide.

Diphenylbenzarsinic acid (*Triphenylarsineoxidecarboxylic acid*)[1], $(C_6H_5)_2AsO{\cdot}C_6H_4{\cdot}CO_2H$, crystalline crusts from alcohol, m.p. 253–254°, insoluble in water or ether, dissolves readily in alcohol, alkalis, or in excess of mineral acids. Diphenyl-*p*-tolylarsine (10 grams) is oxidised with permanganate (13 grams) at 60° for four or five weeks. A more rapid oxidation leads only to tarry substances, although possibly heating with nitric acid (D = 1·2) in sealed tubes might give the product more quickly. *Silver* salt, $OAs(C_6H_5)_2{\cdot}C_6H_4{\cdot}CO_2Ag$, pulverulent precipitate affected by light; *acid barium* salt, white powder.

[1] Michaelis, *Annalen*, 1902, **321**, 192.

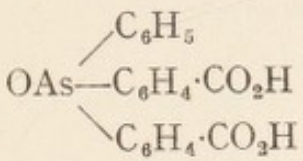
Ethyl diphenylbenzarsinate dichloride,

$$Cl_2As(C_6H_5)_2{\cdot}C_6H_4{\cdot}CO_2{\cdot}C_2H_5,$$

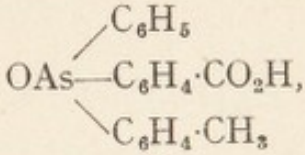
results from the passage of hydrogen chloride through an alcoholic solution of the acid ; well-defined colourless crystals, m.p. 133°.

Diphenyl sulphidobenzarsinic acid, $SAs(C_6H_5)_2{\cdot}C_6H_4{\cdot}CO_2H$, colourless crystals, m.p. 178°, produced by passing sulphuretted hydrogen through an alcoholic solution of the acid ; the product separates in oily drops on evaporating the solvent.

Phenyl di-p-*benzarsinic acid* (*Triphenylarsineoxide-di*-p-*carboxylic acid*), (I),[1]



I.



II.

colourless, crystalline powder from glacial acetic acid, not melting below 300°, is insoluble in water, ether, or chloroform, but dissolves in hot alcohol, glacial acetic acid, or aqueous alkalis.

As the starting material, phenyldi-*p*-tolylarsine is oxidisable in two stages, two products are theoretically possible, and both have been obtained. The dicarboxylic acid represents the final stage involving oxidation of both methyl groups. Alkali permanganate (22 grams) is added gradually to the finely divided tertiary arsine (10 grams) suspended in 500 c.c. of water containing caustic potash. The oxidation proceeds very slowly, and in spite of warming the mixture to 50–60° with repeated shaking it requires eight weeks for completion. The filtrate from manganese hydroxides is concentrated and the dicarboxylic acid precipitated by hydrochloric acid. The basicity of this acid is determined by the composition of its *silver* salt, $O{:}As(C_6H_5)(C_6H_4{\cdot}CO_2Ag)_2$, white, crystalline powder, and *copper* salt,

$$O{:}As(C_6H_5)(C_6H_4{\cdot}CO_2)_2Cu,H_2O,$$

blue powder, losing water at 105°. The *acid barium* salt, $[O{:}As(C_6H_5)(C_6H_4{\cdot}CO_2H)(C_6H_4CO_2)]_2Ba$, colourless crystals, is easily soluble in water.

Ethyl phenyldi-p-*benzarsinate dichloride,*

$$Cl_2As(C_6H_4)(C_6H_4{\cdot}CO_2{\cdot}C_2H_5)_2,$$

warty aggregates of needles, m.p. 176°, has a pungent not dis-

[1] Michaelis, *Annalen*, 1902, **321**, 196.

agreeable odour; it results from the action of alcoholic hydrochloric acid on the dicarboxylic acid.

Phenyl-p-*tolylbenzarsinic acid* (*Diphenyl*-p-*tolylarsineoxide-p-carboxylic acid*) (II), crystalline powder resembling the preceding dicarboxylic acid in not melting below 300°; it is, however, much more soluble in alcohol, this solvent effecting a separation of these two oxidation products. Phenyldi-*p*-tolylarsine (10 grams), oxidised as in the preceding experiment, but with only 12·6 grams of permanganate, yields both acids, but the monocarboxylic acid predominates. The *silver* salt,

$$O{:}As(C_6H_5)(C_7H_7)\cdot C_6H_4\cdot CO_2Ag,$$

needles, turning brown on exposure, indicates the basicity of the acid. *Ethyl phenyl*-p-*tolyl*-p-*benzarsinate dichloride*,

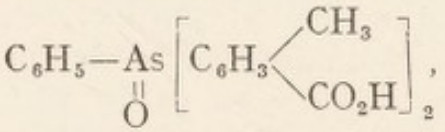
$$Cl_2As(C_6H_5)(C_7H_7)\cdot C_6H_4\cdot CO_2\cdot C_2H_5,$$

hygroscopic, m.p. 94°, results from the simultaneous action of alcohol and hydrogen chloride on the acid.

2.—*Xylene Series.*[1]

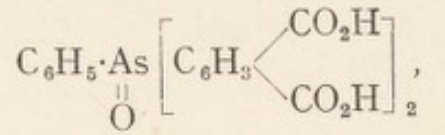
Di-*m*-xylylphenylarsine heated with the calculated amounts of nitric acid (D = 1·2) in sealed tubes at 110–170° gives rise to two acids.

Phenylditolylarsineoxidedicarboxylic acid,



purified from alcohol, crystallises as a pale yellow powder, m.p. 196°, sparingly soluble in water; dibasic.

Triphenylarsineoxidetetracarboxylic acid,



is less soluble in alcohol than the preceding acid, but dissolves moderately easily in hot water; m.p. 213°; tetrabasic.

3.—*Pseudocumene Series.*[2]

Dipseudocumylphenylarsine is not smoothly oxidised by alkaline permanganate, but on heating with increasing quantities

[1] Michaelis, *Annalen*, 1902, **321**, 226.

[2] *Ibid.*, 233.

of dilute nitric acid in sealed tubes at 110–180° it is converted progressively into di-, tetra-, and hexa-carboxylic acids, the final product being the most easily obtained.

Phenyldixylylarsineoxidedicarboxylic acid,

$$C_6H_5\cdot As(=O)[C_6H_2(CH_3)_2\cdot CO_2H]_2,$$

is obtained by heating the arsine (2 grams) with 4·7 grams of nitric acid (D = 1·2) for twelve hours at 120–180°; pale yellow powder, m.p. 199°, very soluble in alcohol, insoluble in water, ether or benzene; it is dibasic.

Phenylditolylarsineoxidetetracarboxylic acid,

$$C_6H_5\cdot As(=O)\left[C_6H_2\begin{matrix}CH_3\\(CO_2H)_2\end{matrix}\right]_2,$$

formed as in the preceding experiment, but using a double proportion of dilute nitric acid.

Triphenylarsineoxidehexacarboxylic acid,

$$C_6H_5\cdot As(=O)[C_6H_2(CO_2H)_3]_2,$$

prepared from the arsine (2 grams) with 16 grams of dilute nitric acid at 110–150° for thirteen hours (1·3 grams obtained); hard, white crystals from hot dilute alcohol, m.p. 275°. The composition of the *silver* salt and *ethyl ester* (silky needles, m.p. 193°) suggests that the acid exists in the form of its partial anhydride, $\{C_6H_5\cdot AsO[C_6H_2(CO_2H)_3][C_6H_2(CO_2H)_2\cdot CO]\}_2O$.

Reduction Products of Benzarsinic Acids.[1]

p-Benzarsinic acid, prepared by oxidising *p*-tolylarsinic acid with nitric acid (D = 1·2) at 150°, is reduced by hydriodic acid and phosphorus to *p*-benzarsenious acid. The latter arsenical compound, when reduced in strong aqueous solution with solid phosphorous acid, yields p-*arsenobenzoic acid*, an insoluble, yellow powder forming soluble alkali salts with a neutral reaction.

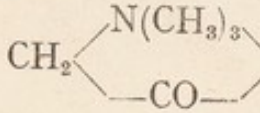
o-*Arsenobenzoic acid* is prepared by a similar series of reactions. Both arsenobenzoic acids are very toxic and cause pronounced glycosuria and albuminuria.

Phenylarsine-p-*carboxylic acid*, $CO_2H\cdot C_6H_4\cdot AsH_2$, colourless prisms, m.p. 79–80°, is prepared by reducing a methyl-alcoholic

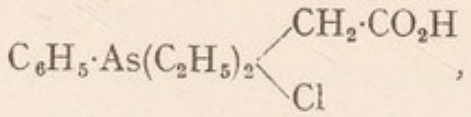
[1] Michaelis, *Ber.*, 1915, **48**, 870.

solution of *p*-benzarsinic acid with hydrochloric acid (D = 1·19) and zinc dust, the product being removed by distillation in steam. It is very sensitive to atmospheric oxygen, becoming oxidised to *p*-arsenobenzoic acid.[1]

Section X.—Betaines of Aromatic Arsenicals.

This section deals with a group of aromatic compounds containing a quinquevalent arsenic atom involved in a cyclic complex analogous to that obtaining in ordinary betaine,  , the naturally occurring trimethylglycine.

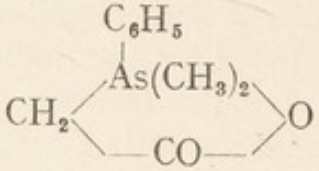
Phenyldiethylarsenibetaine hydrochloride,[2]



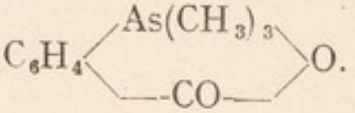
colourless needles from alcohol-ether, m.p. 135°, is obtained by heating for several hours at 100° equal weights of phenyldiethylarsine and chloroacetic acid; *platinichloride*,

$$[C_6H_5\cdot As(C_2H_5)_2(CH_2\cdot CO_2H)]_2PtCl_6,$$

red, lustrous crystals, m.p. 161°. The free *betaine* is isolated by passing carbon dioxide into an alcoholic solution of the hydrochloride and caustic potash. The filtrate from potassium chloride and carbonate contains the betaine, (I). The betaine *ethyl ester*, $C_6H_5As(C_2H_5)_2(CH_2\cdot CO_2\cdot C_2H_5)Cl$, an oil prepared by heating together phenyldiethylarsine and ethyl chloroacetate at 100°, yields a crystalline *platinichloride* (m.p. 125°) and *picrate* (m.p. 90°).



I.



II.

Trimethylarsenibenzobetaine (II). The *hydrochloride*

$$CO_2H\cdot C_6H_4\cdot As(CH_3)_3Cl$$

of this betaine, clusters of colourless needles from water, is produced by oxidising *p*-tolyltrimethylarsonium chloride with

[1] Sieburg, *Arch. Pharm.*, 1916, **254**, 224.
[2] Michaelis, *Annalen*, 1902, **320**, 297.

alkaline permanganate at 50° for ten days. At 400° it decomposes into phenyltrimethylarsonium chloride (*platinichloride*, m.p. 219°) and carbon dioxide. The free *betaine* obtained from its hydrochloride by sodium carbonate crystallises from dilute alcohol in thin plates containing $2\frac{1}{2}H_2O$; this water is evolved at 100°. Prolonged boiling with alcoholic potash decomposes the betaine into trimethylarsineoxide and benzoic acid.

With acids the betaine furnishes well-defined salts:—

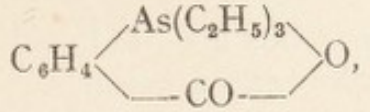
Hydrobromide, $CO_2H{\cdot}C_6H_4{\cdot}As(CH_3)_3Br$, needles decomposed at 270°.

Nitrate, $CO_2H{\cdot}C_6H_4{\cdot}As(CH_3)_3{\cdot}NO_3$, leaflets, m.p. 230°.

Platinichloride, $\overline{B}_2PtCl_6$, pale yellow needles, m.p. 255°.

Aurichloride, $\overline{B}AuCl_4$, golden-yellow needles, m.p. 198°.

Acid sulphate, colourless needles.

Triethylarsenibenzobetaine,  , extremely hygroscopic, tabular crystals with bitter taste, forms no salts with alkalis and, unlike trimethylphosphoribenzobetaine, is very resistant to potassium hydroxide, and is completely decomposed only after twenty hours' boiling with alcoholic potash, yielding trimethylarsineoxide and potassium benzoate. It is prepared by evaporating to dryness a solution of its hydrochloride and sodium carbonate, the residue being extracted with alcohol.

The *hydrochloride* of this substance, the first arsenical betaine to be prepared, is obtained by oxidising *p*-tolyltriethylarsonium chloride with the calculated amount of permanganate in alkaline solution at 50°, the reaction requiring eight to ten days. The filtrate from manganese hydroxides is acidified, evaporated to dryness, and extracted with absolute alcohol, when the salt separates from alcohol or water in very hygroscopic, acicular crystals:—

Platinichloride, $\overline{B}_2PtCl_6$, light yellow leaflets, m.p. 225°.

Aurichloride, $\overline{B}AuCl_4$, golden-yellow needles, m.p. 165°.

Picrate, $(NO_2)_3C_6H_2{\cdot}OH,\overline{B}$, golden-yellow plates, m.p. 155°.

Triphenylarsenibetaine.[1]—The *chloride* of this arsonium base is obtained in quantitative yield by heating equal parts of triphenylarsine and chloroacetic acid at 100° until a homogeneous, viscid mass is obtained, which is rendered solid by

[1] Michaelis, *Annalen*, 1902, **321**, 174.

stirring with ether and crystallised from a mixture of this solvent and alcohol; colourless needles, m.p. 145°; *platinichloride*, light red powder, m.p. 194°.

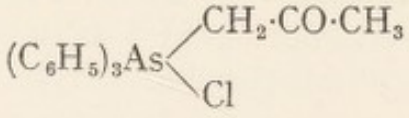
The free betaine, prepared by treating the chloride with alcoholic potash, is isolated, after removing the excess of alkali by carbon dioxide, by concentrating the solution over sulphuric acid. It crystallises from alcohol-ether in colourless needles, m.p. 125°. Its solutions are neutral. At 100° this hydrated betaine loses water and passes into the *anhydride*,

Triphenylarseniketobetaines.[1]

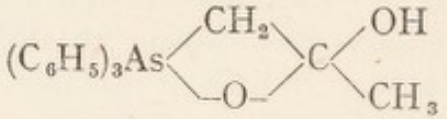
These compounds are produced by condensing triphenylarsine with monohalogenated ketones.

Triphenylacetonylarsonium Chloride (I).—This salt is prepared by heating triphenylarsine (6 grams) with chloroacetone (4 grams) at 120°, and crystallised from alcohol-ether, rectangular crystals very soluble in water or alcohol, m.p. 172°.

The free *triphenylmethylarseniketobetaine* (II)

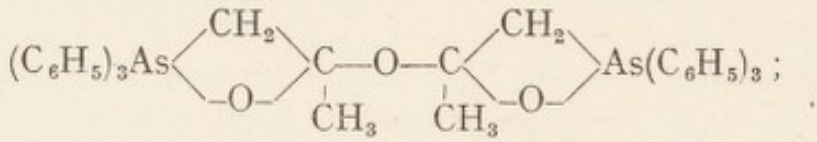


I.



II.

obtained from the chloride by means of aqueous alkali hydroxide or carbonate, separates in nacreous rhombic plates, insoluble in cold water, but dissolving readily in hot water, alcohol, or benzene and sparingly in ether. It melts at 123°, becomes solid on further heating, and melts again at 194°; these changes represent the formation of the anhydride,

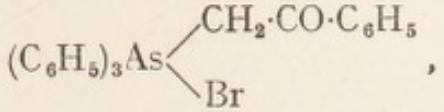


this product crystallises unchanged from benzene, but in hydrated solvents it reverts to the ketobetaine (m.p. 123°).

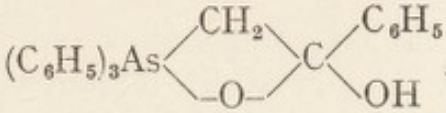
Triphenylacetonylarsonium bromide, $(CH_3\cdot CO\cdot CH_2)\cdot As(C_6H_5)_3Br$, colourless crystals, m.p. 165°, results from the addition of hydrobromic acid to alcoholic solutions of the ketobetaine, precipitated by ether; the *iodide*, m.p. 161°.

[1] Michaelis, *Annalen*, 1902, **321**, 176

Triphenylphenacylarsonium bromide,

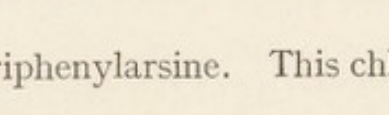


silky, felted needles from water, m.p. 178°, produced by heating equal parts of triphenylarsine and bromoacetophenone on the water-bath. The free *tetraphenylarseniketobetaine,*

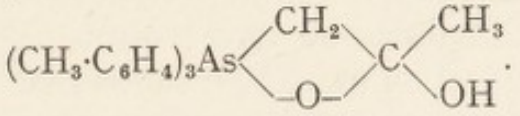


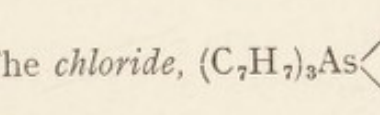
obtained by decomposing the preceding salt with sodium hydroxide or carbonate, crystallises from dilute alcohol in colourless needles, m.p. 176°, characterised by the following salts: *chloride,* m.p. 166°; *platinichloride,* m.p. 191°; *iodide,* m.p. 157°; *nitrate,* colourless needles, m.p. 184°, insoluble in cold water, soluble in alcohol.

Tri-p-*tolylarseniketobetaines.*[1]

Tri-p-*tolylmethylarsenibetaine* is obtained in the form of its *chloride* by heating tri-*p*-tolylarsine on the water-bath with chloroacetic acid; the addition occurs much less readily than with triphenylarsine. This chloride,  , forms a colourless, crystalline mass, m.p. 146°; *platinichloride,* yellow precipitate, m.p. 206°.

Tri-p-*tolylmethylarseniketobetaine,*

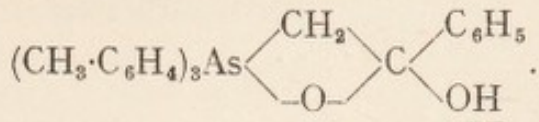


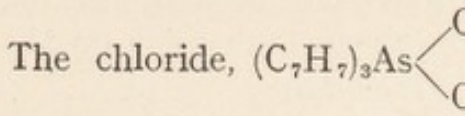
The *chloride,*  , of this ketobetaine is prepared by heating molecular proportions of tri-*p*-tolylarsine and chloroacetone in sealed tubes at 85°, it crystallises from alcohol-ether, m.p. 170°; *platinichloride,* sparingly soluble yellow leaflets, m.p. 210°; *bromide,* needles, m.p. 159°; *iodide,* m.p. 144°.

The free ketobetaine, obtained by the action of alkali on the chloride, is insoluble in water and dissolves in ether, benzene, or alcohol, separating from the last in lustrous needles, m.p. 113°.

[1] Michaelis, *Annalen,* 1902, **321**, 208.

Tri-p-*tolylphenylarseniketobetaine*,



The chloride,  , of this ketobetaine is produced by heating tri-*p*-tolylarsine and chloroacetophenone at 85°, the product being crystallised from alcohol-ether, colourless needles, m.p. 159°; *platinichloride*, yellowish-red needles, m.p. 205°; *bromide*, m.p. 182°; *iodide*, m.p. 148°. The free ketobetaine crystallises from alcohol on adding water in tufts of lustrous needles, m.p. 160°.

Section XI.—Nitro-derivatives of Aromatic Arsenicals.

A separate section is devoted to the nitration products of aromatic arsenical compounds because of their increased importance as starting points in the production of amino-arylarsenicals having useful germicidal properties.

In the earliest experiments made on these derivatives by Michaelis and others the influence of the arsenical group on orientation was not elucidated. But by means of the Béchamp reaction applied to *p*-nitroaniline a nitro-amino-arsinic acid of known constitution has been obtained. Elimination of the amino-group by the agency of the diazo-reaction leaves *m*-nitrophenylarsinic acid, which turns out to be identical with Michaelis's nitro-compound produced by direct nitration of phenylarsinic acid. This identification (page 144) shows that the arsinic group determines the entry of the nitro-group into the meta-position. The stibinic group has been shown to induce the same orientation, and this substitution probably holds for the phosphinic group. These results show that Crum Brown and Gibson's rule for substitution holds not only for the acidic groups NO_2, CO_2H, SO_3H, but also for the univalent acidic groups $-PO_3H_2$, $-AsO_3H_2$, $-SbO_3H_2$. It also holds, in all probability for the bivalent groups

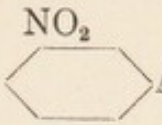
$$>PO\cdot OH, \quad >AsO\cdot OH; \quad >SbO\cdot OH,$$

and for the tervalent groups

$$-P(OH)_2 \quad -As(OH)_2 \text{ and } \quad -Sb(OH)_2,$$

inasmuch as the correctness of this generalisation has been demonstrated in the case of the three antimonial groups (p. 296)

m-*Nitrophenylarsinic acid* [1] (*v.* page 157),



rhombic leaflets from water, no definite melting point ; the acid evolves water on heating and then intumesces, leaving a carbonaceous residue. Easily soluble in hot water at 18°, one part requires 50 parts of water for complete solution. It dissolves in alcohol, only sparingly in benzene or chloroform, and is insoluble in ether or light petroleum. Prepared by adding phenylarsinic acid (10 grams) to absolute nitric acid [2] (100 per cent. HNO_3) and distilling the mixture until two-thirds of the acid has passed over ; the residue is poured into 75 c.c. of water, when nitrophenylarsinic acid separates in small leaflets. This nitration may also be effected with nitric acid dissolved in concentrated sulphuric acid. The acid mother liquors from the first crop of nitrophenylarsinic acid contain a mixture of this acid with the nitrate $C_6H_5 \cdot As(OH)_3 \cdot O \cdot NO_2$; this product is worked up with subsequent nitrations. Aqueous solutions of the nitro-acid give white and blue precipitates with lead acetate and copper sulphate respectively, especially on warming. With silver nitrate and mercuric chloride white precipitates only in ammoniacal solutions ; soluble barium, calcium, and magnesium salts give similar results on warming.

The alkali salts of the acid are not crystallisable. *Calcium* m-*nitrophenylarsinate*, $NO_2 \cdot C_6H_4 \cdot AsO_3Ca, H_2O$, produced on boiling calcium carbonate with an aqueous solution of the acid ; lustrous leaflets still retaining the water of crystallisation at 110°. It probably has the constitution $NO_2 \cdot C_6H_4 \cdot AsO(OH) \cdot OCa \cdot OH$.

Acid *barium* m-*nitrophenylarsinate*, $[NO_2 \cdot C_6H_4 \cdot AsO(OH) \cdot O]_2Ba$, crystalline crusts obtained by dissolving the nitro-acid in excess of baryta water, passing in carbon dioxide and evaporating the filtered solution.

Copper m-*nitrophenylarsinate*, $NO_2 \cdot C_6H_4 \cdot AsO_3Cu, H_2O$, probably $NO_2 \cdot C_6H_4 \cdot AsO(OH) \cdot OCu \cdot OH$, since it does not lose water on heating ; blue, crystalline precipitate produced by boiling together in aqueous solution copper sulphate and nitrophenylarsinic acid.

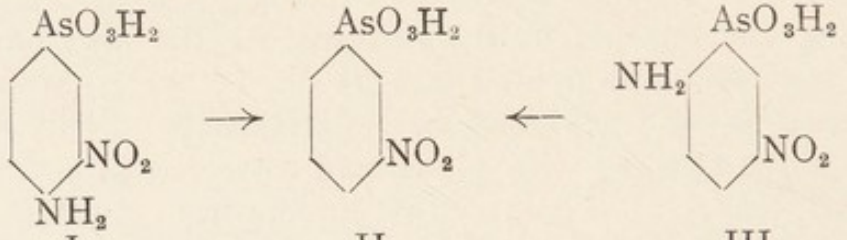
[1] Michaelis and Loesner, *Ber.*, 1894, **27**, 265.

[2] Valentiner and Schwarz, D.R.-P., 63207.

Silver m-*nitrophenylarsinate*, $NO_2 \cdot C_6H_4AsO(OAg)_2$, white, amorphous powder, soluble in ammonia or nitric acid.

The reduction of nitrophenylarsinic acid with tin and hydrochloric acid does not lead to definite products ; stannous chloride yielded on one occasion a small amount of crystalline material, apparently $NH_2 \cdot C_6H_4AsO(OH)_2, HCl, SnCl_2, H_2O$.

Phosphorous acid reduces only the arsinic group, giving dinitroarsenobenzene. Aqueous hydrogen sulphide furnishes nitrophenylarsinic sesquisulphide, whereas ammonium sulphide followed by dilute acid leads to aminophenylarsenious sulphide. The constitution of this nitrophenylarsinic acid (II) has been substantiated by producing it synthetically from two isomeric nitro-arsanilic acids (I) and (III).[1]



I. II. III.

An isomeride of this nitrophenylarsinic acid,[2] insoluble in water, is obtained on heating in sealed tubes for three hours at 155–165° one part of phenylarsinic acid, five parts of concentrated nitric acid, and ten parts of concentrated sulphuric acid. The mixture of acids is extracted with boiling water, when the isomeric acid remains undissolved ; it is produced only in small amount and intumesces on heating without melting.

The production of *m*-nitrophenylarsinic acid from 3-nitro-4-aminophenylarsinic acid is described under *m*-aminophenylarsinic acid. The nitro-acid is also obtained from 5-nitro-2-aminophenylarsinic acid. In this case the 2-amino-group is diazotised by adding 2*N*-sulphuric acid to an aqueous solution of sodium 5-nitro-2-aminophenylarsinate and nitrite. An equal volume of alcohol is added to the diazo-solution and the elimination of the diazo-group is facilitated by the addition of 9 per cent. of copper-bronze The filtered solution is concentrated to a small bulk and the mineral acid neutralised with sodium hydroxide when *m*-nitrophenylarsinic acid separates.[3]

[1] Bertheim and Benda, *Ber.*, 1911, **44**, 3298.
[2] Michaelis, *Annalen*, 1902, **320**, 294.
[3] Bertheim and Benda, *Ber.*, 1911, **44**, 3299.

o-*Nitrophenylarsinic acid*,[1] $NO_2 \cdot C_6H_4 \cdot AsO(OH)_2$, white needles from alcohol or water, intumesces without melting.

Sodium *o*-nitrobenzene*iso*diazo-oxide (1·8 parts) and sodium arsenite (2 parts) are heated in 4 parts of water until nitrogen is no longer evolved. The solution is evaporated to dryness and the product extracted from the residue by alcohol.

p-*Nitrophenylarsinic acid*,[1] $NO_2 \cdot C_6H_4 \cdot AsO(OH)_2$.—An acid or alkaline solution of arsenious acid is added to a solution of *p*-nitrobenzenediazonium chloride, the mixture is warmed, and after evolution of nitrogen has ceased, the filtered solution is evaporated to dryness and the product extracted with alcohol. The yield is better when alkaline arsenite is employed.

Di-p-*nitrodiphenylarsinic acid*, $(NO_2 \cdot C_6H_4)_2AsO \cdot OH$, whitish-yellow precipitate, sparingly soluble in water or alcohol, and giving yellow alkali salts, is prepared by adding an alkaline solution of *p*-nitrophenylarsenious acid to a solution of *p*-nitrodiazonium chloride. Nitrogen is evolved, and acids precipitate the product from the filtered solution. The p-*nitrophenylarsenious acid* required in this condensation is prepared by reducing the preceding compound with sulphurous acid, using hydriodic acid as catalyst. It is an insoluble powder dissolving in caustic soda solution.

m-*Nitrophenylarsenious acid*,[2] $NO_2 \cdot C_6H_4As(OH)_2$, white flocculæ, darkening on heating, and intumescing without melting. Prepared by dissolving nitrophenylarsenious chloride or bromide in aqueous alkalis and then acidifying either by passing in carbon dioxide or preferably by adding hydrochloric acid, taking care to keep the solution cool. It is of interest to compare the composition of the product with that of the substance obtained by acting on phenylarsenious chloride with aqueous alkali. In the latter case phenylarsenious oxide is produced, but no arsenious acid derivative. The presence of the acidic nitro-group in the aromatic nucleus increases the tendency towards the retention of hydroxyl groups and the formation of an aromatic arsenious oxide (compare Benzarsenious acid, p. 131).

Nitrophenylarsenious acid is easily soluble in caustic alkalis, and sparingly though appreciably so in carbonated alkalis ; it is insoluble in water, but soluble in alcohol.

m-*Dinitroarsenobenzene*,[3] $NO_2 \cdot C_6H_4 \cdot As{:}As \cdot C_6H_4 \cdot NO_2$, heavy

[1] H. Bart, D.R.-P., 250264.

[2] Michaelis and Loesner, *Ber.*, 1894, **27**, 269.

[3] *Ibid.*, 268.

yellow powder, intumesces with melting ; insoluble in all volatile organic solvents. Oxidation with nitric acid regenerates nitrophenylarsinic acid. Prepared by heating in a sealed tube for twelve hours at 115° 10 grams of the foregoing acid with water and 40 grams of crystallised phosphorous acid. Combines additively with the halogens and sulphur.

m-*Nitrophenylarsenious chloride*,[1] $NO_2 \cdot C_6H_4 \cdot AsCl_2$, colourless crystals from chloroform, m.p. 46–47°, is not affected by water.

Chlorine passed into a suspension of dinitroarsenobenzene in chloroform leads to complete solution, and, on evaporating the solvent, long needles of nitrophenylarsenic chloride separate, which are rapidly converted by moist air into nitrophenylarsinic acid. When the chloroform solution of nitrophenylarsinic chloride is treated with excess of dinitroarsenobenzene, the oily residue left after removing the solvent by distillation yields the crystalline nitrophenylarsenious chloride,

$$(NO_2 \cdot C_6H_4 \cdot As)_2 + 2NO_2 \cdot C_6H_4 \cdot AsCl_4 = 4NO_2 \cdot C_6H_4 \cdot AsCl_2.$$

m-*Nitrophenylarsenious bromide*, $NO_2 \cdot C_6H_4 \cdot AsBr_2$, white crystals easily soluble in chloroform, sparingly so in petroleum, obtained by adding bromine to dinitroarsenobenzene suspended in light petroleum (b.p. 50°) ; the solution is filtered and concentrated under reduced pressure. The corresponding iodide has not been obtained crystalline.

m-*Nitrophenylarsenic sulphide*,[2] $NO_2 \cdot C_6H_4 \cdot AsS_2$, white powder, melting at 80° (approx.) and intumescing at higher temperatures, is insoluble in water, ether, or chloroform, sparingly soluble in alcohol or benzene, dissolving readily in ammonia or aqueous alkalis. Dinitroarsenobenzene is suspended in water and boiled for one hour with flowers of sulphur ; the mixture is then rendered ammoniacal, filtered and acidified when the sulphide is precipitated.

m-*Nitrophenylarsenic sesquisulphide*,

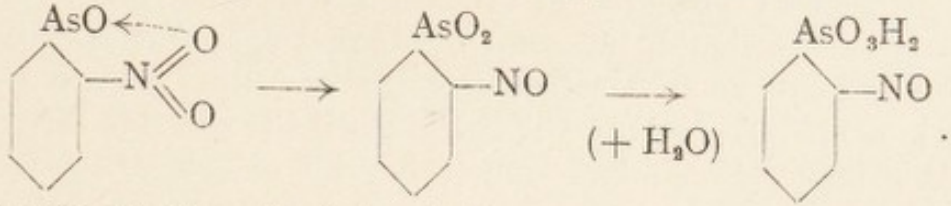
$$NO_2 \cdot C_6H_4 - AsS - AsS \cdot C_6H_4 \cdot NO_2,$$
$$\backslash S /$$

yellow leaflets from benzene-alcohol, melting at 119°, and under boiling water, is prepared by passing hydrogen sulphide repeatedly into a solution of nitrophenylarsinic acid (10 grams) in 200 c.c. of water at 50–60° and allowing the mixture to remain for twelve hours, after which ammonia is added to dissolve out the

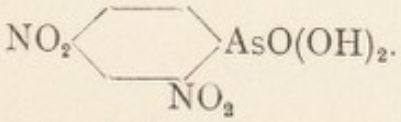
[1] Michaelis and Loesner, *Ber.*, 1894, **27**, 269. [2] *Ibid.*, 270.

sesquisulphide from the precipitated sulphur, the product being precipitated by mineral acid.

o-Nitrophenylarsenious chloride, produced by dissolving *o*-nitrophenylarsenious oxide in wet ether and adding alcoholic hydrochloric acid, forms a faintly yellow solution which on exposure to strong sunlight for several weeks gives a yellowish-brown, crystalline deposit which has the properties of an arsinic acid, but differs from 2-nitrophenylarsinic acid. It is regarded by Karrer as being a highly polymerised form of the nitroso-compound produced by the migration of oxygen from the nitro-group to the arsenious radical in the presence of water.[1]



2 : 4-*Dinitrophenylarsinic acid*,[2]



The introduction of arsinic groups into aromatic nuclei by Bart's process through the diazo-reaction takes place usually in alkaline or neutral solution. With diazotised 2 : 4-dinitro-aniline, however, this synthesis does not occur under these conditions, but on the contrary a good yield of 2 : 4-dinitrophenyl-arsinic acid is obtained when the reaction is carried out in the presence of excess of acid. Dinitroaniline (18·5 grams) is added to a mixture of concentrated sulphuric acid (30 grams) and 23 grams of vitriol containing 59 per cent. of nitrosylsulphate cooled below 25°. The brown solution is poured on to ice (250 grams) and treated with a solution of sodium arsenite (25 grams) in 50 c.c. of water. The evolution of diazo-nitrogen occurs even in the cold and may be completed by heating with steam. So soon as the diazo-reaction has practically disappeared the hot solution is treated with animal charcoal and filtered; 2 : 4-dinitrophenylarsinic acid separates in felted needles (m.p. 199–200°). The product is moderately soluble in cold water and dissolves readily in aqueous alkalis or sodium acetate, glacial acetic acid, or the alcohols. The aqueous solution turns Congo red paper violet.[3]

[1] Karrer, *Ber.*, 1914, **47**, 1783. [2] M. L. and B., D.R.-P., 266944.
[3] M. L. and B., A.P., 1075537, 1075538. Benda, Eng. P., 24667/1912.

Dinitrodiphenylarsinic acid,[1] $(NO_2 \cdot C_6H_4)_2AsO \cdot OH$, aggregates of yellowish-white, monoclinic prisms from glacial acetic acid, m.p. 256° without losing water. Only sparingly soluble in hot water or alcohol, dissolving more readily in hot glacial acetic acid.

The salts with the alkali metals and those of the alkaline earths are soluble. *Barium* salt, $[(NO_2 \cdot C_6H_4)_2 \cdot AsO_2]_2Ba$, yellowish-white scales. *Silver* salt, $(NO_2 \cdot C_6H_4)_2AsO_2Ag$, white precipitate. *Copper* salt has the composition

$$(NO_2 \cdot C_6H_4)_2AsO \cdot OCu \cdot OH.$$

Tetranitrotetraphenyldiarsine, $(NO_2 \cdot C_6H_4)_2As \cdot As(C_6H_4 \cdot NO_2)_2$, glistening leaflets insoluble in all ordinary solvents, m.p. 200° to a pale yellow liquid, prepared by adding a moderate excess of phosphorous acid to a solution of the preceding acid in glacial acetic acid. The mixture is boiled until the diarsine separates. This compound combines additively with chlorine, bromine, or sulphur.

Dinitrodiphenylarsenious sulphide, $[(NO_2 \cdot C_6H_4)_2As]_2S$, warty aggregates of yellow needles, m.p. 156°, produced by warming the preceding compound (in slight excess) with sulphur dissolved in benzene. Excess of sulphur leads to *tetranitrotetraphenyldiarsenious sulphide*, $\begin{matrix}(NO_2 \cdot C_6H_4)_2 \\ (NO_2 \cdot C_6H_4)_2\end{matrix}\!\!\gg\!As_2S_3$, yellow powder, m.p. 69°.

Dinitrodiphenylarsenious chloride, $(NO_2 \cdot C_6H_4)_2AsCl$, yellowish-white needles from benzene-petroleum, m.p. 112°, obtained by passing chlorine into a slight excess of tetranitrotetraphenyldiarsine suspended in benzene. Dinitrodiphenylarsenic chloride is formed as an intermediate product, but, being unstable, it is reduced by the excess of diarsine to the required monochloride. The *bromide* consists of colourless leaflets, m.p. 93°.

Tri-p-*nitrotriphenylarsinic acid*,

This compound is prepared by an extension of Bart's diazo-reaction from *di*-p-*nitrodiphenylarsenious acid*,

$$(NO_2 \cdot C_6H_4)_2AsO(OH)_2,$$

white, felted needles, m.p. 149°, salts unstable; this intermediate product is produced by the mild reduction of di-*p*-nitrodiphenylarsinic acid with hydriodic acid in glacial acetic acid.

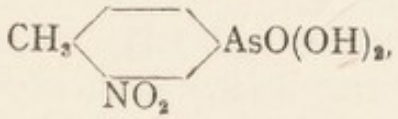
[1] Michaelis, *Annalen*, 1902, **321**, 151.

Sodium *p*-nitrobenzene*iso*diazo-oxide in aqueous solution is added to a solution of sodium di-*p*-nitrodiphenylarsenite the mixture being slowly heated to 75–80°; nitrogen is evolved, and after filtration a brown precipitate is obtained on adding hydrochloric acid. This product is boiled in water with barium carbonate to remove unchanged di-*p*-nitrodiphenylarsenious acid, which becomes soluble. The residue, freed from excess of barium carbonate by hydrochloric acid, is crystallised from glacial acetic acid and alcohol. It is obtained in brown crystals, insoluble in aqueous sodium carbonate, but dissolving in caustic soda to brownish-yellow solutions.[1]

Tri-3-nitrotriphenylarsine oxide,[2] $(NO_2 \cdot C_6H_4)_3AsO$, colourless or slightly yellow crystals, m.p. 254°, intumescing on heating; insoluble in alcohol or ether, easily soluble in glacial acetic acid. Prepared by dissolving triphenylarsine (20 grams) in a warm mixture of fuming nitric acid (40 grams) and concentrated sulphuric acid (100 grams); the product is poured on to ice, extracted with hot alcohol to remove a red, tarry impurity, dissolved in glacial acetic acid and precipitated with alcohol. The reddish product stated by Philips to be an isomeride has not been analysed or identified.

Tri-3-nitrotriphenylarsine,[3] $(NO_2 \cdot C_6H_4)_3As$, yellow, crystalline powder, m.p. 250°, produced by warming trinitrotriphenylarsine oxide in alcohol with crystallised phosphorous acid, is twice as soluble in alcohol as the original oxide. Addition of bromine to a chloroform solution of this arsine gives rise to *trinitrotriphenylarsinedibromide*, reddish-yellow precipitate, m.p. 204°. Addition of chlorine leads to *trinitrotrichlorophenylarsinedichloride*, colourless crystals, m.p. 228°; this product treated with concentrated potassium hydroxide gives the *oxide*, colourless, crystalline mass, m.p. 257°, which by reduction with phosphorous acid furnishes *trinitrotrichlorotriphenylarsine*, white powder, m.p. 252°, moderately soluble in alcohol, chloroform, or glacial acetic acid, characterised by its yellow *dibromide*, m.p. 209°.

3-Nitro-4-tolylarsinic acid,[4]



crystallises from hot water in long, silky, acicular prisms of the

[1] Bart, D.R.-P., 254345.
[2] Philips, *Ber.*, 1881, **19**, 1033. Michaelis, *Annalen*, 1902, **321**, 180
[3] Michaelis, *Annalen*, 1902, **321**, 180. [4] *Ibid.*, **320**, 321.

rhombic system ; it remains unchanged at 300°, intumescing at higher temperatures ; prepared by adding gradually *p*-tolylarsinic acid (5 parts) to a mixture of concentrated sulphuric acid (25 parts) and fuming nitric acid (20 parts) at summer temperature. The mixture is stirred vigorously to prevent local heating and then poured into 6 volumes of cold water, when the nitro-derivative separates slowly in lustrous needles.

Salts : *Alkali* salts not crystallisable ; *silver* salt,

$$NO_2 \cdot C_7H_6 \cdot AsO(OAg)_2,$$

white powder from ammoniacal solution of the acid ; *acid barium* salt, $[NO_2 \cdot C_7H_6 \cdot AsO(OH) \cdot O]_2Ba$, by dissolving the acid in baryta water, precipitating excess of alkali with carbon dioxide and concentrating the filtrate. The *calcium*, *copper*, and *cobalt* salts have the general composition

$$NO_2 \cdot C_7H_6 \cdot AsO_3R,H_2O ;$$

the water of hydration is so tenaciously held that it is not eliminated without partial decomposition of the compound, so that Michaelis suggests the constitution

$$NO_2 \cdot C_7H_6 \cdot AsO(OH) \cdot O \cdot R \cdot OH.$$

Reduction Products of 3-Nitro-4-tolylarsinic Acid.

3 : 3′-*Dinitroarseno*-p-*toluene*, $NO_2 \cdot C_7H_8 \cdot As{:}As \cdot C_7H_6 \cdot NO_2$, yellow powder, m.p. 165° ; insoluble in all solvents, is prepared by the action of phosphorous acid on the preceding nitrotolylarsinic acid. When suspended in chloroform it absorbs bromine (2 mols.), forming 3-*nitro*-4-*tolylarsenious dibromide*, $NO_2 \cdot C_7H_6 \cdot AsBr_2$, lustrous, brownish-white scales from chloroform, m.p. 260°.

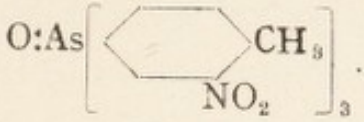
3-*Nitro*-4-*tolylarsenious sulphide*, $NO_2 \cdot C_7H_6 \cdot AsS$, yellow needles, from benzene-alcohol, m.p. 141–142° ; is obtained by passing hydrogen sulphide into an aqueous solution of 3-nitro-4-tolylarsinic acid at 70°. Sulphur and the sulphide are precipitated. The latter is extracted with ammonia and reprecipitated from the filtrate with hydrochloric acid.

3-*Amino*-4-*tolylthioarsinic acid*, $NH_2 \cdot C_7H_6 \cdot S(SH)_2$, is produced by saturating with hydrogen sulphide an ammoniacal solution of 3-nitro-4-tolylarsinic acid, evaporating to dryness, and extracting with very dilute hydrochloric acid. This compound is then precipitated in the form of its sparingly soluble *sulphate* by the addition of dilute sulphuric acid to the acid extract. This salt

decomposes at 155° ; it is insoluble in the ordinary solvents, but is dissolved by dilute alkalis.

3-*Nitrobenzarsinic acid*, $CO_2H{\cdot}C_6H_3(NO_2){\cdot}AsO(OH)_2$, colourless needles, very soluble in water, less so in alcohol, and insoluble in ether or chloroform, m.p. above 300°, is prepared by the oxidation of 3-nitro-4-tolylarsinic acid with alkaline permanganate at 60–70°. The acidified filtrate from manganese hydroxides is evaporated to dryness and extracted with alcohol. The alcoholic extract furnishes the acid, which is purified further by adding strong hydrochloric acid to its concentrated aqueous solution, when it slowly crystallises.

Tri-3-nitrotri-4-tolylarsine oxide,[2]



—Tri-*p*-tolylarsine (10 grams) is added to a cooled mixture of fuming nitric acid (20 c.c.) and concentrated sulphuric acid (40 c.c.) ; the liquid is added to a large volume of cold water, when the nitro-compound separates as a white, flocculent precipitate (12 grams), which is dissolved in alcohol, treated with animal charcoal, and allowed to crystallise from the filtered solution ; yellow, highly refractive monoclinic crystals, m.p. 212°, easily soluble in glacial acetic acid or hot alcohol, sparingly so in cold spirit, insoluble in ether. When the foregoing nitration is performed on tri-*p*-tolylarsine (5 grams) with the warm acids in the foregoing proportions oxidation takes place simultaneously and *trinitrotri*-p-*tolylarsine dinitrate*, $[NO_2{\cdot}C_6H_3(CH_3)]_3As(NO_3)_2$, is obtained, colourless crystals from glacial acetic acid, m.p. 265°, converted by caustic potash into the foregoing oxide (m.p. 212°).

Trinitrotri-p-*tolylarsine*, $[NO_2{\cdot}C_6H_3(CH_3)]_3As$, colourless needles from hot alcohol, m.p. 201°, obtained from the trinitrated oxide and phosphorous acid (large excess) in alcoholic solution. Chlorine passed into its chloroform solution gives rise to *trinitrotrichlorotri*-p-*tolylarsine dichloride*, $[NO_2{\cdot}C_6H_2Cl(CH_3)]_3AsCl_2$, m.p. 170°, By reduction with tin and hydrochloric acid this derivative loses its chlorine and yields triaminotri-*p*-tolylarsine (*v.* p. 223).

Nitro-m-*xylylarsinic acid*,[2] $NO_2{\cdot}C_8H_8{\cdot}AsO(OH)_2$, colourless needles from water, m.p. 207°, sparingly soluble in alcohol or

[1] Michaelis, *Annalen*, 1902, **321**, 211. [2] *Ibid.*, **320**, 334.

ether. Prepared by dissolving *m*-xylylarsinic acid in cold fuming nitric acid. *Silver* salt, $NO_2 \cdot C_8H_8 \cdot AsO(OAg)_2$.

Nitro-p-*xylylarsinic acid*, white needles from alcohol, m.p. 205°, prepared by adding *p*-xylylarsinic acid to a large excess (8–9 parts) of 100 per cent. nitric acid. By heating this acid in sealed tubes with phosphorous acid *nitroarseno*-p-*xylene* is obtained, as a yellow powder sintering at 165°.

CHAPTER IV

Atoxyl

The Béchamp Reaction and its Extensions

It was pointed out in the introduction to the section on aromatic derivatives of arsenic that the earliest observation on this group of substances is due to Béchamp (*loc. cit.*), who during the years 1860–63 isolated a colourless condensation product of the interaction of aniline and arsenic acid. He noted that this substance had the functions of a monobasic acid, giving rise to well-defined metallic salts, and was not hydrolysed by aqueous caustic potash. Nevertheless he concluded that the compound was an anilide or, on account of its acid functions, " phenarsényl-ammonium." In these considerations Béchamp was hindered rather than assisted by the theoretical conceptions current among French chemists of that time. The obscurity in which their theories of molecular configuration involved these organic substances may be shown by giving the formulæ ascribed by Béchamp to the compound and its salts.[1]

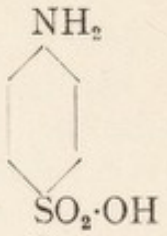
Old Notation.	*Modern Notation.*
p-Arsanilic acid—	
$[(C_{12}H_5H_2AsO_4)N]O,HO.$	$[(C_6H_5H_2AsO_2)N]_2O,H_2O.$
Sodium salt (atoxyl)—	
$[(C_{12}H_5H_2AsO_4)N]O,NaO,10HO.$	$[(C_6H_5H_2AsO_2)N]_2O,Na_2O,10H_2O.$
Silver salt—	
$[(C_{12}H_5H_2AsO_4)N]O,AgO.$	$[(C_6H_5H_2AsO_2)N]_2O,Ag_2O.$

Not only was Béchamp prevented from arriving at a correct interpretation of his experimental results, but other contemporaneous chemists failed to recognise that his arsenical compound of aniline was in reality a true organo-arsenic derivative. It is probably for this reason that in giving a *résumé* of earlier

[1] Béchamp, *Bull. Soc. chim.*, 1863, **5**, 518.

researches on organo-arsenical compounds La Coste and Michaelis, in their first detailed memoir (1880, *loc. cit.*), omit any reference to the work of Béchamp, although they refer to the earlier researches of Cadet and Thénard.

The third period in the history of organic arsenic and antimony compounds commenced in 1907, when Ehrlich and Bertheim demonstrated the true constitution of atoxyl. These workers showed that the action of arsenic acid on aniline is comparable with that of sulphuric acid on the same base. In both cases the acidic group enters the aromatic nucleus, giving rise to *p*-aminophenylarsinic acid and *p*-aminophenylsulphonic acid respectively. The latter of these acids is generally termed sulphanilic acid (I), and, accordingly, the former has been called arsanilic acid (II).



I.

II.

Atoxyl is therefore sodium arsanilate, the commercial product, $NH_2 \cdot C_6H_4AsO(OH) \cdot ONa, xH_2O$, containing an amount of water which varies between 2 and $6H_2O$, depending on the conditions of crystallisation.

The constitution of *p*-arsanilic acid was demonstrated in three stages :—

(i) Its diazotisability showed the presence of a free amino-group.

(ii) Its stability towards boiling aqueous caustic alkalis proved that it was neither an amide nor an anhydride.

(iii) Its conversion into *p*-iodoaniline by boiling hydriodic acid demonstrated the orientation of the arsenic atom in the nucleus with respect to the amino-group.

The proof that this compound is really an organo-metalloidal derivative containing arsenic directly attached to the aromatic nucleus rendered practicable the improvement of the drug by the synthesis of other compounds of similar type. At first the substances contained quinquevalent arsenic, but later syntheses were aimed at the production of derivatives containing arsenic in the more active tervalent condition. The latter are dealt with in a subsequent chapter on salvarsan.

Derivatives containing Quinquevalent Arsenic.

Following on Ehrlich and Bertheim's demonstration, the Béchamp condensation was applied to other aromatic amines having a free para-position. Ortho-toluidine gave rise to 2-aminotolyl-5-arsinic acid, whilst *a*-naphthylamine furnished 1-aminonaphthyl-4-arsinic acid.

It was already known that aniline and phenetidine could be converted by acetylation into less toxic but nevertheless therapeutically active substances, *e.g.* the drugs antifebrin (acetanilide) and phenacetin. Accordingly, atoxyl was treated similarly with acetic anhydride, and the sodium salt of the acetyl derivative thus obtained was introduced as a drug by Messrs. Meister, Lucius, & Brüning under the name of arsacetin, the formula for the salt being

$$CH_3{\cdot}CO{\cdot}NH{\cdot}C_6H_4{\cdot}AsO(OH){\cdot}ONa,3—4H_2O.$$

This product is less toxic than atoxyl, and its solutions can be sterilised by heat without decomposition. Orsudan is the ortho-tolyl analogue of arsacetin.

The use of these drugs led to the preparation of other acyl derivatives of atoxyl. Benzenesulphonylatoxyl,

$$C_6H_5{\cdot}SO_2{\cdot}NH{\cdot}C_6H_4AsO(OH){\cdot}ONa,$$

was described by Mouneyrat in a French patent (No. 401586 of 1908) and introduced as a drug under the name of hectine. At the Seventh Congress of Applied Chemistry, held in 1909, Dr. Martindale and the author described toluene-*p*-sulphonyl-arsanilic acid obtained from arsanilic acid and toluene-*p*-sulphonic chloride, the latter reagent being a by-product in the manufacture of saccharin. Iodoacetyl-arsanilic acid, $CH_2I{\cdot}CO{\cdot}NH{\cdot}C_6H_4AsO(OH)_2$, and its homologues have been patented by Messrs. Schering (D.R.-P., 268983). Allied to the acyl derivatives of atoxyl are the glycine derivatives patented by Messrs. Meister, Lucius, & Brüning (D.R.P., 204664).

Phenylglycinearsinic acid,

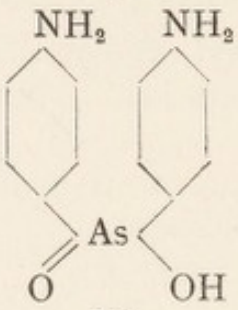
is produced by either of the following processes :—(1) Interaction

of arsanilic acid and chloroacetic acid ; (2) hydrolysis of the nitrile, $CN{\cdot}CH_2{\cdot}NH{\cdot}C_6H_4{\cdot}AsO(OH)_2$, produced by condensing together arsanilic acid, formaldehyde, and prussic acid.

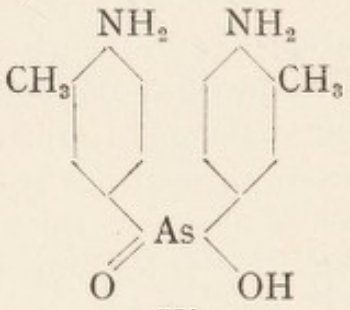
The alkyl derivatives of atoxyl have been examined, but without finding therapeutic employment. Dimethylarsanilic acid was obtained by Michaelis on oxidising dimethylaniline-arsenious oxide with mercuric oxide or alkaline permanganate.

$$N(CH_3)_2{\cdot}C_6H_4{\cdot}AsO \longrightarrow N(CH_3)_2{\cdot}C_6H_4{\cdot}AsO(OH)_2.$$

The Béchamp condensation was studied systematically by Benda and by Pyman and Reynolds, who discovered independently that in this process by-products were formed by the introduction of a second aromatic nucleus into the arsenic acid complex. From aniline and *o*-toluidine were obtained respectively, in small amount, di-*p*-aminodiphenylarsinic acid (III.) and 2-diaminoditolyl-5-arsinic acid (IV.).



III.



IV.

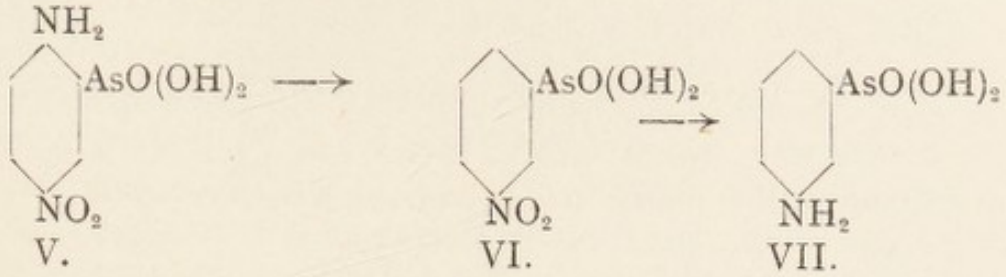
These acids had no marked effect on trypanosomes, although their reduction products, the corresponding oxides, *e.g.*, $HO{\cdot}As(C_6H_4{\cdot}NH_2)_2$, were very active *in vitro* (*Ber.*, 1908, **41**, 1672 ; *Chem. Soc. Trans.*, 1908, **93**, 1180).

Benda next extended Béchamp's condensation to the case of para-substituted amines, such as para-toluidine, and found that small yields of aromatic arsinic acids could be obtained containing the arsinic radical in the ortho-position with respect to the amino-group (*Ber.*, 1909, **42**, 3619).

Contrary to expectation, *p*-nitroaniline reacted readily with arsenic acid, giving rise to 2-amino-5-nitrophenyl-1-arsinic acid (V.) ; diazotisation followed by elimination of the diazo-complex and the reduction of the resulting *m*-nitrophenylarsinic acid (VI.) led to meta-arsanilic acid (VII.), which was also obtained by nitrating Michaelis's phenylarsinic acid and reducing the nitro-compound (VI.) with sodium amalgam.

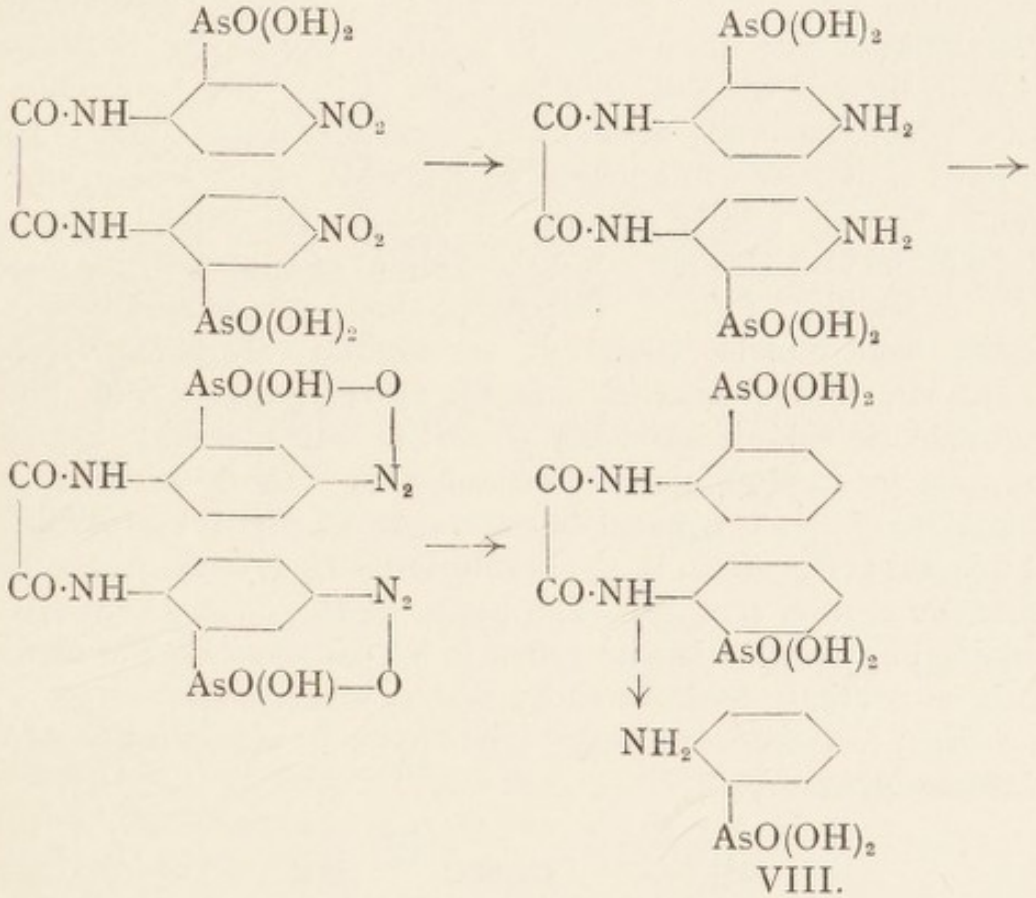
This synthesis of *m*-arsanilic acid demonstrates incidentally the constitution of the nitrophenylarsinic acid (p. 143) first

obtained by Michaelis and Loesner and shows that the arsinic group favour substitution in the meta-position. It therefore resembles the other acyl groups, CO_2H, SO_3H, and NO_2, and, like these complexes, conforms to Crum Brown and Gibson's rule of substitution.



V. VI. VII.

Benda obtained the remaining isomeride, *o*-arsanilic acid (XIV., *Ber.*, 1911, **44**, 3304), by converting 2-amino-5-nitrophenyl-1-arsinic acid into its oxanilide, and then carrying out the following succession of chemical changes :—



VIII.

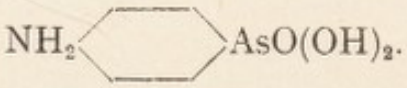
Comparative experiments with the three (ortho-, meta- and para-) arsanilic acids showed that the para-compound was the most efficacious trypanocide.

The diazo-derivatives of *p*-arsanilic acid and its homologues couple with phenols and aromatic amines, forming coloured

azo-derivatives (Ehrlich and Bertheim, *Ber.*, 1907, **40**, 3297; Barrowcliff, Pyman, and Remfry, *Chem. Soc. Trans.*, 1908, **93**, 1893). But neither these azo-derivatives nor the phenazines produced by oxidising arsanilic acid with persulphuric acid had any very marked effect on trypanosomes.

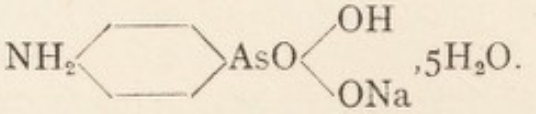
Section I.—p-*Arsanilic Acid and its* N-*Acyl and* N-*Alkyl Derivatives.*

4-Aminophenyl-1-arsinic acid[1] (p-*Arsanilic Acid*),



—Aniline (186 grams), mixed with 140 grams of arsenic acid, is slowly heated up to 170–200° in a vessel fitted with an efficient stirrer, the temperature being maintained at 190–200° for one to two hours. The product is mixed with water, rendered alkaline, and the excess of base distilled off in steam. The residue is allowed to cool, filtered, concentrated, and neutralised with hydrochloric acid, when the crude arsinic acid separates on cooling. This product is dissolved in aqueous caustic soda; the solution, which should be only faintly alkaline, is boiled with animal charcoal and filtered into alcohol, when the sodium salt (atoxyl) separates in a crystalline form. The by-product, di-4-aminodiphenylarsinic acid, remains dissolved, its sodium salt being soluble in alcohol. Free p-*arsanilic acid*, liberated from atoxyl by dilute hydrochloric acid, is sparingly soluble in water or ethyl alcohol, more so in methyl alcohol, insoluble in ether, benzene, or chloroform.[2] It is appreciably amphoteric, dissolving in excess of mineral acid. From this acid solution it is, however, reprecipitated by sodium acetate. The hydrochloride, $C_6H_8O_3NAs,HCl$, obtained by evaporating its generators to dryness on the water-bath, is partially hydrolysed by water.

Sodium p-*Arsanilate, Atoxyl.* Synonyms[2]: *Arsamin, Soamin, Natrium Arsanilicum.*



—The content of water in this salt is somewhat variable. Ehrlich and Bertheim state that the salt is obtainable with 2 and $6H_2O$,

[1] O. and K. Adler, *Ber.*, 1908, **41**, 932; Benda and Kahn, *ibid.*, 1674, 2370.

[2] Ehrlich and Bertheim, *Ber.*, 1907, **40**, 3292.

according to the solvent used in crystallising the compound. The more hydrated forms lose water by efflorescence and commercial specimens give amounts of water ranging from 3 to $5H_2O$. The product introduced by Burroughs Wellcome and Co. under the name of " Soamin " takes the form of well-defined, colourless crystals containing $5H_2O$. Dr. Martindale's preparation contains approximately $3H_2O$.[1]

The adherence of arsinic groups to the aromatic nucleus has been studied by E. Schmitz, who heated solutions of atoxyl with various proportions of aqueous alkalis at 100° and at 130°. The maximum decomposition was obtained by heating solutions containing one molecule of *p*-arsanilic acid with 0·8 molecule of sodium hydroxide. This instability rapidly diminishes when more alkali is added and the salt approaches its maximum stability when an extra half-molecule of sodium hydroxide is present. With an extra molecule of alkali there is no hydrolysis. The instability of the molecule of atoxyl is traced to some interaction between the amino-group and the second hydroxyl radical of the arsinic complex. Other alkalis, such as lithia, and even carbamide, behave similarly and the stabilising effect is due to the saturation by the alkali of the second hydroxyl radical. The acyl derivatives of atoxyl are more stable inasmuch as the combining power of the amino-group is diminished considerably by acylation.[2]

Alkaloidal Salts of p-*Arsanilic Acid.*[3]

Quinine *p*-arsanilate, produced by mixing solutions of atoxyl and quinine hydrochloride ; white needles, m.p. 202°, soluble in hot alcohol or methyl alcohol. Solubilities 1 in 635 water, 1 in 534 physiological salt solution, and 1 in 133 glycerol. Cinchonine salt decomposes at 180°, soluble in alcohol, insoluble in water or anhydrous solvents.

Mercuric p-*arsanilate,*[4] *" Asyphil,"* $[NH_2 \cdot C_6H_4AsO(OH) \cdot O]_2Hg$, a white powder, sparingly soluble in water, dissolves in aqueous sodium chloride, and is accordingly useful for injections ; prepared

[1] Congress of Applied Chemistry, 1909, (Pharmaceutical Chemistry Section).

[2] Schmitz, *Ber.*, 1914, **47**, 363.

[3] Vereinigte chemische Werke, Aktiengesellschaft in Charlottenburg, D.R.-P., 203081.

[4] May and Baker and Bates, Eng. P., 8959 and 24428/1908 ; Fr. P., 396192, Allschul, A. P., 938939. M. L. and B., D.R.-P., 237787.

by triturating *p*-arsanilic acid with freshly precipitated mercuric oxide or by double decomposition from atoxyl and mercuric chloride. A basic mercuric salt, $NH_2 \cdot C_6H_4 \cdot AsO(OH) \cdot OHg \cdot OH$, has also been prepared.

N-*Acyl Derivatives of* p-*Arsanilic Acid.*[1]

Formyl-p-*arsanilic acid*, $COH \cdot N \cdot C_6H_4 \cdot H \cdot AsO(OH)_2$, colourless needles from hot water or methyl alcohol, insoluble in ether. Prepared by heating atoxyl dried at 140° with excess of formic acid for two hours in a reflux apparatus, afterwards distilling off excess of volatile acid.

Acetyl-p-*arsanilic acid*, $CH_3 \cdot CO \cdot NH \cdot C_6H_4 \cdot AsO(OH)_2$, colourless leaflets from water, prepared either by warming atoxyl with acetic anhydride or by heating this salt with glacial acetic acid in a reflux apparatus. Easily soluble in aqueous sodium carbonate, dissolving only sparingly in dilute hydrochloric acid.

Sodium Acetyl-p-*arsanilate*, "*Arsacetin*," "*Acetylatoxyl*,"

$$CH_3 \cdot CO \cdot NH \cdot C_6H_4 \cdot AsO(OH) \cdot ONa, 3\text{–}4H_2O,$$

solubility 1 in 10 parts of cold water, insoluble in alcohol. Acetyl-*p*-arsanilic acid is also obtained by Bart's reaction by adding aqueous sodium arsenite to *p*-aminoacetanilide diazotised in dilute hydrochloric acid. The mixture is rendered just alkaline by caustic soda and warmed. The filtered solution is concentrated until sodium acetyl-*p*-arsanilate separates. The salt crystallises from dilute methyl alcohol in colourless needles.[2]

Chloroacetyl-p-*arsanilic acid*, $CH_2Cl \cdot CO \cdot NH \cdot C_6H_4 \cdot AsO(OH)_2$, prepared by dissolving *p*-arsanilic acid in warm chloroacetyl chloride and adding the solution to water ; the product is soluble in cold aqueous sodium carbonate and reprecipitated with hydrochloric acid: *iodoacetyl*-p-*arsanilic acid* (needles decomposing at 196°) and *iodopropionyl* derivative (needles decomposing at 214°).[3]

Butyryl-p-*arsanilic acid*, $C_3H_7 \cdot CO \cdot NH \cdot C_6H_4AsO(OH)_2$, prepared by (1) warming atoxyl with butyric anhydride or (2) adding butyryl chloride to an equal weight of *p*-arsanilic acid dissolved in 10 parts of dry pyridine. After 16 hours in the cold the product is precipitated with ether and the precipitate treated successively with water and dilute hydrochloric acid, the final residue being the butyryl derivative.

[1] Ehrlich and Bertheim (M. L. and B.), U.S.P., 907016/1908.
[2] H. Bart, D.R.-P., 250264 ; Eng. P., 568/1911.
[3] Schering, D.R.-P., 268983.

The *carbamide* derivative, $CO[NH{\cdot}C_6H_4AsO(OH)_2]_2$, is prepared by shaking a well-cooled 10 per cent. aqueous solution of atoxyl with the calculated amount of carbonyl chloride dissolved in toluene (20% solution). The resulting paste is washed successively with water and alcohol, and the residual carbamide dissolved in aqueous sodium carbonate and precipitated by hydrochloric acid.

Malonyl-p-*arsanilic acid* is obtained by heating *p*-arsanilic acid and ethyl malonate in a reflux apparatus.

Benzoyl-p-*arsanilic acid* is prepared by the Schotten-Baumann reaction from *p*-arsanilic acid, benzoyl chloride and aqueous sodium hydroxide, and separated from benzoic acid after acidifying by extraction with hot alcohol, in which the latter acid is more soluble.

Oxalyl-p-*aminophenylarsinic acid, Oxalyl*-p-*arsanilic acid*,[1]

$$CO_2H{\cdot}CO{\cdot}NH{\cdot}C_6H_4{\cdot}AsO(OH)_2,$$

white, crystalline powder not melting below 360°, soluble in hot water, caustic or carbonated alkalis, sparingly so in methyl alcohol, but insoluble in acids. Prepared by heating to 120–130° an intimate mixture of 347 grams of crystallised atoxyl (sodium *p*-arsanilate) and 378 grams of crystallised oxalic acid until the greater part of the water is eliminated. The pasty mass is then heated further to 160° until it becomes pulverulent. The crude product is mixed with 3 litres of water and 350 c.c. of hydrochloric acid (D = 1·12) and the precipitate then dissolved in 700 c.c. of cold water and 200 c.c. of 10*N*-caustic soda. The filtered solution, when acidified with 390 c.c. of hydrochloric acid (D = 1·12), yields the oxalyl derivative as a white, crystalline meal.

Allylthiocarbamino-p-*arsanilic acid*,

$$C_3H_5{\cdot}NH{\cdot}CS{\cdot}NH{\cdot}C_6H_4{\cdot}AsO_3H_2,$$

m.p. 185° (decomp.), and the homologue (decomp. 170°) from methyl-*p*-arsanilic acid are produced by treating the arsenical acid with allylthiocarbimide in methyl alcohol. The products have the combined therapeutic action of allyl and arsenic compounds without the toxic character of the latter.[2]

Carbamino-p-*arsanilic acid* (I.).[3]—Glacial acetic acid (480 c.c.)

[1] M. L. and B., D.R.-P., 206037, 231969. [2] Thoms, D.R.-P., 294632.

[3] M. L. and B., D.R.-P., 213155, addition to D.R.-P., 191548. Fr. P., 392857, Eng. P., 17139/1908. Ehrlich and Bertheim, U.S.P., 937929. A. Mouneyrat, Fr. P., 401586.

is added to an aqueous solution (3·6 litres) of sodium *p*-arsanilate (620 grams) and potassium cyanate (480 grams). After 24 hours the solution is acidified with 1560 c.c. of hydrochloric acid (D = 1·124). The crystallisation of the product is promoted by rubbing the side of the vessel.

I.

II.

Thiocarbamino-p-*arsanilic acid* (II.).—A solution of 60 grams of potassium thiocyanate and 78 c.c. of hydrochloric acid (D = 1·124) is saturated with *p*-arsanilic acid (about 83 grams) and evaporated to dryness. The residue is heated on the water-bath for two hours and mixed with 300 c.c. of water and 150 c.c. of 10*N*-caustic soda, the product being precipitated from the filtrate by means of dilute hydrochloric acid.

Methylcarbamino-p-*arsanilic acid*,

$$CH_3{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}C_6H_4{\cdot}AsO_3H_2,$$

is prepared by adding 14 grams of methyl *iso*cyanate to atoxyl (40 grams) in 240 c.c. of water, the solution being cooled in ice. After twelve hours in the ice-chest 52 c.c. of hydrochloric acid (D = 1·12) are added to precipitate the crystalline product.

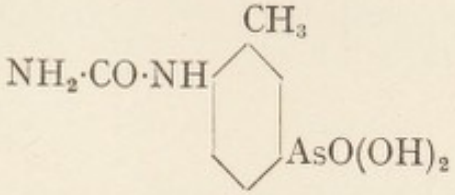
Phenylcarbamino-p-*arsanilic acid*,

$$C_6H_5{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}C_6H_4{\cdot}AsO_3H_2,$$

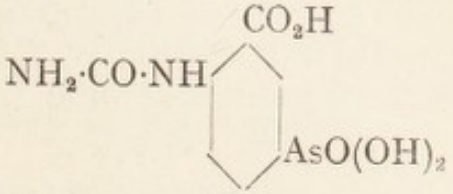
results from the addition of phenyl *iso*cyanate (18 grams) to 31 grams of atoxyl in 300 c.c. of water. The mixture is well stirred and kept ice-cold for twelve hours, being then extracted with ether, and the solution filtered. The aqueous layer is acidified with 40 c.c. of hydrochloric acid (D = 1·14), when the phenylcarbamino-derivative is precipitated. A further quantity is obtained by extracting the insoluble products with aqueous sodium carbonate and afterwards acidifying the alkaline extract.

Methyl-atoxyl and its carboxyl oxidation product, when treated with potassium cyanate and acetic acid, and after twenty-four hours with excess of hydrochloric acid, yield respectively

2-carbaminomethyl-5-arsinic acid (I.) and *2-carbamino-1 : 5-benzarsinic acid* (II.).

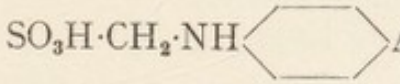


I.



II.

p-*Sulphomethylaminophenylarsinic acid*,



needles, decomposing at 148°, prepared by treating atoxyl with formaldehyde and sodium bisulphite in concentrated aqueous solution. The free acid is precipitated by hydrochloric acid. It is much less toxic than atoxyl, but also much less trypanocidal.[1]

Phthalyl-p-*arsanilic acid*, $CO_2H \cdot C_6H_4 \cdot CO \cdot NH \cdot C_6H_4 \cdot AsO(OH)_2$, is prepared by the Schotten-Baumann reaction, using phthalyl chloride ; the product is precipitated by adding concentrated hydrochloric acid very slowly to the alkaline solution.[2]

Benzenesulphonyl-p-*arsanilic acid*,[3]

$$C_6H_5 \cdot SO_2 \cdot NH \cdot C_6H_4 \cdot AsO(OH)_2,$$

prepared by the Schotten-Baumann reaction, using benzenesulphonic chloride. *Sodium* salt, "*Hectine.*"

p-*Toluenesulphonyl*-p-*arsanilic acid*,[4]

$$C_7H_7 \cdot SO_2 \cdot NH \cdot C_6H_4 \cdot AsO(OH)_2,$$

colourless crystals from hot water, prepared by the Schotten-Baumann reaction, using toluene-*p*-sulphonic chloride. *Sodium* salt, very soluble in water, slightly so in alcohol.

The foregoing acyl-*p*-arsanilates no longer give the following characteristic reactions of atoxyl :—

(1) *p*-Dimethylaminobenzaldehyde in hydrochloric acid forms, with atoxyl, an intensely yellow condensation product.

(2) *β*-Naphthaquinone-4-sulphonic acid and atoxyl in the presence of aqueous sodium carbonate yield an intense reddish-orange coloration of a naphthaquinone derivative soluble in alkalis and dissolving only sparingly in acids. The acyl-*p*-arsanilic acids are hydrolysed by warming with 30 per cent.

[1] Abelin, *Biochem. Zeitsch.*, 1916, **78**, 191. [2] D.R.-P., 191548.

[3] Mouneyrat, Fr. P., 401586/1908.

[4] Martindale and Morgan, Seventh International Congress of Applied Chemistry, 1909.

sulphuric acid or concentrated aqueous alkalis, when the regenerated atoxyl gives the above colour reactions.

The toxicity of these acyl derivatives of atoxyl is generally stated to be less than that of the latter salt itself. In trypanocidal effect they are somewhat similar.

Aldehydic Condensation Products of Atoxyl.

The condensation of aldehydes with *p*-arsanilic acid leads to products having diminished toxicity.

p-*Hydroxybenzylidene*-p-*arsanilic acid*,

$$HO{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}C_6H_4{\cdot}AsO(OH)_2,$$

yellow crystals insoluble in ether, sparingly soluble in water or alcohol, dissolving readily in aqueous sodium carbonate but hydrolysed by concentrated caustic soda. Prepared by heating at 140° a mixture of *p*-arsanilic acid and *p*-hydroxybenzaldehyde in molecular proportions. Similar products are obtainable from *p*-arsanilic acid and dimethyl-*p*-aminobenzaldehyde or resorcylaldehyde and from other aliphatic and aromatic aldehydes.[1]

p-*Dimethylaminophenylarsinic acid*,[2]

crystallises from water or alcohol in colourless needles, subliming without melting; produced by heating together dimethylaminophenylarsenious oxide and red mercuric oxide (slight excess) suspended in water; the acid separates from the filtrate on evaporation.

$$(CH_3)_2N{\cdot}C_6H_4AsO + HgO + H_2O =$$
$$(CH_3)_2N{\cdot}C_6H_4{\cdot}AsO(OH)_2 + Hg.$$

A more convenient method of preparing this acid is as follows: A mixture of 15 grams of dimethylaniline and 25 grams of arsenious chloride heated for two hours on the water-bath is poured into 300–400 c.c. of cold water. Excess of aqueous caustic soda is added until *p*-dimethylaminophenylarsenious oxide is dissolved. After removing unaltered dimethylaniline with light petroleum, excess of 30 per cent. hydrogen peroxide is added and *p*-dimethylaminophenylarsinic acid precipitated by acetic acid. It is sparingly soluble in cold water or

[1] D.R.-P., 193542, Kuratorium des Georg und Franziska Speyerschen Studienstiftung in Frankfurt A/M.

[2] Michaelis, *Annalen*, 1902, **320**, 295.

alcohol, dissolving readily in hot alcohol, hot dilute acetic acid, mineral acids or alkalis. *Sodium* salt, (N-*Dimethylatoxyl*), $(CH_3)_2N{\cdot}C_6H_4{\cdot}AsO(OH)ONa,5H_2O$, leaflets.[1]

Phenylglycinearsinic Acid and its Homologues.

Phenylglycine-p-*arsinic acid*,

This important derivative of *p*-arsanilic acid is prepared by the following methods —

(1) Atoxyl (27·5 parts) dissolved in 80 parts of hot water is mixed with chloroacetic acid (16 parts) in 20 parts of water, the mixture being heated in a reflux apparatus for six to eight hours. On cooling, the glycine derivative crystallises and is washed with dilute hydrochloric acid to remove unchanged arsanilic acid. The residual phenylglycine-*p*-arsinic acid is sparingly soluble in cold, easily so in hot, water. It is easily soluble in concentrated hydrochloric acid, but in the dilute acid only on warming; it dissolves readily in alkali hydroxides, carbonates and acetates.

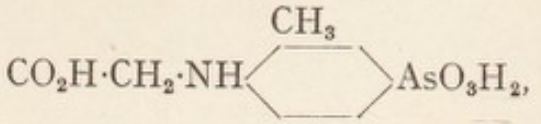
(2) *p*-Arsanilic acid (7 parts), sodium cyanide (2 parts), and 2·2 parts of 40 per cent. formalin solution are dissolved in 35 parts of water and heated in an autoclave at 100° for one to two hours. After cooling the solution is neutralised cautiously with dilute hydrochloric acid; the *nitrile*, $CN{\cdot}CH_2{\cdot}NH{\cdot}C_6H_4{\cdot}AsO(OH)_2$, crystallises and is boiled with aqueous sodium hydroxide, when ammonia is evolved. The alkaline solution on acidifying with dilute hydrochloric acid yields phenylglycine-*p*-arsinic acid. The homologous arylglycinearsinic acids from 2-aminotolyl-5-arsinic acid, 5-aminotolyl-2-arsinic acid, and 2-amino-*p*-xylyl-5-arsinic acid are obtained in a similar manner.

These glycine derivatives are distinguished from atoxyl by their feebler toxicity. Although an *N*-acetyl group lowers the toxicity of atoxyl, this diminution of toxic effect is noticeable only in certain animal species and not with horses or guinea pigs. In these cases the animal organism exerts a more or less complete hydrolysis of the acetyl compound, but the glycine group is more firmly attached and resists this hydrolytic action.[2]

[1] Michaelis, D.R.-P., 200065; *Ber.*, 1908, **41**, 1514.

[2] M.L. and B., D.R.-P., 204664. *Berliner Klinischen Wochenschrift*, 1907, **44**, 283.

o-*Tolylglycine*-p-*arsinic acid*,

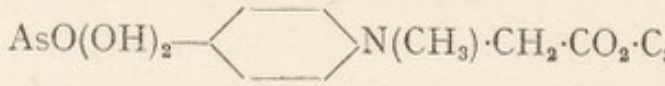


melts and decomposes at 220°, crystallises from hot water, soluble in alcohol or aqueous alkalis, insoluble in hydrochloric acid.

Phenylmethylglycine-p-*arsinic Acid and its C-Esters*.[1]

The starting materials for these arsenical compounds are obtained by heating dimethylaniline with the esters of chloroacetic acid, the product being fractionated *in vacuo*: C-*ethylphenylmethylglycine*-4-*arsinic acid* $AsO(OH)_2 \cdot C_6H_2N(CH_3) \cdot CH_2 \cdot CO_2 \cdot C_2H_5$, boils at 171°/30 mm., the *propyl* ester boils at 174°/20 mm.; both are colourless liquids having a faint agreeable odour.

C-*Propylphenylmethylglycine*-4-*arsinic acid*,

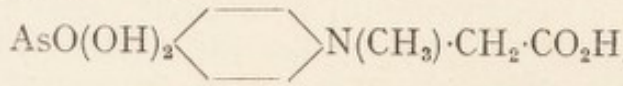


white, crystalline mass, m.p. 153–154°, blackening at 190°; sparingly soluble in water, ether, or mineral acids, but dissolving more readily in alcohol, acetone, or acetic acid; prepared by heating the propyl ether of phenylmethylglycine (200 grams) for 1½ hours at 90–110° with arsenious chloride (250 grams) or arsenious bromide (430 grams). The hot solution is then poured into water and the intermediate product,

$$AsCl_2 \cdot C_6H_4N(CH_3) \cdot CH_2 \cdot CO_2 \cdot C_3H_7,$$

or the corresponding bromide is oxidised with hydrogen peroxide. The crystalline precipitate is dissolved in aqueous sodium carbonate, the solution decolorised with animal charcoal and acidified with excess of hydrochloric acid, when the precipitated arsinic acid is crystallised from 20 per cent. acetic acid.

Phenylmethylglycine-4-*arsinic acid*,[2]



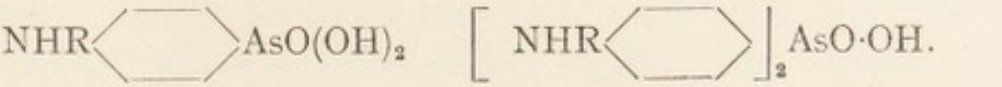
white, crystalline powder evolving carbon dioxide at high temperatures and yielding 4-dimethylaminophenylarsinic acid.

The foregoing propyl ester or the corresponding amyl compound (50 grams) is dissolved in 4 per cent. aqueous sodium hydroxide

[1] Poulenc and K. Oechslin, Fr. P., 450214. [2] *Ibid.*, Fr. P., 462276.

(200 c.c.), 100 grams of 36 per cent. alkali are added, and the mixture heated to 60°. Amyl alcohol separates and the acidified aqueous solution yields the free glycine.

p-*Alkylaminophenylarsinic* and *Bis*-p-*alkylaminophenylarsinic acids*,[1]



—In addition to the dialkylanilines studied by Michaelis and Rabinerson, it was found subsequently that the monoalkylanilines and arylglycines also undergo condensation with arsenious chloride to furnish derivatives of phenylarsenious dichloride, $NHR{\cdot}C_6H_4{\cdot}AsCl_2$,, and diphenylarsenious chloride,

$$(NHR{\cdot}C_6H_4)_2AsCl,$$

especially in the presence of pyridine.

Amylaniline (163 grams) dissolved in at least 79 grams of dry pyridine is added to arsenious chloride (180 grams) and the mixture heated for one to two hours at 106–108° for the monophenyl derivative and at 115–120° for the diphenyl compound. The solution is poured into water (400 c.c.) and oxidised in acid or alkaline solution with hydrogen peroxide in moderate excess. The alkali soluble product is reprecipitated by mineral acid added till the mixture is faintly acid to Congo red. The monophenylated acid is isolated by dissolving the mixture in absolute alcohol and then adding ether, when it separates in a crystalline mass which recrystallised from hot water forms colourless lamellæ decomposing at 172°. It is slightly soluble in water, but dissolves in alcohol, acids or alkalis. The diphenylated acid remaining in the ether-alcohol mother liquors is very soluble in alcohol but insoluble in water ; it dissolves in acids or alkalis.

Similar products are obtainable from methyl- and ethylaniline and from phenylglycine and phenylmethylglycine.

Section II.—Isomerides of p-*Arsanilic Acid.*

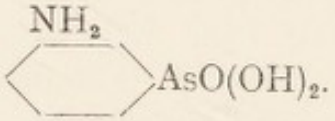
m-*Aminophenylarsinic Acid* (m-*Arsanilic Acid*).[2]

p-Oxanilarsinic acid is produced by heating a mixture of *p*-arsanilic acid (21·7 grams) and oxalic acid (37·8 grams) heated

[1] Poulenc and K. Oechslin, Fr. P., 473704.
[2] Benda, *Ber.*, 1909, **42**, 3619.

to 130–140° until the liquid mass thickens when the temperature is raised to 160°. The fused mass is extracted with water acidified with hydrochloric acid to remove unchanged *p*-arsanilic acid and the crude oxanilic compound dissolved in aqueous sodium hydroxide and reprecipitated with hydrochloric acid. The product crystallised from 50 per cent. acetic acid has the composition $AsO_3H{\cdot}C_6H_4{\cdot}NH{\cdot}CO{\cdot}CO_2H,H_2O$, m.p. above 200°. A solution of 116 grams of this substance dissolved in 300 c.c. of concentrated sulphuric acid is nitrated at 15–20° with 26 c.c. of nitric acid (D = 1·4) and 26 c.c. of concentrated sulphuric acid. The nitration solution is poured into 1·5 litres of water and the whole mixture boiled in a reflux apparatus, when 3-nitro-4-aminophenylarsinic acid is produced, the yield being 86 per cent. of theory.

When dissolved in 400 c.c. of water and 100 c.c. of 10*N*-caustic soda the foregoing nitro-acid (131 grams) is diazotised with sodium nitrite (35 grams) in 175 c.c. of water. The diazo-solution when diluted with 650 c.c. of water and 390 c.c. of hydrochloric acid (D = 1·12) is added to 265 grams of sodium hypophosphite in 500 c.c. of water and 325 c.c. of hydrochloric acid (D = 1·12). The *m*-nitrophenylarsinic acid, produced by eliminating the diazo-group, is isolated successively through the barium, zinc, and sodium salts, when by this synthetic method the yield of 45 per cent. is obtained.[1]



m-Arsanilic acid containing the amino-group in the meta-position to the arsinic radical is obtained by the reduction of *m*-nitrophenylarsinic acid, produced either by the foregoing process from *p*-arsanilic acid or by direct nitration of phenylarsinic acid (p. 143). A practical difficulty arises in this operation owing to the tendency of the arsinic group to undergo reduction simultaneously with the nitro-group.

m-Nitrophenylarsinic acid (99 grams) dissolved in 2 litres of methyl alcohol is treated with 4 per cent. sodium amalgam at 50° until the evolution of hydrogen ceases. The filtrate from mercury is distilled to remove methyl alcohol; the residue extracted with 8–9 litres of water, the solution neutralised with

[1] Bertheim and Benda, *Ber.*, 1911, **44**, 3298.

acetic acid, excess of zinc acetate added, and the precipitated zinc *m*-aminophenylarsinate decomposed with sodium carbonate. The filtrate from zinc carbonate is neutralised with hydrochloric acid and acidified with glacial acetic acid, when *m*-aminophenyl-1-arsinic acid separates as a white powder.

m-Arsanilic acid, or 3-aminophenyl-1-arsinic acid, is sparingly soluble in hot water, and crystallises therefrom in colourless prisms melting at 212–214°; it is moderately soluble in methyl alcohol, sparingly so in ethyl alcohol, glacial acetic acid, or ether, and dissolves readily in aqueous alkalis or mineral acids. With magnesia mixture this acid gives a white precipitate; moreover, the acid is readily diazotised.

When *m*-nitrophenylarsinic acid is reduced with ammonium sulphide in alcoholic solution, the nitro- and arsinic groups are both affected, a sulphur-containing compound, $NH_2 \cdot C_6H_4 \cdot AsS$, being produced. The sulphur in this substance can be eliminated in the following manner. A solution of *m*-nitrophenylarsinic acid (200 grams) in 1·4 litres of 25 per cent. ammonia is saturated with hydrogen sulphide and heated for twelve hours on the water-bath, the treatment with hydrogen sulphide being repeated several times. The solution is evaporated to dryness, the residue is extracted repeatedly with very dilute hydrochloric acid, the extract diluted to 10 litres and heated to boiling after adding 1·4 litres of 10*N*-sodium hydroxide. Decinormal copper sulphate is added till a filtered portion gives no precipitate of lead sulphide on boiling with lead acetate. The precipitate of copper sulphide is removed, the filtered solution neutralised with acetic acid, and *m*-arsanilic acid obtained through the zinc salt.[1]

In the reduction with sodium amalgam and methyl alcohol the roundabout purification through the zinc salt may be avoided by distilling off the alcohol, adding water and 1½ vols. of strong hydrochloric acid. Sodium chloride and by-products are precipitated, and sodium acetate is added to the filtrate until the colour of Congo red paper is no longer changed. On rubbing the sides of the vessel *m*-arsanilic acid separates and is purified by crystallisation from water.[2]

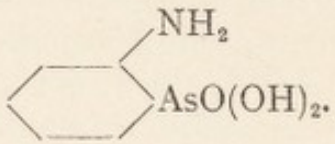
[1] M.L. and B., D.R.-P., 206344. *Cf.* Michaelis, *Ber.*, 1894, **27**, 265 and 271; *Annalen*, 1902, **320**, 277 and 294.

[2] *Ber.*, 1908, **41**, 1657, and 1911, **44**, 3299.

m-*Aminophenylarsenious sulphide*,[1] $NH_2 \cdot C_6H_4 \cdot AsS$, white, uncrystallisable powder, softening at 182° and melting at 188° to a yellow liquid. Nitrophenylarsinic acid dissolved in strong aqueous ammonia is saturated with hydrogen sulphide and the solution warmed on the water-bath. Fresh ammonia is added and the whole operation repeated. Finally the solution is taken to dryness, the residue extracted with water and acidified in the cold with dilute hydrochloric acid. The filtrate from precipitated sulphur, rendered ammoniacal, gives aminophenylarsenious sulphide as a voluminous white precipitate (11 grams). Probably ammonium aminophenylthioarsinate is the intermediate product which is decomposed by acid.

$$NH_2 \cdot C_6H_4 \cdot AsS(SNH_4)_2 + 2HCl = NH_2 \cdot C_6H_4AsS + S + H_2S + 2NH_4Cl.$$

o-*Aminophenylarsinic acid* (o-*Arsanilic acid*),[2]



—5-Nitro-2-aminophenylarsinic acid (104 grams) is converted into the corresponding oxanilide (*v.* p. 157) by heating with oxalic acid (200 grams) and 40 c.c. of *N*-sodium hydroxide at 110–130° and finally at 160–165°; this product is reduced with iron powder and dilute acetic acid. The oxanilide of 2 : 5-diaminophenylarsinic acid containing a free (5-) amino-group is diazotised and the diazo-compound warmed at 55–60° with alcohol and copper-bronze. The product, which separates in the filtrate as a brown, crystalline precipitate, is hydrolysed with 2*N*-sulphuric acid, when *o*-arsanilic acid is produced and purified through its barium salt. This ortho-isomeride of *p*-arsanilic acid melts at 152–153°, and is very soluble in water even at the ordinary temperature. It dissolves readily in aqueous alkalis or acids, in the alcohols, and in glacial acetic acid. Its *silver* salt shows a characteristic reaction. Silver nitrate added to sodium *o*-arsanilate gives a caseous, white precipitate which in a few seconds and without stirring changes suddenly into well-defined lustrous needles. *o*-Arsanilic acid. when warmed at 80° with potassium iodide and dilute sulphuric acid, rapidly yields *o*-iodoaniline.

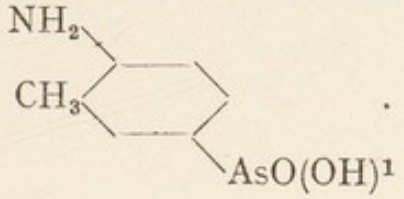
[1] Michaelis and Loesner, *Ber.*, 1894, **27**, 271.
[2] Benda, *Ber.*, 1911, **44**, 3304.

Section III.—Homologues and Substitution Products of p-*Arsanilic Acid.*

1. *Homologues.*

The Aminotolylarsinic Acids.[1]

2-Aminotolyl-5-arsinic Acid,



—Powdered arsenic acid (24 parts) is added to *o*-toluidine (90 parts) heated at 100° in a vessel fitted with stirrers. The temperature is gradually raised so that after one hour the fused mass is at 165–168° ; water and *o*-toluidine distil off, the temperature is increased further and maintained for one hour at 185–190°. The solution is cooled to 150° and blown into water, neutralised with sodium hydroxide and rendered strongly alkaline with calcium or barium hydroxide. The excess of *o*-toluidine is distilled off in steam, the residual solution saturated with sodium chloride and filtered after 24 hours. Hydrochloric acid and a few drops of methyl-orange are now added till the colour of the solution changes to red, a tarry by-product separates, and after 20 hours or longer 2-aminotolyl-5-arsinic acid crystallises and is dissolved in a little hot water The solution neutralised with sodium hydroxide is cleared with animal charcoal and treated with 1½ volumes of alcohol, when the sodium salt separates in crystalline form. On acidifying with hydrochloric acid a concentrated aqueous solution of the sodium salt, 2-aminotolyl-5-arsinic acid (m.p. 198–200°) crystallises in needles, sparingly soluble in cold, more soluble in hot, water. This acid dissolves sparingly in alcohol and is insoluble in benzene or ether ; it is easily soluble in excess of dilute mineral acids or in aqueous solutions of alkali hydroxides or carbonates. The diazo-derivative of the acid, which is prepared in the usual way, couples with alkaline phenols.

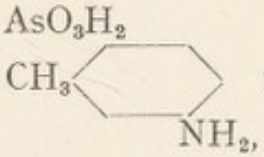
[1] M.L. and B., D.R.-P., 219210 (20/7/07); Eng. P., 14937 (14/7/08). L. Benda and M.L. and B., U.S.P., 913940 (2/3/09). H. S. Wellcome and F. L. Pyman, Eng. P., 855 (14/1/08). O. and R. Adler, *Ber.*, 1908, **41**, 931. Benda and Kahn, *Ber.*, 1908, **41**, 1672.

Sodium 2-aminotolyl-5-arsinate, " Kharsin,"

$$NH_2 \cdot C_6H_3(CH_3) \cdot AsO(OH) \cdot ONa,$$

dissolves readily in water, but is more sparingly soluble in alcohol; it is insoluble in ether or benzene. From water this salt separates with $5H_2O$ of crystallisation, but when its concentrated aqueous solution is mixed with three volumes of alcohol it is obtained in glistening, tabular crystals containing $3\frac{1}{2}H_2O$.

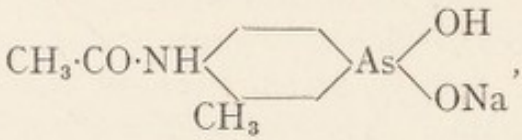
5-*Aminotolyl-2-arsinic acid,*



m.p. 180°.

—The interaction of arsenic acid and *m*-toluidine at 170–190° gives rise to 5-aminotolyl-2-arsinic acid, which is extracted from the mixture in the same manner as its isomeride.

Sodium Acetyl-2-aminotolyl-5-arsinate, " Orsudan," [1]



, 5 or $7H_2O$.

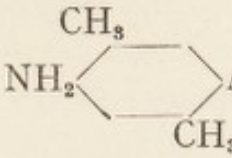
—Acetyl-2-aminotolyl-5-arsinic acid is prepared by (1) adding acetic anhydride to sodium 2-aminotolyl-5-arsinate or (2) treating 2-aminotolyl-5-arsinic acid with this anhydride and a little concentrated sulphuric acid. The free acetylamino-acid crystallises from water in acicular prisms; at 260° it turns brown and decomposes with frothing at 306°.

The sodium salt introduced into pharmacy by Messrs. Burroughs Wellcome & Co. under the name of " orsudan " crystallises from 50 per cent. alcohol with $5H_2O$ and from water with $7H_2O$.

Acetyl-5-aminotolyl-2-arsinic acid is prepared by mixing 5-aminotolyl-2-arsinic acid (50 grams), acetic anhydride (100 c.c.), and 2·5 c.c. of concentrated sulphuric acid, the mixture being warmed on the water-bath till a clear solution is produced. This acetyl derivative, which is more soluble than the foregoing isomeride, crystallises from water in colourless prisms which become discoloured at 240°, but not entirely melted at 350°.

[1] Pyman and Reynolds, *Chem. Soc. Trans.*, 1908, **93**, 1181; Wellcome and Pyman, Eng. P, 855/1908.

2-Amino-p-*xylyl-5-arsinic Acid*,

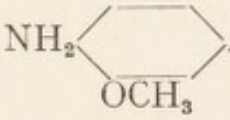


—*p*-Xylidine contains an unsubstituted hydrogen atom in the para-position to the amino-group, and accordingly a mixture of this base and arsenic acid when heated for several hours at 170–190° yields 2-amino-*p*-xylyl-5-arsinic acid, the properties of which resemble closely those of *p*-arsanilic acid.

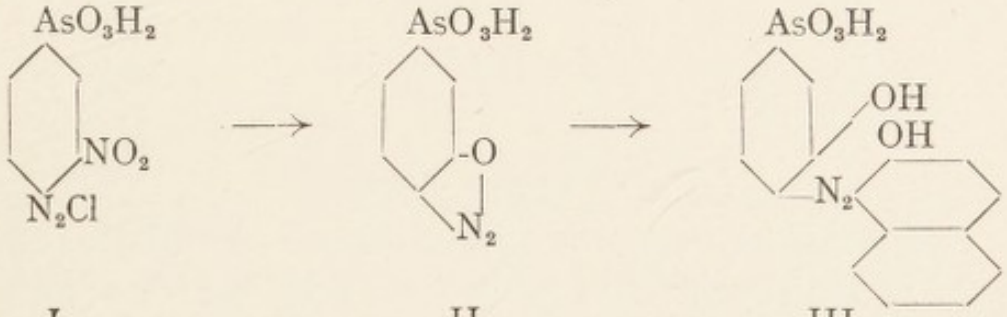
The *acetyl* derivative crystallises from water in prisms, becoming brown at 240° and decomposing with frothing at 278°.

2. *Alkoxyaryl Derivatives.*

o-*Anisidine-4-arsinic Acid* (*4-Amino-3-methoxyphenylarsinic Acid*),[1]



—When subjected to Béchamp's reaction *o*-anisidine yields only a very small amount of arsinic acid, so that this derivative is preferably obtained by an indirect process from 3-nitro-4-amino-phenylarsinic acid. This nitroamine is diazotised and treated with excess of sodium acetate until the diazo-derivative (I.) has lost its capacity for coupling with R-salt and yields a red instead of a yellow azo-compound with resorcinol. This change arises from the elimination of the nitro-group. At this stage the diazo-product (II.) is coupled with alkaline β-naphthol when the sodium salt of a crystalline, coppery-red azo-β-naphthol derivative (III.) is precipitated.

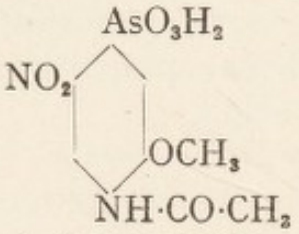


I. II. III.

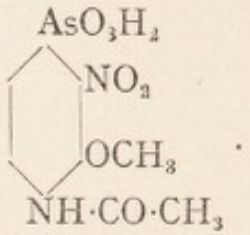
This azo-compound is methylated with methyl toluene-*p*-sulphonate in methyl alcohol containing sodium carbonate.

[1] Benda, *Ber.*, 1914, **47**, 995.

On reducing the methylated azo-derivative with alkaline hydrosulphite, *o*-anisidine-4-arsinic acid is obtained in lustrous, colourless needles easily soluble in hot water. Its diazo-derivative is quite colourless. The acetyl compound produced by the action of acetic anhydride on an alkaline solution of *o*-anisidine-4-arsinic acid furnishes on nitration the following isomeric nitro-derivatives :

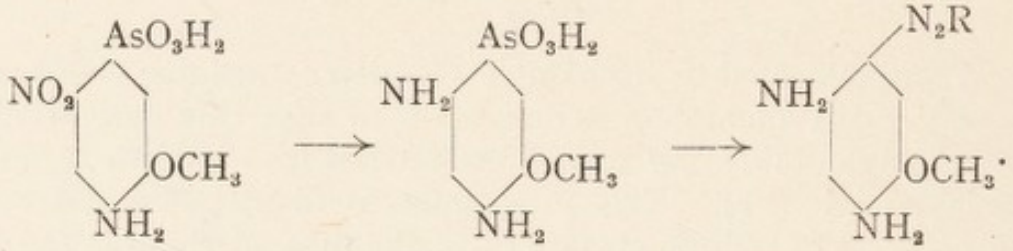


I. Less soluble.

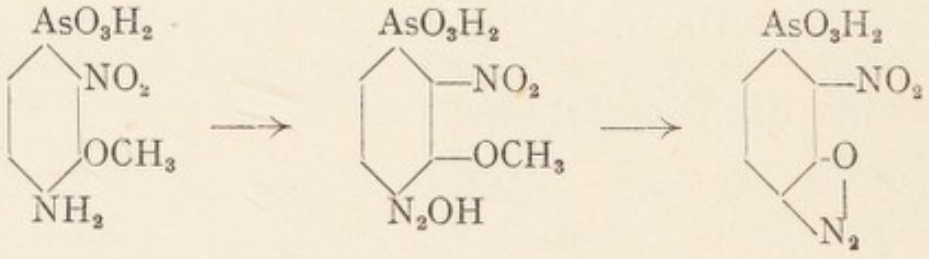


II. More soluble.

These isomerides on alkaline hydrolysis yield the corresponding nitro-*o*-anisidine-4-arsinic acids. The amino-derivative from I. reduces to a diaminoarsinic acid which loses the arsenical group on treatment with diazo-compounds



The amino-derivative from II. yields a diazo-derivative which on warming to 40–50° loses its methoxyl group and passes into a deep orange diazo-oxide.



3. *Naphthalene Homologue.*

1-*Aminonaphthyl-4-arsinic acid*,[1] $NH_2 \cdot C_{10}H_6 \cdot AsO(OH)_2$, prisms, m.p. 173–175°, produced by heating to 190° four parts of α-naphthylamine and three parts of arsenic acid ; the mixture is stirred thoroughly and next heated till the mass is violet red. The

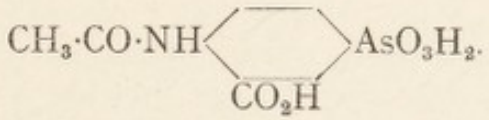
[1] W. Adler, D.R.-P., 205775 ; O. and R. Adler, *Ber.*, 1908, **41**, 934 ; Benda and Kahn, *ibid.*, 1676.

melt is extracted with aqueous alkali, the solution filtered from α-naphthylamine and concentrated when the arsinic acid is precipitated with mineral acid. The product is easily soluble in hot water or alcohol, sparingly so in ether, insoluble in petroleum or chloroform. The alkali salts are very soluble in water, being precipitated in a crystalline form by alcohol.

4. *The Aminobenzarsinic Acids.*

The acylamino-derivatives of the benzarsinic acids are prepared by the general method first employed by La Coste in the production of the unsubstituted benzarsinic acids (*v.* p. 129). The introduction of a carboxyl group into the aromatic nucleus of the acylaminoarylarsinic acids results in a lessened toxicity of the product. These acylaminoarylbenzarsinic acids are colourless, well-crystallised substances, sparingly soluble in cold water, dissolving more readily in hot water or alcohol, insoluble in ether. With alkali carbonates they form well-defined salts. On hydrolysis they yield the aminobenzarsinic acids.

2-Acetylamino-1 : 5-benzarsinic acid,



—Potassium permanganate (10 parts) in aqueous solution is added with stirring to acetyl-2-aminotolyl-5-arsinic acid (8·2 parts) dissolved in 900 parts of water at 75°. Oxidation is completed in three hours by warming to 85–90°. The mixture is then heated to boiling, the manganese hydroxides separated, and the concentrated filtrate acidified with acetic acid to precipitate any unaltered tolylarsinic acid ; the product is precipitated in the final filtrate by hydrochloric acid.

2-Acetylamino-1 : 5-benzarsinic acid decomposes at 230° ; acid or alkaline hydrolysis leads to 2-amino-1 : 5-benzarsinic acid, $NH_2 \cdot C_6H_3(CO_2H) \cdot AsO_3H_2$, decomposing at 245°.

3-Acetylamino-1 : 6-benzarsinic acid decomposes at about 260° ; it is produced from *m*-toluidine through the intermediary of 3-aminotolyl-6-arsinic acid.

p-Xylidine gives rise successively to 2-amino-*p*-xylyl-6-arsinic acid and the acetyl derivative of this compound. The latter substance on oxidation furnishes successively *3-acetylamino-1-methyl-4 : 6-benzarsinic acid*, decomposing at 255°, and *2-acetyl-*

aminoterephthal-6-arsinic acid, turning brown and decomposing at 340°.[1]

5. *Halogen Derivatives of* p-*Arsanilic Acid.*

2-Chloro-1-aminophenyl-4-arsinic acid, $NH_2 \cdot C_6H_3Cl \cdot AsO(OH)_2$, white crystals, m.p. 305°; prepared from *o*-chloroaniline and arsenic acid.[2] Also obtained by chlorinating acetyl-*p*-arsanilic acid either with chlorine in glacial acetic acid or with sodium hypochlorite in presence of water. It is sparingly soluble even in hot water, but more so in the alcohols.

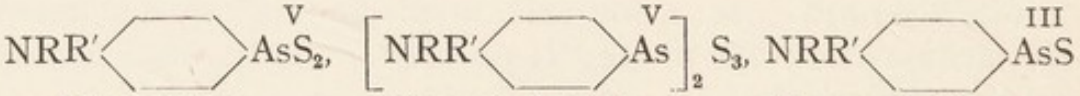
2-Bromo-1-aminophenylarsinic acid, prepared by treating *p*-arsanilic acid in glacial acetic acid with half the calculated amount of bromine; white needles, not melting below 255°.

The *iodo*-compound is obtained in colourless needles by iodinating *p*-arsanilic acid with iodine in methyl alcohol in the presence of mercuric oxide,

Dichloro-p-*arsanilic acid*, produced by chlorinating *p*-arsanilic acid in glacial acetic acid; the *dibromo*-compound is prepared from *p*-arsanilic acid and aqueous sodium hypobromite; the *di iodo*-compound is obtained by adding a 4 per cent. potassium iodide solution to a hot solution of *p*-arsanilic acid, potassium iodate, and sulphuric acid; these dihalogenated *p*-arsanilic acids crystallise in colourless needles, not melting below 250°.[3]

6. *Thio-derivatives of* p-*Arsanilic Acid and its Homologues and Derivatives.*[4]

These thio-derivatives are of three types:—



Disulphides. Sesquisulphides. Monosulphides.

They are white or yellowish-white substances, to some extent crystallisable from organic media, soluble in alkali sulphides or hydroxides and reprecipitated by acids, dissolving only sparingly in aqueous alkali carbonates and accordingly precipitated by carbon dioxide from alkaline solutions (unless containing

[1] M.L. and B., D.R.-P., 203717; O. and R. Adler, *Ber.*, 1908, **41**, 933.
[2] Benda, *Ber.*, 1908, **41**, 1676. [3] Bertheim, *Ber.*, 1910, **43**, 530.
[4] M.L. and B., D.R.-P., 205617; *cf. Ber.*, 1882, **15**, 1955; 1894, **27**, 270.

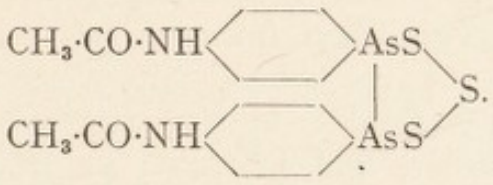
carboxyl or sulphonic substituents). On heating they melt without decomposition. These properties are comparable with those of the non-aminic organic sulphides of arsenic (*v.* pp. 75 and 82), and are further illustrations of the well-known affinity of this metalloid for sulphur.

These *p*-aminoarylarsenical sulphides have a higher toxicity than the corresponding oxygen compounds, and show a higher trypanocidal action.

p-*Aminophenylarsenious sulphide*, $NH_2 \cdot C_6H_4 \cdot AsS$, yellowish-white, crystalline powder, sinters at 165°, m.p. 180°; sparingly soluble in alcohol or acetone, easily so in aniline or pyridine, insoluble in benzene, chloroform, carbon bisulphide, or glacial acetic acid, is prepared by dissolving *p*-arsanilic acid in hydrochloric acid (D, 1·19 in $2OH_2O$) and saturating the solution with sulphuretted hydrogen. Reduction and thionation proceed concurrently, so that sulphur and monosulphide are both precipitated; the former is extracted with carbon bisulphide. The latter is also prepared by dissolving *p*-aminophenylarsenious oxide[1] in cold methyl alcohol and passing in sulphuretted hydrogen so long as a precipitate is produced. This monosulphide dissolves in warm aqueous caustic alkalis and is precipitated therefrom by mineral acids, which redissolve it in excess. Concentrated hydrochloric acid precipitates the *hydrochloride* $AsS \cdot C_6H_4 \cdot NH_2,HCl$.

It was formerly stated that arsenic is so lightly held in atoxyl that arsenious sulphide is produced by the action of sulphuretted hydrogen.

Acetyl-p-*aminophenylarsenic sesquisulphide*,



—Acetyl-*p*-arsanilic acid (80 grams) dissolved in 800 c.c. of 25 per cent. ammonia; the solution saturated with sulphuretted hydrogen diluted with water to 8 litres and acidified with hydrochloric acid. The snow-white precipitate when crystallised from alcohol separates in lustrous needles, m.p. 208°. The sesquisulphide dissolves readily in aniline or pyridine, less in alcohol or glacial acetic acid, and sparingly in toluene or chloroform.

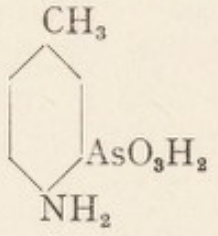
Phenylglycine-p-*arsenic disulphide*, $CO_2H \cdot CH_2 \cdot NH \cdot C_6H_4 \cdot AsS_2$,

[1] Eng. P., 17619/1907.

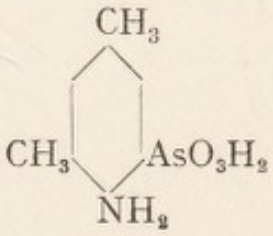
yellowish-white powder, sintering at 70°, decomposing at 142°, is prepared by dissolving phenylglycine-*p*-arsinic acid (p. 165) in 50 parts of water and saturating the solution with sulphuretted hydrogen. The disulphide is only sparingly soluble in organic media, excepting the basic solvents ; it turns yellow on exposure to light.

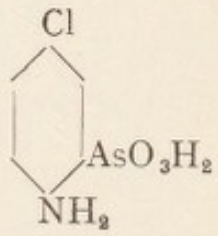
Section IV.—Homologues and Derivatives of o-*Arsanilic Acid.*

4-*Aminotolyl-3-arsinic acid* (I) [1]



I.





II.

p-Toluidine (240 grams) is melted and mixed with powdered arsenic acid (60 grams) at 60–70° ; the temperature of the mass is then raised to 195–200° within half an hour. Water and *p*-toluidine distil away and the residue is added to water and rendered alkaline with caustic soda. The unchanged *p*-toluidine is removed partly mechanically and partly with ether ; the aqueous solution is freed from arsenious and arsenic acids by addition of barium hydroxide. The filtrate is saturated with sodium chloride and just neutralised by hydrochloric acid (slight reddening of methyl-orange paper). The tarry impurity is rapidly removed when the clarified solution yields 4-aminotolyl-2-arsinic acid. Recrystallised from 50 per cent. alcohol, this product separates in colourless, felted needles, melting at 176.° It is easily soluble in hot water or the alcohols, sparingly so in ether, and insoluble in benzene. Reduced with sodium hydrosulphite, it yields a yellow arseno-derivative.

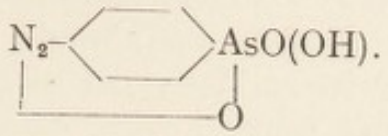
4-*Amino*-1 : 3-*xylyl*-5-*arsinic acid* (II), from *m*-xylidine by the Béchamp reaction, is a microcrystalline precipitate, m.p. 199–200°. It is converted by potassium iodide and dilute sulphuric acid at 100° into 5-iodo-4-amino-1 : 3-xylene.

4-*Chloro*-o-*arsanilic acid* (III) from *p*-chloroaniline. This and the foregoing acid have properties similar to those of 4-aminotolyl-3-arsinic acid.

[1] Benda, *Ber.*, 1909, **42**, 3621.

Section V.—Nitroso-, Azo-, Diazo-, and Triazo-phenylarsinic Acids and their Derivatives.

Benzenediazonium-4-arsinate,[1]



—*p*-Arsanilic acid is diazotisable in the ordinary way to a soluble diazonium compound which is precipitated as a sparingly soluble white double salt by phosphotungstic acid. The diazo-derivative gives the usual reactions of diazonium salts : (1) on boiling with dilute sulphuric acid it furnishes phenolarsinic acid ; (2) copper powder and hydrochloric acid lead to 4-chlorophenyl-arsinic acid ; (3) it couples with phenols and reactive aromatic bases (*e.g.*, 2 : 4-tolylenediamine).

p-*Nitrosophenylarsinic acid*, $NO \cdot C_6H_4 \cdot AsO_3H_2$.—Atoxyl (10 grams) is added to an ice-cold solution of neutralised Caro's acid (monopersulphuric acid, H_2SO_5, 200 c.c. = 1·67 O_2) and the liquid rendered faintly alkaline by sodium carbonate. After 30 minutes sufficient acid is added to redissolve any unchanged atoxyl, whilst the nitroso-compound separates in yellow crystals (yield 50 per cent. of theory). *p*-Nitrosophenylarsinic acid is readily soluble in alkalis, but dissolves only sparingly in the organic media. It reacts quantitatively with phenylhydrazine (2 mols.), setting free the nitrogen ($2N_2$) from this reducing agent. It is reduced by alkaline hydrosulphite and magnesium chloride to 4 : 4′-diaminoarsenobenzene.[2] This nitrosoarsinic acid has no curative properties.

Azo-derivatives of p-*Arsanilic Acid.*[3]

Diseases produced by the absorption and development in the system of certain pathogenic protozoa—as in sleeping sickness—have been treated on the one hand with a series of azo-dyes (*e.g.*, trypan red) and on the other with aromatic arsenicals (particularly atoxyl), and with the object of combining these two modes of attack azo-dyes have been prepared from the diazotisable *p*-arsanilic acid containing arsenic attached to benzene nuclei.

Monoazo-dyes.—*p*-Arsanilic acid is diazotised and coupled

[1] Kuratorium der Georg und Franziska Speierschen Studienstiftung in Frankfort A/M., D.R.-P., 205449. [2] Karrer, *Ber.*, 1912, **45**, 2065.

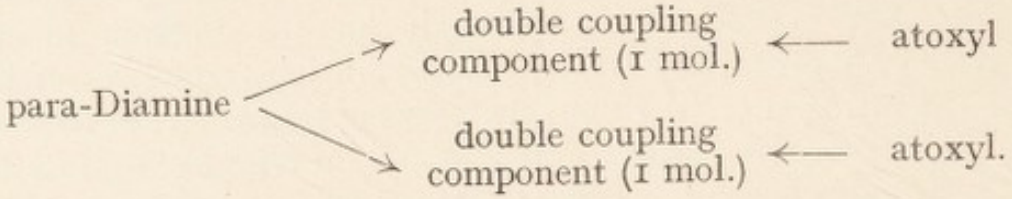
[3] Aktien Gesellschaft für Anilin Fabrikation, D.R.-P., 212018, 212304, 222063, 216223 ; *cf.* Noelting, *Bull. Soc. chim.*, 1916 [iv], **19**, 361 (Mordant dyes from *p*-arsanilic acid).

with alkaline β-naphthol, β-naphthol-3 : 6-disulphonic acid (R salt), 8-amino-α-naphthol-3 : 6-disulphonic acid (H acid in alkaline or acid solution), or naphthionic acid.

Polyazo-dyes.—A para-diamine, such as benzidine, diazotised and coupled with 8-amino-α-naphthol-3 : 6-disulphonic acid (H acid) in acid solution. The violet diazo-dye is dissolved in sodium carbonate and coupled with diazotised atoxyl (1 or 2 mols.). An isomeric dye is produced by coupling diazotised atoxyl with H acid in acetic acid and then treating the resulting monoazo-dye (2 mols.) with diazotised benzidine (1 mol.).

Further variations in the composition of these polyazo-dyes are produced by changing the diamine (replacing benzidine by tolidine or dichlorobenzidine) and by substituting for H acid some other double coupling middle component such as 2-amino-5-naphthol-7-sulphonic acid (J acid), 1 : 8-aminonaphthol-4-sulphonic acid (S acid), and 1 : 8-dihydroxynaphthalene-3 : 6-disulphonic acid (chromotrope acid).

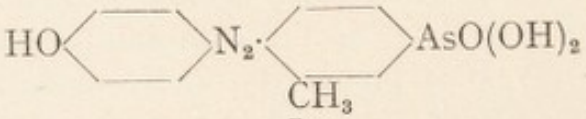
The following diagram gives a general representation of the constitution of these polyazo-dyes containing arsenic : the arrows indicate the direction in which the diazotised component is coupled.



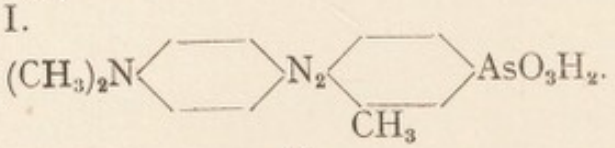
These polyazo-arsenical dyes have a greater trypanocidal action than the monoazo-dyes and are 2½ times less lethal than atoxyl to the host of the trypanosomes.

The following monoazo-derivatives of 2-aminotolyl-5-arsinic acid are only slightly active towards trypanosomes.[1]

4-*Hydroxybenzene-2-azotoluene-5-arsinic acid* (I.),



I.



II.

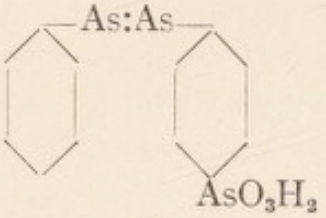
[1] Barrowcliff, Pyman, and Remfry, *Chem. Soc. Trans.*, 1908, **93**, 1899.

4-Dimethylaminobenzene-2'-azotoluene-5'-arsinic acid (II.).

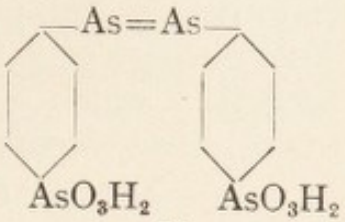
Nitrosophenylarsinic acid[1] (p. 179) serves for the preparation of azo-derivatives of *p*-arsanilic acid.

Azobenzene-4-arsinic acid (I.), brown, amorphous powder, soluble in alkalis, is prepared by condensing the nitroso-derivative with aniline in boiling glacial acetic acid.

Azobenzene-4 : 4'-diarsinic acid (II.)



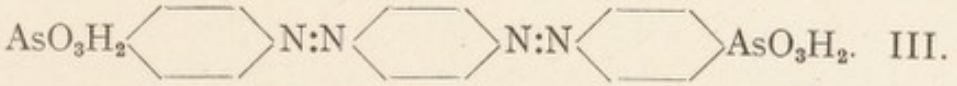
I.



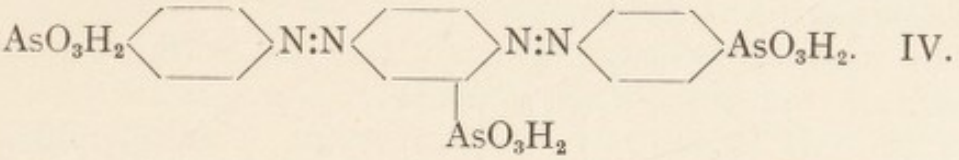
II.

is similarly obtained from the nitroso-derivative and *p*-arsanilic acid, a dark brown powder easily soluble in alkalis to a yellowish-green solution.

Disazobenzene-4 : 4'-diarsinic acid (III.) *and Disazobenzene-4 : 2'' : 4'''-triarsinic acid* (IV.) are prepared from the nitroso-derivative and *p*-phenylenediamine and *p*-phenylenearsinic acid respectively.

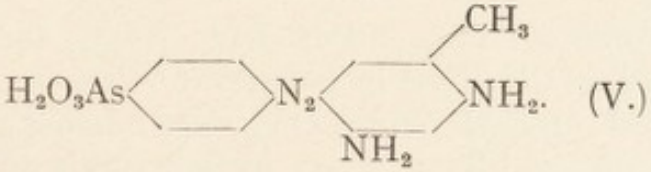


III.



IV.

Benzeneazo-2 : 4-tolylenediamino-4'-arsinic acid (V.),



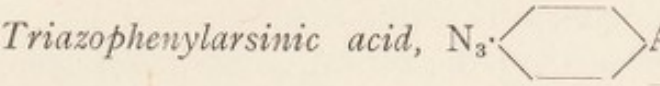
(V.)

—Prepared by coupling *p*-diazobenzenearsinic acid and *m*-tolylenediamine or by condensing this base with nitrosophenylarsinic acid and hydroxylamine in alkaline solution. Of the foregoing azoarsinic acids, No. V. is the most toxic and No. II. the least.[2]

[1] Karrer, *Ber.*, 1912, **45**, 2065.

[2] *Monoazo*-derivatives of *p*-arsanilic acid, *v.* Ehrlich and Bertheim, *Ber.*, 1907, **40**, 3297; D.R.-P., 205449; Eng. P., 3929/1907; L. Benda, *Ber.*, 1911, **44**, 3878, 3295, 3300.

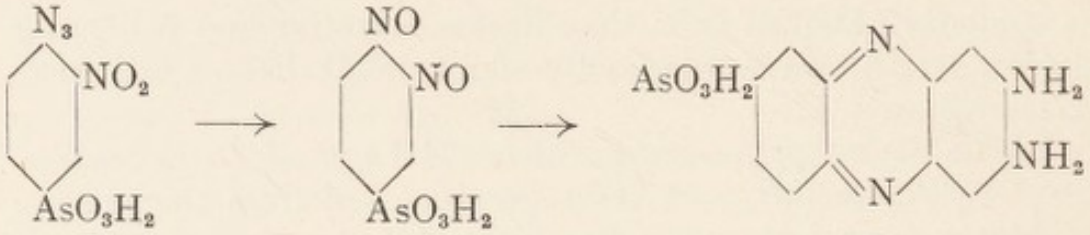
Triazo-derivatives of Phenylarsinic Acid.

4-*Triazophenylarsinic acid*,  , stout, colourless crystals obtained by adding sodium azide to diazophenylarsinic acid.

3-*Nitro-4-triazophenylarsinic acid* (I.), yellow, crystalline powder from diazotised 3-nitro-4-aminophenylarsinic acid and sodium azide, loses nitrogen at 75° and changes into 3 : 4-*dinitrosophenylarsinic acid* (II.), which in turn condenses with dimethylamine to form 2 (or 3)-*dimethylaminophenazine-7-arsinic acid*,

$$C_{14}H_{12}O_3N_3As,$$

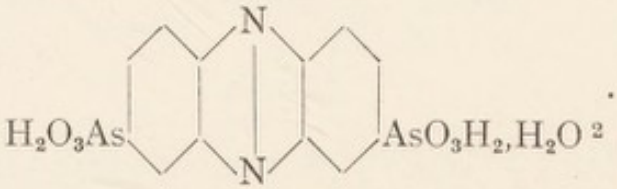
a blue dye soluble in acetic acid or in aqueous alkalis.



I. II. III.

3-Nitro-4-triazophenylarsinic acid and *o*-phenylenediamine condense in acetic acid to the brick-red acetate of the yellow base 2 : 3-*diaminophenazine-7-arsinic acid* (III.).[1]

Phenazine-2 : 7-bisarsinic acid,



—Powdered ammonium persulphate (23 grams) is slowly added to *p*-arsanilic acid dissolved in warm water (100 c.c.) and 15 c.c. of concentrated sulphuric acid. On gently heating a brisk evolution of gas occurs and light brown, leafy crystals separate. This phenazine derivative is insoluble in water and dissolves only sparingly in alcohol or acetic acid ; it does not melt below 300°. Its homologue from 2-aminotolyl-5-arsinic acid is prepared by the same method and has similar properties. Both acids give a deep red coloration with concentrated sulphuric acid. They have but little trypanocidal action.

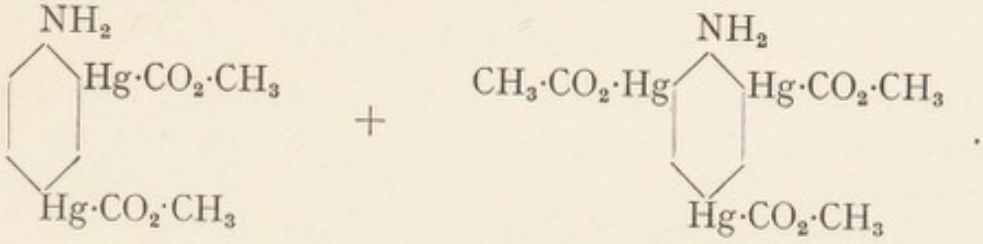
[1] Karrer, *Ber.*, 1913, **46**, 249; *cf.* Barrowcliff.

[2] Pyman and Remfry, *Chem. Soc. Trans.*, 1908, **93**, 1893.

Section VI.—Organo-mercurial Compounds of p-*Arsanilic Acid and its Derivatives.*

The beneficial results accruing in syphilis from the joint application of mercurial drugs and organic arsenical compounds have led to attempts to combine these useful effects in the same drug. With this end in view atoxyl and its derivatives have been condensed with mercuric acetate, it being well known that mercuriacetate groups are readily introduced into the aromatic nucleus when amino- and hydroxy-groups are already present.

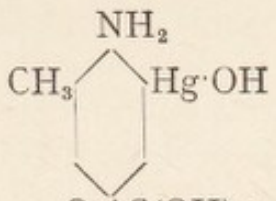
Aniline, for instance, when heated with mercuric acetate gives rise to a mixture of di- and tri-mercuriacetate derivatives,



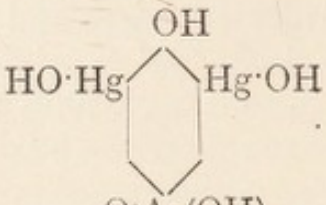
Atoxyl (329 grams) in water (1700 c.c.) is mixed with mercuric acetate (636 grams) dissolved in 1800 c.c. of water. The mixture is heated at 100° for five hours, the precipitated solid—a mercuric salt of the organomercurial compound—is boiled with 1200 c.c. of 10 per cent. aqueous sodium hydroxide, and the filtered solution is acidified with 120 grams of glacial acetic acid. The complex organomercurial acids thus precipitated are dissolved in a slight excess of aqueous sodium hydroxide ; the solution when gradually concentrated, yields successively *sodium* 3 : 5-*dihydroxymercuri*-4-*aminophenylarsinate*, $C_6H_6O_5NAsHg_2Na_2,4H_2O$, sparingly soluble needles, and *sodium* 3-*hydroxymercuri*-4-*aminophenylarsinate*, $C_6H_6O_4NAsHgNa_2,14H_2O$, readily soluble crystals. The corresponding free acids have the following constitutional formulæ :—

They are obtained in flattened crystals on treating the foregoing sodium salts with acetic acid. A similar treatment applied to methylatoxyl (Kharsin) leads to the production of a monohy-

droxymercuri-compound of which the free acid 3-hydroxymercuri-2-aminotolyl-5-arsinic acid has the composition I.; its *sodium* salt, $C_7H_8O_4NAsHgNa_2,9H_2O$, needles, is soluble in one part of water.



I.



II.

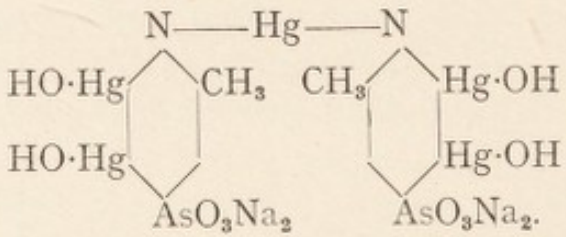
4-Hydroxyphenylarsinic (phenol-4-arsinic) acid yields 3:5-dihydroxymercuri-4-hydroxyphenylarsinic acid, II., a crystalline, insoluble compound forming a *sodium* salt,

$$C_6H_4O_6AsHg_2Na_3,5H_2O,$$

soluble in 3 parts of water. Similar mercuri-derivatives were obtained from 2-hydroxytolyl-5-arsinic acid and from the azo-compound, $HO\cdot C_6H_4N_2\cdot C_6H_3(CH_3)\cdot AsO(OH)_2$, having respectively the compositions $HO\cdot HgC_6H_3(CH_3)(OH)\cdot AsO(OH)_2$ and the latter $(HO\cdot Hg)_2C_6H_2(OH)\cdot N_2\cdot C_6H_3(CH_3)\cdot AsO(OH)_2$. The sodium salts of these insoluble acids are readily soluble in water.[1]

The mercury in the foregoing compounds is in a non-ionised condition. These compounds, which do not coagulate albumin, are satisfactory as regards toxicity and are suitable for hypodermic injection.

A further addition to the list of organomercurials is the product of the interaction of mercuric oxide and "orsudan." This complex derivative, which has been tested clinically under the name of "Hydryl," has the composition



On physiological tests this substance gave promising results but clinical experiments failed to establish its value in protozoal diseases.[2]

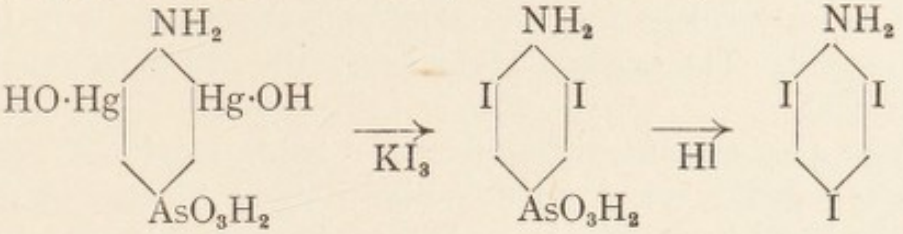
The orientation of the hydroxymercuri-group in the foregoing compounds is ascertained by treatment of the sodium salts

[1] Wellcome and Barrowcliff, Eng. P., 12472/1908.

[2] Jowett, private communication.

with iodine dissolved in aqueous potassium iodide when the mercuri-groups were displaced by iodine. Further treatment with hot hydriodic acid leads to the removal of the arsenical group, this giving rise to a polyiodo-compound of known constitution.

These reactions take the following course in the case of the dihydroxymercuri-derivative of *p*-arsanilic acid,



The other mercurated arsenical compounds undergo similar successive iodinations.

Section VII.—4 : 4′-*Diaminodiarylarsinic Acids.*

These acids were discovered as the result of a systematic study of the Béchamp reaction as applied to aniline and *o*-toluidine,

4 : 4′-*Diaminodiphenylarsinic acid*, $(NH_2 \cdot C_6H_4)_2AsO \cdot OH$, colourless matted needles, m.p. 248–249° (232°), is very sparingly soluble in water or the ordinary organic solvents. It is moderately soluble in glacial acetic acid and readily so in dilute alkalis or mineral acids in excess.

This acid is a by-product of the Béchamp condensation with aniline arsenate and aniline at 180°. The crude product is extracted with 10 per cent. aqueous sodium carbonate, the extract concentrated and acidified with hydrochloric acid. The precipitate digested with just sufficient aqueous caustic soda to give a faintly alkaline solution leaves undissolved the crude diaminodiphenylarsinic acid, which is converted into barium salt, the latter being crystallised from water with addition of animal charcoal until colourless. The purified barium salt is then decomposed with the calculated amount of hydrochloric acid, when the acid is obtained as a dense, white precipitate of matted needles. The yield is about 2–3 per cent. of the calculated quantity.[1] This by-product [2] is also isolated by dissolving the whole of crude arsinic acids in hot caustic soda, decolorising with animal charcoal and pouring the filtered solution into 2 volumes of alcohol, when sodium *p*-arsanilate (atoxyl) is for the most part precipitated, whereas the secondary diphenylarsinate remains entirely

[1] Pyman and Reynolds, *Chem. Soc. Trans.*, 1908, **93**, 1184.

[2] Benda, *Ber.*, 1908, **41**, 2367.

dissolved. After twelve hours the atoxyl is collected, the filtrate evaporated to a small bulk and treated with excess of alcohol to precipitate the remainder of the primary arsinate. The filtrate is evaporated to remove alcohol and treated with hydrochloric acid when the crude secondary arsinic acid evaporates. This material is redissolved in dilute caustic soda and reprecipitated in pulverulent form by acidifying cautiously with hydrochloric acid. The product is then crystallised from 50 per cent. acetic acid.

With 4:4′-diaminodiphenylarsinic acid, sulphuric acid and potassium iodide yield *p*-iodoaniline; silver nitrate in neutral solution furnishes a white precipitate, barium chloride gives no precipitate, and magnesia mixture in ammoniacal solution gives no precipitate even on warming (unlike *p*-arsanilic acid).

Sodium 4:4′-diaminodiphenylarsinate,

$$(NH_2 \cdot C_6H_4)_2AsO \cdot ONa, 2,5\text{–}6H_2O,$$

monoclinic plates soluble in an equal weight of water to an alkaline solution and very soluble in alcohol. *Barium* salt, $Ba[O \cdot OAs(C_6H_4 \cdot NH_2)_2]_2, 7\frac{1}{2}H_2O$, soluble in twice its weight of water and sparingly soluble in alcohol.

Diacetyl derivative, rosettes of needles, m.p. 275°, readily soluble in hot water, crystallising therefrom with $3H_2O$. *Sodium* salt, prismatic needles, contains $9H_2O$.

2:2′-Diaminoditolyl-5-arsinic acid,

$$[NH_2 \cdot C_6H_3(CH_3)]_2AsO \cdot OH,$$

highly refractive acicular prisms from hot water or 35 per cent. acetic acid, m.p. 247–249°.

The yield of this acid is about 3 per cent. from the Béchamp condensation with 200 grams of *o*-toluidine arsenate and 400 grams of *o*-toluidine at 180–190°. The product is extracted with 10 per cent. aqueous sodium carbonate and the solution concentrated to the crystallising point. Sodium 2-aminotolyl-5-arsinate separates and is washed with alcohol; the filtrates are concentrated and the crude secondary arsinic acid precipitated by hydrochloric acid. The precipitate is dissolved in aqueous sodium hydroxide and the sodium salt allowed to separate, after which it is recrystallised from water. The acid, when boiled with dilute sulphuric acid and potassium iodide, furnishes a good yield of 5-iodo-*o*-toluidine.

The *sodium* salt, $[NH_2 \cdot C_6H_3(CH_3)]_2AsO \cdot ONa, 7\frac{1}{2}H_2O$, dissolves in $1\frac{1}{2}$ times its weight of water to an alkaline solution; it dissolves very readily in alcohol.

Diacetyl-2 : 2′-diaminotolyl-5-arsinic acid,

$$[CH_3{\cdot}CO{\cdot}NH{\cdot}C_6H_3(CH_3)]_2As{\cdot}OH,$$

from hot water in refractive prisms, m.p. 242–244°, containing $2/3H_2O$. The *sodium* salt is soluble in twice its weight of cold water and is very soluble in alcohol ; it contains $6H_2O$.

Triaminotriarylarsine Oxides.[1]

A small yield of an uncrystallisable substance having the properties of a *triaminotriphenylarsine oxide* was obtained by prolonged boiling of aniline (750 grams) and arsenious chloride (150 grams) in benzene (500 grams) or in toluene. This triamine yielded a *tribenzoyl* and a *triacetyl* derivative melting respectively at 130–140° and 140–150°.

Section VIII.—Mixed Aromatic-aliphatic p-*Amino-arsinic Acids.*[2]

p-*Aminophenylmethylarsinic acid,*

$$NH_2{\cdot}C_6H_4As(CH_3)O{\cdot}OH,$$

crystalline powder, m.p. 201°, is obtained by the general method from *p*-aminophenylarsenious oxide and methyl iodide. The iodine is preferably removed by the moist silver chloride method, the arsinic acid obtained direct from the filtrate and crystallised from alcohol-ether.

Acetyl-p-*aminophenylmethylarsinic acid,*

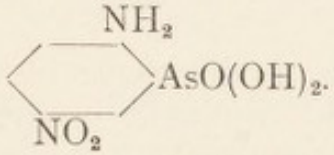
$$CO{\cdot}CH_3{\cdot}NH{\cdot}C_6H_4As(CH_3)O{\cdot}OH,$$

prepared in good yield by the general method, crystallises from hot water in prisms melting at 260°.

These secondary arsinic acids are all well crystallised compounds extremely resistant to oxidation by the action of nitric acid.

Section IX.—Nitro-derivatives of the Arsanilic Acids.

5-*Nitro-2-aminophenylarsinic acid,*[3]



Although, as a rule, para-substituted aromatic bases give

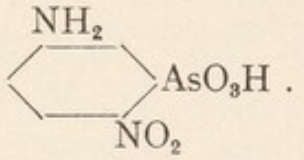
[1] Morgan and Micklethwait, *Chem. Soc. Trans.*, 1909, **95**, 1474.

[2] Bertheim, *Ber.*, 1915, **48**, 350.

[3] M.L. and B. 243693 and Eng. P., 29196/1911 ; Benda, *Ber.*, 1911, **44**, 3294.

unfavourable results in the Béchamp condensation (*v.* p. 178), yet *p*-nitroaniline behaves exceptionally in giving a relatively good yield of arsinic acid. This base (70 parts) is thoroughly mixed with arsenic acid (20 parts) and heated to 210°. Water distils off ; the viscid mass is then added to water (250 parts) and rendered alkaline with sodium carbonate (20 parts). The filtered solution is saturated with salt, extracted with ether and then carefully acidified with hydrochloric acid, when 5-nitro-2-aminophenylarsinic acid separates as a lemon-yellow powder crystallising from hot water in yellow needles, m.p. 235–236°. It is readily soluble in ammonia, in alkali hydroxides, carbonates or acetates, or in warm alcohol ; sparingly soluble in cold mineral acids. The diazonium compound, prepared by adding sodium nitrite to the arsinic acid suspended in acid, is almost colourless and couples readily to form azo-derivatives.

2-Nitro-5-aminophenylarsinic acid[1] (*6-Nitro*-m-*arsanilic acid*),

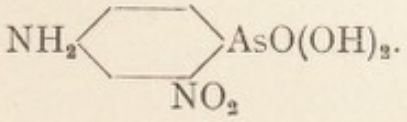


3-Aminophenylarsinic acid (*m*-arsanilic acid) is converted into its *oxalyl* derivative, which crystallises from water in acicular aggregates. When dissolved in 3 parts by weight of concentrated sulphuric acid and nitrated at 0° to 5° with the calculated amount of nitric–sulphuric acid (26 per cent. HNO_3) this oxalyl compound is converted into a nitro-derivative isolated by pouring the mixture on to ice. 6-Nitro-3-aminophenylarsinic acid is prepared by boiling this product with 10 parts of 2*N*-hydrochloric acid when it separates from solution in light yellow needles. By boiling this compound with strong aqueous caustic potash, the amino-group is eliminated and 2-nitro-5-hydroxyphenylarsinic acid is obtained, which, with warm sodium hydrosulphite, undergoes reduction to 2 : 2′-diamino-5 : 5′-dihydroxyarsenobenzene, an isomeride of salvarsan.

The mother liquors of the above nitration contain a very small amount of the isomeric 2-nitro-3-aminophenylarsinic acid.

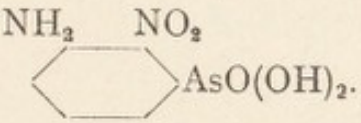
[1] M.L. and B., D.R.-P., 261643.

2-Nitro-4-aminophenylarsinic acid,[1]



—2-Nitro-4-acetyl-*p*-phenylenediamine [2] (4 kilos.) dissolved in concentrated hydrochloric acid (10 litres) and water (15 litres) is diazotised with sodium nitrite and treated with sodium arsenite (5 grams) in 10 litres of water, the mixture being gradually warmed by the introduction of steam. So soon as the diazo-reaction has disappeared, the filtered solution is heated in a reflux apparatus for several hours, when 2-nitro-4-aminophenylarsinic acid separates on cooling in orange-yellow needles, darkening at 240°, decomposing at 258°. This compound is sparingly soluble in cold water, dilute mineral acids, or alcohol, dissolving more readily in methyl alcohol, glacial acetic acid, alkalis or sodium acetate. The acetyl derivative which arises as an intermediate product in the foregoing reaction crystallises in yellowish-white, acicular crystals readily soluble in hot water, alcohol, glacial acetic acid, or alkalis, and only sparingly so in dilute mineral acids.

2-Nitro-3-aminophenylarsinic acid,[3]



—The compound is obtained indirectly from *m*-aminophenylarsinic acid, which is converted into *urethane* derivative,

$$AsO(OH)_2 \cdot C_6H_4 \cdot NH \cdot CO_2 \cdot C_2H_5,$$

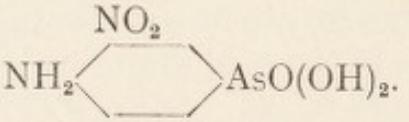
by adding ethyl chlorocarbonate to its solution in dilute hydrochloric acid at 0° to 5°. This product is precipitated with more hydrochloric acid ; it crystallises from hot water in well-defined needles, decomposing at 180°.

This urethane derivative (289 grams) is dissolved in 5 parts of cold concentrated sulphuric acid and nitrated at 0° to 5° with 245 grams of nitric–sulphuric acid (26 per cent. HNO_3). After an hour at 15° the solution is poured on to ice, when the nitro-urethane derivative slowly separates as a yellow, crystalline powder, sparingly soluble in water, dissolving easily in alkalis to yellowish-red solutions. This product is hydrolysed by heating with 8–10 parts of concentrated sulphuric acid at 70–80° until the

[1] M.L. and B., D.R.-P., 267307. [2] *Ber.*, 1897, **30**, 980.
[3] M.L. and B., D.R.-P., 256343.

evolution of carbon dioxide ceases, when the solution is poured on to ice. 2-Nitro-3-aminophenylarsinic acid separates and is purified by dissolving in dilute aqueous alkali, and reprecipitating with acid it forms orange-yellow needles sparingly soluble in hot water or in dilute mineral acids.

3-*Nitro-4-aminophenylarsinic acid*,[1]



—The nitration of acetyl-*p*-arsanilic acid does not proceed smoothly and no homogeneous nitro-product is obtainable, but the reaction is readily effected with oxalyl-*p*-arsanilic acid (p. 161). A mixture of 26 c.c. of nitric acid (D = 1·4) and 26 c.c. of concentrated sulphuric acid is slowly added with stirring to 115·6 grams of oxalyl-*p*-arsanilic acid in 300 c.c. of concentrated sulphuric acid at 10–20°. The strongly acidic solution is then added to 1500 c.c of water, when a white, crystalline mass of the mononitro-compound, $CO_2H{\cdot}CO{\cdot}NH{\cdot}C_6H_3(NO_2){\cdot}AsO(OH)_2$, separates. The mixture is boiled in a reflux apparatus for one hour and the yellow solution filtered, when 3-nitro-4-aminophenylarsinic acid separates on cooling as a bulky precipitate of pale sulphur-yellow needles. It is moderately soluble in methyl alcohol or 50 per cent. acetic acid, sparingly so in glacial acetic acid or acetone, and dissolves readily in aqueous alkalis or hot concentrated hydrochloric acid.

3-Nitro-4-aminophenylarsinic acid is also prepared through the urethane derivative of *p*-arsanilic acid.

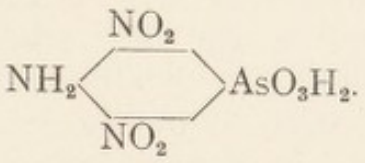
Urethane derivative, $C_2H_5{\cdot}O{\cdot}CO{\cdot}NH{\cdot}C_6H_4{\cdot}AsO(OH)_2$.—*p*-Arsanilic acid (217 grams) and 57 grams of caustic soda solution (D = 1·375) are dissolved in 1 litre of ice-cold water and treated with 130 grams of ethyl chlorocarbonate and 114 grams of caustic soda solution (D = 1·375) so that the liquid remains alkaline. The urethane is precipitated by acid in felted needles, decomposing at 230–240°. This compound (289 grams) dissolved in 1500 grams of concentrated sulphuric acid is treated at 0–5° with 245 grams of concentrated nitric–sulphuric acids containing 26 per cent. HNO_3. The mixture is stirred at 15° for half an hour and then poured on to ice, when the nitro-urethane derivative separates as a pale yellow powder crystallising from alcohol in yellowish needles, sparingly soluble in hot water and dissolving readily in aqueous

[1] M.L. and B., D.R.-P., 231969, 232879; Bertheim, *Ber.*, 1911, **44** 3093.

alkalis to an intensely yellow solution. It is hydrolysed by heating at 60–80° with 10 parts of concentrated sulphuric acid till all the carbon dioxide has been evolved. The solution is then poured on to ice and the crude 3-nitro-4-aminophenylarsinic acid crystallises from dilute acetic acid in yellow needles, deflagrating on heating.

3-Nitro-4-aminophenylarsinic acid[1] is also obtained by heating *o*-nitroaniline and arsenic acid at 200–210° for ten minutes, being extracted from the mixture with 10 per cent. aqueous caustic soda and reprecipitated by acid. Crystallised from hot water it is a yellow, microcrystalline powder soluble in the ordinary organic solvents. When treated with hydriodic acids it yields successively 2-nitro-1-aminophenylarsenious iodide and 4-iodo-2-nitroaniline.

3 : 5-*Dinitro*-p-*arsanilic acid*,[2]



—*p*-Arsanilic acid (44 grams) dissolved at 5–10° in concentrated sulphuric acid (120 c.c.) is nitrated with 56 grams of mixed nitro-sulphuric acid (44·7 per cent. HNO_3), the temperature rising to 10–15°. After three hours the mixture is added to 500 grams of ice ; the solid product consists of 3 : 5-dinitro-*p*-arsanilic acid and 2 : 4 : 6-trinitroaniline, the latter being removed by ether whilst the liquid contains *p*-diazobenzenearsinic acid.

3 : 5-Dinitro-*p*-arsanilic acid purified by dissolving in alkali, reprecipitating by mineral acid and crystallising from 50 per cent. acetic acid, separates in brownish-yellow needles or leaflets.

With 40-50 per cent. caustic potash this dinitro-compound develops a violet coloration changing to brownish-red. It is not diazotisable and gives no characteristic coloration with alcoholic potash. Bromine added to an alkaline solution removes the arsenical group, producing 4-bromo-2 : 6-dinitroaniline.

Nitro-derivatives of p-*Dimethylaminophenylarsinic Acid*.[3]

p-Dimethylaminophenylarsinic acid nitrates smoothly to a series of definite compounds, and in this respect differs greatly

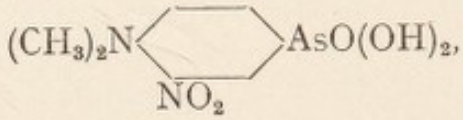
[1] Mameli, *Boll. Chim. Farm.*, 1909, **48**, 682.

[2] Benda, *Ber.*, 1912, **45**, 53.

[3] Poulenc and K. Oechslin, Fr. P., 449373, 451078; *Cf.* Eng. P., 22521/1914.

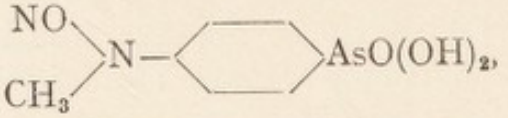
from *p*-arsanilic acid, the nitro-derivatives of which are obtainable only by a circuitous route, generally through the oxanilido-compound. The importance of these nitrations lies in the facts that (1) *p*-dimethylaminophenylarsinic acid is readily prepared from easily accessible reagents, dimethylaniline and arsenious chloride; (2) the dimethylamino-complex is removable quantitatively by hydrolysis, the products being nitrophenolarsinic acids available for the preparation of salvarsan and its analogues (*v.* p. 230).[1]

4-*Dimethylamino*-3-*nitrophenylarsinic acid*,



golden-yellow needles, m.p. 204°, sparingly soluble in alcohol or hot water. In its preparation a mixture of nitric acid (D 1·49, 35 grams) and 60 per cent. sulphuric acid (150 grams) is added slowly to *p*-dimethylaminophenylarsinic acid (100 grams) dissolved in 60 per cent. sulphuric acid (250 grams). The temperature is allowed to rise to 35–40°; the mixture is maintained for half an hour at 30–35°, and then poured on to broken ice. The yellow precipitate is dissolved in aqueous sodium carbonate, reprecipitated from the filtered solution by very dilute mineral acid, and the product purified further by crystallisation from hot water. When heated with dilute aqueous sodium hydroxide this compound is hydrolysed to 3-nitro-4-hydroxyphenylarsinic acid (*v.* p. 201). The foregoing nitration may also be effected in concentrated sulphuric acid by keeping the temperature below 15°; the same proportions of reagents are employed, and the purification is carried out in a similar manner.

4-*Methylnitrosoaminophenylarsinic acid*,



almost colourless crystals, decomposing at 190°, obtained by nitrating *p*-dimethylaminophenylarsinic acid in more dilute solutions. A solution of sodium nitrate (190 grams) in 1 litre of sulphuric acid (1 to 4) is added to 500 grams of p-dimethylaminophenylarsinic acid in 2 litres of dilute sulphuric acid (1 to 4), the mixture being slowly heated to 85–90°. The

[1] Meyer and Oechslin, Fr. P., 474056.

yellow solution assumes a brown colour, and after one hour the liquid is allowed to cool, when the nitrosoamine separates in yellowish-brown, spear-shaped crystals. This product is dissolved in aqueous sodium carbonate and reprecipitated from the filtered solution by dilute mineral acid. The mother liquor from which the nitrosoamine has separated contains a certain amount of the preceding nitro-compound.

In the first of the patents cited and in the provisional specification of the English patent this nitrosoamine is described as an isomeric dimethylaminonitrophenylarsinic acid (*v.* p. 191).

4-Methylnitrosoaminophenylarsinic acid[1] is prepared in a state of purity and free from nitro-compounds by adding sodium nitrite (84 grams) in 500 c.c. of 60 per cent. sulphuric acid to *p*-dimethylaminophenylarsinic acid dissolved in 300 c.c. of 60 per cent. sulphuric acid at 0°. The reaction is accompanied by evolution of gas, and the liquid when poured on to ice gives a precipitate of the almost colourless nitrosoamine. The concentration of the sulphuric acid may be varied considerably, or it may be replaced by hydrochloric acid.

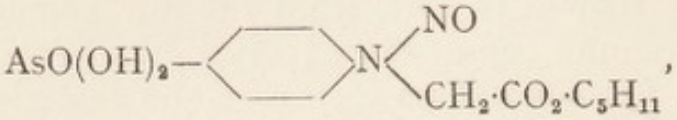
Isomeric 4-Dimethylaminodinitrophenylarsinic Acids.

Nitric acid (1400 c.c. of 30 per cent. HNO_3) is added to 100 grams of *p*-dimethylaminophenylarsinic acid in 600 c.c. of dilute sulphuric acid (1 to 4). The mixture is heated at 40° for two hours, then left in the cold for three days, when a golden-yellow precipitate is obtained. This product dissolved in aqueous sodium carbonate, reprecipitated by dilute sulphuric acid and crystallised from hot water, alcohol, or acetone, separates in rosettes of bright yellow, prismatic crystals and melts at 161° with decomposition.

The mother liquor from the yellow dinitro-compound yields small, red, four-sided plates, less soluble than the yellow compound in hot water, and melting with decomposition at 158°. Both products are dinitro-compounds, but it has not been ascertained whether they are chromo-isomerides having the same orientation of substituent groups or whether the nitro-groups occupy different positions in the aromatic nucleus.

[1] Poulenc, Eng. P., 22522/1914, Fr. P., 479646.

The *amyl ester* of N-*nitrosophenylmethylglycine-4-arsinic acid*,

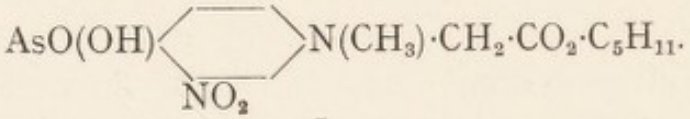


colourless crystals from hot dilute acetic acid (1 : 4) decomposing at 150°, is prepared by adding sodium nitrite to phenylmethylglycine-4-arsinic acid in dilute sulphuric acid. The intermediate product is obtained by warming dimethylaniline with amyl chloroacetate when methyl chloride is eliminated. These nitrosoamines of phenylarsinic acid lose the nitroso-group by heating with strong hydrochloric acid and yield *N*-monoalkylaminophenylarsinic acids. On reduction they yield hydrazine derivatives.

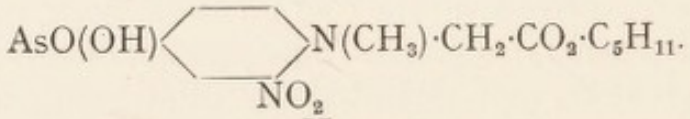
Ortho- and Meta-nitro-derivatives of Phenylalkylglycinearsinic Acids and their Reduction Products.[1]

The phenylalkylglycinearsinic acids and their *C*-esters (esterified in the glycine group) are readily nitrated in sulphuric acid, and the orientation of the nitro-group depends on the concentration of this acid.

The following esters are produced by nitrating the *C*-amyl ester of phenylmethylglycinearsinic acid.



I.

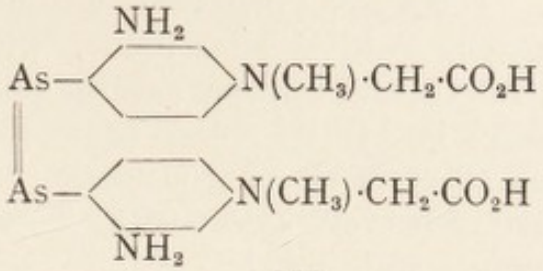


II.

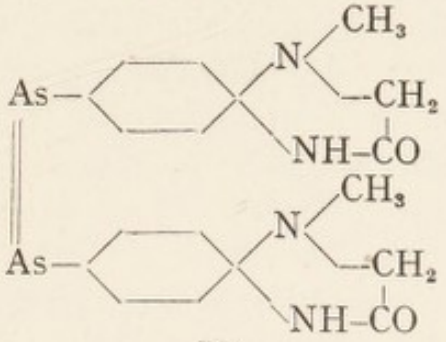
No. I. is produced by adding nitric acid (1 mol.) in 30 grams of sulphuric acid (3 : 2) to the *C*-amyl ester (50 grams) dissolved in 228 grams of strong sulphuric acid and 152 grams of water. It is an intensely yellow substance, sparingly soluble in hot water, dissolving easily in alcohol, and melting at 130°. No. II. is produced by adding nitric acid (1 mol.) in 30 grams of sulphuric acid (1 : 3) to the *C*-amyl ester (50 grams) dissolved in 300 grams of sulphuric acid and 100 grams of water. When hydrolysed with excess of aqueous sodium hydroxide these esters yield the corresponding free glycinearsinic acids. These substances behave very differently on reduction with alkaline sodium hydrosulphite.

[1] Poulenc and K. Oechslin, Fr. P., 473705.

The free acid of No. I. gives rise to the reduction product III., whilst the acid of No. II. furnishes an internal amide which is



III.



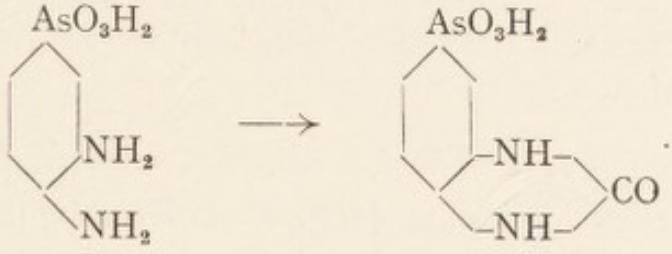
IV.

insoluble in the acids, alkalis, and ordinary organic solvents. Reduction product No. III. is soluble in alkalis and its alkali salt is precipitated by alcohol.

Section X.—Diaminophenylarsinic Acids.

2 : 3-*Diaminophenylarsinic acid*,[1] $(NH_2)_2C_6H_3 \cdot AsO_3H_2$, melting and decomposing at 205–208°, is produced by the mild reduction of 2-nitro-3-aminophenylarsinic acid (p. 189) with sodium hydrosulphite at the ordinary temperature. This diamine gives an azoimide with nitrous acid.

3 : 4-*Diaminophenylarsinic acid*,[2]



I. II.

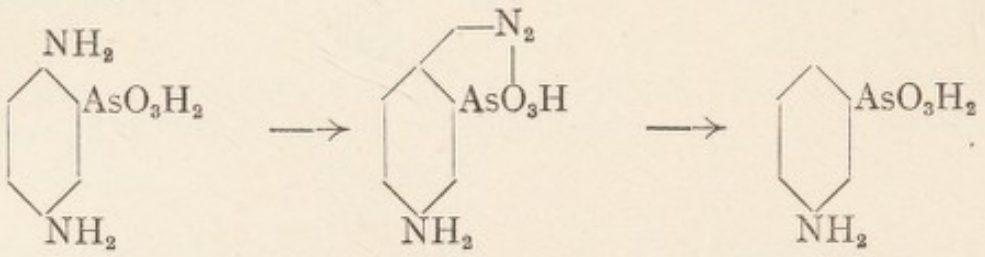
—3-Nitro-4-aminophenylarsinic acid is reduced with alkaline hydrosulphite at −1°, the temperature rising to +28°. After boiling with animal charcoal the filtered solution is cooled,

[1] M. L. and B., D.R.-P., 256343. [2] Bertheim, *Ber.*, 1911, **44**, 3092.

neutralised with hydrochloric acid, and concentrated when 3 : 4-diaminophenylarsinic acid (I.) separates in colourless prisms containing $\frac{1}{2}H_2O$. The product behaves as a typical *orthodiamine* yielding with nitrous acid a diazoimine, with phosgene a *carbamide* derivative II., and with phenanthraquinone an azine.

This diamino-acid is 25 times less toxic than atoxyl; it exhibits a healing effect in sleeping sickness, but the curative dose produces certain nervous disorders as a secondary action.

p-*Phenylenediaminearsinic acid*,[1]



I. II. III.

—5-Nitro-2-aminophenylarsinic acid (78 grams) dissolved in water (900 c.c.) and 10*N*-sodium hydroxide (480 c.c.) is treated slowly with 500 c.c. of 20·6 per cent. ferrous chloride solution, the mixture being kept alkaline to turmeric. The filtrate treated with sulphuric acid until it turns Congo red paper brown slowly deposits *p*-phenylenediaminearsinic acid in colourless needles soluble in hot water, dilute mineral acids, alkalis, or aqueous sodium acetate, but dissolving only sparingly in alcohol. At 210–215° it decomposes; when exposed to light it assumes a violet tint. When diazotised it requires only one molecular proportion of nitrite; its diazo-derivative II. couples readily with resorcinol and β-naphthol, but only slowly with R-salt. The aqueous solution of diazo-compound when treated in the cold with alcohol and copper powder is decomposed, yielding *m*-arsanilic acid, which is purified by diazotising, coupling with alkaline β-naphthol and reducing the azo-derivative with alkaline hydrosulphite.

Section XI.—The Hydroxyphenylarsinic Acids.

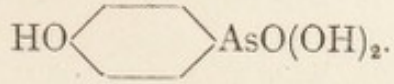
Phenol-p-*arsinic Acid and its Homologues.*[2]

An extension of Béchamp's reaction to phenol showed that arsenic can be introduced into the aromatic nucleus of this compound under experimental conditions similar to those obtaining in the *p*-arsanilic acid condensation.

[1] Benda, *Ber.*, 1911, **44**, 3300; M. L. and B., D.R.-P., 248047.

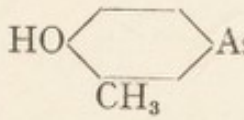
[2] M. L. and B., D.R.-P., 205616.

Phenol-p-*arsinic acid*,



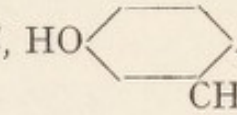
—Phenol (94 parts) and crystallised arsenic acid (151 parts) are stirred together and heated at 150° for four hours. The dark mass obtained is extracted with 1,000 parts of warm water and the filtered solution evaporated in a vacuum and the residue extracted repeatedly with cold acetone. After evaporating off this solvent the crude arsinic acid is left as an oil which gradually solidifies. It crystallises from glacial acetic acid in small, yellow prisms, decomposing at 173–174°; it is readily soluble in cold water, alcohol, acetone, or dilute mineral acids, and slightly soluble in ether or ethyl acetate. The *alkali* salts are readily soluble in water and crystallise in needles from alcohol.[1] They are useful in purifying the crude free acid, which is otherwise inclined to remain syrupy. This acid is identical with the compound obtained by boiling the diazo-derivative of *p*-arsanilic acid with acidified water. Hence it is the para-compound. Sodium nitrite (74 parts) is added to *p*-arsanilic acid (217 parts) in 4,000 parts of 5 per cent. sulphuric acid, the solution being heated on the water-bath till all the nitrogen is evolved. The sulphuric acid is removed with barium hydroxide, the filtrate evaporated to dryness *in vacuo*, and the residue extracted with dilute alcohol; the sodium salt crystallising from this medium is decomposed with the calculated amount of sulphuric acid, and the free phenol-*p*-arsinic acid is extracted with acetone from the residue after evaporation.[2]

A third method of preparation of phenol-*p*-arsinic acid is available, based on Bart's reaction. *p*-Aminophenol is diazotised in hydrochloric acid and warmed with alkaline sodium arsenite. The neutralised solution is filtered, boiled with animal charcoal, and concentrated; sodium phenol-*p*-arsinate separates and is crystallised from alcohol.[3]

o-*Cresol*-4-*arsinic acid*,  — *o*-Cresol (108 parts) and 151 parts of powdered arsenic acid are thoroughly mixed and heated to 140°. A reaction sets in and the mass, which soon solidifies, is heated for 15 minutes,

[1] Mouneyrat, Eng. P., 3087/1915; Kay, Eng. P., 6322/1915.
[2] M. L. and B., D.R.-P. 205616. [3] D.R.-P., 250264, 268172.

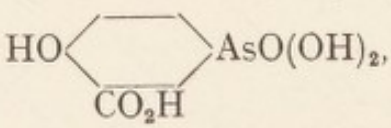
cooled, powdered, and extracted with aqueous sodium carbonate. The aqueous solution is extracted with ether to remove unaltered *o*-cresol, then rendered acid to Congo red and evaporated to dryness in a vacuum. The arsinic acid is extracted from the residue with acetone, and after removing this solvent the crude product is crystallised from glacial acetic acid, when it separates in yellowish crystals, sintering at 150° and decomposing at 172°; *o*-cresol-4-arsinic acid is sparingly soluble in cold water, insoluble in benzene, but readily soluble in alcohol, acetone, aqueous alkalis, or mineral acids. *o*-Cresol-4-arsinic acid is also prepared by boiling in acidified water the diazo-compound of 2-aminotolyl-5-arsinic acid; this preparation melts at 180°, but in all other respects is identical with the product of the Béchamp condensation.[1]

m-*Cresol-4-arsinic acid*,  , is prepared as

in the foregoing example, the condensation occurring at 170°; it sinters at 160°, decomposes at 183–185°, and resembles the preceding isomeride in its physical and chemical properties.

α-*Naphthol-4-arsinic acid*,[2] $\cdot HO \cdot C_{10}H_6 \cdot AsO(OH)_2$, colourless leaflets or needles, is produced by adding an ice-cold solution of sodium nitrite (250 grams) to a solution of one kilogram of 1-aminonaphthyl-4-arsinic acid dissolved at 5° in 10 litres of 15 per cent. sulphuric acid. Steam is blown in to decompose the diazo-compound, the red product is converted into sodium salt, the latter precipitated with alcohol and decomposed with acid. The free acid is readily soluble in hot water or alcohol, but insoluble in ether, chloroform, or petroleum; its alkali salts are readily soluble in water, its salts with the heavy metals are insoluble. The sodium salt crystallises from alcohol in well-defined; colourless needles.

2-*Hydroxy*-1 : 5-*benzarsinic acid*[3] (*salicyl-4-arsinic acid*),

 ,

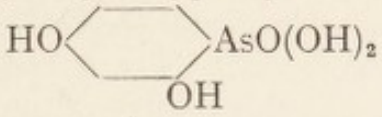
colourless needles, m.p. over 300°, is prepared by the following series of reactions: 2-acetylaminotolyl-5-arsinic acid is oxidised by alkaline permanganate to 2-acetylamino-1 : 5-benzarsinic acid;

[1] Benda and Kahn, *Ber.*, 1908, **41**, 1678.
[2] O. and R. Adler, *Ber.*, 1908, **41**, 933.
[3] W. Adler, D.R.-P., 215251.; O. and R. Adler, *Ber.*, 1908, **41**, 933.

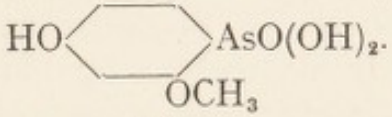
the latter is hydrolysed to 2-amino-1 : 5-benzarsinic acid with hot 10 per cent. caustic soda. The amino-compound is diazotised in dilute sulphuric acid, and the diazo-compound decomposed by blowing steam into the solution. On concentrating this solution 2-hydroxy-1 : 5-benzarsinic acid separates and is purified by crystallisation from hot water or alcohol. It is moderately soluble in methyl alcohol or acetone. Its alkali salts are very soluble and are precipitated in crystalline form by alcohol; the copper, iron, silver, and barium salts are sparingly soluble in hot water. The sodium salt is less toxic than atoxyl.

Under the name of "*enesol*," *mercuric salicylarsinate* has been employed in the combined arseno-mercurial treatment of syphilis.

2 : 4-*Dihydroxyphenylarsinic acid* (*Resorcinolarsinic acid*),

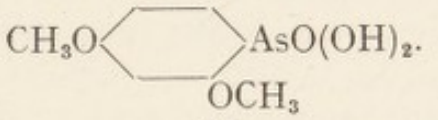


I.



II.

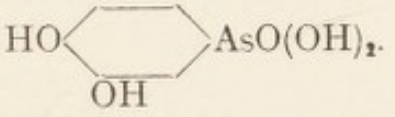
—This acid I. is prepared by heating resorcinol with arsenic acid for two days on the water-bath, the solid product being recrystallised from dilute acetic acid,



III.

2-*Methoxy-4-hydroxyphenylarsinic acid* (II.) and 2 : 4-*dimethoxy phenylarsinic acid* (III.) are prepared by heating the corresponding mono- and di-ethers of resorcinol with arsenic acid at 100° for several days.[1]

3 : 4-*Dihydroxyphenylarsinic acid*,[2]



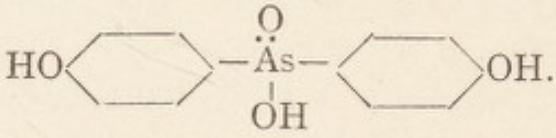
—Phenol-4-arsinic acid (120 grams) in 1800 c.c. of water is treated successively with 10*N*-caustic soda (200 c.c.) and 135 grams of powdered potassium persulphate. After being stirred for 48 hours the liquid is mixed with 650 c.c. of hydrochloric acid (D = 1·12) and heated to boiling for 15 minutes. The solution is mixed with concentrated ammonia (500 c.c.) and excess of magnesia mixture, stirred at the ordinary temperature with animal charcoal,

[1] Bauer, *Ber.*, 1915, **48**, 509; *cf.* M. L. and B., D.R.-P., 272690.

[2] M. L. and B., D.R.-P., 271892.

filtered, and heated to boiling, when magnesium 3 : 4-dihydroxyphenylarsinate separates as a microcrystalline powder. The free acid is obtained by mixing 11 grams of the salt with 13 c.c. of hydrochloric acid (D = 1·12), when it crystallises out on stirring. This arsinic acid is extremely soluble in water, and differs from phenol-4-arsinic acid in its powerful reducing action on cold ammoniacal silver solution, and by giving with acid ferric chloride the green coloration characteristic of a catechol derivative.

4 : 4′-*Dihydroxydiphenylarsinic acid*,

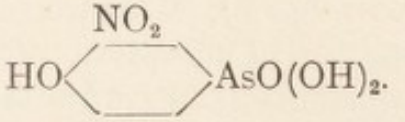


—4 : 4′-Diaminodiphenylarsinic acid (p. 185) is diazotised in dilute hydrochloric or sulphuric acid, and the diazo-derivative decomposed in solution by blowing in steam. The solution is then saturated with sodium chloride and the acidity diminished by adding sodium acetate. The dihydroxyarsinic acid, which is thus precipitated, is crystallised from 50 per cent. acetic acid, when it separates in thin plates with cracked surfaces, m.p. 239°. It is readily soluble in boiling water, warm *N*-hydrochloric acid, alcohol, or glacial acetic acid. Magnesia mixture gives no precipitate.[1]

2 : 2′-*Dihydroxyditolyl-5-arsinic acid*, $HO{\cdot}AsO(C_6H_3{\cdot}OH)_2$, colourless, crystalline powder from 75 per cent. acetic acid, m.p. 247°, is prepared by a similar process to that of the former compound from 2 : 2′-diaminoditolyl-5-arsinic acid, but, being less soluble, it is precipitated without the use of sodium chloride. It is only sparingly soluble in hot water, but dissolves more readily in warm alcohol, hot glacial acetic acid, or *N*-hydrochloric acid.

Section XII.—Nitro-derivatives of the Hydroxyphenylarsenic Acids.

3-*Nitro-4-hydroxyphenylarsinic acid*[2] (*2-Nitrophenol-4-arsinic acid*),



—A mixture of 39 c.c. of nitric acid (D = 1·4) and 39 c.c.

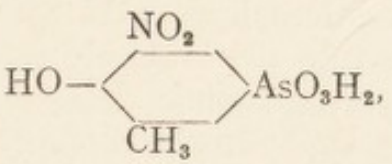
[1] Benda, *Ber.*, 1908, **41**, 2371.

[2] M. L. and B., D.R.-P., 224953; Benda and Bertheim, *Ber.*, 1911, **44**, 3445, 3451.

of concentrated sulphuric acid is added slowly to a solution of 144 grams of sodium phenolarsinate, $HO{\cdot}C_6H_4{\cdot}As(OH){\cdot}ONa$, dried at 80° and dissolved in 450 c.c. of concentrated sulphuric acid at 0°. After the addition of the nitric acid the temperature is allowed to rise to +10° and the acid solution poured into 2,250 c.c. of cold water. 3-Nitro-4-hydroxyphenylarsinic acid, collected after 24–48 hours, is a yellowish-white powder deflagrating on heating ; it is moderately soluble in hot water, and dissolves readily in alcohol, acetone, or glacial acetic acid. Its soluble alkali salts are intensely yellow. Yield 65–75 per cent. of the calculated quantity. This compound is also obtainable from 3-nitro-4-aminophenylarsinic acid by warming the latter with aqueous caustic potash (D = 1·324) at 80° until it is no longer diazotisable. The solution is diluted with water and saturated with hydrogen chloride, when 3-nitro-4-hydroxyphenylarsinic acid separates.[1] Furthermore, 3-nitro-4-hydroxyphenylarsinic acid can be synthesised by Bart's diazo-reaction from alkaline arsenite and diazotised *o*-nitro-*p*-aminophenol.[2]

3-Nitro-4-hydroxyphenylarsinic acid[3] can be obtained by a third process from the readily prepared 4-dimethylaminophenylarsinic acid, which is smoothly nitrated to 4-dimethylamino-3-nitrophenylarsinic acid (p. 192). This nitro-compound (500 grams) is dissolved in aqueous potassium hydroxide (500 grams KOH to 1,500 c.c. H_2O), and the solution maintained at 80–90° until the mixture becomes nearly solid ; ice-cold water (2,000 c.c.) and concentrated hydrochloric acid are added successively, the precipitate is dissolved in hot water, and the filtered solution treated with sodium acetate (1 mol.) and washed animal charcoal. The final filtrate is acidified with hydrochloric acid, when 3-nitro-4-hydroxyphenylarsinic acid separates either in yellow, rhombohedral plates or in tufts of almost colourless needles. The foregoing preparations also exhibit this dimorphism.

3-*Nitro-2-hydroxytolyl-5-arsinic acid*,

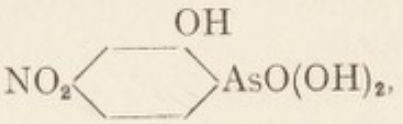


a yellowish-white powder intumescing on heating, is produced as

[1] M. L. and B., D.R.-P., 235141. [2] Bart, D.R.-P., 250264.
[3] Oechslin and Poulenc, Fr. Pat., 451078.

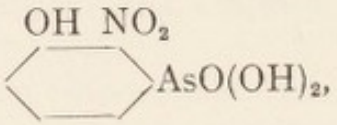
in the foregoing nitration. It is sparingly soluble in cold water, dissolving more readily in hot water, alcohol, or glacial acetic acid ; yield 90 per cent.

4-*Nitro-2-hydroxyphenylarsinic acid*,



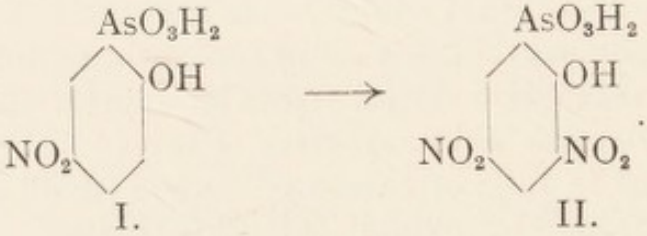
pale yellow crystals from alcohol, decomposing violently on heating ; prepared by Bart's method by diazotising 4-nitro-2-aminophenol in hydrochloric acid and warming the diazo-solution with alkaline sodium arsenite till the diazo-nitrogen is all evolved. The solution is neutralised, filtered, and evaporated to dryness with excess of hydrochloric acid. The residue is extracted with alcohol, and the solution boiled with animal charcoal and evaporated to the crystallising point.[1]

2-*Nitro*-3-*hydroxyphenylarsinic acid*,[2]



is produced by heating the corresponding nitroamino-acid (p. 189) with strong caustic potash solution. On exhaustive reduction with sodium hydrosulphite this compound is converted into 2 : 2′-*diamino*-3 : 3′-*dihydroxyarsenobenzene*, an isomeride of salvarsan base.

5-*Nitro-2-hydroxyphenylarsinic acid*,



I. II.

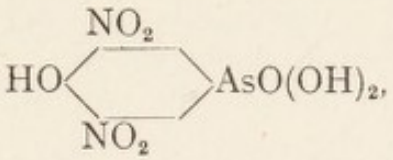
—5-Nitro-2-aminophenylarsinic acid (20 grams), when warmed with 90 c.c. of potassium hydroxide solution (36° Bé.), loses ammonia and passes into the intensely yellow dipotassium salt of 5-nitro-2-hydroxyphenylarsinic acid. The monopotassium salt is obtained by adding hydrochloric acid to an ice-cold solution of the dipotassium salt, when it separates in almost colourless needles or leaflets containing $1H_2O$. The free acid (I.) separates

[1] Bart, D.R.-P., 250264. [2] M. L. and B., D.R.-P., 256343.

from more strongly acidified solutions of the foregoing salts in the form of amber-yellow crystals sparingly soluble in cold water; it decomposes at 247–248°.

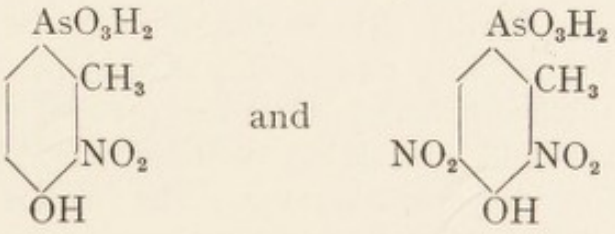
3:5-*Dinitro-2-hydroxyphenylarsinic acid* (II.)[1] separates in the form of pale yellow needles (m.p. 237–238°) on pouring on to ice the product of the nitration of the foregoing compound with nitric and sulphuric acids. Its solution in alkali is even more intensely coloured than that of the mononitro-compound, and addition of a little hydrosulphite develops a deep red coloration due to reduction to nitroamino-derivatives.

3:5-*Dinitro-4-hydroxyphenylarsinic acid*[2] (2:6-*Dinitrophenol-4-arsinic acid*),



lustrous, pale yellow leaflets decomposing with a flash on heating, sparingly soluble in cold water, and dissolving easily in hot water or methyl alcohol to a yellow solution. Prepared by nitrating phenol-*p*-arsinic acid with excess of nitric acid (D = 1·52) in concentrated sulphuric acid at 15–20°. Its alkaline solution is reddened by sodium hydrosulphite (distinction from mononitrophenol-*p*-arsinic acid). This acid is also produced by heating 3:5-dinitro-*p*-arsanilic acid with 10 per cent. caustic potash at 90° until ammonia is eliminated, the product being precipitated on adding hydrochloric acid.[3] It dyes wool in clear yellow shades much more intense than those obtained by means of the isomeric 3:5-dinitro-2-hydroxyphenylarsinic acid.[4]

4-Hydroxy-2-methylphenylarsinic acid[5] nitrates to yield successively the following nitro-compounds:—



The second of these, on warming with aqueous caustic soda,

[1] Benda, *Ber.*, 1911, **44**, 3294.

[2] M. L. and B., D.R.-P., 224953; Benda and Bertheim, *Ber.*, 1911, **44**, 3448.

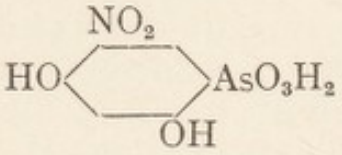
[3] Benda, *Ber.*, 1912, **45**, 58.

[4] Benda, *Ber.*, 1911, **44**, 3296.

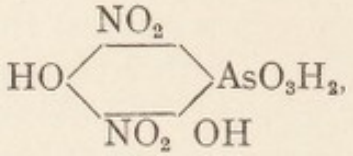
[5] Karrer, *Ber.*, 1915, **48**, 307.

yields stilbene colouring matters; the former compound does not undergo this change, and for this reason the nitro-group is regarded as being in the 3-position rather than in the 5-position.

5-Nitro-2 : 4-dihydroxyphenylarsinic acid [*5-Nitroresorcinol-arsinic acid* (I.)],

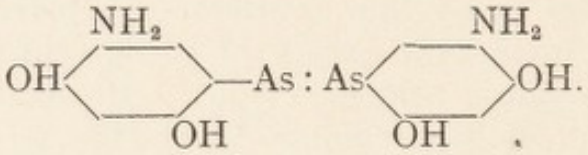


I.



II.

is prepared by nitrating resorcinolarsinic acid below 0°. Above 60° 3 : 5-*dinitro-2 : 4-dihydroxyphenylarsinic acid* (II.) is produced. Alkaline hydrosulphite reduces the mononitro-compound to an *amino-acid* of which the *acetyl* derivative is freely soluble in water. Further reduction leads to 5 : 5′-*diamino-2 : 4 : 2′ : 4′-tetrahydroxyarsenobenzene,*



The hydrochloride is freely soluble in water. Caustic soda precipitates the base, which redissolves in excess to a solution which becomes blue on exposure to air. The foregoing acetyl compound dissolved in hypophosphorous acid containing a trace of hydriodic acid becomes reduced to the diacetylated arsenobenzene.

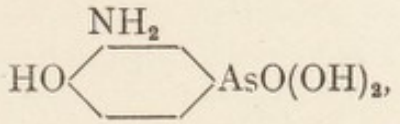
The dinitro-compound reduces to 3 : 5 : 3′ : 5′-tetramino-2 : 4 : 2′ : 4′-tetrahydroxyarsenobenzene, the hydrochloride of which gives with alkalis the very oxidisable base soluble in excess to solutions rapidly undergoing oxidation.

2-Methoxy-4-hydroxyphenylarsinic acid (p. 199) is reduced with hypophosphorous acid containing potassium iodide to 2 : 2′-*dimethoxy-4 : 4′-dihydroxyarsenobenzene.* The methoxy-compound nitrates to *5-nitro-2-methoxy-4-hydroxyphenylarsinic acid,* which on reduction with hydrosulphite gives the *hydrochloride* of 5 : 5′-*diamino-2 : 2′-dimethoxy-4 : 4′-dihydroxyarsenobenzene.* This hydrochloride on boiling with water loses its arsenic, yielding *2-aminoresorcinol-5-methyl ether.* [1]

[1] Bauer, *Ber.*, 1915, **48**, 509; *cf.* M. L. and B., D.R.-P., 272690.

Section XIII.—Arsinic Acids of the Aminophenols.

3-Amino-4-hydroxyphenylarsinic acid [1] (*2-Amino-phenol-4 arsinic acid*),



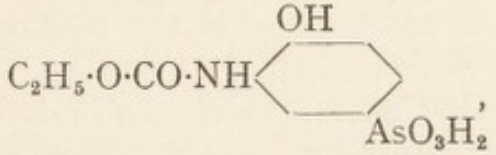
colourless leaflets or minute prisms darkening and decomposing at 170° without melting. Prepared by the action of reducing agents on 3-nitro-4-hydroxyphenylarsinic acid.

Sodium amalgam (840 grams of 4 per cent. Na) is added to the nitro-acid (31·6 grams) in 600 c.c. of methyl alcohol at 60–70°. About 5/6ths of the alcohol is distilled off, the residue taken up with 120 c.c. of water, and after removing mercury, the solution is acidified with 150 c.c. of hydrochloric acid (D = 1·19). After twelve hours the impurity is filtered off, the filtrate boiled with animal charcoal, and the clear solution treated with 52 c.c. of 10*N*-caustic soda, when 3-amino-4-hydroxyphenylarsinic acid crystallises. It is very slightly soluble in water or organic solvents, but dissolves easily in ammonia, caustic or carbonated alkali, or in mineral acids. Alkaline hypochlorite develops a deep green coloration, whilst acid bichromate produces an intense red coloration.

This reduction is also effected by adding with continuous stirring 130–140 grams of dry sodium hydrosulphite to 2-nitrophenol-4-arsinic acid (66 grams) in 700 c.c. of water containing 125 c.c. of 2*N*-sodium hydroxide. The hydrosulphite is added till the yellow colour is destroyed, and throughout reduction the temperature is not allowed to exceed 30°. The solution on cooling to 0°, deposits 2-aminophenol-4-arsinic acid, especially on seeding with crystals of the same substance.

The *sodium* salt, $C_6H_7O_4NAsNa$, is very soluble in water to a neutral solution and less so in alcohol ; it crystallises with one or two molecules of water.

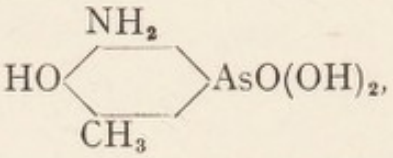
The *urethane* derivative,



[1] M. L. and B., D.R.-P., 224953; Ehrlich and Bertheim, U.S.P. 986148. *Cf.* Benda and Bertheim, *Ber.*, 1908, **41**, 1657; Bertheim and Benda, *Ber.*, 1911, **44**, 3299.

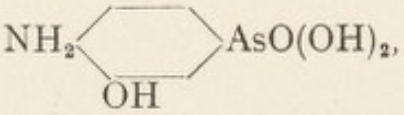
is obtained by adding alkaline sodium arsenite and copper paste to a diazotised solution of 5-amino-2-hydroxyphenylurethane.[1]

3-*Amino*-2-*hydroxytolyl*-5-*arsinic acid* (3-*Amino*-o-*cresol*-5-*arsinic acid*),



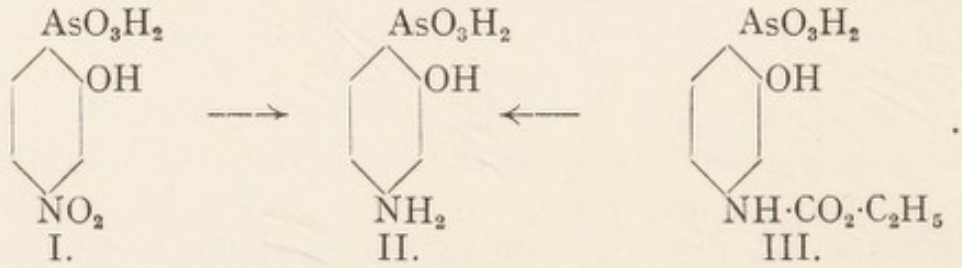
prepared in a similar manner to its lower homologue, is more easily soluble in water than the latter and is salted out from aqueous solution.

4-*Amino*-3-*hydroxyphenylarsinic acid*,[2]



colourless crystals sparingly soluble in cold water or alcohol, easily so in alkalis, ammonia, and excess of dilute acids, prepared by reducing the azo-compound (p. 232) from 3-nitro-4-aminophenylarsinic acid with alkaline sodium hydrosulphite, and after removing the 1-amino-α-naphthol, allowing the solution to become oxidised by air or oxygen. On acidifying, the arsinic acid is precipitated.

(4-*Amino*-2-*hydroxyphenylarsinic acid* 3-*Aminophenol*-6-*arsinic acid* II.),



—1. From *m*-aminophenol. This compound is converted into the carbethoxyl derivative by dissolving (2 mols.) in ether and adding ethyl chlorocarbonate.

A violent reaction sets in and *m*-aminophenol hydrochloride is precipitated, the filtrate is distilled, and carbethoxy-*m*-aminophenol (m.p. 97°) is precipitated in the residue on adding light petroleum.

Carbethoxy-3-*aminophenol*-6-*arsinic acid* (III.) is prepared by heating on the water-bath for a week carbethoxy-*m*-aminophenol and syrupy arsenic acid (83 per cent.). The hard product, after

[1] Bart, D.R.-P., 268172.

[2] M. L. and B., D.R.-P., 244166; Benda, *Ber.* 1911, **44**, 3580.

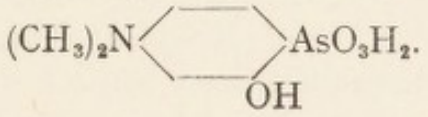
washing with water to remove arsenic acid, is dissolved in aqueous ammonia, and the liquid saturated with ammonia gas. The ammonium salt separates and is converted into the free arsinic acid (m.p. 213°) by addition of mineral acid.

3-Aminophenol-6-arsinic acid is produced from the preceding compound by alkaline hydrolysis (dilute NaOH) and precipitated on addition of 2*N*-sulphuric acid. Crystallised from water it melts at 173°. It is also soluble in the alcohols and in acetone.

2. From 3-nitro-6-aminophenol. This aminophenol (77 grams) in hydrochloric acid (170 c.c. of D = 1·12) and 350 c.c. of water is diazotised with sodium nitrite (36 grams). The red, sparingly soluble diazo-oxide is mixed with aqueous sodium arsenite (65 grams) and gradually rendered alkaline with 2*N*-sodium hydroxide. A dark solution results accompanied by elimination of nitrogen. Acidification with hydrochloric acid throws down a slight impurity. The filtrate is rendered ammoniacal and heated to boiling after adding magnesia mixture. The yellow magnesium salt of the 3-nitrophenol-6-arsinic acid (I.) is precipitated and treated with hydrochloric acid, when the free acid crystallises out on rubbing (yield 72 grams); m.p. 250° with decomposition.

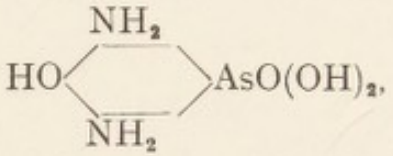
This nitro-compound when reduced with iron filings and dilute acetic acid yields 3-aminophenol-6-arsinic acid (II.).[1]

4-Dimethylamino-2-hydroxyphenylarsinic acid,[2]



2-Nitro-4-dimethylaminophenylarsinic acid (1 part) is added to 0·5 part of carbamide in 10 parts of 60 per cent. sulphuric acid. Carbon dioxide and nitrogen are evolved, and after partial neutralisation 4-dimethylamino-2-hydroxyphenylarsinic acid is precipitated.

3 : 5-*Diamino-4-hydroxyphenylarsinic acid*,[3]



silver grey needles darkening and decomposing at 170°, easily soluble in aqueous alkalis or dilute acids. Chromic acid develops a dark olive green coloration. The diamino-acid is prepared by reducing 3 : 5-dinitro-4-hydroxyphenylarsinic acid with sodium amalgam or sodium hydrosulphite at low temperatures.

[1] H. Bauer, *Ber.*, 1915, **48**, 1579. [2] Meyer and Oechslin, Fr. P., 474056.
[3] M. L. and B., D.R.-P., 224953.

CHAPTER V

SALVARSAN

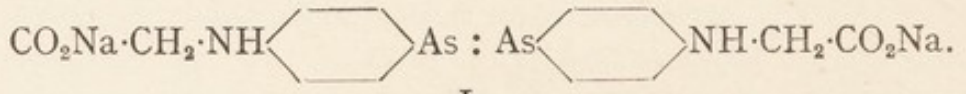
Aromatic Derivatives containing Tervalent Arsenic

PART I

BUNSEN found that the cacodyl derivatives containing tervalent arsenic were much more active physiologically than cacodylic acid and its salts in which the arsenic is a pentad. A similar connection was traced by Ehrlich among the aromatic derivatives of arsenic, those containing tervalent arsenic being much more potent trypanocides and spirochætocides than the compounds of quinquevalent arsenic.

The aromatic compounds with tervalent arsenic are usually obtained by the reduction of atoxyl and its derivatives. After trying 605 arsenical preparations Ehrlich arrived at salvarsan (No. 606).

Phenylglycinearsinic acid, which has already been mentioned, yields on reduction with sodium hydrosulphite the therapeutically important compound arsenophenylglycine. Its sodium salt is the drug "spirarsyl" (I.), No. 418 in Ehrlich's experimental series, which, on account of its low toxicity and high trypanocidal power, constituted an important advance on atoxyl and its immediate derivatives.



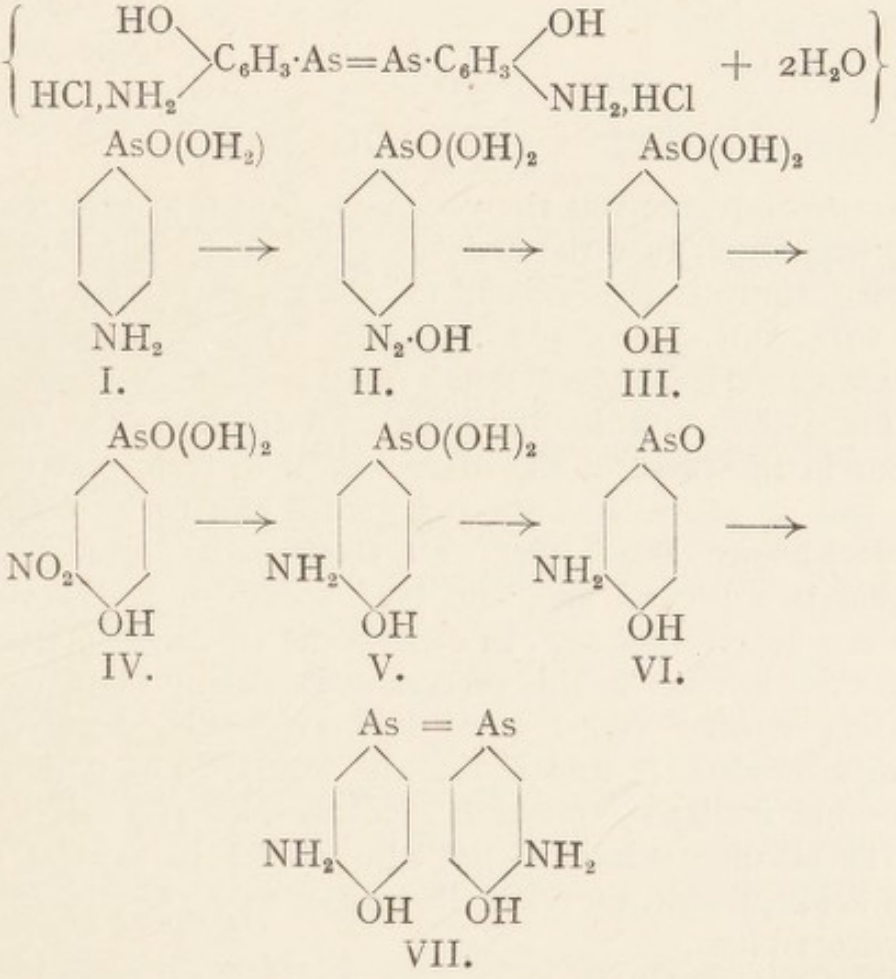
I.

Early in the study of these arsenicals it was found by Bertheim, Benda, and Kahn, in Germany, and independently by Barrowcliff, Pyman, and Remfry, in England, that *p*-hydroxyarsinic acid (III.) is produced by boiling in aqueous solution the diazocompound (II.) of *p*-arsanilic acid (I.), the homologues of this amino-

acid giving rise to the homologous hydroxyarsinic acids (*Ber.*, 1908, **41**, 1678, 1854 ; *Chem. Soc. Trans.*, 1908, **93**, 1893).

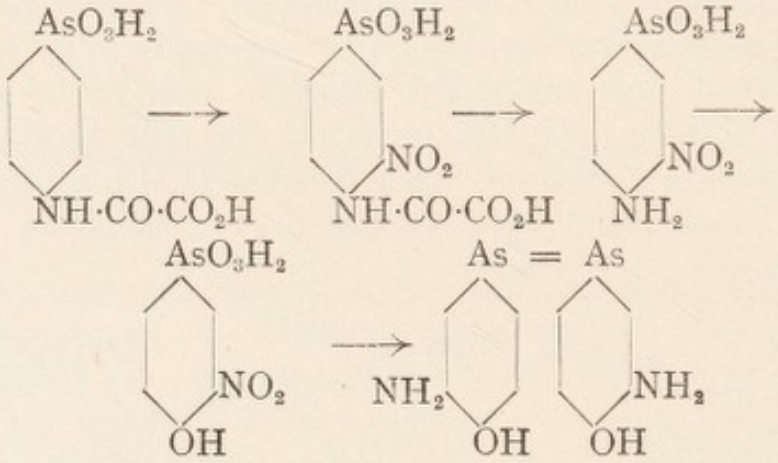
It was also found by Messrs. Meister, Lucius, and Brüning that *p*-hydroxyarsinic acid (III.) and its homologues can be obtained directly from arsenic acid and phenol, and its homologues by the Béchamp condensation.

On nitration, *p*-hydroxyarsinic acid yields a mono-nitro-compound (IV.), which can undergo reduction in various ways. With reagents affecting only the nitro-group the first reduction product is 3-amino-4-hydroxyphenylarsinic acid (V.). Further reduction leads to 3-amino-4-hydroxyphenylarsenious oxide (VI.), a highly toxic substance, and finally the complete removal of oxygen leads to a doubling of the molecule and the formation of 3 : 3′-diamino-4 : 4′-dihydroxyarsenobenzene (VII.), or salvarsan (No. 606), introduced into pharmacy in the form of its dihydrochloride,



Several variations on this process have been patented (*v.* pp 224-231), and five isomerides of salvarsan have been synthesised (p. 232).

Acetylatoxyl or arsacetin is not readily nitrated, but oxalylatoxyl furnishes a mono-nitro compound, in quantitative yield. In this product the oxalylamino-group is in a sympathetic ortho-para-position with respect to the acidic nitro- and arsinic groups. This orientation renders the oxalylamino-complex very labile, alkaline hydrolysis removes first the oxalic group, and then the amino-group itself, giving rise to 3-nitro-4-hydroxyarsanilic acid. This compound when reduced at 55–60° with excess of sodium hydrosulphite yields salvarsan.

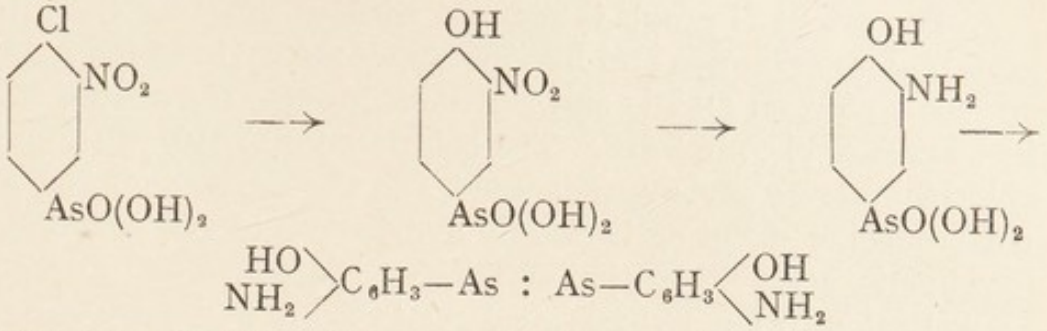


The next advance was the very important discovery made by Bart, who found that the arsinic group can be introduced into the ring through the agency of the diazo-reaction (Eng. P., 568, 1911, D.R.-P., 250264, 254345). When benzenediazonium chloride or preferably potassium *iso*diazo-oxide is treated with alkaline sodium arsenite the arsinic group enters the aromatic nucleus in the place of the diazo-radical to form phenylarsinic acid, just as other elements and groups can be introduced by the well-known Sandmeyer and Gattermann reactions. The reaction is a general one, and both mono- and di-arylarsinic acids can be synthesised. In general the *iso*-diazo- (*anti*-diazo-) compounds interact in this process more readily than the corresponding normal (*syn*-) diazo-derivatives. If, however, the aromatic nucleus is substituted, the reactivity of both normal diazo- and *iso*diazo-compounds is increased. The reaction goes best in alkaline solutions, but also occurs in neutral media. With acids present, the yield diminishes with the concentration of hydrogen ions.

$$C_6H_5N_2\cdot OK + K_2HAsO_3 \rightarrow N_2 + C_6H_5AsO(OH)OK$$
$$C_6H_5N_2\cdot OK + C_6H_5As(OK)_2 \rightarrow N_2 + (C_6H_5)_2AsO\cdot OK$$

In this way *p*-chloroaniline can be converted into *p*-chloro-

phenylarsinic acid; this substance can be nitrated, and the following series of changes again leads to salvarsan.



The introduction of the arsenical group is facilitated by the presence of copper compounds (Sandmeyer reaction), and in these circumstances the interaction between alkali arsenite and alkali aryldiazo-oxide takes place in the absence of free alkali.[1]

The use of metallic catalysts, copper, silver, nickel, or cobalt (Gattermann reaction) as well as their salts, facilitates the removal of diazo-nitrogen at low temperatures and obviates the formation of by-products.[2]

Progressive Reduction of Aromatic Compounds containing Quinquevalent Arsenic.

The progressive reduction of aromatic nitro-arsenicals furnishes an exceptionally interesting illustration of the action of different reducing agents on aromatic compounds.

p-Arsanilic acid and its homologues and derivatives containing quinquevalent arsenic are reducible to derivatives of tervalent arsenic, the chemical nature of the products depending on the reducing agent employed.

Sulphurous acid, with hydriodic acid as catalyst, phenylhydrazine, thionyl chloride and phosphorus trichloride give aminoarylarsenious oxides, *e.g.*, $NH_2 \cdot C_6H_4 \cdot AsO$.

Electrolytic reduction [3] or various metals and concentrated acid solutions, especially in the presence of methyl or ethyl alcohol, lead to derivatives of the aromatic primary arsines.[4]

By a judicious selection of reducing agent, reduction of either nitro-group or arsenical radical can be effected at will, more drastic treatment leading to simultaneous reduction of both these oxygenated complexes.

1. The chief difficulty is to reduce the nitro-group without affecting the arsenical complex. This reduction is brought about

[1] Fabr. Heyden, D.R.-P., 264924.
[2] Bart, D.R.-P., 268172.
[3] Bart, D.R.-P., 270568.
[4] D.R.-P., 251571 and 267082.

by ferrous compounds, especially ferrous hydroxide, or by using the calculated amount of sodium amalgam.

2. The arsenical group is reduced without affecting the nitro-group by phosphorous and hypophosphorous acids which have a specific action on arsinic and arsenious groups, converting these into arsenoaryl complexes. The calculated quantity of stannous chloride reduces arylarsenious oxides to the same condition, and this reducing agent activated by hydriodic acid will also reduce arylarsinic acids to a similar extent. Sulphuretted hydrogen in neutral solution reduces arylarsinic acids and arylarsenious oxides to sesqui- and mono-sulphides without altering the nitro-group. In acid and alkaline solutions this group becomes involved.

3. In the reduction of both nitro- and arsino-groups the catalytic agent of hydriodic acid is very noteworthy. In addition to its employment with sulphurous acid it is used in conjunction with stannous chloride and with great advantage, in activating hypophosphorous acid, preferably in acetic acid solution.

Sodium hydrosulphite is the specific reducing agent used in the production of salvarsan and similar arsenoaryl compounds. The metals (tin and zinc) and concentrated acids lead to primary arsines, but it is claimed that, in the presence of sulphurous acid, reduction stops at the arsenobenzene stage.

These aminoaryl derivatives containing tervalent arsenic are of great therapeutic interest. *In vitro* atoxyl in 1 per cent. solution did not kill a certain strain of trypanosomes, which, however, were destroyed by *p*-aminophenylarsenious oxide in dilutions of 1 in 1,000,000. Mice affected with very virulent trypanosomes (*Nagano ferox*) were healed with atoxyl (1 in 300) only in 5-6 per cent. of cases studied ; all cases were healed with *p*-arsenophenylglycine (1 in 600), and this arsenical drug kills in the organism parasites which are immune to atoxyl.

Section I.—Reduction Products of p-*Hydroxyphenylarsinic Acid (Phenol*-p-*arsinic Acid) and its Derivatives.*

p-*Hydroxyphenylarsenious oxide,*

white, crystalline mass unchanged by heat below 240°, easily soluble in water, methyl or ethyl alcohol, acetone, glacial acetic acid or ethyl acetate, sparingly so in benzene, chloroform,

or carbon bisulphide. Prepared by saturating with sulphur dioxide at 18°, a solution of sodium phenol-*p*-arsinate and potassium iodide acidified by dilute sulphuric acid. The solution is then saturated with sodium chloride and extracted with ether; the ethereal extract is shaken with saturated sodium carbonate to remove phenolarsinic acid and the ethereal solution concentrated till the product crystallises.

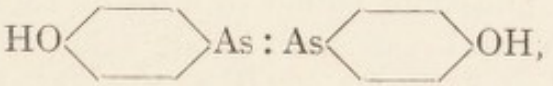
Other mild reducing agents, such as phenylhydrazine, thionyl chloride, or phosphorus trichloride, reduce phenol-*p*-arsinic acid to *p*-hydroxyphenylarsenious oxide, and this substance warmed with a neutral solution of sodium hydrosulphite gives yellow flakes of arsenophenol.[1]

The Arsenophenols.[2]

Phenol-*p*-arsinic acid and its homologues and derivatives are reducible to arsenophenols by strong reducing agents, such as stannous chloride, tin and hydrochloric acid and sodium hydrosulphite. Milder reducing agents, such as hydriodic acid, sulphurous acid, and phenylhydrazine, give rise to hydroxyarylarsenious oxides, which by further treatment, for instance with sodium amalgam, are reduced ultimately to arsenophenols.

From the phenolarsinic acids, these arsenophenols (in the form of their soluble alkali derivatives) are distinguished by their greater biological action, toxicity, and trypanocidal power (effect on trypanosomes and spirilla). Animals greatly infected with trypanosomes are healed by a single injection of sodium arsenophenoxide. Their alkyl ethers, arseno-*p*-anisole and arseno-*p*-phenetole (p. 93), on the contrary, are inactive compounds, insoluble in water, and unsuitable for use in therapeutics.

p-*Arsenophenol*,



yellowish-brown powder, darkening and decomposing above 200°, is easily soluble in alcohol, acetone, ether, or aqueous caustic alkali, insoluble in benzene, chloroform, or dilute mineral acids. Prepared by adding phenol-*p*-arsinic acid (10 grams) dissolved in water to a solution of sodium hydrosulphite (50 grams) in 250 c.c. of water neutralised with 25 grams of crystallised

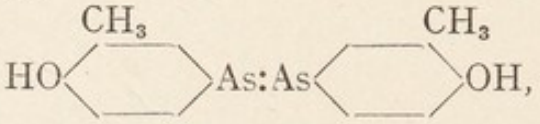
[1] M. L. and B., D.R.-P., 213594.

[2] M. L. and B., D.R.-P., 206456; Eng. P., 9855/1908; Ehrlich and Bertheim (M. L. and B.), U.S. P., 907978 and 909380.

magnesium chloride and 12 c.c. of 10*N*-caustic soda. On warming (not boiling) the mixture for three-quarters of an hour the product separates in yellow flakes.

Sodium p-*arsenophenoxide* is a yellow powder precipitated by alcohol from concentrated aqueous solutions, sparingly soluble in methyl or ethyl alcohol, dissolving readily in water.

4-*Arseno*-o-*cresol*,



yellowish-red powder, produced by digesting at 50° an aqueous solution of sodium *o*-cresol-4-arsinate and 10 parts of sodium hydrosulphite neutralised by magnesium hydroxide.

Halogenated Arsenophenols.[1]

The halogenated arsenophenols yield neutral soluble alkali salts having a more pronounced bactericidal action than the unhalogenated compounds. They are produced by successively halogenating *p*-hydroxyphenylarsinic acid (phenol-*p*-arsinic acid) and its homologues and reducing the product to the arseno-stage.

Sodium *p*-hydroxyphenylarsinate in 10 per cent. aqueous solution is added to dilute hypochlorous or hypobromous acid solutions containing four atomic proportions of the halogen. After twelve hours the solution is cooled and stirred with hydrochloric acid. After separating the trihalogenated phenol with ether the precipitate consists of *dichloro-* or *dibromo*-p-*hydroxyphenylarsinic acid*, sparingly soluble in cold water, insoluble in ether or chloroform, dissolving readily in acetone or the alcohols, not decomposed at 260°.

The *di-iodo*-compound $HO{\cdot}C_6H_2I_2{\cdot}AsO_3H_2$ is prepared by adding aqueous potassium iodide to a dilute solution of sodium phenol-*p*-arsinate and potassium iodate acidified with sulphuric acid and heated at 80°. On cooling, the di-iodo-compound is precipitated. Its solubilities are similar to those of the other dihalogenated products.

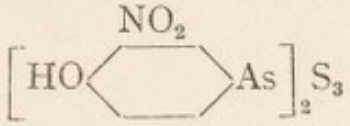
Tetrachloroarsenophenol,

An aqueous solution (1500 c.c.) of sodium hydrosulphite (285

[1] M. L. and B., D.R.-P., 235430.

grams) and magnesium chloride (58 grams) is added to dichlorophenol-*p*-arsinic acid (58 grams) and sodium hydroxide (12 grams) in 1150 c.c. of water. The mixture is digested at 50° until the deposition of the arseno-compound is complete. Tetrachloro-, tetrabromo-, and tetraiodo-arsenophenol are yellow precipitates dissolving in aqueous alkalis to form salts with a neutral reaction.

3-Nitro-4-hydroxyphenylarsenic sesquisulphide,



is produced by saturating with sulphuretted hydrogen at the ordinary temperature an aqueous solution of sodium 3-nitro-4-hydroxyphenylarsinate. The product is crystallised from acetone-water and from boiling xylene; it separates in hard, warty aggregates of yellow crystals, decomposing at 160°, and dissolving in alkalis to a reddish-brown solution.

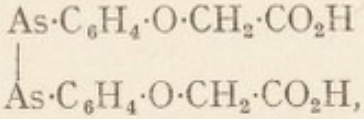
The reduction product of the foregoing nitro-sulphide is obtained from 3-amino-4-hydroxyphenylarsinic acid with sulphuretted hydrogen in acid or alkaline solutions; the product furnishes a sparingly soluble sulphate, and loses its sulphur on boiling with lead sulphate in alkaline solution.

m-Aminophenylarsenious sulphide,[1] even in large doses, has no curative action, and the sulphide from *p*-aminophenylarsinic acid manifests a slight healing effect in quantities which are close to the lethal dose. The aminohydroxysulphide derived from 3-nitro-4-hydroxyphenylarsinic acid and its reduction products heal with doses only one-third of the lethal amount.

Glycyl Derivatives of Arsenophenol and Arsenothiophenol.

The following arsenobenzene derivatives possess such pronounced trypanocidal powers that they cure animals infected with highly resistant strains of trypanosomes.[2]

Arsenobenzene-bis-4-oxymethylenecarboxylic acid,



is a yellow, voluminous precipitate reducing ammoniacal silver solutions in the cold; it dissolves in aqueous alkalis to yield

[1] M. L. and B., D.R.-P. 253757.

[2] M. L. and B., D.R.-P., 216270, addition to D.R.-P., 206456.

the yellow alkali (sodium) salts which are readily soluble in water and only sparingly so in alcohol.

Anhydrous sodium hydrosulphite (80 grams) and magnesium chloride (40 grams) are dissolved in 400 c.c. of water and mixed with 20 grams of 10*N*-caustic soda. To the solution, after filtering off magnesium hydroxide, is added the sodium salt of glycyloxyphenyl-4-arsinic acid and the mixture thoroughly stirred for one hour at 45°. The precipitated arseno-compound is purified through its sodium salt.

Carboxymethyleneoxyphenyl-4-arsinic acid,

$$CO_2H{\cdot}CH_2{\cdot}O{\cdot}C_6H_4{\cdot}AsO_3H,$$

spicules or plates from water or glacial acetic acid, sinters at 150° and carbonises at higher temperatures. It is prepared by adding successively chloroacetic acid (188 grams) in 300 c.c. of water and 400 grams of 35 per cent. caustic soda to sodium phenol-*p*-arsinate (240 grams) in 480 c.c. of water. The mixture is heated for three hours in a reflux apparatus, then cooled and cautiously acidified with hydrochloric acid; the product which crystallises from water is also soluble in the alcohols, but not in ether or benzene.

Carboxymethylenethiophenyl-4-arsinic acid,

$$CO_2H{\cdot}CH_2{\cdot}S{\cdot}C_6H_4{\cdot}AsO_3H,$$

yellowish needles from water, sintering at 170° and melting with decomposition at 187°. It is prepared from *p*-arsanilic acid by the following application of the diazo-reaction.

Sodium nitrite (74 grams) is added to *p*-arsanilic acid (217 grams) dissolved in 2 litres of water and 260 grams of concentrated hydrochloric acid at 4–8°. The diazo-solution is introduced into a solution of potassium xanthate (217 grams) and sodium carbonate (420 grams) in 4·2 litres of water at 80°. Caustic soda (126 grams) is then added, and the mixture warmed for several hours at 90–100°, and afterwards treated with a solution of chloroacetic acid (282 grams) and 35 per cent. caustic soda solution (430 grams) in 650 c.c. of water, the whole solution being evaporated to a small bulk. Carboxymethylenethiophenyl-*p*-arsinic acid separates on acidification with hydrochloric acid.

Arsenobenzene-bis-4-thiomethylenecarboxylic acid,

$$\begin{array}{l} As{\cdot}C_6H_4{\cdot}S{\cdot}CH_2{\cdot}CO_2H \\ \quad\| \\ As{\cdot}C_6H_4{\cdot}S{\cdot}CH_2{\cdot}CO_2H, \end{array}$$

a yellow powder dissolving in aqueous alkalis to yellow salts,

readily soluble in water and sparingly so in alcohol. This arsenobenzene derivative is obtained by reducing the preceding compound either with sodium hydrosulphite, or, in two stages, by phenylhydrazine to the arylarsenious oxide and to the arsenoaryl stage by sodium amalgam.

Section II.—Aminoaryl Derivatives containing Tervalent Arsenic.

p-*Aminophenylarsenious oxide*,[1] $NH_2 \cdot C_6H_4 \cdot AsO, 2H_2O$, well-defined, colourless needles softening at 80°, sparingly soluble in ammonia, sodium carbonate, ether, chloroform, or benzene, dissolving readily in aqueous caustic alkalis, dilute acids, alcohol, acetone, or glacial acetic acid. Prepared by reducing atoxyl with sulphurous and hydriodic acids. Atoxyl (311 grams) is dissolved in 1·8 litres of water containing 520 grams of potassium iodide, 1 litre of sulphuric acid (1 : 5) is added, and sulphur dioxide passed in until the colour of iodine has disappeared. The reduction product crystallises from the solution when rendered slightly alkaline with ammonia.

Hydrochloric acid (420 c.c. of D = 1·12) is added to atoxyl (62 grams) dissolved in 100 c.c. of hot water; the precipitated sodium chloride is removed and the solution saturated with sulphur dioxide. After twelve hours, crystallisation of the compound $AsCl_2 \cdot C_6H_4 \cdot NH_2, HCl$ commences; the solution is then saturated with hydrochloric acid, the precipitated hydrochloride is added to 200 c.c. of cold water and treated with strong aqueous caustic soda till alkaline. The solution is saturated with sodium chloride and the product collected after several hours.

p-Arsanilic acid dissolved in 12 parts of methyl alcohol is boiled for two hours with phenylhydrazine, nitrogen is evolved, the alcohol is removed, and water and ether added to the residue; the latter removes phenylhydrazine, and the aqueous solution, on evaporation, deposits *p*-aminophenylarsenious oxide.

Ās-*Dihydroxydi*-p-*aminoarsenobenzene*,[2]

$$NH_2 \cdot C_6H_4 \cdot As(OH) \cdot As(OH) \cdot C_6H_4 \cdot NH_2,$$

pale yellow flakes, m.p. 227°, soluble in hydrochloric acid, an intermediate stage in the production of diaminoarsenobenzene, is obtained by adding sodium amalgam to a methyl-alcoholic solution of *p*-aminophenylarsenious oxide. The molecular weight of the product corresponds with the above formula.

[1] M. L. and B., D.R.-P., 206057. [2] M. L. and B., D.R.-P., 206057.

p-*Acyl Derivatives of* p-*Aminophenylarsenious Oxide.*

p-Arsanilic acid and ethyl chlorocarbonate yield a urethane derivative; this substance furnishes a nitro-compound. The two substances on reduction give rise to the carbethoxy-compounds,

$$C_2H_5\cdot O\cdot CO_2\cdot NH\cdot C_6H_4\cdot AsO \text{ and}$$
$$C_2H_5\cdot O\cdot CO_2\cdot NH\cdot C_6H_3(NH_2)_2\cdot AsO.$$

These products are stated to be useful in the treatment of swine fever.[1]

2-Aminotolyl-5-arsenious oxide,[2] $NH_2\cdot C_6H_3(CH_3)\cdot AsO$, white crystals softening under 100°, melting at about 160° to a clear liquid. Prepared by adding to 156 grams of sodium 2-amino-tolyl-5-arsinate dissolved in $2\frac{1}{2}$ litres of water 500 c.c. of 6*N*-sulphuric acid and 30 grams of potassium iodide in strong aqueous solution. The mixture is cooled and sulphur dioxide passed in until precipitation begins, when, on cooling and rendering ammoniacal, the oxide is precipitated. This product is soluble in hot water, alcohol, acetone, dilute hydrochloric acid, or aqueous caustic alkalis.

2-Acetylamino-1 : 5-benzarsenious oxide,

$$CH_3\cdot CO\cdot NH\cdot C_6H_3(CO_2H)\cdot AsO,$$

is produced when equal parts of 2-acetylamino-1 : 5-benzarsenic acid and phenylhydrazine are boiled together for two hours in methyl-alcoholic solution. After removing the greater part of the solvent, the residue is dissolved in water and extracted with ether to remove phenylhydrazine. The aqueous portion, concentrated *in vacuo* at 30–40°, is saturated with sodium chloride, cooled in ice and acidified with dilute acetic acid, when the product separates as a white, crystalline precipitate, decomposing at about 300°, easily soluble in hot dilute hydrochloric acid or aqueous alkalis, slightly soluble in water or glacial acetic acid, insoluble in alcohol or ether.

Displacement of Arsenic from Aromatic Arsenicals.[3]

It was shown by La Coste and Michaelis (p. 78) that mercury di-aryls and arsenious chloride give rise to aromatic arsenicals containing tervalent arsenic. The reverse change is practicable, and triadic arsenic can be replaced by mercury in its aromatic

[1] Parke Davis & Co., U.S. P., 1119279.
[2] M. L. and B., D.R.-P., 212205, addition to D.R.-P., 206057.
[3] M. L. and B., D.R.-P., 272289; Eng. P., 2314/1914.

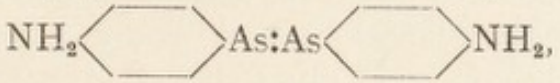
compounds. This displacement takes place in alkaline, neutral, or acid solutions, and the mercury derivatives produced belong to one or other of the types ArHgX or Ar–Hg–Ar (where Ar = aryl and X = negative radical), depending on the nature of the original aryl-arsenical.

1. Phenylarsenious oxide boiled with mercuric chloride in aqueous caustic soda yields mercury diphenyl.

2. *p*-Aminophenylarsenious oxide, mercuric oxide, and aqueous caustic soda yield mercury dianiline, $Hg(C_6H_4 \cdot NH_2)_2$.

3. Phenylglycine-4-arsenious chloride and mercuric chloride yield phenylglycine-4-mercuric chloride, $CO_2H \cdot CH_2 \cdot NH \cdot C_6H_4 \cdot HgCl$.

4 : 4′-Diaminoarsenobenzene,[1]



pale yellow flakes, m.p. 130–140°, insoluble in water and the ordinary organic media, dissolving in dilute hydrochloric acid.

1. Atoxyl (250 grams) dissolved in 1·4 litres of water is added to 800 grams of crystallised stannous chloride in 800 c.c. of hydrochloric acid (D = 1·19) and the solution digested for several days at a temperature not exceeding 40°. The yellow double tin salt which separates is dissolved in hot *N*-hydrochloric acid, and sufficient caustic soda is added to decompose this salt and redissolve tin hydroxide when the product is precipitated in yellow flakes.

2. On mixing dilute hydrochloric acid solutions of 4-aminophenylarsine (p. 263) and 4-aminophenylarsenious oxide (p. 257) the liquid assumes a yellow colour, and the addition of sodium acetate in the cold determines the precipitation of 4 : 4′-diaminoarsenobenzene.[2]

4 : 4′-Dioxalyldiaminoarsenobenzene,

$$CO_2H \cdot CO \cdot NH \cdot C_6H_4 \cdot As{:}As \cdot C_6H_4 \cdot NH \cdot CO \cdot CO_2H.$$

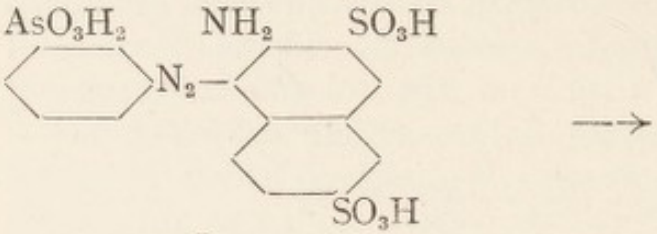
—Oxalyl-*p*-arsanilic acid (100 grams) and 150 grams of crystallised sodium acetate in 500 c.c. of water are added to 1 litre of saturated sodium chloride solution. One kilogram of sodium hydrosulphite in 4 litres of water is mixed with 10 litres of saturated sodium chloride. The two solutions, cooled to −15°, are mixed and the mixture left for 24 hours at this temperature, when the product separates as a pale yellow precipitate insoluble in organic media, soluble in aqueous alkalis and converted into an insoluble compound on warming these solutions.

[1] M. L. and B., D.R.-P., 206057. [2] M. L. and B., D.R.-P., 254187.

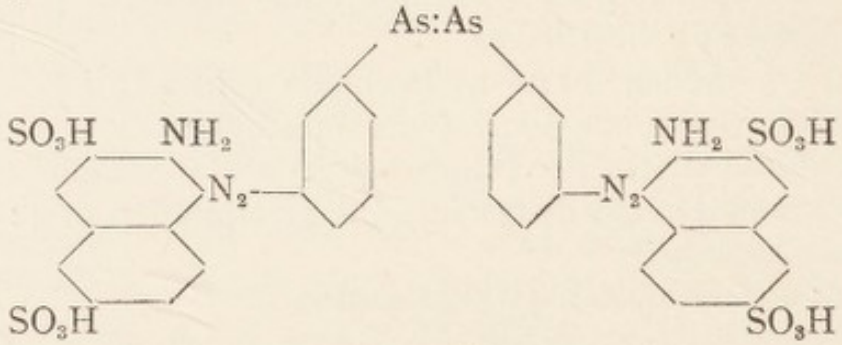
Azo-compounds containing an Arsenobenzene Residue.

Aminoarsenobenzene and its derivatives are not readily diazotised and converted into azo-colouring matters because the nitrous acid acts as an oxidising agent towards the arseno-group. The azo-derivatives of arsenobenzene can, however, be readily obtained by starting out from the aminoarsinic acids and the corresponding aminoarsenious oxides. These amino-derivatives are diazotised, coupled with phenols or reactive amines, and the resulting azo-compound reduced with hypophosphorous acid. This reducing agent acts preferentially on the arsinic or arsenious radical without affecting the azo-group, and in this way complex azo-dyes based on arsenobenzene are produced.

m-Arsanilic acid diazotised and coupled with β-naphthylamine-3:6-disulphonic acid gives the azo-dye I., and this compound, reduced by boiling with aqueous hypophosphorous acid yields the arseno azo-dye II.



I.



II.

Similar products are obtainable from diazotised *p*-arsanilic acid and 1-amino-8-naphthol-3:6-disulphonic acid (H acid) and from 3-amino-4-hydroxyphenylarsinic acid and phloroglucinol.[1]

p - *Dimethylaminophenylarsenious oxide*[2] (*Dimethylanilinearsenious oxide*), $(CH_3)_2N{\cdot}C_6H_4{\cdot}AsO$, white powder, m.p. 75°, easily soluble in chloroform or hot alcohol, insoluble in water, is produced by mixing dimethylaniline (15 grams) and arsenious chloride (25 grams). Considerable heat is generated, and the reaction is

[1] M. L. and B., D.R.-P., 271271.

[2] Michaelis and Rabinerson, *Annalen*, 1892, **270**, 139.

completed on the water-bath. The resulting syrupy liquid is poured into 700 c.c. of water, treated with excess of aqueous caustic soda, and filtered from a small residue of hexamethyltriaminotriphenylarsine. The filtrate is acidified with hydrochloric acid and the main product precipitated with aqueous sodium carbonate. *p*-Dimethylaminophenylarsenious oxide is basic towards dilute acids, and behaves as a weak acid with strong bases, for this reason dissolving in excess of concentrated aqueous caustic soda.

p-*Dimethylaminophenylarsenious chloride hydrochloride,*

$$AsCl_2 \cdot C_6H_4N(CH_3)_2,HCl,$$

colourless needles, m.p. 116°, is obtained by adding concentrated hydrochloric acid to a saturated solution of the foregoing oxide in dilute hydrochloric acid; the corresponding *hydrobromide,*

$$AsBr_2 \cdot C_6H_4N(CH_3)_2,HBr,$$

is similarly prepared; the *hydriodide* is a yellow precipitate rapidly undergoing decomposition.

p-*Dimethylaminophenylarsenious sulphide,* $(CH_3)_2N \cdot C_6H_4 \cdot AsS$, colourless needles, m.p. 187°, dissolving in cold dilute hydrochloric acid without change; strong hydrochloric acid evolves hydrogen sulphide and gives the preceding hydrochloride. Prepared by passing hydrogen sulphide either into an alcoholic solution of the oxide or into a neutral solution of the hydrochloride. The sulphide is insoluble in water or aqueous alkalis.

Tetramethyldiaminoarsenobenzene,

$$(CH_3)_2 \cdot N \cdot C_6H_4 \cdot As{:}As \cdot C_6H_4 \cdot N(CH_3)_2,$$

yellow, granular, crystalline powder, m.p. 202°, insoluble in water or alcohol, readily soluble in chloroform or dilute acids. Prepared by shaking a warm alcoholic solution of dimethylaminophenylarsenious oxide with a large excess of 3–4 per cent. sodium amalgam. After twelve hours the precipitated arseno-derivative is collected, dissolved in chloroform, and precipitated therefrom with alcohol. It is easily oxidised in the air either when dry or in solution, regenerating dimethylaminophenylarsenious oxide. With concentrated hydrochloric acid in sealed tubes at 150° it is completely decomposed, giving dimethylaniline, arsenious chloride, and elemental arsenic. Its *hydrochloride* is a red, crystalline mass easily soluble in water and very oxidisable to the salt of the foregoing arsenious oxides.

Diethylaminophenylarsenious oxide, $(C_2H_5)_2N \cdot C_6H_4 \cdot AsO$, light

yellow powder, m.p. 58°, easily soluble in hot alcohol or dilute mineral acid. *Diethylaminophenylarsenious chloride hydrochloride*, $AsCl_2 \cdot C_6H_4 \cdot N(C_2H_5)_2,HCl$, snow-white needles, extremely soluble in water, m.p. 139°.

Diethylaminophenylarsenious sulphide, $N(C_2H_5)_2 \cdot C_6H_4 \cdot AsS$, white needles, m.p. 155°, very soluble in chloroform, insoluble in alcohol.

Tetraethyldiaminoarsenobenzene,

$$(C_2H_5)_2N \cdot C_6H_4 \cdot As{:}As \cdot C_6H_4 \cdot N(C_2H_5)_2,$$

yellow, crystalline powder, m.p. 180°, very soluble in chloroform, but not in alcohol; *hydrochloride*, a red, crystalline salt easily oxidised by air to the foregoing oxide. In the case of diethylaniline the tertiary arsine base was not obtained (*cf.* p. 224).

3 : 3′-*Diaminodiphenylarsenious sulphide*,

$$\begin{matrix}(NH_2 \cdot C_6H_4)_2As \\ (NH_2 \cdot C_6H_4)_2As\end{matrix}\!\!\diagdown\!\!\diagup S,$$

white, amorphous powder, m.p. 110°, obtained by the reduction of 3 : 3′-dinitrodiphenylarsinic acid with ammonium sulphide.

$$(NO_2 \cdot C_6H_4)_2AsO \cdot ONH_4 + 8(NH_4)_2S \longrightarrow (NH_2 \cdot C_6H_4)_2AsS \cdot SNH_4.$$

On adding hydrochloric acid to the solution in the cold the aminosulphide is obtained in the form of its soluble hydrochloride,

$$2(NH_2 \cdot C_6H_4)_2AsS \cdot SNH_4 + 6HCl =$$
$$[(NH_2 \cdot C_6H_4)_2As]_2S,4HCl + 2NH_4Cl + H_2S + S_2.$$

The filtrate, rendered ammoniacal, yields the monosulphide as a voluminous, white precipitate; the *sulphate*, $(R_2As)_2S,2H_2SO_4$, snow-white needles; the *acetyl* derivative (m.p. 175°),

$$[(CH_3 \cdot CO \cdot NH \cdot C_6H_4)_2As]_2S,$$

Tetraminotetraphenyldiarsine, $(NH_2 \cdot C_6H_4)_2As \cdot As(C_6H_4 \cdot NH_2)_2$, uncrystallisable, white flocculæ, readily becoming grey, is obtained by reducing tetranitrotetraphenyldiarsine with excess of phosphorous acid in glacial acetic acid solution. A portion becomes acetylated and separates as a more stable, white powder, m.p. 162°.

Tri-3-*aminotriphenylarsine*,[1] $(NH_2 \cdot C_6H_4)_3As$, crystalline, m.p. 176° (Philips), white, flocculent precipitate turning grey in the air (Michaelis), insoluble in water, moderately soluble in alcohol, produced by treating with tin and hydrochloric acid, a solution of 3 : 3′ : 3″-trinitrotriphenylarsine oxide in glacial acetic acid.

[1] Michaelis, *Annalen*, 1902, **321**, 183.

Its *hydrochloride* is $(NH_2 \cdot C_6H_4)_3As,3HCl$, crystalline and readily soluble in water or alcohol. *Platinichloride,*

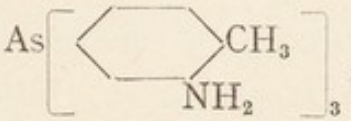
$$[(NH_2 \cdot C_6H_4)_3As,3HCl]_2(PtCl_4)_3,$$

yellow precipitate; *acid sulphate,* $2(NH_2 \cdot C_6H_4)_3As,3H_2SO_4$, crystalline, very insoluble in water, but dissolving readily in dilute hydrochloric acid. *Triacetyl* derivative,

$$(CH_3 \cdot CO \cdot NH \cdot C_6H_4)_3As,$$

colourless needles, m.p. 233°, sparingly soluble in alcohol, more so in acetic acid; prepared by treating the preceding triamine with acetic anhydride; *tribenzoyl* derivative, crystalline powder, m.p. 276°, insoluble in all ordinary solvents. Sulphuretted hydrogen passed into a glacial acetic acid solution of trinitrotriphenylarsine produces partial reduction to form the nitroamine, $NH_2 \cdot C_6H_4 \cdot As(C_6H_4 \cdot NO_2)_2$, m.p. 205°.

Tri-3-amino-tri-4-tolylarsine,[1]



—Tri-3-nitrotri-4-tolylarsine oxide is reduced with hydrochloric acid and two parts by weight of tin (10 grams of nitro-compound yield 7 grams of aminoarsine). This amino-derivative is precipitated from acid solution by caustic soda and crystallised from hot alcohol; colourless prisms, stable on exposure, m.p. 198°, almost insoluble in ether or water. The *hydrochloride,*

$$As[C_6H_3(CH_3) \cdot NH_2]_3,3HCl,$$

colourless needles, is precipitated by concentrated hydrochloric acid; the *sulphate,* $2As[C_6H_3(CH_3) \cdot NH_2]_3,3H_2SO_4$, a crystalline precipitate, is almost insoluble in water and dissolves only sparingly in hot dilute hydrochloric acid.

The *triacetyl* derivative, $As(C_7H_6 \cdot NH \cdot CO \cdot CH_3)_3$, prepared by dissolving the aminoarsine in acetic anhydride, crystallises from alcohol, m.p. 228°; the *sulphide,* $(NH_2 \cdot C_7H_6)_3AsS$, insoluble in all organic solvents, dissolves in dilute mineral acids, obtained by saturating successively with ammonia and sulphuretted hydrogen, a hot alcoholic solution of the aminoarsine.

Hexamethyl-4:4′:4″-triaminotriphenylarsine, $[(CH_3)_2N \cdot C_6H_4]_3As$, colourless needles from alcohol, m.p. 240°, very soluble in chloroform, sparingly so in cold alcohol, dissolved by dilute acids and reprecipitated unchanged by alkalis. Prepared by mixing dimethylaniline (15 grams) and arsenious chloride (25 grams)

[1] Michaelis, *Annalen*, 1902, **321**, 213.

without application of external heat. The syrupy mass is stirred into water, the solution filtered and mixed with excess of concentrated caustic soda. The tertiary base, precipitated as a white, caseous mass, is taken up with chloroform.

Hexamethyltriaminotritolylmethylarsonium iodide,

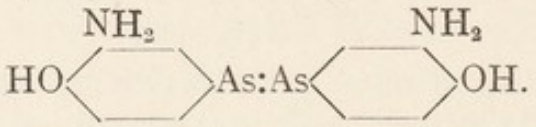
$$[(CH_3)_2N\cdot C_7H_6]_3As(CH_3)I,$$

is produced by heating the aminoarsine with methyl iodide in a reflux apparatus. After removing excess of iodide, the residue dissolved in water is precipitated with caustic soda; white powder, m.p. 135°, easily soluble in alcohol, but dissolving only sparingly in water.

Section III.—Salvarsan.

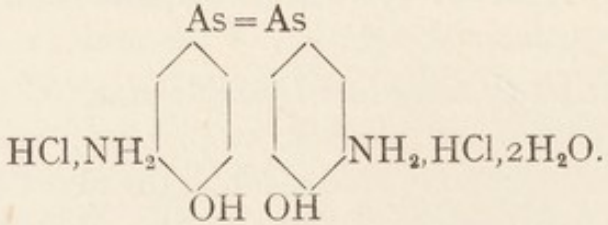
Synonyms: *Kharsivan, Arsenobenzol, Arsenobillon. Ehrlich* 606.

3 : 3′-*Diamino*-4 : 4′-*dihydroxyarsenobenzene,*[1]



—The free base of salvarsan is a pale yellow powder, soluble in dilute hydrochloric acid or aqueous sodium hydroxide or carbonate, and reprecipitated from alkaline solutions by acetic acid.

The observation that 4-hydroxyphenylarsinic acid and its reduction product, *p*-arsenophenol, has a beneficial influence on the spirilla (relapsing fever) of mice [2] led Ehrlich to examine many other substances of similar constitution with the object of increasing this spirillocidal effect to a maximum, while at the same time diminishing the harmful effect on the host of the spirilla to a minimum. The atomic grouping $HO\cdot C_6H_4\cdot As$ was varied in many ways, and ultimately it was found that the most beneficial results were obtained, not only in relapsing fever but also in human syphilis, with the *hydrochloride* of 3 : 3′-*diamino*-4 : 4′-*dihydroxyarsenobenzene* (*Salvarsan*),



[1] M. L. and B., D.R.-P., 224953; Eng. P., 13485/1910.

[2] P. Ehrlich and S. Hata, "Experimental Chemotherapy of Spirilloses," 1911, 18.

Ehrlich and Bertheim[1] obtained this product from 3-nitro-4-hydroxyphenylarsinic acid (p. 200) by reducing the nitro-compound either in successive stages or in one operation. Although many experimental modifications of these processes have been devised and new methods of synthesis discovered, it is from this nitro-compound that salvarsan has hitherto been manufactured.

Progressive Reduction of 3-Nitro-4-hydroxyphenylarsinic Acid.

The first two stages lead successively to 3-amino-4-hydroxyphenylarsinic acid and 3-amino-4-hydroxyphenylarsenious oxide, and these processes are described under the heading of these compounds (pp. 205, 228).

Salvarsan is obtainable from the second of these reduction products by the following method, in addition to processes based on the use of stannous chloride or sodium hydrosulphite. Sodium amalgam (28·8 grams of 4 per cent. Na) is added to 30 c.c. of water and 32 c.c. of 2*N*-acetic acid containing 4·98 grams of 3-amino-4-hydroxyphenylarsenious oxide. A yellow precipitate is produced, and when the amalgam is used up a further addition is made of 25 c.c. of 2*N*-acetic acid and 28·8 grams of sodium amalgam. This treatment is again repeated. The reduction is now complete, as shown by a test with hydrosulphite. The precipitate is dissolved in 60 c.c. of methyl alcohol, the calculated amount of methyl-alcoholic hydrochloric acid is added, and the salvarsan hydrochloride is precipitated by adding ether to the filtered solution; the yield is 56 per cent. of theory. This preparation contains methyl alcohol and has the composition

$$[HCl,NH_2\cdot C_6H_3(OH)As:]_2,CH_3\cdot OH.$$

It blackens and decomposes at 185–195°.

Direct Reduction of 3-Nitro-4-hydroxyphenylarsinic Acid.

An enamelled vessel (30 litres capacity) placed in a water-bath and fitted with a wooden cover, stirring gear, and thermometer, is charged with water (13 litres), crystallised magnesium chloride (513 grams), and sodium hydrosulphite (2950 grams of 80 per cent.). Into this mixture is introduced a cold solution of 3-nitro-4-hydroxyphenylarsinic acid (197 grams, 0·75 mol.) in water (4·5 litres) and 10*N*-caustic soda (135 c.c.). The tempera-

[1] *Ber.*, 1912, **45**, 756.

ture is raised to 55–60° when a microcrystalline, yellow precipitate begins to form. The reduction, which is tested by warming a filtered sample until no further deposit occurs, is usually completed in 1½–2 hours, the mixture being thoroughly stirred throughout the operation. The precipitate is washed with water and pressed. At this stage the crude diaminodihydroxyarsenobenzene is contaminated by mineral ash, sulphurous acid, and small quantities of sulphurised arsenical compounds. The moist preparation is dissolved in 1700 c.c. of methyl alcohol and the calculated quantity of methyl-alcoholic hydrochloric acid (0·75 mol. HCl) is added; ether added to the filtered solution precipitates salvarsan hydrochloride, which is collected and dried *in vacuo* or in an inert atmosphere, the average yield being 82 per cent. of theory.

3 : 3′-Diamino-4 : 4′-dihydroxyarsenobenzene dihydrochloride.—The commercial product, which is now made in 1500-gram batches, appears in the market as a bulky, pale yellow, microcrystalline powder, permanent when dry and preserved in loosely-stoppered vessels. This salt is easily soluble in water, methyl alcohol, ethylene-glycol, or glycerol, slightly so in ethyl alcohol, very slightly so in glacial acetic acid, acetone, ether, or concentrated hydrochloric acid.

Commercial samples of salvarsan contain impurities and vary one from another in respect of their arsenic content. In few cases does the composition of the product agree with the formula

$$C_{12}H_{12}O_2N_2As_2,2HCl,2H_2O.$$[1]

The yellow, aqueous solution is acid to litmus and turns Congo red to a violet hue. On adding gradually sodium or potassium hydroxide there is at first no turbidity; but precipitation begins when 1 mol. of caustic alkali has been employed for 1 mol. of dihydrochloride. When 2 mols. of caustic alkali are added the free base 3 : 3-diamino-4 : 4′- dihydroxyarsenobenzene is precipitated, the liquid being neutral. With further caustic alkali the precipitate begins to dissolve and a clear solution is reached with sufficient alkali to form the monosodium phenoxide

$$HO{\cdot}C_6H_3(NH_2){\cdot}As{:}As{\cdot}C_6H_3(NH_2){\cdot}ONa.$$[2]

The clear, moderately alkaline solution yields a precipitate with carbon dioxide, and for this reason becomes turbid in the air.

[1] Ewins, *Chem. Soc. Trans.*, 1916, **109**, 1355.

[2] Neutralisation of salvarsan; *cf.* Bongrand, *J. Pharm. Chim.*, 1913, [vii], **7**, 49.

The free diaminodihydroxyarsenobenzene is only slightly soluble in sodium carbonate ; it is insoluble in sodium bicarbonate. Its *sulphate* is very sparingly soluble in water, and even in dilute solutions the hydrochloride yields a yellowish-white precipitate with sulphuric acid and soluble sulphates.

With *p*-dimethylaminobenzaldehyde in dilute hydrochloric acid, salvarsan gives an orange coloration and then an orange precipitate. This reaction is noticeable even at considerable dilution ; it is rendered sharper by adding mercuric chloride, and is then suitable for detecting salvarsan in animal tissues.

Like other derivatives of arsenobenzene, salvarsan is very oxidisable in air. This point is of extreme importance in connection with its employment as a drug, because the oxidation product, 3-amino-4-hydroxyphenylarsenious oxide, is 20 times as toxic as salvarsan. Oxidation with iodine or hydrogen peroxide converts salvarsan into 3-amino-4-hydroxyphenylarsinic acid, the yield being about 66·5 per cent. of theory. Although stable in the dry condition when kept in closed vessels, salvarsan is very decomposable in aqueous, methyl-alcoholic. and especially in alkaline solutions, even in the absence of air, These liquids become red, ultimately depositing intense reddish-brown precipitates which have completely new properties. It is important to realise that these changes represent the later phases of a decomposition process. The earliest stages are scarcely to be detected by physical and chemical means. Biological and toxicological tests, however, are capable of detecting the slightest alteration in salvarsan by a rise in the toxicity of the preparation. The toxic properties vary considerably and unexpectedly. Colour is no criterion of safety, for, when tested on rabbits, samples of clear yellow tint have sometimes proved so toxic that the experimental animals have succumbed during injection.

Sodium salvarsan is prepared by precipitating with alcohol a solution of salvarsan in aqueous sodium hydroxide in the presence of a stabiliser, which may be sodium hydrosulphite, sodium formaldehyde-sulphoxylate, mannitol, or other polyhydric alcohol containing more than three hydroxyl groups. This preparation is stated to have proved satisfactory in the ambulatory treatment of syphilis.[1]

[1] M. L. and B., Eng. P., 15931/1912, 24152/1914 ; *Münch. Med. Wochenschr.*, 1915, 177.

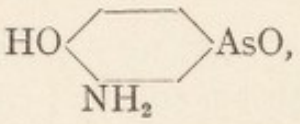
Copper salvarsan, useful in sleeping sickness, is prepared by adding sodium hydroxide to a solution of salvarsan and a copper salt (*cf.* co-ordination compounds, p. 280).[1]

Various albumin compounds of salvarsan are of therapeutic utility.[2]

2. *p*-Arsanilic acid, when diazotised in excess of hydrochloric acid and treated with *copper* powder, yields 4-chlorophenylarsinic acid,[3] which, when nitrated in concentrated sulphuric acid, gives rise to *3-nitro-4-chlorophenylarsinic acid*, white leaflets from dilute alcohol. The nitro-compound, when boiled with 5 parts of aqueous caustic potash (D = 1·32) for several hours, loses its chlorine and gives an intense yellowish-red solution, which, on acidifying, gives 3-nitro-4-hydroxyphenylarsinic acid (p. 200). The reduction of this product leads again to salvarsan. This synthesis is valid for the next homologue. 5-Amino-tolyl-2-arsinic acid diazotised and decomposed in the presence of cuprous chloride gives *5-chlorotolyl-2-arsinic acid*, m.p. 180°. This substance nitrates to 5-chloro-4-nitrotolyl-2-arsinic acid (needles from alcohol, m.p. 310°), which, on boiling with caustic alkali, yields 5-hydroxy-4-nitrotolyl-2-arsinic acid.[4] On reducing this hydroxy-compound with sodium hydrosulphite, *methyl-salvarsan* is produced.

3. 4-Hydroxy-3-aminophenylarsinic acid (230 grams) in 2000 c.c. of water and 1000 c.c. of 2*N*-sulphuric acid with 50 grams of potassium iodide in 50 c.c. of water is reduced to 4-hydroxy-3-aminophenylarsenious oxide by saturating the solution with sulphur dioxide. 4-Hydroxy-3-aminophenylarsine (185 grams) is dissolved in 2000 c.c. of alcohol, and 2000 c.c. of *N*-hydrochloric acid. The two solutions are mixed in the cold, when 3 : 3′-diamino-4 : 4′-dihydroxyarsenobenzene is precipitated forthwith as a greyish-yellow precipitate.[5]

3-Amino-4-hydroxyphenylarsenious oxide,[6]



a colourless, microcrystalline precipitate, is obtained on reducing 3-amino-4-hydroxyphenylarsinic acid by saturating its cold dilute

[1] M. L. and B., Eng. P., 1247/1914. [2] Dering, D.R.-P., 261542.
[3] *Ber.*, 1908, **41**, 1856. [4] M. L. and B., D.R.-P., 245536.
[5] M. L. and B., D.R.-P., 251571 and 254187.
[6] M. L. and B., D.R.-P., 235391.

sulphuric or hydrochloric acid solution containing potassium iodide with sulphur dioxide. The solution is rendered distinctly ammoniacal and the deposition of the oxide is completed by the addition of common salt.[1]

This oxide yields a very soluble hydrochloride, giving a neutral reaction. The salt condenses with sodium β-naphthaquinonesulphonate to a dark red product, soluble in alkali, and also yields condensation products with phenol-aldehydes.

4.[2] This method of preparation contains an improvement in the mode of reduction. Phosphorous or hypophosphorous acid, used in conjunction with hydriodic acid and preferably in the presence of acetic acid, reduces very readily and smoothly the generators of salvarsan containing nitro-groups.

i. 3-Nitrophenol-4-arsinic acid (20 grams), hypophosphorous acid (100 c.c. of 25 per cent. solution), and 70 c.c. of glacial acetic acid are heated in a stirring apparatus. 3:3′-Dinitro-4:4′-dihydroxyarsenobenzene separates as a yellow, crystalline magma; potassium iodide (12 grams) is now added, a vigorous reaction ensues, and the precipitate redissolves to a pale yellow solution. Phosphorous acid may be employed instead of hypophosphorous acid.

ii. The foregoing reduction goes even more readily with 3-nitro-hydroxyphenylarsenious oxide.

The reduction product of the foregoing processes is isolated in one or other of three ways.

i. The solution is neutralised with sodium carbonate when salvarsan base is precipitated. It is washed with water and converted into the dihydrochloride by methyl-alcoholic hydrochloric acid.

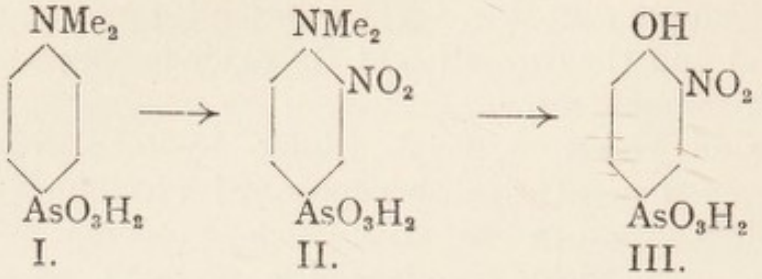
ii. The reduction solution is poured into alcohol when salvarsan hypophosphite separates as a yellowish-white powder soluble in water, alkalis, or dilute hydrochloric acid.

iii. The reduction solution is added to concentrated hydrochloric acid; salvarsan dihydrochloride separates and is washed with strong hydrochloric acid, alcoholic hydrochloric acid, and finally with ether.

[1] Ehrlich and Bertheim, *Ber.*, 1912, **45**, 761.

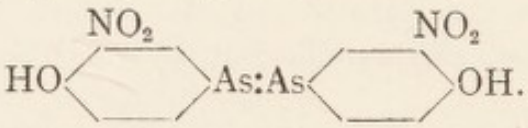
[2] M. L. and B., D.R.-P., 271894, addition to D.R.-P., 206456; compare D.R.-P., 216270, 235430, 269886, 269887.

5. *Alternative method of reduction.*[1]



—The 3-nitro-4-hydroxyphenylarsinic acid (III.) required in this alternative method may be prepared by the methods outlined on p. 200, or by Oechslin and Poulenc's method from dimethyl-*p*-arsanilic acid (I.). One hundred grams are dissolved in 500 c.c. of water with sufficient sodium hydroxide to produce a neutral solution, 50 grams of zinc chloride or acetate are then added, followed successively by a concentrated solution of sodium sulphite (100 grams), glacial acetic acid (150 c.c.), and zinc dust (200 grams), the emulsion being thoroughly stirred. Five hundred c.c. of hydrochloric acid (18 per cent.) are then added very slowly, the temperature being between 25° and 35°. The resulting clear solution is warmed to 50° and treated gradually with a further 570 c.c. of hydrochloric acid (18 per cent.). After 20–30 minutes the solution is filtered rapidly and the product precipitated by adding magnesium sulphate, when bright yellow 3 : 3′-diamino-4 : 4′-dihydroxyarsenobenzene sulphate is obtained. It is claimed that in this process the presence of sulphurous acid prevents the reduction going beyond the arsenobenzene stage to primary arsine.

3 : 3′-*Dinitro*-4 : 4′-*dihydroxyarsenobenzene*,[2]



—This compound, which is referred to incidentally in the fourth preparation of salvarsan (p. 229), is prepared in the following way :—

3-Nitro-4-hydroxyphenylarsinic acid (5·3 grams), dissolved in 20 c.c. of methyl alcohol, is added slowly, with stirring, to a well-cooled solution of stannous chloride (10 grams) in 40 c.c. of hydrochloric acid (D = 1·19) and 1 c.c. of hydriodic acid (D = 1·7).

Precipitation of 3 : 3′-dinitro-4 : 4′-dihydroxyarsenobenzene

[1] Poulenc, Eng. P., 21421/1914 ; *cf.* Eng. P., 11625/1911.
[2] M. L. and B., D.R.-P., 269886.

commences immediately, and the product, when washed with methyl alcohol and dried *in vacuo*, is a bright yellow powder which becomes electrified by friction and is insoluble in water, but dissolves in dilute aqueous alkalis, the salts being somewhat sparingly soluble in excess of these reagents. The compound requires careful handling, as when quite dry it is prone to spontaneous inflammation. It can also be conveniently prepared from 3-nitro-4-hydroxyphenylarsenious oxide by reduction with the calculated amount of stannous chloride in methyl alcohol at −15° to −10°. In this instance the addition of hydriodic acid as catalyst is unnecessary. A yield of 77·5 per cent. of the calculated amount is obtainable. This reduction [1] is also brought about by adding 10 grams of 3-nitro-4-hydroxyphenylarsinic acid or 3-nitro-4-hydroxyphenylarsenious oxide to 50 grams of hypophosphorous acid (D = 1·15) and 50 c.c. of water, the mixture being stirred and heated on the water-bath in the absence of air. After one hour's heating the mixture is poured into 2 litres of warm water.

Salvarsan from Dimethylaniline.

3-*Nitro-4-dimethylaminophenylarsinic acid.*—Finely powdered *p*-dimethylanilinearsinic acid (23·5 grams) is suspended in glacial acetic acid (300 c.c.) and dissolved with 62 per cent. nitric acid (9·8 grams) added at the ordinary temperature. The solution becomes yellow on adding 20 c.c. of acetic anhydride and rapidly deposits a thick precipitate of the pure nitro-compound (yield 20 grams).

3-Nitro-4-hydroxyphenylarsinic acid is obtained in good yield by warming the preceding compound with $2\frac{1}{2}$ parts of 40 per cent. aqueous caustic soda at 85° for 3–4 hours; it is reduced to salvarsan as in the foregoing preparations.

When the nitrodimethylamino-compound is reduced with alkaline hydrosulphite in the presence of magnesium chloride, 4 : 4′-*tetramethyl*-3 : 4 : 3′ : 4′-*tetraminoarsenobenzene* is produced and precipitated by methyl-alcoholic hydrochloric acid as its tetrahydrochloride.

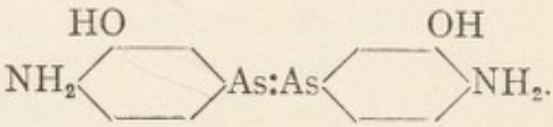
This arsenobenzene derivative has no curative effect on mice affected with *Trypanosoma brucei*. Methylation of salvarsan greatly reduces its healing powers.[2]

[1] D.R.-P., 269887. [2] Karrer, *Ber.*, 1913, **46**, 515.

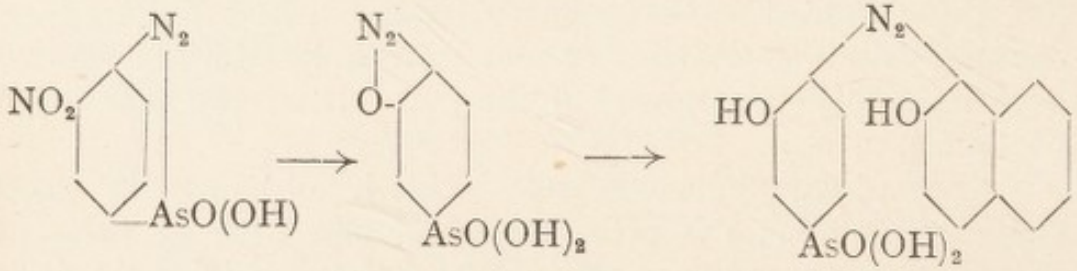
Section IV.—Isomerides of Salvarsan.

Of the nine theoretically possible isomerides of salvarsan having a symmetric constitution, the two aromatic nuclei being similarly substituted, the following have been prepared. In every instance the curative value of the isomeride is decidedly less than that of salvarsan itself.

4 : 4′-*Diamino*-3 : 3′-*dihydroxyarsenobenzene*,



—3-Nitro-4-aminophenylarsinic acid (130 grams) is dissolved in 400 c.c. of 2*N*-sodium carbonate and 500 c.c. of *N*-sodium nitrite and treated with 2550 c.c. of 2*N*-sulphuric acid at the ordinary temperature, after which 1400 grams of crystallised sodium acetate are added and the diazo-solution kept at 18° until coupling with R-salt (β-naphthol-3 : 6-disulphonic acid) no longer occurs. The brown solution is then poured into an alkaline solution of 80 grams of β-naphthol containing 556 c.c. of 10*N*-caustic soda, 500 grams of sodium carbonate, and 3 litres of water, the mixture being stirred at 20–25° for two hours, when the azo-colour is partly precipitated and partly separated by adding hydrochloric acid and salt.



The azo-compound (100 grams) is dissolved in 1½ litres of water and 100 c.c. of 10*N*-caustic soda with 500 c.c. of 2*N*-sodium acetate at 25° ; 500 grams of dry sodium hydrosulphite are added and warmed to 35–38°. When the colour disappears the solution is cooled to −10° and the precipitated 1-amino-β-naphthol separated. The filtrate is saturated with carbon dioxide, more amino-β-naphthol is removed, and the filtrate warmed to 65–70°, when 4 : 4′-diamino-3 : 3′-dihydroxyarsenobenzene gradually separates in yellow flakes.

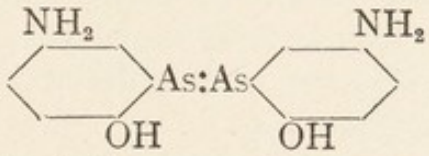
This preparation may be varied by isolating 4-amino-3-hydroxyphenylarsinic acid (*v.* p. 205) and then reducing this substance

with alkaline hydrosulphite at 60–65°, when yellow flakes of the arseno-compound are deposited.[1]

The dried product is a yellow powder scarcely soluble in water, but very easily so in aqueous alkalis or dilute acids. The hydrochloride is best prepared by dissolving the arseno-derivative in alcoholic hydrochloric acid and precipitating the salt from the filtered solution with ether (air being excluded). From solutions of the hydrochloride, sodium carbonate or acetate precipitates the free base. The hydrochloride diazotises to an intensely yellow diazo-derivative which couples to a blue azo-colour with 1-amino-8-hydroxynaphthalene-4-sulphonic acid in alkaline solution. The very sparingly soluble sulphate is precipitated by adding sulphuric acid or a soluble sulphate to the solution of hydrochloride.

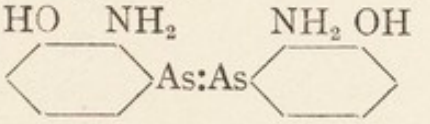
4-Amino-3-hydroxyphenylarsenious oxide, a white powder, is obtained from the corresponding arsinic acid by reducing the latter with sulphurous acid and a small amount of hydriodic acid.

5 : 5′-Diamino-2 : 2′-dihydroxyarsenobenzene,[2]



—The dihydrochloride of this compound is isomeric with salvarsan. It is produced by drastic reduction of 5-nitro-2-hydroxyphenylarsinic acid with alkaline hydrosulphite. The free base is a yellow powder, soluble in acids or aqueous caustic alkalis. The alkaline solution oxidised together with *p*-xylenol by sodium hypochlorite develops an intense cornflower blue coloration of the corresponding indophenolarsinic acid.

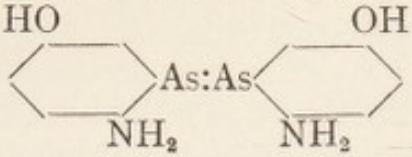
2 : 2′-Diamino-3 : 3′-dihydroxyarsenobenzene,[3]



—This isomeride is produced indirectly from 2-nitro-3-aminophenylarsinic acid (p. 189). This substance on boiling with strong aqueous caustic potash loses its amino-group, becoming 3-nitro-3-hydroxyphenylarsinic acid, and the latter on reduction with alkaline hydrosulphite yields the consecutively substituted diaminodihydroxyarsenobenzene.

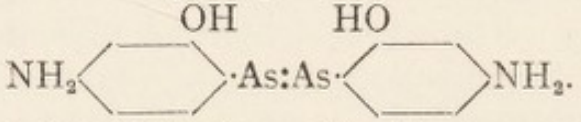
[1] M. L. and B., D.R.-P., 243648, 244166, 244789, 244790; Benda, *Ber.*, 1911, **44**, 3582. [2] Benda, *Ber.*, 1911, **44**, 3296. [3] D.K.-P., 256343.

2 : 2′-*Diamino*-5 : 5′-*dihydroxyarsenobenzene*,



—2-Nitro-5-aminophenylarsinic acid becomes converted into 2-nitro-5-hydroxyphenylarsinic acid by boiling with strong aqueous caustic potash, and the latter hydroxyarsinic acid on reduction with warm alkaline hydrosulphite yields the arseno-derivative (*cf.* p. 188).

4 : 4′-*Diamino*-2 : 2′-*dihydroxyarsenobenzene*,[1]



—The hydrochloride of this isomeride of salvarsan is obtained by reducing 3-aminophenol-6-arsinic acid (p. 206) in hydrochloric acid at −5° with stannous chloride, glacial acetic acid, and a small amount of hydriodic acid. The product is drained in an atmosphere of carbon dioxide and washed with acetic acid and alcohol.

This hydrochloride dissolves to a light yellow solution. Sodium hydroxide sets free the base as a yellow precipitate soluble in excess to a yellow solution. The sulphate of the arseno-base is sparingly soluble.

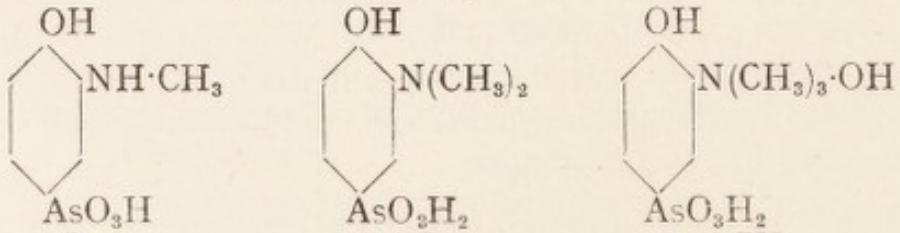
Its carbethoxy-derivative is obtained by the reduction of carbethoxy-3-aminophenol-6-arsinic acid as a yellow precipitate soluble in aqueous caustic soda to a yellow solution. The therapeutic value of 4 : 4′-diamino-2 : 2′-dihydroxyarsenobenzene is far less than that of its isomeride, salvarsan.

Section V.—Derivatives and Homologues of Salvarsan.

1. N-*Methyl Derivatives of Salvarsan.*[2]

The starting point in the production of *N*-alkylated salvarsans is preferably 3-amino-4-hydroxyphenylarsinic acid, direct alkylation of the arsenobenzene derivative being attended by complications due to the unsaturated nature of this compound.

3-*Methylamino*-4-*hydroxyphenylarsinic acid* I.

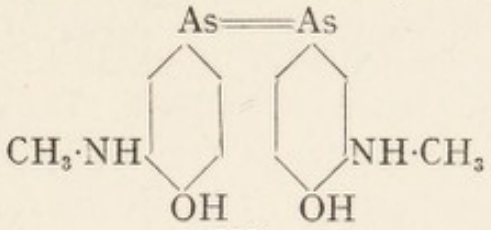


I. II. III.

[1] Bauer, *Ber.*, 1915, **48**, 1581. [2] Bertheim, *Ber.*, 1912, **45**, 2130.

—This compound is produced by adding dimethyl sulphate (0·2 mol.) to an alkaline solution of 3-amino-4-hydroxyphenylarsinic acid (0·4 mol.); crystallisation sets in, and after the mixture has become heated, it is cooled again, when hydrochloric and acetic acids are added and the unchanged aminohydroxyphenylarsinic acid separated by filtration. The filtrate, on concentration *in vacuo*, yields the crystalline methyl compound separating with $\frac{1}{2}H_2O$. The product is very soluble in water, the alcohols, acetic acid, aqueous alkalis, and mineral acids; it melts with decomposition at 263–263·5°, and its aqueous solution is oxidised by air, giving coloured tarry products.

Sym.-3 : 3′-*Dimethylamino*-4 : 4′-*dihydroxyarsenobenzene* (IV.).



IV.

—The foregoing methylated arsinic acid is reduced in the customary manner (p. 225) with hydrosulphite and the precipitated arsenobase converted into dihydrochloride, a greyish or yellowish-white microcrystalline powder. With *p*-dimethylaminobenzaldehyde it gives a brownish-orange liquid, but, unlike salvarsan, no subsequent precipitate. Its solution yields with sulphuric acid a sparingly soluble sulphate; caustic soda furnishes a precipitate of the free base which passes into a yellow solution with more of the alkali.

3-*Dimethylamino*-4-*hydroxyphenylarsinic acid* (II.).—3-Amino-4-hydroxyphenylarsinic acid (46·6 grams) in water (300 c.c.) and 10*N*-sodium hydroxide (21·2 c.c.) is mixed with 20 c.c. of dimethyl sulphate at the ordinary temperature. Heat is generated, and as the mixture cools crystallisation commences, and a further 20 c.c. of alkali and 20 c.c. of dimethyl sulphate are added. When crystallisation no longer occurs, glacial acetic acid (12 c.c.) is added, and the solution is seeded with a little of the starting material. After two days a crop of 3-amino-4-hydroxyphenylarsinic acid is removed, and the filtrate yields totally dissimilar transparent prisms when concentrated *in vacuo*, the total yield being 53·7 per cent. of theory. The dimethylated acid is soluble in water, the alcohols, or acetic acid, but dissolves only slightly in acetone, and is insoluble in ether; its decomposition point is 119–121°.

3 : 3′-*Tetramethyldiamino*-4 : 4′-*dihydroxyarsenobenzene* results from the hydrosulphite reduction of the preceding compound ; its dihydrochloride is a yellowish-grey powder, easily soluble in water or methyl alcohol. Sulphuric acid precipitates it from aqueous solution, but only slowly.

3-*Trimethylammonium*-4-*hydroxyphenylarsinic acid* (III.), lustrous, colourless prisms decomposing at 262–264°. 3–Amino-4-hydroxyphenylarsinic acid (21 grams) is shaken with methyl alcohol (210 c.c.), 10*N*-sodium hydroxide (9 c.c.), and methyl iodide (6 c.c.). After several hours, a further addition of the same quantities of alkali and iodide is made, and after a day this addition is repeated. The crystals separating (25·3 grams) are a mixture of quaternary iodide and quaternary base, and these constituents are separated by crystallisation from water when the more soluble iodide remains dissolved. The quaternary ammonium compound loses water at 110–114°, passing probably into the inner anhydride, $AsO_3H_2 \cdot C_6H_3 \begin{cases} N(CH_3)_3 \\ | \\ O \end{cases}$.

The ammonium hydroxide itself dissolves readily in water with an acid reaction ; it is less soluble in the alcohols or acetone ; it dissolves readily in aqueous alkalis or acids. Unlike the unmethylated and mono- and di-methylated arsinic acids, it does not give a red coloration with a drop of bichromate in acid solution. Reduced with hydrosulphite it furnishes 3 : 3′-*hexamethyldiammonium*-4 : 4′-*dihydroxyarsenobenzene*, a light yellow powder, insoluble in water, but dissolving in dilute hydrochloric acid or aqueous caustic soda.

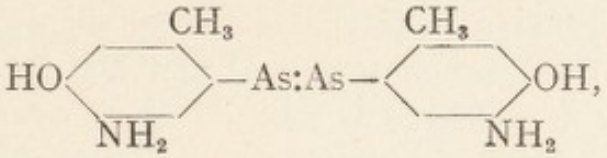
These methylated salvarsans are all much more toxic than salvarsan itself. The di- and tetra-methyl derivatives have equal toxicity and are 10 times as toxic on mice as salvarsan. The hexamethyl compound is about 3–5 times as toxic as the latter drug. The curative effect on trypanosomes is diminished by methylation. The hexamethylsalvarsan is inactive on these organisms. The tetramethyl compound in half the lethal dose gives very little useful result ; a similar concentration of dimethylsalvarsan renders animals free from trypanosomes only for a few days, whereupon recurrence sets in. These results may be correlated with the influence of methyl groups in general, not only in the arsenical drugs but in the rosaniline and acridine series. A methyl group produces a dystherapeutic effect.

2. C-*Methyl Derivatives of Salvarsan.*

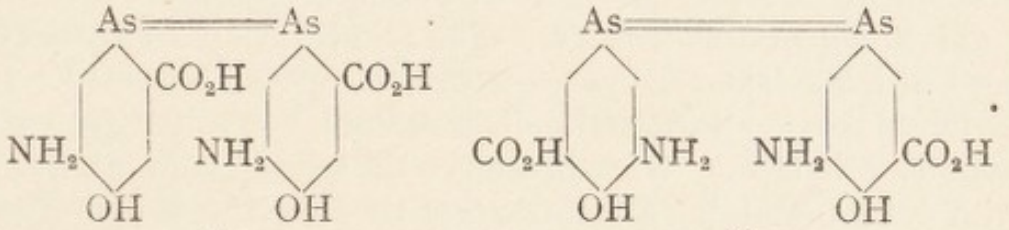
3 : 3′-*Diamino*-2 : 2′-*dihydroxy*-5 : 5′-*arsenotoluene,*

a pale yellow powder, melting and decomposing at 165–167°, is prepared in a similar manner to salvarsan ; it is sparingly soluble in water or organic media, but dissolves readily in aqueous alkalis or dilute acids.[1]

4 : 4′-*Diamino*-5 : 5′-*dihydroxy*-2 : 2′-*arsenotoluene* (*v.* p. 228),



3. *Carboxylated Derivatives of Salvarsan,*[2]



I. II.

The starting material for the first of these carboxylic acids is 5-nitroanthranilic acid, of which 18 grams diazotised in 100 c.c. of hydrochloric acid and 50 c.c. of water give, on treatment with sodium arsenite (26 grams) in 50 c.c. of water and careful addition of sodium hydroxide till the acid reaction on Congo red has disappeared, a granular precipitate of *2-carboxy-4-nitrophenylarsinic acid* (yield 22 grams). This nitro-acid dissolved in aqueous caustic soda is added at once to a solution of ferrous sulphate. The concentrated filtrate from iron hydroxides, rendered acid, is decanted from separated sodium chloride, and the *2-carboxy-4-aminophenylarsinic acid* diazotised in solution and the diazo-compound decomposed by heating on the water-bath. The resulting 2-carboxy-4-hydroxyphenylarsinic acid is reduced in solution with 35 per cent, hypophosphorous acid containing potassium iodide, when 2 : 2′-*dicarboxy*-4 : 4′-*dihydroxy*-

[1] M. L. and B., D.R.-P., 224953; Ehrlich and Bertheim, U.S. P., 986148.

[2] Karrer, *Ber.*, 1915, **48**, 1058.

arsenobenzene separates as a yellow precipitate. This substance, when freed by washing from all inorganic impurities, is oxidised with 30 per cent. cooled hydrogen peroxide, yielding *2-carboxy-4-hydroxyphenylarsinic acid*, which is produced but not isolated in an earlier stage of the synthesis. This compound (3·9 grams), which crystallises in very soluble colourless needles, is dissolved in 20 c.c. of concentrated sulphuric acid, cooled below 0°, and treated with 1·3 grams of nitric acid (D = 1·42) and 5 c.c. of water. The temperature rises to 10°, and the mixture is poured on to 75 grams of ice. *5-Nitro-2-carboxy-4-hydroxyphenylarsinic acid* separates in colourless needles decomposing at 350–355°.

5 : 5′-Diamino-4 : 4′-dihydroxy-2 : 2′-dicarboxyarsenobenzene (I.) is preferably obtained from the preceding nitro-compound by reduction with hypophosphorous acid and hydriodic acid. The nitro-compound (2·2 grams) is mixed with 20 c.c. of hypophosphorous acid (25 per cent.) and 10 c.c. of glacial acid and heated to boiling with stirring.

The arsenical group is reduced and dinitrodihydroxydicarboxyarsenobenzene is precipitated. On adding 2–3 grams of potassium iodide a violent action sets in. The acid is then partially neutralised with alkali and the yellow arseno-compound collected. It is easily soluble in alkalis and sodium acetate, but only slightly so in hydrochloric acid. When heated on the water-bath for ten hours with water containing sodium acetate the substance is hydrolysed, losing its arsenic and yielding 4-amino-3-hydroxybenzoic acid.

The isomeride (II.) of the foregoing substance is produced from 4-aminosalicylic acid by arsinating this substance to salicylarsinic acid and successively nitrating and reducing this compound to the arsenobenzene stage.

The toxic dose of isomeride I. on mice is 1/1500 gram per 20 grams of body weight.

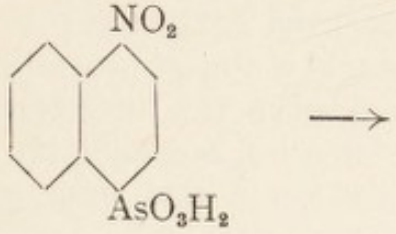
4. *Chloro-derivative of Salvarsan.*

5 : 5′-Dichloro-4 : 4′-diamino-3 : 3′-dihydroxyarsenobenzene.—The diazo-solution from 3 : 5-dichloro-*p*-arsanilic acid diluted with ice-cold water is treated with sodium acetate and stirred till the coupling with R-salt (sodium *β*-naphthol-3 : 5-disulphonate) no longer takes place. At this stage the diazo-oxide is produced by removal of one chlorine atom. The product is now coupled with alkaline *β*-naphthol, the azo-compound collected, redissolved in water, and the free azo-acid precipitated by mineral acid.

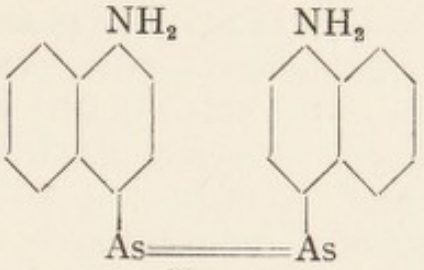
This product dissolved in sodium hydroxide containing sodium acetate is reduced with sodium hydrosulphite at 40–50°. The cooled liquid precipitates 1-amino-β-naphthol, and the filtrate reduced further with more hydrosulphite at 60° gradually deposits the arseno-compound in yellow flakes. The product is soluble in aqueous caustic soda or mineral acid, the hydrochloride being precipitated by concentrated hydrochloric acid.

5. *Arsenonaphthalene Derivatives.*[1]

1-Nitronaphthyl-4-arsinic acid (I).



I.

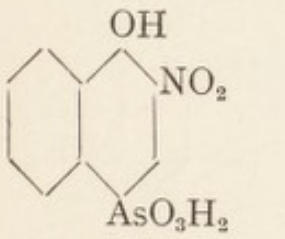


II.

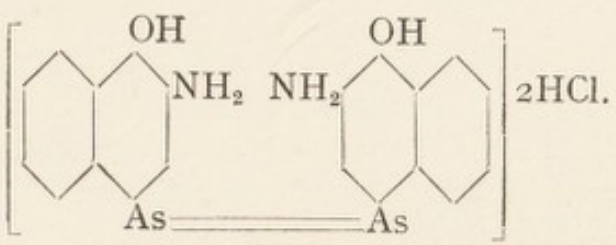
The nitration of α-naphthylarsinic acid leads to 1-nitronaphthyl-4-arsinic acid, crystallising in yellow needles and containing the arsenical group so firmly attached that it is not replaced by iodine and only slightly by bromine. With concentrated hydrochloric acid at 120° α-nitronaphthalene is produced; alkali fusion leads to α-naphthol, and treatment with phosphorus pentachloride to 4-chloro-1-nitronaphthalene.

4 : 4′-*Diamino-α-arsenonaphthalene* (II.), produced by reducing the preceding compound with acid stannous chloride in methyl-alcoholic solution; its *hydrochloride* is a pale yellow powder readily oxidised in moist air.

3 : 3′-*Diamino*-4 : 4′-*dihydroxy-α-arsenonaphthalene dihydrochloride* (II.), the naphthalene analogue of salvarsan, is a brownish-yellow powder produced by nitrating 4-hydroxy-α-naphthylarsinic acid and reducing the nitro-compound (III.) with acid stannous chloride.



III.

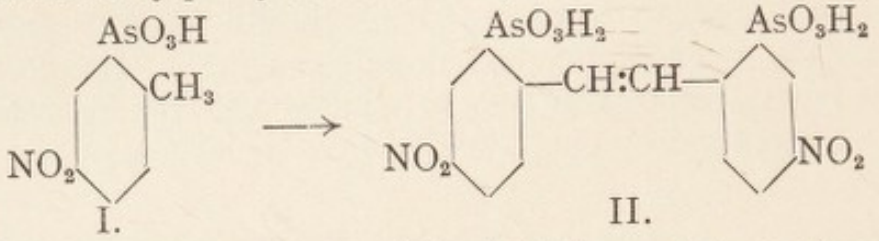


IV.

[1] N. Andrew, *J. Russ. Phys. Chem. Soc.*, 1913, **45**, 1980.

6. *Stilbene Analogues of Salvarsan.*

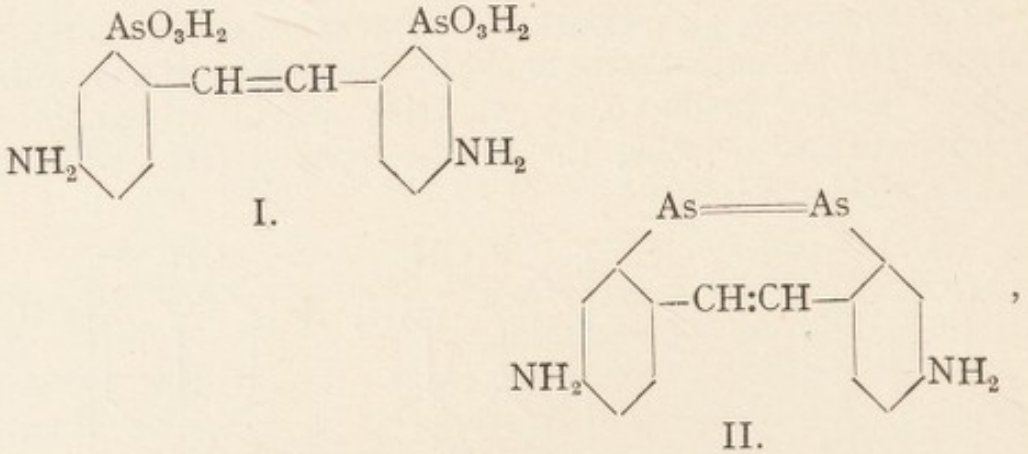
5-Nitro-2-methylphenylarsinic acid (I.),[1]



I. II.

—*o*-Tolylarsinic acid (5 grams) is added to a mixture of concentrated sulphuric acid (25 grams) and nitric acid (20 grams, D = 1·49) at 20–35°, and after 15 minutes the mixture is poured into 6 volumes of water. The sulphuric acid is almost neutralised with concentrated caustic soda solution, when the nitro-arsinic acid separates on cooling in white, felted needles, becoming brown at 230° and melting at 261°. This nitroarsinic acid undergoes a series of complicated changes when heated at 90° with aqueous alkalis, giving rise to arsenicated stilbene dyes of the Mikado brown type. These reactions are due to intramolecular oxidation of the methyl group by the nitro-group in the presence of alkalis, the resulting products being a mixture of dinitroso-, azoxy-, and azo-stilbenediarsinic acids. A homogeneous product is obtained by heating to 90° for five minutes 5-nitro-2-methylphenylarsinic acid (5 grams), 50 c.c. of 10*N*-caustic soda, 50 c.c. of water, and 35 c.c. of sodium hypochlorite (Cl = 5·5 per cent.), when acid precipitates a thick, crystalline mass of colourless 5 : 5′-*dinitro*-2 : 2′-*stilbene*-1 : 1′-*arsinic acid* (II.).

[2] 5 : 5′-*Diamino*-2 : 2′-*stilbene*-1 : 1′-*diarsinic acid* (I.) and 5 : 5′-*diamino*-1 : 1′-*arseno*-2 : 2′-*stilbene* (II.),



I. II.

—The arsenicated stilbene colouring matters obtained in solution

[1] Karrer, *Ber.*, 1915, **48**, 311. [2] *Ibid.* 313.

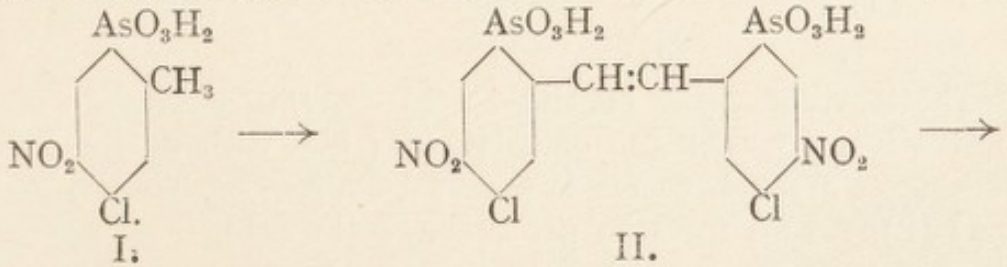
by heating at 90° with caustic alkali, are reduced by the addition of zinc dust until the decolorised solution no longer becomes brown on exposure to air. Sodium hydrosulphite is introduced, and the hot solution added to excess of dilute hydrochloric acid. The brown precipitate is redissolved in aqueous sodium carbonate, and boiled with more hydrosulphite until the solution is completely decolorised, when the filtrate on cooling deposits the disodium salt of 5 : 5′-diamino-2 : 2′-stilbene-1 : 1′-diarsinic acid. The free acid (I.) separates from an acid solution of the salt in yellow flakes; it yields a Schiff base with *p*-dimethylaminobenzaldehyde.

5 : 5′-*Diamino*-1 : 1′-*arseno*-2 : 2′-*stilbene* (II.) is produced by the energetic reduction of the preceding compound with excess of hydrosulphite; it separates in yellow flakes insoluble in alkalis and dissolving only sparingly in excess of mineral acid.

o-*Tolylarsinic acid* is conveniently prepared by Bart's synthesis in the following manner: *o*-toluidine (53 grams) in 500 c.c. of water and 165 c.c. of hydrochloric acid (D = 1·19) is diazotised at 5° with sodium nitrite (35 grams) in 140 c.c. of water. To this diazo-solution are added successively with continual stirring, sodium arsenite (130 grams) in 260 c.c. of water and 100 c.c. of 10*N*-sodium hydroxide. The mixture is then left for several hours, decanted from tar, and treated successively with strong ammonia (300 c.c.), 30 per cent. hydrogen peroxide (75 c.c.), and 2/3*N*-magnesia mixture (2 litres), when all the inorganic arsenic present is precipitated as magnesium ammonium arsenate. The filtrate on boiling deposits magnesium *o*-tolylarsinate, which is sparingly soluble in hot water. The free acid crystallises in colourless needles (m.p. 160°) on decomposing this salt with moderately strong hydrochloric acid, the yield being 20 grams.

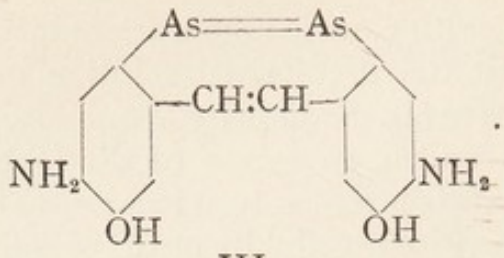
5-*Chlorotolyl*-2-*arsinic acid*, $CH_3 \cdot C_6H_3Cl \cdot AsO_3H_2$, white needles, softening at 195° and melting at 199°, is prepared by the foregoing process from 5-chloro-2-toluidine, 45 grams of this base yielding 8 grams of the magnesium salt.[1]

5 : 5′-*Diamino*-4 : 4′-*dihydroxy*-1 : 1′-*arseno*-2 : 2′-*stilbene* (III.),[2]



I. II.

[1] P. Karrer, *Ber.*, 1915, **48**, 310, 314. [2] Karrer, *Ibid.*, 314.



III.

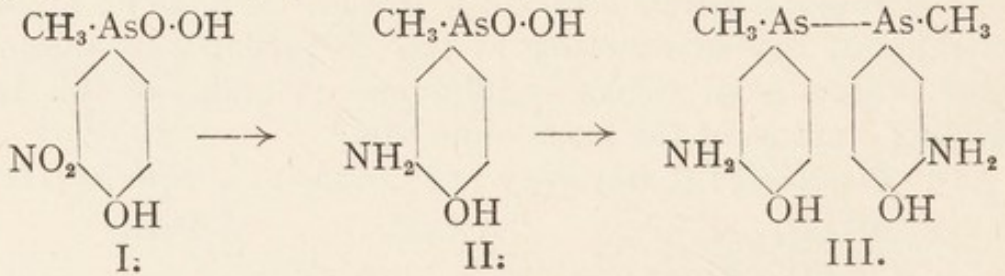
—5-Chlorotolyl-2-arsinic acid is nitrated at 30–40° by a mixture of concentrated nitric and sulphuric acids, the product being isolated by pouring the acid solution into water.

4-*Nitro*-5-*chlorotolyl*-2-*arsinic acid* (I.), crystallising from hot water in colourless, lustrous leaflets, m.p. 215°, undergoes the stilbene condensation on heating on the water-bath for 20 minutes with 5*N*-sodium hydroxide and an equal volume of sodium hypochlorite (Cl = 5·5 per cent.), the hot solution being then acidified with hydrochloric acid, when 4 : 4′-*dichloro*-5 : 5′-*dinitro*-2 : 2′-*stilbene*-1 : 1′-*diarsinic acid* (II.) is precipitated as a white, crystalline powder.

5 : 5′-*Diamino*-4 : 4′-*dihydroxy*-1 : 1′-*arseno*-2 : 2′-*stilbene* (III.), an analogue of salvarsan, containing its arsenic in an eight-membered ring, is produced by heating the preceding compound with 10*N*-sodium hydroxide and a little sodium hypochlorite, precipitating 5 : 5′-dinitro-4 : 4′-dihydroxy-2 : 2′-stilbene-diarsinic acid and reducing the latter with alkaline hydrosulphite or stannous chloride containing potassium iodide. The resulting yellowish-brown arseno-compound is insoluble in acids, and dissolves in aqueous caustic soda.

7. *Mixed Aromatic-aliphatic Cacodyl Analogue of Salvarsan.*

3 : 3′-*Diamino*-4 : 4′-*dihydroxydiphenyldimethyldiarsine* (III.),[1]



I. II. III.

—The starting point of this mixed aromatic-aliphatic cacodyl derivative, an analogue of salvarsan, but without the double linking of arsenobenzene, is 3-*nitro*-4-*hydroxyphenylmethylarsinic acid* (I.), prisms from 50 per cent. acetic acid, m.p. 232–233°,

[1] Bertheim, *Ber.*, 1915, **48**, 357.

prepared in good yield by Ehrlich and Bertheim's general method from 3-nitro-4-hydroxyphenylarsenious oxide, methyl-alcoholic caustic soda, and methyl iodide. Its reduction is preferably effected in two stages. The nitro-arsinic acid (1 part) caustic soda (2 mols.), dissolved in 10 parts of water at 5°, and treated at once with 2½ parts of sodium hydrosulphite. The warm filtered solution mixed with 1 part of concentrated hydrochloric acid yields the crude *3-amino-4-hydroxyphenylarsinic acid* (II.), which, when crystallised from water, decomposes at 206–207°. With sodium nitrite it gives a lemon-yellow, soluble diazo-compound.

3 : 3′ - *Diamino* - 4 : 4′ - *dihydroxydiphenyldimethyldiarsine* is obtained in the form of its colourless, crystalline hypophosphite by treating the preceding aminoarsinic acid with hypophosphorous acid (D=1·136) containing 1 per cent. of strong hydriodic acid. This hypophosphite dissolves readily in aqueous caustic alkalis or acids. With sodium nitrite it yields a yellow diazo-derivative. When shaken with methyl-alcoholic hydrochloric acid the hypophosphite is converted into hydrochloride, which is precipitated as a white, crystalline powder on adding excess of strong hydrochloric acid. This salt dissolves in water to a clear solution neutral to Congo red paper. Both the hypophosphite and hydrochloride have an irritating effect on the mucous membrane. This substituted aromatic diarsine and its salts differ from salvarsan and its salts in being devoid of colour and highly crystalline. The toxicity of the diarsine is much greater than that of salvarsan, whilst its therapeutic effect is less. Since the aromatic nuclei are similarly substituted in both compounds, the foregoing differences are to be attributed to the disappearance of the arsenical double linking in the diarsine series.

Section VI.—Tetraminoarsenobenzenes.

Reduction Products of 2 : 4-Dinitrophenylarsinic Acid.[1]

2 : 4-*Dinitrophenylarsenious oxide*, $(NO_2)_2C_6H_3 \cdot AsO$, crystalline, yellow crusts obtained by adding phosphorus trichloride to 2 : 4-dinitrophenylarsinic acid suspended in ether. The ethereal solution is washed with water (2 vols.), then shaken up with 3 vols. of water, and the mixture allowed to evaporate. The product is soluble in ether or alcohol containing hydrochloric acid with the formation of 2 : 4-dinitrophenylarsenious chloride ;

[1] Karrer, *Ber.*, 1914, **47**, 2275.

it is, however, insoluble in water or dilute acids. In excess of aqueous sodium hydroxide it dissolves to a yellow solution.

2 : 4 : 2′ : 4′-*Tetranitroarsenobenzene*,

$$(NO_2)_2C_6H_3\cdot As{:}As\cdot C_6H_3(NO_2)_2,$$

is produced in reddish-brown flakes by shaking an alkaline solution of the preceding compound with excess of hypophosphorous acid and a few drops of aqueous potassium iodide as catalyst at 50–60°. On account of the oxidisability of the product the reduction goes best in an inert atmosphere.

2 : 4 : 2′ : 4′-*Tetraminoarsenobenzene*,

$$(NH_2)_2\cdot C_6H_3\cdot As{:}As\cdot C_6H_3(NH_2)_2,$$

is an extremely oxidisable substance obtained in the form of its double tin salt (yellowish-white flakes) by warming at 70–80° 2 : 4-dinitrophenylarsinic acid with stannous chloride in hydrochloric acid containing a few drops of potassium iodide solution. The liquid is cooled to 40° and poured into glacial acetic acid when the double chloride is precipitated. This compound is not stable in aqueous solution, but the arseno-compound is produced from it by dissolving in 2–3*N*-hydrochloric acid and adding successively excess of glacial acetic acid and ether until a bulky, yellowish-white precipitate separates.

This tetraminoarsenobenzene behaves like a meta-diamine, coupling with diazo-compounds (without loss of arsenic) and yielding with nitrous acid an azo-dye of the Bismarck brown type. It is rapidly decomposed hydrolytically by cold water, yielding arsenious and arsenic acids, *m*-phenylenediamine (25 per cent. of the theoretical amount), and a reddish-brown, insoluble product containing a large amount of combined arsenic. Like other aromatic meta-diamines, whether containing arsenic or not, the foregoing base is soluble in excess of carbonic acid, this solubility being probably due to the formation of a complex carbamic acid.

3 : 5 : 3′ : 5′-*Tetramino*-4 : 4′-*dihydroxyarsenobenzene*,[1]

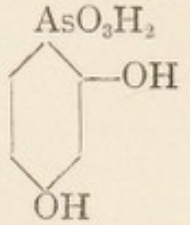
pale yellow powder, decomposing and blackening at 155–157°, insoluble in water or organic media, and dissolving readily in aqueous alkalis or dilute acids, is obtained by reducing 3 : 5-dinitro-4-hydroxyphenylarsinic acid.

[1] M. L. and B., D.R.-P., 224953.

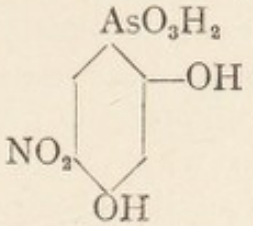
Section VII.—*5 : 5′-Diamino-2 : 4 : 2′ : 4′-tetrahydroxyarsenobenzene and its Derivatives.*

These compounds are obtained from resorcinol and its methyl ethers.

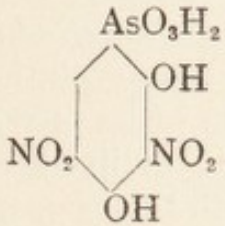
2 : 4-Dihydroxyphenylarsinic acid (I.),[1]



I.



II.



III.

—Resorcinol (110 grams) heated on the water-bath with arsenic acid solution (180 grams of 75° Bé., 83 per cent.) forms a solution from which crystals slowly separate in the course of several hours. After two days a yield of 145 grams of 2 : 4-dihydroxyphenylarsinic acid is obtained. This acid crystallises from dilute acetic acid; it is very soluble in water and the alcohols, but insoluble in ether, benzene, or petroleum. With ferric chloride it gives a dark red coloration, but does not reduce warm ammoniacal silver nitrate. It nitrates in stages to yield successively *5-nitro-2 : 4-dihydroxyphenylarsinic acid* (II.) and *3 : 5-dinitro-2 : 4-dihydroxyphenylarsinic acid* (III.). These products on bromination lose their arsenical complex, giving rise respectively to 2 : 6-dibromo-4-nitroresorcinol and 2 : 4-dinitro-6-bromo-resorcinol. The arsenical group is also removed by coupling the compounds with diazotised *p*-nitroaniline.

The foregoing nitro-compounds on drastic reduction give rise to derivatives of arsenobenzene.

5-Amino-2 : 4-dihydroxyphenylarsinic acid (needles, decomposing at 150°) is an intermediate compound obtained from the mononitro-acid and alkaline hydrosulphite. Acetylation of the sodium salt gives *5-acetylamino-2 : 4-dihydroxyphenylarsinic acid*, which on reduction with hypophosphorous acid (D = 1·136) and a small amount of hydriodic acid furnishes *5 : 5′-diacetyldiamino-2 : 4 : 2′ : 4′-tetrahydroxyarsenobenzene*, a yellow, insoluble powder dissolving in aqueous caustic soda.

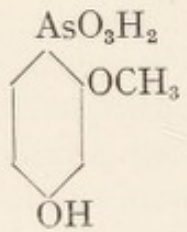
5 : 5′-Diamino-2 : 4 : 2′ : 4′-tetrahydroxyarsenobenzene is produced by reducing the mononitro-acid to the amino-acid by stannous chloride, afterwards activating this reducing agent with hydriodic

[1] M. L. and B., D.R.-P., 272690; Bauer, *Ber.*, 1915, **48**, 509.

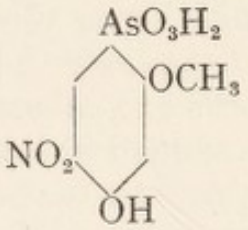
acid so that the arsinic group is also reduced. In the presence of acetic and hydrochloric acids the arsenobenzene derivative is precipitated in the form of its yellow dihydrochloride. This salt is easily soluble in water; sodium hydroxide precipitates the free base, but redissolves it in excess, this solution turning blue on exposure to air.

3:5:3′:5′-*Tetramino*-2:4:2′-4′-*tetrahydroxyarsenobenzene*, precipitated from solutions containing excess of hydrochloric acid in the form of its tetrahydrochloride, is produced by reducing the foregoing dinitro-acid first with stannous chloride alone, and then with this reagent activated by hydriodic acid. The product is a dull yellow powder dissolving in water to a dark yellow solution. The solution in hydrochloric acid is light yellow, but on warming, the arseno-compound is hydrolysed, losing arsenic and yielding 2:4-diaminoresorcinol. In mineral acid the arsenobenzene derivative gives a light yellow diazo-derivative coupling to a red azo-dye with resorcinol. With acetic acid and sodium nitrite it furnishes a deep brown precipitate, which is probably an aminoazo-dye of the Bismarck brown type.

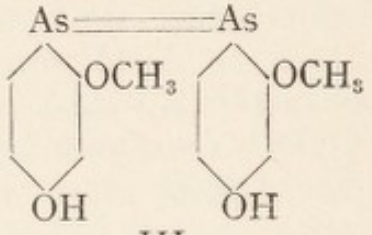
2-*Methoxy*-4-*hydroxyphenylarsinic acid* (I.),



I.



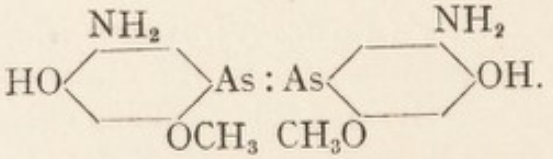
II.



III.

—Resorcinol monomethyl ether (100 grams) heated for fifty hours with arsenic acid (160 grams of 75° Bé.) on the water-bath yields on extraction with acetic acid 63 grams of arsinic acid (m.p. 209°, crystallised from water). Nitration of this product is effected preferably in acetic acid and leads to 5-*nitro*-2-*methoxy*-4-*hydroxyphenylarsinic acid* (II.). Unlike resorcinol-4-arsinic acid, the monomethyl ether can be reduced with hypophosphorous and hydriodic acids to a stable arsenobenzene derivative (III.), separating as a yellow powder, soluble in caustic but not in carbonated alkali.

5:5′-*Diamino*-2:2′-*dimethoxy*-4:4′-*dihydroxyarsenobenzene*,



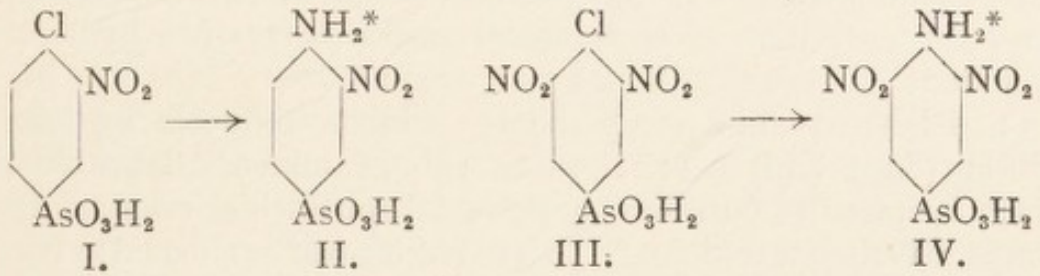
—This arsenobenzene derivative is produced by reducing 5-nitro-2-methoxy-4-hydroxyphenylarsinic acid in two stages. The first with alkaline hydrosulphite leads to *5-amino-2-methoxy-4-hydroxyphenylarsinic acid*, colourless needles with $2H_2O$, darkening at 120°, sparingly soluble in water. The second stage, effected on the preceding aminoarsinic acid with hypophosphorous acid and potassium iodide, furnishes the arseno-compound precipitated as hypophosphite by adding acetone, or as hydrochloride by excess of hydrochloric acid. The latter salt in warm solution undergoes hydrolysis to 4-aminoresorcinol 1-methyl ether, thus demonstrating the accuracy of the foregoing formula.

2 : 4-*Dimethoxyphenylarsinic acid* is obtainable in good yield by heating resorcinol dimethyl ether and syrupy arsenic acid on the water-bath for eight days. It crystallises from water in silky needles, m.p. 242–243°. This arsinic acid is also produced by the methylation of resorcinol-4-arsinic acid with dimethyl sulphate (excess) in presence of aqueous caustic soda at 90–100°.

Section VIII.—Hexaminoarsenobenzene and its Derivatives.

Since the introduction of salvarsan much activity has been shown in the production of other analogously constituted derivatives of arsenobenzene. Among these researches a promising field has been opened up in the polyaminoarsenobenzenes, which exhibit useful therapeutic properties.

The starting points in these syntheses are the nitrated *p*-arsinic and alkyl-*p*-arsinic acids, produced either by direct nitration of *p*-arsinic acid or its alkyl and acyl derivatives, or by replacing chlorine by amino- and alkylamino-groups in the nitrated *p*-chlorophenylarsinic acids (I. and III.).

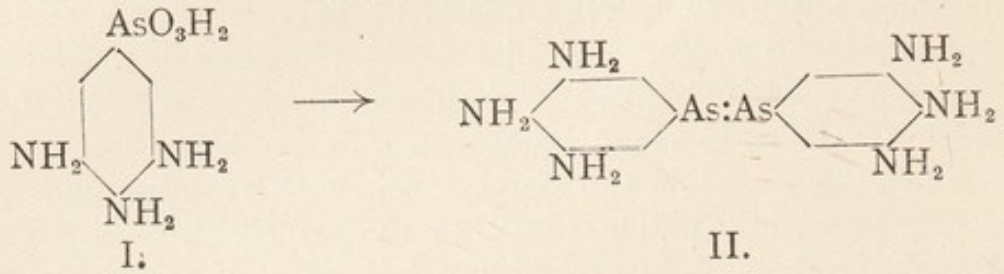


I. II. III. IV.

The NH_2 group (asterisked) is alternatively replaceable by NHR or NR_2 groups.[1]

[1] C. F. Boehringer and Söhne, Eng. P., 29546/1913.

3 : 4 : 5 : 3′ : 4′ : 5′-*Hexaminoarsenobenzene* (II.),[1]



I. II.

—The starting material for this arsenobenzene derivative is 3 : 5-dinitro-*p*-arsanilic acid (p. 203), this substance being reducible in two stages.

3 : 4 : 5-*Triaminophenylarsinic acid* (I.).—The dinitro-compound (92·4 grams) is dissolved in water (1400 c.c.) and 10*N*-caustic soda (200 c.c.) at the ordinary temperature and reduced with an acid ferrous chloride solution (1050 c.c. of 19·6 per cent. Fe) diluted with 2000 c.c. of water. During addition of the iron solution the mixture is kept alkaline to turmeric by means of caustic soda. The filtered solution is acidified, concentrated, partially neutralised with caustic soda, a dark impurity removed by filtration, and the mineral acid neutralised by more alkali (Congo red test); the arsinic acid separates in brown needles (total yield 72 per cent. of theory). When recrystallised it becomes colourless (decomposing point 170–175°); it is very sparingly soluble in cold, more so in hot, water, almost insoluble in alcohol, but dissolves in dilute mineral acids, aqueous alkalis, warm sodium acetate and 50 per cent. acetic acid.

Nitrous acid produces a yellow diazo-compound; oxidising agents (K_3FeCy_6 and NaClO) give red, transient colorations; the ammoniacal solution reduces silver nitrate, and a drop of nitric acid added to the solution in concentrated sulphuric acid develops a brown coloration, changing quickly to olive green and blue. This triamino-acid and its generator, the dinitro-compound, are both reducible to the arsenobenzene derivative by acid reduction.

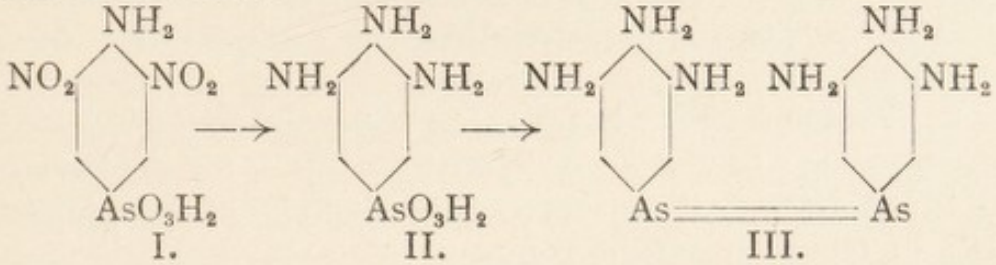
3 : 5-Dinitro-4-aminophenylarsinic acid is reduced in acid solution (Sn + HCl) to 3 : 4 : 5 : 3′ : 4′ : 5′-hexaminoarsenobenzene, which is stated to possess very powerful spirillicidal effects with comparatively low toxicity.[2] This reduction can be effected in two or more stages.[3] Sodium hydrosulphite leads to 3 : 4 : 5-triaminobenzenearsinic acid, reducible further by hypophosphorous acid

[1] Benda, *Ber.*, 1914, **47**, 1316.
[2] Eng. P., 7488 and 8041/1913.
[3] Eng. P., 8137/1913.

to the hexamino-base. Furthermore, 3 : 5-dinitro-4-aminophenylarsinic acid is reduced to 4 : 4′-diamino-3 : 5 : 3′ : 5′-tetranitroarsenobenzene by 50 per cent. alcoholic phosphorous acid, the final stage to hexamino-base being effected by stannous chloride and hydrochloric acid.

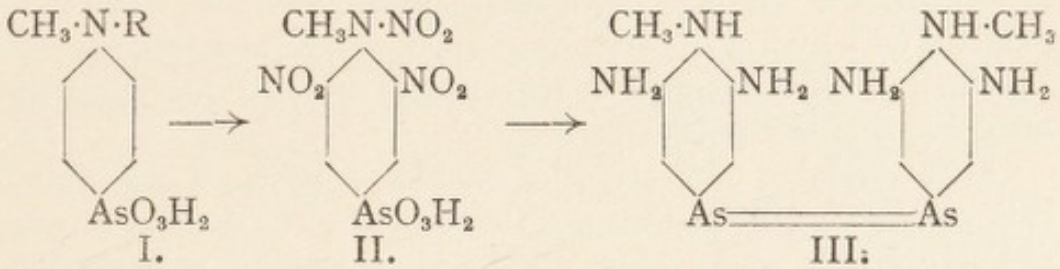
The hexamino-base (III.) is obtainable from 3 : 5-dinitro-4-aminophenylarsinic acid I. by various other methods of reduction.[1]

Both triaminophenylarsinic acid (II.) and the hexamino-base are comparatively slightly toxic, and the latter has a powerful spirillocidal action.



3 : 5-Dinitro-4-methylaminophenylarsinic acid reduced with tin and hydrochloric acid furnishes 4 : 4′-*dimethyl*-3 : 4 : 5 : 3′ : 4′ : 5′-*hexaminoarsenobenzene* decomposing at 95°.[2]

3 : 5-Dinitro-4-methylnitroaminophenylarsinic acid (II.) affords another means of obtaining this base (III.).



It is prepared from any arsinic acid of the type I. when R = hydrogen, methyl, or an acyl group.[3] The hydrochloride $C_{14}H_{20}N_6As_2,4HCl$ is yellowish-green. The base has a pronounced action on trypanosomes and other pathogenic protozoa; its toxic effect on the human organism is less marked than that of other organic arsenicals.

The nitroamino-acid (II.) when reduced with acid stannous chloride below 50° yields an intermediate complex hydrazine,

$$[NH_2{\cdot}N(CH_3){\cdot}C_6H_2(NH_2)_2{\cdot}As=]_2,$$

which also exhibits pronounced trypanocidal action.[4]

[1] F. Boehringer and Söhne, D.R.-P., 286854, 286855.
[2] C. F. Boehringer and Söhne, U.S. P., 1075279, 1081079.
[3] Swiss P., 64347. [4] D.R.-P., 285572, 285573.

This base has the remarkable property discovered by Karrer and Giemsa of dissolving in soluble bicarbonates to form a complex carbonate, which can be isolated by precipitation by alcohol or acetone.[1] This carbonate is very stable, whilst that from hexaminoarsenobenzene decomposes in a few seconds.

The bismethylamino-base (III.), which has valuable therapeutic properties, is obtainable from its generator (II.) in a great variety of ways.[2]

3 : 5-dinitro-4-dialkylaminophenylarsinic acids when reduced yield 4 : 4′-tetralkyldiamino-3 : 5 : 3′ : 5′-tetraminoarsenobenzenes having a higher therapeutic value and more pronounced action on certain pathogenic parasites than the corresponding dialkyl compounds.

4 : 4′-*Tetramethyl*-3 : 4 : 5 : 3′ : 4′ : 5′-*hexaminoarsenobenzene*, the corresponding *tetraethyl* derivative, and 4 : 4′-*dipiperidino*-3 : 5 : 3′ : 5′-*tetraminoarsenobenzene* are examples of this promising series of tervalent arsenic compounds.[3]

Halogenated Polyaminoarsenobenzenes.

2-*Chloro*-4-*dimethylaminophenyl*-1-*arsinic acid* is prepared by condensing *m*-chlorodimethylaniline with arsenious chloride, the intermediate 2-*chloro*-4-*dimethylaminophenylarsenious oxide* being oxidised with hydrogen peroxide, permanganate, or mercuric oxide. The final product has greater therapeutic activity than dimethylatoxyl and is less poisonous.[4]

Other alkylated derivatives of *m*-chloroaniline are utilisable in this condensation, for instance those having the general formula $Cl \cdot C_6H_4 \cdot NR_1R_2$, where R_1 = alkyl and R_2 = alkyl or hydrogen.[5]

This product, halogenated in the ortho-position with respect to the arsinic group, can be nitrated to yield dinitro-alkylaminoarsinic acids which are reducible to polyaminoarsenobenzene derivatives[6] containing halogen atoms in the aromatic nuclei.

[1] D.R.-P., 269660; Eng. P., 1667/1914 and 8759/1915.
[2] D.R.-P., 286667 and 286668. [3] M. L. and B., D.R.-P., 294276.
[4] C. F. Boehringer and Söhne, D.R.P., 286546.
[5] M. L. and B., U.S. P., 1156045. [6] D.R.-P., 285604, 292546.

CHAPTER VI

Neosalvarsan

Aromatic Derivatives containing Tervalent Arsenic

Part II

On account of its combined phenolic and feebly basic properties, salvarsan fails to give neutral salts with either mineral acids or alkali bases. In the form of the free base it is very insoluble in water or in physiological salt solution. The preparation of an approximately neutral solution from salvarsan dihydrochloride is a matter of careful adjustment to be made immediately before the drug is injected intravenously. This preliminary neutralisation complicates the use of the substance in therapeutics, and on this account many attempts have been made to convert salvarsan into a substance yielding soluble salts giving a neutral reaction in solution. From these endeavours have come the drugs "Neosalvarsan," "Galyl," and "Ludyl."

The idea of using an arsenobenzene derivative sufficiently acidic to furnish soluble neutral salts is foreshadowed in the employment by Ehrlich, of the drug arsenophenylglycine in the form of its sodium salt, "Spirarsyl" or "418." This substance was the most successful remedy among the arsenicals which preceded salvarsan. For this reason arsenophenylglycine has been grouped with the neosalvarsan series.

Section I.—Neosalvarsan.

"Ehrlich 914."

Synonyms: *Neokharsivan, Novarsenobillon, Novarsenobenzol. Sodium 3 : 3'-Diamino-4 : 4'-dihydroxyarsenobenzene-N-methylene-sulphinate.*

Salvarsan dihydrochloride (25 grams) in 250 c.c. of water, is treated successively with sodium formaldehyde-sulphoxylate

(12·5 grams = 1 mol.) in 10 per cent. aqueous solution, and after one hour with 80 c.c. of 10 per cent. sodium carbonate and then with 100 c.c. of 12 per cent. hydrochloric acid ; 3 : 3′-diamino-4 : 4′-dihydroxyarsenobenzene-*N*-methylenesulphinic acid is precipitated. This acid is also obtained if in the foregoing condensation 2 molecular proportions of sodium formaldehyde-sulphoxylate are employed. The sodium salt of this acid is obtained by mixing 20 grams of the complex sulphinic acid in 80 c.c. of water with 20 c.c. of 2*N*-caustic soda ; the solution poured in a thin stream into 1 litre of alcohol gives a precipitate of the sodium salt (neosalvarsan).

Salvarsan base (21 grams) is added to sodium formaldehyde-sulphoxylate (25 grams) in 60 grams of water, the mixture is heated on the water-bath until a clear solution is obtained and 25 c.c. of concentrated hydrochloric acid are added to precipitate the product. In these circumstances, the precipitated acid contains two methylenesulphinic groups.[1]

The formation of neosalvarsan is facilitated by operating in solutions of the mono- and poly-hydric alcohols, the following solvents being cited : methyl and ethyl alcohols, ethylene glycol, and glycerol.

Sodium formaldehyde-sulphoxylate (31 parts) dissolved in 150 parts of water is stirred into 50 parts of salvarsan (dihydrochloride) in 200 parts of ethylene glycol. Sodium carbonate is added till the solution is neutral. Alternatively, the salvarsan base may first be set free with (12·5 per cent.) aqueous sodium carbonate added to salvarsan dissolved in ethylene glycol containing 12 per cent. of water and the suspension stirred with the foregoing proportion of sodium formaldehyde-sulphoxylate (50 per cent. aqueous solution) until the precipitate is dissolved. These solutions when added to acetone, alcohol, or ether-alcohol give a light yellow precipitate of neosalvarsan. The foregoing reactions can also be effected in the entire absence of water.[2]

The starting material in the production of neosalvarsan need not necessarily be the very oxidisable salvarsan ; the preparation can be simplified by operating directly on 3-nitro-4-hydroxybenzenearsinic acid (p. 200) or the corresponding amino-derivative (p. 205).[3] The nitro-compound (1 part) dissolved as sodium salt in 5 parts of water is gently warmed with sodium formaldehydesulphoxylate (2 parts) in 10 parts of water, when a yellow

[1] M. L. and B., D.R.-P., 245756 ; Eng. P., 7865/1912.
[2] M. L. and B., D.R.-P., 260235. [3] D.R.-P., 263460.

precipitate of the free sulphinic acid of neosalvarsan slowly separates.

Sodium 3-amino-4-hydroxyphenylarsinate is similarly reduced with 2 parts of sodium formaldehydesulphoxylate, the free sulphinic acid of neosalvarsan being precipitated by mineral acid.

The arylarsenious oxides corresponding with the starting materials of the preceding preparations also furnish a means of arriving at neosalvarsan[1], and its homologues. *3-Nitro-4-hydroxyphenylarsenious oxide*, produced from the above nitroarsinic acid with sulphurous and hydriodic acids, is dissolved as mono-sodium salt and reduced with 2 parts of sodium formaldehydesulphoxylate in warm aqueous solution for about two hours. After cooling, the free acid of neosalvarsan is precipitated by dilute mineral acids. 3-Amino-4-hydroxyphenylarsenious oxide (p. 228) is similarly reduced with formaldehydesulphoxylate at 50–60° and the product precipitated as before.[2]

Another useful variant on the foregoing preparations arises from the use of the stable 3 : 3′-dinitro-4 : 4′-dihydroxyarsenobenzene (p. 230), 1 part of which, warmed in 5 per cent. aqueous solution with sodium hydroxide (2 parts) and sodium formaldehydesulphoxylate (2 parts) for two hours, yields neosalvarsan, the product (free acid) being precipitated by dilute sulphuric acid from the cold filtered solution.

Neosalvarsan or *sodium 3 : 3′-diamino-4 : 4′-dihydroxyarsenobenzene*-N-*methylenesulphinate*, as produced by the foregoing processes, is a pale yellow powder usually containing somewhat less arsenic (about 24 per cent.) than is required by the formula $C_{13}H_{13}O_4N_2As_2SNa$ (with $2H_2O$). Commercial samples generally contain small proportions of inorganic salts; the aqueous solutions are quite neutral. Neosalvarsan may be prepared from salvarsan and the crude formaldehyde additive compound of sodium hydrosulphite, as well as from sodium formaldehydesulphoxylate (rongalite). As in practice the arsenical content of the drug is rather lower than that of salvarsan, the average dose is somewhat larger, but on account of the greater simplicity of its application, neosalvarsan is becoming the more popular remedy. The curative effect is very similar in both cases. The efficacy of the preparations must always be ascertained by the intravenous injection of samples into live animals. Rabbits used in these tests are injected through a prominent vein in the ear.

Among the earlier attempts made to convert salvarsan into

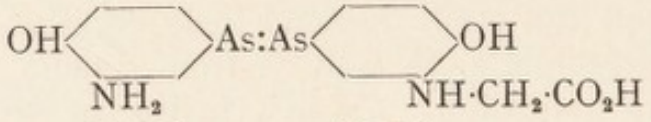
[1] M. L. and B., D.R.-P., 264014, 271893. [2] *Ibid.*

substances yielding neutral solutions in water may be cited the following examples. The first product appears to be a *N*-methylene-sulphonate, and the second an intermediate additive compound. The processes are, however, only of historic interest.

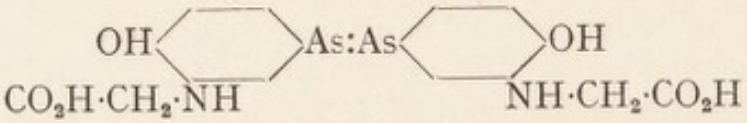
Salvarsan [1] (1 part) suspended in water (3 parts) with 0·3 part of formalin solution (40 per cent.) and 1 part of sodium bisulphite (40 per cent.) was gently warmed on the water-bath till dissolved to a clear solution. Hydrochloric acid precipitates a monosulphonic acid, $NH_2 \cdot C_6H_3(OH) \cdot As{:}As \cdot C_6H_3(OH) \cdot NH \cdot CH_2 \cdot SO_3H$, as a yellowish-red powder insoluble in water, alcohol, ether, benzene, acetone, or acids, dissolving readily in alkali hydroxides or carbonates to yellowish-red or reddish-brown salts, precipitated from strong aqueous solutions by alcohol or acetone. The alkali salts of this *N*-methylenesulphonate dissolve in water to a neutral solution.

Another attempt to convert salvarsan into a stable material dissolving in water to a neutral solution consisted in converting salvarsan dihydrochloride in methyl alcohol into its soluble disodium salt by means of 10*N*-caustic soda (4 mols.), then adding sodium formaldehydesulphoxylate and pouring the ice-cold mixture into ether-alcohol. In this way the disodium salt of salvarsan and the alkali sulphoxylate are co-precipitated. The preparation is carried out in an inert atmosphere, and the product, when dried over sulphuric acid *in vacuo*, is a light yellow powder readily soluble in water with alkaline reaction. Salvarsan is regenerated by treating the product successively with hydrochloric acid and sodium carbonate.[2]

The Glycine Derivatives of Salvarsan.[3]



I.



II.

These compounds are of interest as giving with alkalis readily soluble salts with a neutral reaction. They were originally suggested as substitutes for salvarsan in therapeutics.

The former (I.) is prepared by adding chloroacetic acid in water

[1] M. L. and B., D.R.-P., 249726. [2] M. L. and B., D.R.-P., 264266.
[3] M. L. and B., D.R.-P., 250745.

to salvarsan dihydrochloride dissolved in methyl alcohol neutralised with caustic soda (2 mols.). The mixture is warmed at 60–65° in an inert atmosphere, the reaction being accelerated by the addition of potassium iodide. The precipitated salvarsan base passes into solution, and on partial neutralisation of the acid solution with caustic soda, the product is precipitated. Sodium chloroacetate may be used in this condensation instead of chloroacetic acid. The alkaline solution, slightly acidified, yields the monoglycine derivative as a yellow powder soluble in alkalis or in excess of acids, but insoluble in organic media.

The *sodium* salt gives a yellowish-brown solution with neutral reaction, insoluble in alcohol or acetone. The *potassium* and *ammonium* salts are similar, but the latter slowly dissociates at the ordinary temperature.

The *diglycine* derivative (II.) is obtained by further action of chloroacetic or bromoacetic acid on the monoglycine. Its *disodium* salt is yellowish-brown, readily soluble to a neutral aqueous solution; insoluble in alcohol or acetone. A higher homologue of the monoglycine is produced by condensing salvarsan base suspended in methyl alcohol with α-bromopropionic acid at 60–65° until the base dissolves. After cooling, aqueous caustic soda is added until the solution is slightly acid, when the product is precipitated as a yellow powder insoluble in the ordinary media, but dissolving readily in alkali or excess of acid.

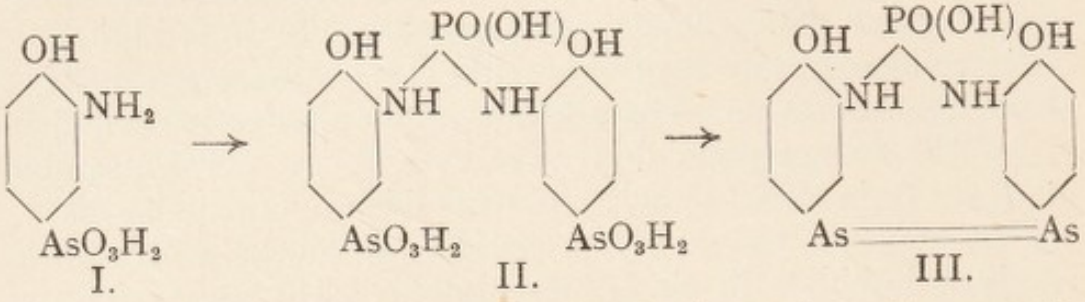
Section II.—Galyl. 4 : 4′-*Dihydroxyarsenobenzene*-3 : 3′-*phosphamic Acid* (*"No.* 1116 *" of Mouneyrat's Series*).

This arsenical medicament, which was discovered by Mouneyrat, belongs to the neosalvarsan series of drugs inasmuch as it is an acidic substance dissolving in aqueous sodium carbonate to a neutral solution. This property renders the preparation a very suitable solution for intravenous injection in the treatment of syphilis and other protozoal diseases.

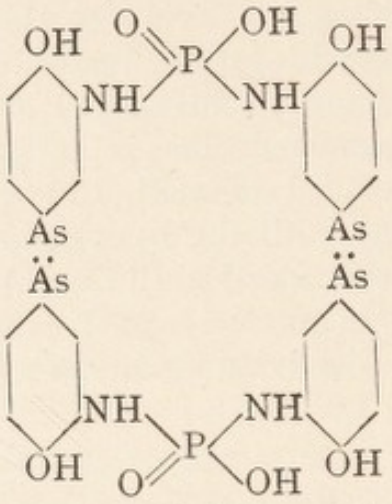
Galyl is prepared from 3-amino-4-hydroxyphenylarsinic acid (I.), which for this purpose is obtained by Mouneyrat by the electrolytic reduction of 3-nitro-4-hydroxyphenylarsinic acid[1] (alkaline solution) in a double cell (2 amperes at 3·5–4 volts) with mercury cathode and nickel anode. Condensation with phosphorus oxychloride in the presence of aqueous caustic soda converts the aminohydroxy-acid into a phosphamic acid

[1] Mouneyrat, Eng. P., 3087/1915.

derivative (II.), and this compound, on reduction with sodium hydrosulphite, yields the phosphamic acid derivative of salvarsan, namely, *Galyl* (III.). This compound, dissolved in sodium carbonate, gives a precipitate of its *sodium* salt on adding alcohol or sodium chloride.[1]



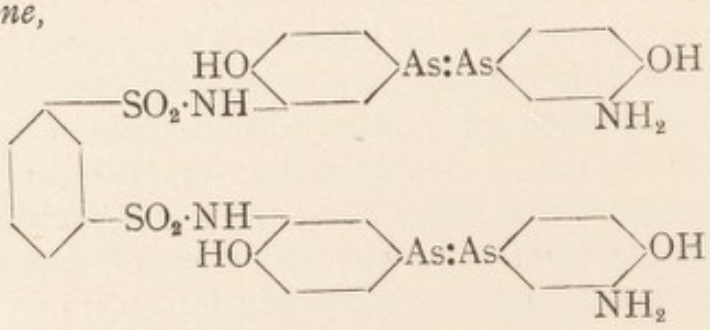
In the foregoing reduction it is obvious that the arsenic atoms of two separate molecules of compound II. may coalesce, giving rise to a more complex molecule which has also been



ascribed to this substance. Galyl contains 35·3 per cent. of arsenic and 7·2 of phosphorus; it is very slightly toxic and has marked spirillicidal and trypanocidal properties.

Ludyl ("1151" *of Mouneyrat's Series*).

Benzene-m-3′ : 3′-*disulphamino-bis*-3-*amino*-4 : 4′-*dihydroxy-arsenobenzene*,



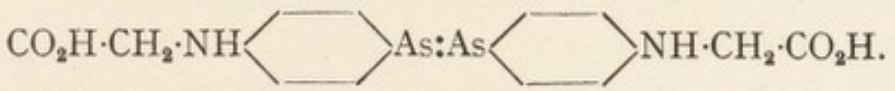
[1] Eng. P., 9234/1915.

is a yellow or yellowish-grey powder insoluble in water, but dissolving in aqueous sodium carbonate to a yellowish-brown solution. This complex disulphonamide is produced by the Schotten-Baumann reaction from benzene-*m*-disulphonic chloride and salvarsan. The product, "*ludyl*," belongs to the neosalvarsan series of arsenical drugs, since it is an acidic substance yielding alkali salts having a neutral solution. When air is excluded this solution remains unchanged for several days and yields a precipitate of the *sodium* salt of ludyl on the addition of alcohol or sodium chloride. With ferric salts, sodium ludyl gives a violet-brown coloration. This drug is administered like galyl by intravenous injection and is recommended for the treatment of protozoal diseases.

Galyl and ludyl are prescribed in the treatment of syphilis; they have a very energetic spirillicidal action, are feebly toxic, and are well tolerated. They show an absence of congestive action on the organs of the body and have no secondary ill effect on the nervous system. Their action on the blood and on general nutrition is favourable.

Section III.—Arsenoarylglycines.

Arsenophenyl-p-*glycine*,[1]



—Phenylglycine-*p*-arsinic acid (200 grams) dissolved in 4 litres of boiling water is added to a solution of 2 kilos. of sodium hydrosulphite in 10 litres of water after the latter solution has been previously treated successively with 600 c.c. of 10*N*-sodium hydroxide and 1 kilo. of crystallised magnesium chloride and filtered from magnesium hydroxide. After three-quarters of an hour on the water-bath the precipitate is separated and dissolved in excess of very hot dilute aqueous sodium carbonate. On adding acetic acid, arsenophenyl-*p*-glycine is obtained as a reddish-brown precipitate, drying to a reddish-brown powder easily soluble in aqueous sodium carbonate to a yellow solution; it dissolves in aniline or pyridine, but not in alcohol, ether, benzene, or dilute mineral acids.

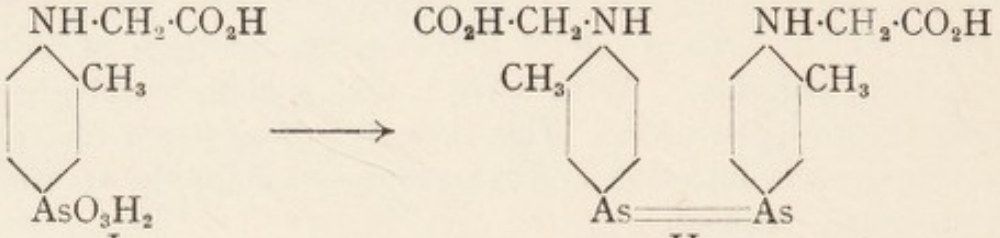
Sodium arsenophenylglycinate, "*Spirarsyl*," "418" (in Ehrlich's experimental series),[2] $As_2(C_6H_4{\cdot}NH{\cdot}CH_2{\cdot}CO_2Na)_2$, is the yellow,

[1] M. L. and B., D.R.-P., 206057; Eng. P., 17619/1907. Ehrlich and Bertheim (M. L. and B.), U.S. P., 888321 and 907016/1908.

[2] Ehrlich, *Ber.*, 1909, **42**, 36.

soluble sodium salt of arsenophenylglycine ; it gives in water a neutral yellow solution and has a pronounced trypanocidal and spirillicidal action with low toxicity.

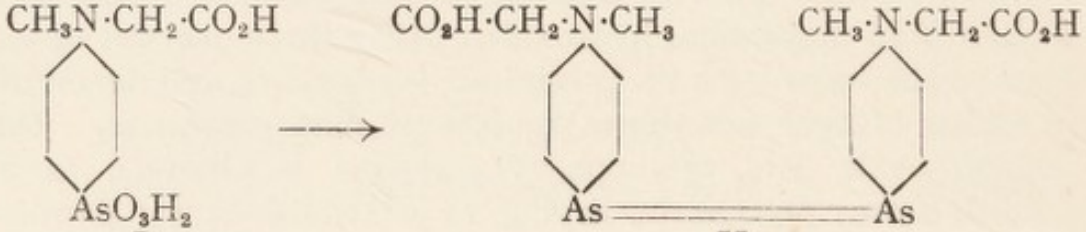
p-*Arseno*-o-*tolylglycine* (II.), the next homologue of *arsenophenyl*-p-*glycine*, is prepared by reducing o-*tolylglycine*-5-*arsinic acid* (I.) with alkaline hydrosulphite in the presence of magnesium chloride.[1]



I. II.

p-*Arsenophenyl*-N-*methylglycine* (II.),[2] is a yellow powder insoluble in acids or the ordinary organic solvents, but dissolving in aqueous alkalis. Phenylmethylglycine-*p*-arsinic acid (I.) (30 grams), in 300 c.c. of water and 210 c.c. of *N*-sodium hydroxide, is added to a solution of sodium hydrosulphite (300 grams) in 1200 c.c. of water previously neutralised with sodium carbonate. After warming for three hours at 55° the clear yellow solution is treated with glacial acetic acid (120 c.c.), when the product is obtained as a flocculent, yellow precipitate. From the golden-yellow neutral solutions of this substance in sodium hydroxide or carbonate, alcohol or acetone precipitates the sodium salt, which readily becomes pulverulent.

Arsenophenylmethylglycine (II.) shows marked trypanocidal action when injected into mice affected with *Trypanosoma Evansii* and *Tr. Rhodesiense*.[3]



I. II.

Acyl Derivatives of Arseno-p-*phenylglycine*.[4]

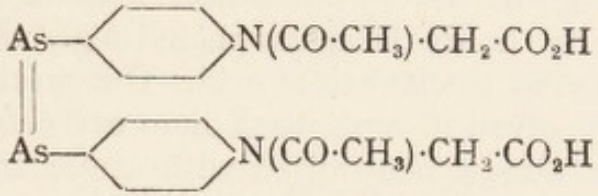
Arsenophenylglycine and its salts become coloured very rapidly on exposure to the air, but their acyl derivatives are much more stable either when dry or in solution.

[1] D.R.-P., 212205. [2] Poulenc and K. Oechslin, Fr. P., 462276.

[3] Oechslin, *Ann. Chim.*, 1914 [ix], **1**, 239. Poulenc and K. Oechslin, Fr. P., 473704. [4] Poulenc, Eng. P., 18/1915.

Diacetylarseno-p-*phenylglycine.*

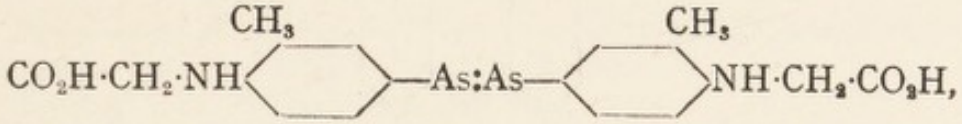
Acetylanilinoacetonitrile, $C_6H_5 \cdot N\langle^{CO \cdot CH_3}_{CH_2 \cdot CN}$, prepared by the interaction of acetanilide, formaldehyde, and hydrocyanic acid, is condensed with arsenious chloride. The complex chloride, $AsCl_2 \cdot C_6H_4 \cdot N(CO \cdot CH_3) \cdot CH_2 \cdot CN$, is oxidised to the corresponding arsinic acid and the nitrile group hydrolysed without removing the acetyl radical. The resulting acetylphenylglycine-*p*-arsinic acid (50 grams) is reduced with sodium hydrosulphite (500 grams) in 2500 c.c. of water for two hours at 45–55°. The addition of acetic acid (70 c.c.) precipitates diacetylarsenophenylglycine in light yellow flakes.



Alternatively, arseno-*p*-phenylglycine (100 grams) is dissolved in 1000 c.c. of 8 per cent. sodium carbonate, excluding air ; the solution is cooled to 5°, and 100–150 c.c. of acetic anhydride are gradually added with vigorous shaking. The addition of excess of 10 per cent. hydrochloric acid precipitates the acetylated arseno-*p*-phenylglycine as a light yellow powder not changing in the air.

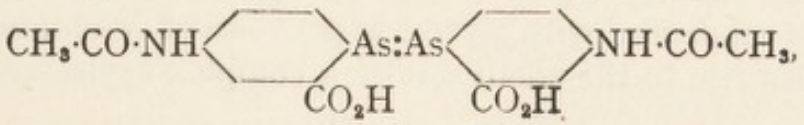
These reactions have been generalised.

5-*Arsenotolyl-2-glycine*,[1]



yellowish-brown, insoluble powder, is obtained by adding tolyl-2-glycine-5-arsinic acid (39 grams) dissolved in 800 c.c. of water and 150 c.c. of *N*-sodium hydroxide to 400 grams of sodium hydrosulphite in 2 litres of water neutralised with magnesium hydroxide. The mixture is digested at 50° until a filtered sample remains clear on boiling, when the precipitated arseno-derivative is collected ; it is easily soluble in aqueous alkalis and sparingly so in the ordinary organic media except aniline and pyridine.

2 : 2′-*Diacetyldiamino*-5-*arsenobenzoic acid*,



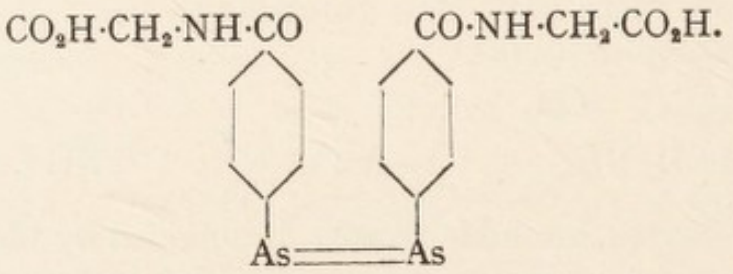
[1] M. L. and B., D.R.-P., 212205.

a pale yellow, insoluble powder dissolving in aqueous alkalis, and also in alcohol when freshly precipitated, is obtained by dissolving 100 grams of 2-acetylamino-1 : 5-benzarsinic acid and 150 grams of crystallised sodium acetate in 1·25 litres of hot water, cooling to 50°, and adding the solution to 1 kilogram of sodium hydrosulphite in 4 litres of cold water, the mixture being digested at 30–40° till no further precipitation occurs.

*Formaldehyde Derivative of Arsenophenyl-*p*-glycine.*[1]

The object of this preparation is to increase the stability of arsenophenyl-*p*-glycine. Phenylglycine-arsinic acid (10 grams) is reduced with 80 grams of sodium hydrosulphite in 350 c.c. of water containing 8 grams of dry sodium carbonate. After warming at 45–48° for two hours the arsenophenyl-*p*-glycine is precipitated with 20–25 c.c. of glacial acetic acid. The precipitate, collected quickly, is dissolved in aqueous sodium carbonate (6 per cent.), the liquid is almost neutralised with acetic acid, and treated with 5 c.c. of formaldehyde solution (40 per cent.). The solution is poured into 60 c.c of cooled absolute alcohol, which precipitates a light yellow salt far more stable than the salt of arsenophenyl-*p*-glycine.

Section IV.—Arsenohippuric Acid,



The starting point in the synthesis of arsenohippuric acid is *p*-benzarsinic acid, first prepared by La Coste by permanganate oxidation from *p*-tolylarsinic acid (p. 129). Successive treatment of this oxidation product with phosphorus tri- and penta-chlorides leads to *p*-dichloroarsinobenzoyl chloride,

$$AsO(OH)_2\cdot C_6H_4\cdot CO_2H \xrightarrow{PCl_3} AsCl_2\cdot C_6H_4\cdot CO_2H \xrightarrow{PCl_5} AsCl_2\cdot C_6H_4\cdot COCl$$

a mobile fuming liquid (b.p. 189–190°/19 mm.). This acid chloride condensed with glycine in presence of *N*-sodium hydroxide, gives rise to the alkali salt of a complex arylarsenious acid,

[1] Poulenc, Eng. P., 17/1915.

the free acid, $As(OH)_2 \cdot C_6H_4 \cdot CO \cdot NH \cdot CH_2 \cdot CO_2H$ (with benzarsenious acid), being precipitated with dilute hydrochloric acid. This mixture oxidised with alkaline hydrogen peroxide gives *hippuroarsinic acid* $AsO(OH)_2 \cdot C_6H_4 \cdot CO \cdot NH \cdot CH_2 \cdot CO_2H$ (with *p*-benzarsinic acid). The former remains in solution, and on adding successively caustic soda and alcohol, *trisodium hippuroarsinate,* $Na_2AsO_3 \cdot C_6H_4 \cdot CO \cdot NH_2 \cdot CH_2 \cdot CO_2Na, 4H_2O$ is precipitated in colourless needles. Hippuroarsinic acid when reduced with hydrosulphite by Ehrlich and Bertheim's method yields *arsenohippuric acid,* a yellow powder giving unstable solutions with alkali carbonates or phosphates, but stable solutions with caustic alkalis in absence of air. Arsenohippuric acid has a toxicity similar to that of salvarsan.[1]

p-Arsenobenzoic acid injected into the animal organism is eliminated partly in the form of hippuroarsinic acid. *p*-Dichloroarsinobenzoyl chloride has been condensed with the following degradation products of albumin: alanine, phenylalanine, tyrosine, leucine, aspartic acid, glutamic acid, pentamethylenediamine. The products, $R \cdot NH \cdot CO \cdot C_6H_4 \cdot AsO$, are oxidised to the corresponding crystalline arsinic acids, $R \cdot NH \cdot CO \cdot C_6H_4 \cdot AsO(OH)_2$, and reduced to yellow, amorphous arseno-compounds,

$$As_2[C_6H_4 \cdot CO \cdot NHR]_2.$$

p-Dichloroarsinobenzoyl chloride condenses in benzene solution in the presence of pyridine with the higher alcohols, myricyl alcohol and cholesterol; the resulting arsine oxides are oxidised to arsinic acids and reduced to arseno-compounds.[2]

[1] Fourneau and Oechslin, *Bull. Soc. chim.*, 1912 [iv], **11**, 909. Hugounenq and Morel, *J. Pharm. Chim.*, 1913 [vii], **7**, 383.

[2] Sieburg, *Arch. Pharm.*, 1916, **254**, 224.

CHAPTER VII

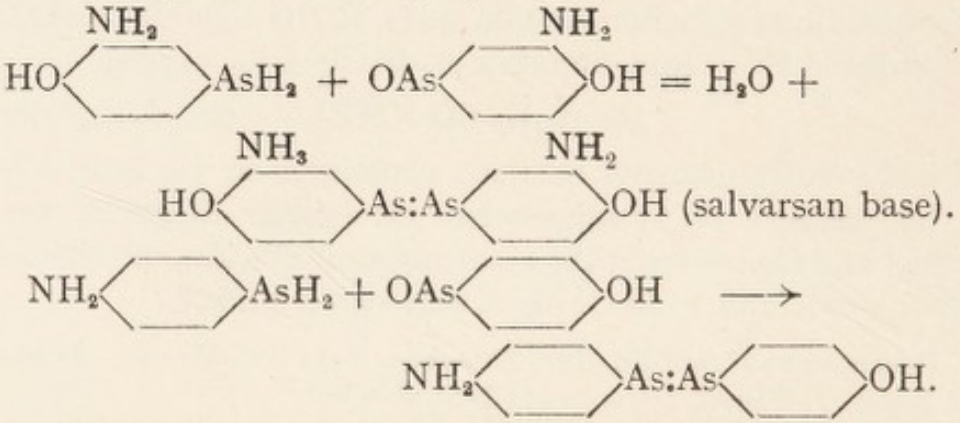
Aromatic Primary Arsines

Synthesis of Dissymmetric Arsenobenzene Derivatives

The preparation of phenylarsine by the energetic reduction of phenylarsinic acid, an important discovery due to Palmer and Dehn (*v.* p. 89), has since led to a valuable synthetic method of preparing complex derivatives of arsenobenzene. The most characteristic property of the primary aromatic arsines is their extreme oxidisability. Exposure to atmospheric oxygen rapidly leads to the production of symmetrical arsenoaryl compounds,

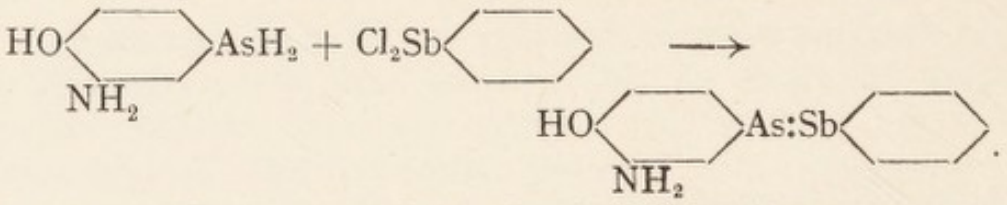
$$2R{\cdot}AsH_2 + O = R{\cdot}As{:}AsR + H_2O.$$

They also react with arylarsenious oxides or chlorides, giving rise to symmetrically or dissymmetrically substituted arsenoaryls, as illustrated by the following equations: [1]

1. 

2.

The reactivity of these primary arsines has been utilised, moreover, in the synthesis of mixed arsenostibino-derivatives.[2]



It can readily be seen from the foregoing illustrations that these condensations increase very considerably the means of synthesising homologues and analogues of salvarsan and its derivatives.

Salvarsan and its nine symmetrically substituted isomerides

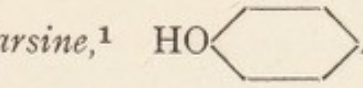
[1] M. L. and B., D.R.-P., 251571, 254187.

could be thus synthesised, and, providing that the ten theoretically possible compounds of the formulæ

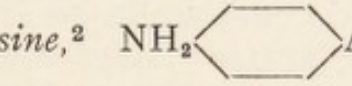
$$HO{\cdot}C_6H_3(NH_2){\cdot}AsH_2 \quad \text{and} \quad HO{\cdot}C_6H_3(NH_2){\cdot}AsO$$

are available, then in addition no fewer than 45 dissymmetrically substituted isomerides of salvarsan could also be produced.

Section I.—Substituted Primary Arylarsines.

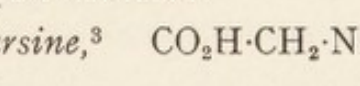
4-*Hydroxyphenylarsine*,[1]  white powder, darkening at 70° and decomposing at 135°, sparingly soluble in water, alcohol, or ether, dissolving in aqueous caustic soda.

Phenol-*p*-arsinic acid (218 grams) is dissolved in 2,500 c.c. of methyl alcohol, and zinc dust (400 grams) is added and 1·5 litres of hydrochloric acid (D 1·19) slowly introduced with stirring. The filtrate from undissolved zinc is extracted with ether, the ethereal extract shaken with aqueous caustic soda, and the primary arsine precipitated from the alkaline solution by passing in carbon dioxide. The product on oxidation becomes yellow and finally red owing to the formation of 4:4′-dihydroxyarsenobenzene.

4-*Aminophenylarsine*,[2]  colourless, very oxidisable oil, b.p. 132°/10 mm., readily soluble in ether, alcohol, or glacial acetic acid, dissolving sparingly in water.

Zinc dust and strong hydrochloric acid are added successively to *p*-arsanilic acid dissolved in methyl alcohol. The filtrate from zinc is rendered alkaline, distilled in steam, and the distillate extracted with ether. The oily product left after distilling off the solvent speedily becomes oxidised to 4:4′-diaminoarsenobenzene.

It is noteworthy that this *p*-aminoarsine, unlike its analogue *p*-phenylenediamine, is volatile in steam from aqueous solutions. Its *N*-acetyl derivative, $NHAc{\cdot}C_6H_4{\cdot}AsH_2$, forms a co-ordination compound with cupric chloride.

Phenylglycine-p-*arsine*,[3]  pale yellow precipitate, rapidly darkening on exposure to air, decomposed at 100°; it is sparingly soluble in water, alcohol, or ether.

[1] M. L. and B., D.R.-P., 269743, 269744.

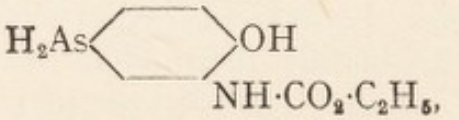
[2] and [3] M. L. and B., D.R.-P., 251571.

Phenylglycine-*p*-arsinic acid is reduced with zinc dust and strong hydrochloric acid in the cold; a yellow precipitate forms, dissolving to a yellow solution which finally becomes colourless. The filtered solution yields, on addition of sodium acetate, the white, insoluble zinc salt of phenylglycine-*p*-arsine. This product is warmed with aqueous sodium carbonate; the solution, filtered from zinc carbonate, is acidified when the free phenylglycine-*p*-arsine is precipitated.

3-*Amino-4-hydroxyphenylarsine*,[1]

—3-Nitro-4-hydroxyphenylarsinic acid is reduced with strong hydrochloric acid and zinc dust, keeping the mixture cool. The precipitate first formed dissolves to a dark solution. Water is added and the solution warmed until colourless. On cooling the filtered solution the double zinc salt separates as a white precipitate, soluble in water. This compound is decomposed with sodium acetate and the product extracted with ether; the arsine is removed from the ether by caustic soda, and then precipitated by acetic acid from the alkaline solution as a greyish-white powder, darkening at 100° and decomposing completely at 135°; soluble in caustic alkali, acid, alcohol, or ether, dissolving only sparingly in water.

The *urethane* derivative of the foregoing arsine is



a crystalline, white powder, m.p. 155–160°, is produced by the electrolytic reduction of the corresponding substituted arsinic acid, $C_2H_5{\cdot}CO_2{\cdot}NH{\cdot}C_6H_3(OH){\cdot}AsO_3H_2$. Treatment with sulphurous acid, followed by hydrolysis, gives rise to the foregoing base.[2]

Co-ordination Compounds.

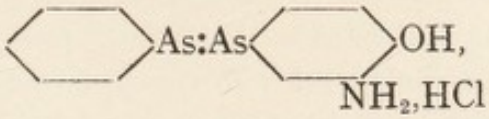
The urethane derivative gives a co-ordination compound with palladous chloride, and 3-amino-4-hydroxyphenylarsine combines with auric chloride, silver nitrate, and copper chloride.[3]

[1] M. L. and B., D.R.-P., 275216. [2] H. Bart, D.R.-P., 267082.
[3] M. L. and B., D.R.-P., 275216.

Section II.—Dissymmetrically Substituted Arsenobenzenes.

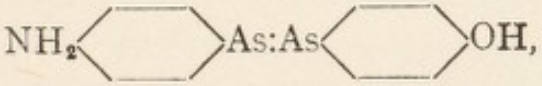
1. *Synthesis from Primary Arsines.*

3-Amino-4-hydroxyarsenobenzene hydrochloride,



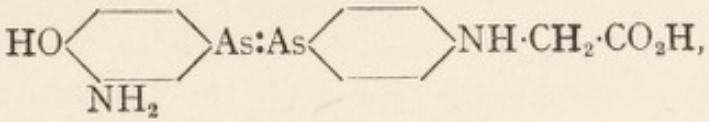
a yellow powder, is obtained by adding 3-amino-4-hydroxyphenylarsine, dissolved in alcohol containing hydrogen chloride, to a cooled benzene solution of phenylarsenious oxide. The yellow, caseous precipitate is soluble in water or alkali, and with an equivalent of caustic soda it gives a precipitate of free 3-amino-4-hydroxy-arsenobenzene, dissolving in excess of alkali.

4-Amino-4′-hydroxyarsenobenzene,



yellow powder, decomposing at 200°, soluble in hydrochloric acid or caustic soda, insoluble in water and the ordinary organic media, is prepared by mixing 4-hydroxyphenylarsenious oxide (methyl-alcoholic solution) and 4-aminophenylarsine (dissolved in dilute hydrochloric acid). After several hours the product is precipitated by sodium acetate.[1]

3-Amino-4-hydroxyarsenophenyl-4′-glycine,



yellow powder, darkening at 120° and decomposing completely at 150°; insoluble in water, alcohol, or the ordinary organic media, but dissolving in hydrochloric acid or aqueous alkalis.

i. Phenylglycine-*p*-arsinic acid (275 grams), dissolved in methyl alcohol (2·5 litres) and 2*N*-sulphuric acid (1 litre), is reduced by adding potassium iodide (50 grams) in an equal weight of water and saturating the solution with sulphur dioxide. To the cold solution of phenylglycine-*p*-arsenious oxide thus produced is added 4-hydroxy-3-aminophenylarsine (185 grams) dissolved in 2 litres of alcohol and 1 litre of *N*-hydrochloric acid. The product separates as a brownish-yellow precipitate.

[1] M. L. and B., D.R.-P., 254187.

ii. *Phenylglycine*-p-*arsenious chloride hydrochloride*,

$$AsCl_2 \cdot C_6H_4 \cdot NH \cdot CH_2 \cdot CO_2H, HCl,$$

white crystals, decomposing at 120°, easily soluble in water, methyl-alcohol, or aqueous alkalis, is precipitated by saturating with sulphur dioxide at −10° a solution of phenylglycinearsinic acid in concentrated hydrochloric acid containing a small amount of hydrogen iodide. This salt is dissolved in water and added to 3-amino-4-hydroxyphenylarsine in methyl-alcoholic hydrochloric acid. After twelve hours 3-amino-4-hydroxyarsenophenyl-4′-glycine is precipitated by sodium acetate.[1]

2. *Synthesis from Two Dissimilar Arylarsinic Acids or Arylarsenious Oxides.*

The arylarsinic acids and arylarsenious oxides give on reduction symmetrically substituted arsenoaryls,

$$\left.\begin{array}{l} 2R \cdot AsO_3H_2 \\ 2R \cdot AsO \end{array}\right\} \longrightarrow R \cdot As{:}As \cdot R.$$

When a pair of dissimilar compounds is employed in the foregoing reductions, dissymmetrically substituted arsenoaryls are produced.

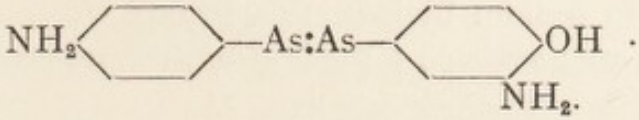
$$\left.\begin{array}{l} R \cdot AsO_3H_2 + R' \cdot AsO_3H_2 \\ R \cdot AsO \quad + R' \cdot AsO \end{array}\right\} \longrightarrow R \cdot As{:}As \cdot R'.$$

This interaction gives a method of synthesis for these arsenoaryls which is supplementary to the general method based on the employment of aromatic primary arsines (*v.* p. 264). The practicability of the method is greater than might at first sight be expected, inasmuch as the tendency to form the dissymmetric compound R·As:AsR′ is much greater than that leading to the production of the two symmetric derivatives R·As:As·R and R′·As:As·R′.

3-Amino-4-hydroxyarsenobenzene,[2]  , a pale yellow powder, insoluble in water, chloroform, benzene, or aqueous sodium carbonate and dissolving in alcohol, acetone, dilute hydrochloric acid, or caustic soda, is prepared by reducing a mixture of phenylarsenious oxide and 3-amino-4-hydroxyphenylarsenious oxide.

[1] M. L. and B., D.R.-P., 254187. [2] M. L. and B., D.R.-P., 251104.

3 : 4′-*Diamino-4-hydroxyarsenobenzene*,[1]



—1. This compound is obtained in the form of its dihydrochloride by adding at −10° to −5° solution *a* of mixed arsinic acids to solution *b*, containing the reducing agents.

a. 4-Aminophenylarsinic acid (21·7 grams) and 3-amino-4-hydroxybenzenearsinic acid (23·3 grams) in methyl alcohol (100 c.c.) and 39 c.c. of hydrochloric acid (D 1·12).

b. Stannous chloride (100 grams) and hydriodic acid (10 c.c. of D = 1·7) in alcohol (300 c.c.) and 500 c.c. of alcoholic hydrochloric acid saturated at 15°. The dihydrochloride obtained as a yellow, microcrystalline precipitate is washed with alcoholic hydrochloric acid and ether. It is very slightly soluble in organic media, but dissolves in water to a clear solution which gives no precipitate on neutralisation with alkali, thus indicating the complete absence of the symmetrically constituted salvarsan base. Dilute sulphuric acid gives an insoluble, light yellow, flocculent sulphate.

2. The dihydrochloride is even more readily obtained by mixing the following solutions *a* and *b* at −10°.

a. 4-Aminophenylarsenious oxide (21·9 grams) and 3-amino-4-hydroxyphenylarsinic acid (23·3 grams) in alcohol (90 c.c.) and alcoholic hydrochloric acid (60 c.c.).

b. Stannous chloride (75 grams) and 5 c.c. of hydriodic acid (D 1·7) in alcohol (200 c.c.) and alcoholic hydrochloric acid (400 c.c.).

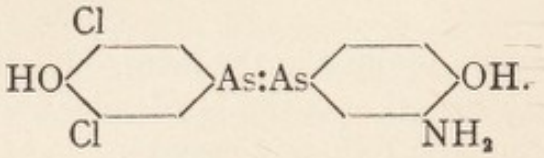
3-*Amino-4-hydroxyarsenophenyl-4′-glycine*,

—A solution of 3-amino-4-hydroxyphenylarsenious oxide (24·9 grams) and phenylglycine-*p*-arsenious chloride hydrochloride (41·6 grams) in 200 c.c. of methyl alcohol is mixed with 500 c.c. of *N*-sodium hydroxide and diluted with 2 litres of water. Anhydrous sodium hydrosulphite (200 grams) is added while the solution is thoroughly stirred, when the arseno-compound separates as yellowish-brown paste. The product is an amphoteric substance ; as an amine it dissolves in dilute hydro-

[1] M. L. and B., D.R.-P., 251104.

chloric acid, and as a carboxylic acid it is soluble in aqueous alkalis, even in sodium hydrogen carbonate.

3′: 5′-*Dichloro*-3-*amino*-4 : 4′-*dihydroxyarsenobenzene*,

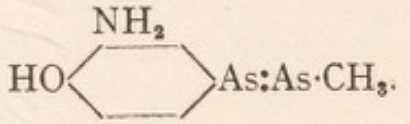


—Anhydrous sodium hydrosulphite (200 grams) is added, with stirring, to a solution of 3 : 5-dichloro-4-hydroxyphenylarsenious oxide (33·9 grams) and 3-amino-4-hydroxyphenylarsenious oxide (24·9 grams) in methyl alcohol (200 c.c.), *N*-sodium hydroxide (125 c.c.), and water (2300 c.c.). The solution sets to a yellow paste of arseno-compound, insoluble in water, dissolving in acetone, alcohol, ether, dilute hydrochloric acid, or aqueous alkalis.

3 : 5-*Dichloro*-4-*hydroxyphenylarsenious oxide*, colourless prisms sparingly soluble in water, and dissolving easily in alcohol or aqueous alkalis, is prepared by the mild reduction of 3 : 5-dichloro-4-hydroxyphenylarsinic acid (p. 214).

The foregoing examples suffice to show the application of the second synthetic method of preparing dissymmetric arsenoaryls, but this reaction is not restricted to the aromatic series. Mixed aliphatic-aromatic arseno-derivatives can be obtained, and, what is even more remarkable, the oxygenated arylarsenical derivatives can be reduced in the presence of inorganic compounds of arsenic to give rise to reduction products containing a large proportion of combined arsenic. These products are of therapeutic interest and have been tried in trypanosomiasis.

3-*Amino*-4-*hydroxybenzenearsenomethane*,[1]



—This product, a yellow powder soluble in dilute hydrochloric acid or aqueous caustic soda, is prepared by the following methods :—

1. 3-Amino-4-hydroxyphenylarsenious oxide (20 grams) in methyl alcohol (100 c.c.) and methylarsenious oxide (10·6 grams) in 50 c.c. of the same solvent are added to 2·5 litres of water and reduced together by adding 200 grams of anhydrous sodium hydrosulphite, when the product separates as a light yellow precipitate.

[1] M. L. and B., D.R.-P., 253226.

2. 3-Amino-4-hydroxyphenylarsinic acid (sodium salt) and sodium methylarsinate, ($CH_3 \cdot AsO_3Na_2, 6H_2O$), in aqueous solution, are reduced together with sodium hydrosulphite in presence of magnesium chloride at 50° until the precipitation is complete.

3. The hydrochloride of 3-amino-4-hydroxybenzenearsenomethane is obtained by reducing 3-amino-4-hydroxyphenylarsinic acid and methylarsenious oxide with stannous chloride and hydriodic acid at −20° to −10° in acetone and methyl-alcoholic solution containing hydrochloric acid. The product is obtained as a yellow precipitate.

3. *Synthesis by Intermolecular Rearrangement from Two Symmetrical Arsenobenzene Derivatives.*

Aromatic arsenobenzene derivatives of dissymmetric constitution are produced by (1) condensation between a primary arsine and an arylarsenious oxide,

$$RAsH_2 + R'AsO = RAs{:}AsR' + H_2O.$$ [1]

(2) Simultaneous reduction of two arylarsenious oxides or two arylarsinic acids,

$$RAsO_3H_2 + R'AsO_3H_2 + 4H_2 = RAs{:}AsR' + 6H_2O.$$ [2]

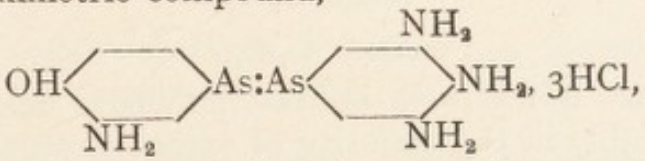
This second method may in reality be a variant of the third process, inasmuch as the two symmetric arsenoaryls would interact to give the dissymmetric arseno-derivative.

(3) Interaction of two symmetrically constituted arsenobenzenes in warm solution.

$$RAs{:}AsR + R'As{:}AsR' = 2R{\cdot}As{:}AsR'.$$

The third process goes remarkably readily and to a quantitative extent.[3]

The dissymmetric compound,



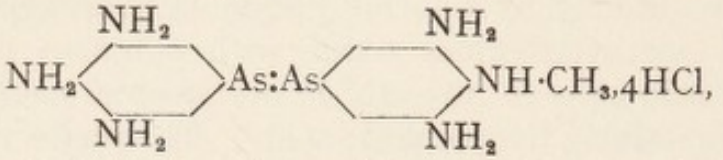
is produced quantitatively by warming rapidly to 80° 3 : 4 : 5 : 3′ : 4′ : 5′-hexaminoarsenobenzene tetrahydrochloride (20 grams) and 3 : 3′-diamino-4 : 4′-dihydroxyarsenobenzene dihydrochloride (salvarsan) in 400 c.c. of water. The solution poured into 4 litres of hydrochloric acid (D = 1·12) yields

[1] D.R.-P., 254187. [2] D.R.-P., 251104.

[3] Karrer, *Ber.*, 1916, **49**, 1648; M. L. and B., Eng. Pat., 17482/1915.

the trihydrochloride in light yellow flakes. The product resembles salvarsan in its solubility in aqueous caustic soda; it is also like the hexaminoarsenobenzene in dissolving in aqueous sodium bicarbonate.

The dissymmetric compound,



is prepared similarly from hexaminoarsenobenzene hydrochloride and 4 : 4′-dimethylamino-3 : 5 : 3′ : 5′-tetraminoarsenobenzene hydrochloride; it forms a stable bicarbamate derivative.

Section III.—Polyarsenical Compounds containing Aromatic Groups. [1]

These compounds are trypanocides and also serve as starting materials in the production of other active substances.

One molecular proportion of an arylarsinic acid or oxide can be condensed on reduction with one or more molecules of inorganic arsenical compounds. The higher the content of arsenic in the product the darker is its colour.

1. *a*. Phenylarsinic acid (20 grams) in water (400 c.c.) and 2*N*-sodium hydroxide (50 c.c.).

b. Sodium arsenite (13 grams) in 500 c.c. of water.

Solutions *a* and *b* are mixed, neutralised with 50 c.c. of 2*N*-acetic acid, and their contents reduced with 200 grams of sodium hydrosulphite and magnesium chloride (40 grams) dissolved in a litre of water. After 24 hours' stirring the light yellow precipitate is collected, washed with water, and dried *in vacuo*.

$$\begin{array}{l} As{:}As{\cdot}C_6H_5 \\ | \\ As{:}As{\cdot}C_6H_5. \end{array}$$

The product is insoluble in water, mineral acids or alkalis, sparingly soluble in the majority of organic solvents, dissolving most readily in chloroform; it contains 54 per cent. of arsenic.

2. Molecular proportions of 3-amino-4-hydroxyphenylarsinic acid and sodium arsenite are dissolved in water containing a slight excess of caustic soda; the solution is neutralised with dilute acetic acid and added to a solution of sodium hydrosulphite and magnesium chloride, the mixture being digested

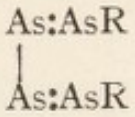
[1] M. L. and B., D.R.-P., 270254.

and stirred at 50–60° until there is no further precipitation of the orange-yellow polyarsenide. This product, which contains 48·9 per cent. of arsenic, is readily soluble in aqueous caustic soda or dilute hydrochloric acid and forms a sparingly soluble sulphate.

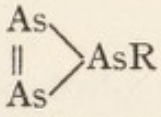
3. The reagents of example 2 are taken, but with two molecular proportions of sodium arsenite to one of the arylarsinic acid. The polyarsenide is darker and dries to a brownish-red powder (As = 57 per cent.). It is readily soluble in dilute caustic soda, and the solution remains clear when acidified with hydrochloric acid ; this acid solution gives a precipitate with sulphuric acid.

4. Molecular proportions of *p*-aminophenylarsenious oxide and arsenious chloride are dissolved in methyl alcohol and added to a well-cooled solution of stannous chloride in methyl alcohol and concentrated hydrochloric acid. The product separates as a brownish-yellow precipitate (As = 45 per cent.), dissolving in moist pyridine or hot dilute hydrochloric acid ; the latter solution yields precipitates with dilute sulphuric acid or caustic soda.

Although the arsenic contents of these polyarsenides do not agree with any simple formulation for these products, yet it is at least possible that they are compounds of tervalent arsenic corresponding with the two following general types :—



I.

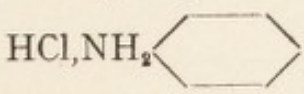


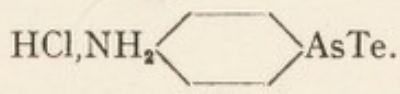
II.

The first results from the interaction of molecular proportions of $R{\cdot}AsO_3H_2$ and sodium arsenite (or arsenious chloride) ; the second from the simultaneous reduction of $R{\cdot}AsO_3H_2$ (1 molecule) and sodium arsenite (2 molecules).

Aromatic Arseno-phosphides, Polyarsenides, Arseno-antimonides, Arseno-selenides, and Arseno-tellurides.[1]

p-*Aminophenylarseno-selenide and -telluride Hydrochlorides,*





—These compounds are produced respectively by passing a rapid stream of hydrogen selenide or hydrogen telluride through an alcoholic solution of *p*-aminophenylarsenious oxide or *p*-amino-

[1] M. L. and B., D.R.-P., 269699, 269700.

phenylarsenious chloride hydrochloride. The selenide is an orange powder and the telluride a reddish-brown compound; both are moderately soluble in dilute hydrochloric acid.

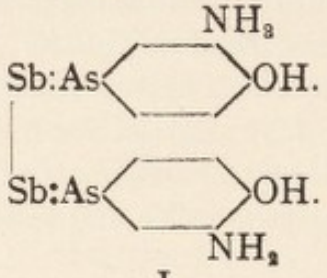
Under similar conditions hydrogen phosphide and antimonide yield arylarseno-phosphides and arylarseno-antimonides, whilst hydrogen arsenide gives rise to aryl polyarsenides, also producible by the reduction method (see p. 270).

Co-ordination compounds of the aryl arseno-phosphides [1] and arylarseno-antimonides are stated to be of therapeutic value.

Arsenoantimonides containing Aromatic Radicals. [2]

The synthetic method of reduction illustrated in the preceding section (p. 270) has been extended to the preparation of mixed stibino-arsenicals containing aromatic radicals which exhibit a marked curative effect in diseases induced by protozoal parasites.

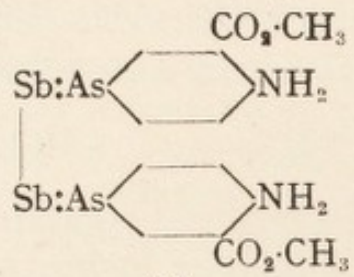
Bis-3-*Amino*-4-*hydroxyphenylarsenoantimonide* (I.).



I.

3-Amino-4-hydroxyphenylarsinic acid (23·3 grams) in 400 c.c. of water and 60 c.c. of 2*N*-caustic soda is mixed with tartar emetic (33·2 grams) in 650 c.c. of water and the resulting solution added to sodium hydrosulphite (500 grams) and magnesium chloride (100 grams) in 2·5 litres of water; the mixture is digested and stirred at 50–53° until precipitation is complete. The product is a reddish-brown powder soluble either in dilute hydrochloric acid or aqueous caustic soda.

The complex arseno-antimonide (II.),



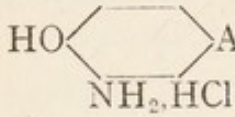
II.

[1] M. L. and B., D.R.-P., 270259. [2] M. L. and B., D.R.-P., 270255.

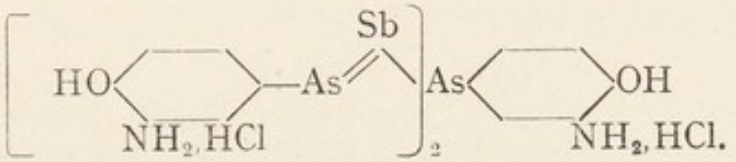
is a brown powder sparingly soluble in water or methyl alcohol, produced from antimony oxychloride in glacial acetic acid and *methyl anthranilylarsine* (a yellow, sparingly soluble powder).[1]

The hydrochloride of a similar arsenostibino-compound is produced by the agency of the primary arylarsine synthesis.[2]

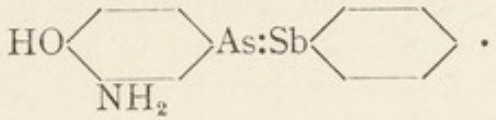
A methyl-alcoholic solution of 3-amino-4-hydroxyphenylarsine (p. 264) containing a small proportion of hydrogen chloride is mixed with antimony trichloride (1 mol.) dissolved in the same solvent. The solution assumes an intense brownish-red colour, and ether precipitates the product as a reddish-brown powder soluble in water, caustic alkalis, dilute hydrochloric acid, the alcohols, glycerin, and glycol. It forms a sparingly soluble sulphate. The product is probably a mixture of



and



3-*Amino-4-hydroxyarsenostibinobenzene*,[3]



—This compound is obtained in the form of its hydrochloride by bringing together in methyl alcohol containing hydrochloric acid molecular proportions of 3-amino-4-hydroxyphenylarsine and phenylstibine dichloride. The brownish-red solution, when poured into ether, yields the hydrochloride as a yellowish-brown, flocculent precipitate, easily soluble in water, aqueous alkali, dilute mineral acid, and the hydroxylic solvents.

The free base is prepared by reducing a mixture of the appropriate pair of aromatic arsenic and antimony derivatives as follows :—

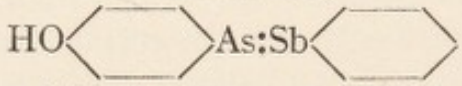
Solution *a*.—3-Amino-4-hydroxyphenylarsenious oxide (10 grams) in 60 c.c. of methyl alcohol, 200 c.c. of water, and 50 c.c. of *N*-sodium hydroxide.

Solution *b*.—Phenylstibinic acid (12·3 grams) in 300 c.c. of water and 50 c.c. of *N*-sodium hydroxide.

[1] M. L. and B., D.R.-P., 269744.
[2] Ehrlich and Karrer, *Ber.*, 1913, **46**, 3569.
[3] M. L. and B., D.R.-P., 269743.

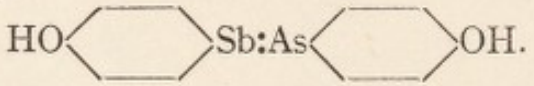
Solutions *a* and *b* are mixed and stirred at the ordinary temperature with sodium hydrosulphite (200 grams) and magnesium chloride (40 grams) in 1 litre of water until a filtered sample remains clear on warming. The brownish-yellow precipitate, obtained in quantitative yield, is readily soluble in moist pyridine, aqueous caustic soda, or methyl alcohol containing hydrochloric acid.[1] The hydrochloride yields co-ordination compounds with gold and osmium chlorides, which are respectively yellowish-brown and brownish-green powders insoluble in ether and dissolving readily in water.[2]

4-Hydroxyphenylarsenostibinobenzene,[3]



is a brown powder soluble in aqueous alkali produced by adding phenylstibine oxide dissolved in hot glacial acetic acid to a methyl-alcoholic solution of *p*-hydroxyphenylarsine.

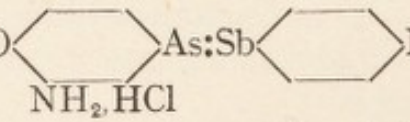
4:4'-Dihydroxystibinoarsenobenzene,[4]



—Molecular proportions of sodium phenol-*p*-arsinate and sodium phenol-*p*-stibinate in dilute aqueous solution are reduced with sodium hydrosulphite until precipitation is complete. The product, a brownish-black powder, is insoluble in water, but dissolves in alcohol, acetone, pyridine, or aqueous caustic soda.

4'-Acetylaminophenylstibinoarseno-4-phenylglycine,[5]

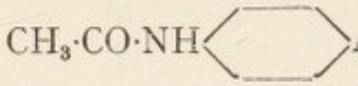
—This compound, a brownish-black powder, is produced by reducing with sodium hydrosulphite a solution containing molecular proportions of phenylglycine-*p*-arsinic acid and 4-acetylaminophenylstibinic acid in slight excess of aqueous caustic soda. The product is insoluble in water, alcohol, or acetone, but dissolves in aqueous alkalis or in moist pyridine.

3-Amino-4-hydroxyarseno-4'-acetylaminostibinobenzene hydrochloride,[6]  is an amorphous, dark brown powder produced by adding 3-amino-4-hydr-

[1] M.L. and B., D.R.-P., 270255; U.S. P., 1111821.
[2] M. L. and B., D.R.-P., 270259. [3] M. L. and B., D.R.-P., 269744.
[4] M. L. and B., D.R.-P., 270255. [5] M. L. and B., D.R.-P., 270255.
[6] Ehrlich and Karrer, *Ber.*, 1913, **46**, 3568.

oxyphenylarsine (0·8 gram) in methyl-alcoholic hydrochloric acid to *p*-acetylaminophenylantimonious iodide, $NH\overline{Ac}\cdot C_6H_4SbI_2$, (1·64 grams), in glacial acetic acid. It is precipitated by ether and is soluble in water or methyl alcohol, dissolving in alkalis to a clear solution. Of the arsenostibine aryls, this compound gives the best therapeutic results on animals infected with trypanosomes.

4-*Acetylaminophenylarsenoantimonious bromide*,



—The 4-*acetylaminophenylarsine*, $CH_3\cdot CO\cdot NH\cdot C_6H_4\cdot AsH_2$, required in this preparation is a white powder, soluble in methyl alcohol or dilute hydrochloric acid, obtained by reducing acetyl-*p*-arsanilic acid with zinc dust and hydrochloric acid.

When mixed in molecular proportions with antimony tribromide in methyl alcohol containing hydrochloric acid, the foregoing arsine yields the condensation product, a reddish-brown powder precipitated by ether and soluble in water or dilute hydrochloric acid.[1]

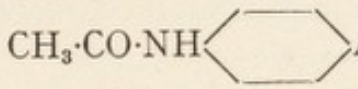
The corresponding arsenoantimonious chloride yields a co-ordination compound with cupric chloride, which is easily soluble in aqueous alkalis or dilute mineral acids.[2]

3-*Amino*-4-*hydroxyphenylarsenoantimonious acetate hydrochloride*,

$$CH_3\cdot CO\cdot OSb{:}As\cdot C_6H_3(OH),NH_2,HCl.$$

—Antimony oxy-salts as well as antimony halides can condense with primary aromatic arsines, and, in the present instance, the compound results from the interaction of 3-amino-4-hydroxy-phenylarsine in methyl alcohol and tartar emetic dissolved in hot glacial acetic acid. The product, a brownish-yellow, flocculent precipitate, is very soluble in water, aqueous alkalis, or dilute hydrochloric acid. Sulphuric acid yields a sparingly soluble sulphate and dimethylaminobenzaldehyde a slightly soluble Schiff base.[3]

Aromatic Arseno-bismuth Halides,[4]



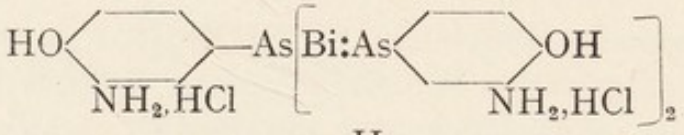
I.

p-*Acetylaminophenylarsenobismuth bromide* (I.), a black, sparingly soluble powder, is obtained by bringing together bismuth

[1] M. L. and B., D.R.-P., 269743. [2] D.R.-P., 270259.
[3] D.R.-P., 269744. [4] M. L. and B., D.R.-P., 269745.

bromide and *p*-acetylaminophenylarsine (prepared by reducing acetyl-*p*-arsanilic acid) in methyl-alcoholic hydrobromic acid, the product being precipitated by ether.

Tris-3 - *amino* - 4 - *hydroxyphenylarsenodibismuthdihydrochloride* (II.), a black precipitate, sparingly but completely soluble in water, is prepared by the interaction of 3-amino-4-hydroxyphenylarsine and bismuth chloride in methyl alcohol containing hydrogen chloride. It is decomposed by alkalis or acids or by boiling the aqueous solution.[1]



II.

Arsenobenzene and its Analogues.

In addition to the aromatic stibino-compounds described in a later chapter (p. 323), we are now acquainted with the following six types of organic compounds containing doubly-linked atoms of the nitrogen family of elements :—

R·N:N·R′ red azo-chromophor.	R·P:P·R′ light yellow phospho-chromophor.	R·As:As·R′ yellow arseno-chromophor.
R·As:Sb·R′ orange to yellowish-brown arseno-stibino-chromophor.	R·Sb:Sb·R′ yellow stibino-chromophor.	R·As:Bi·R′ black arseno-bismutho-chromophor.

The aromatic azo-compounds contain a well-marked chromophor. The weaker colour effect in the phospho- and arseno-compounds is possibly due to the greater tendency to polymerisation which would result in the disappearance of the double linking.[2]

The weakest chromophor of the whole series is the phospho-group, P:P, and from this group to the arseno-bismutho-group the colour increases as the unsaturated character of the molecule becomes more pronounced.[3]

[1] Ehrlich and Karrer, *Ber.*, 1913, **46**, 3569.

[2] Michaelis and Schäfer found by the cryoscopic method in dry phenol that in this solvent the molecular weight of arseno-*p*-toluene corresponds with $C_7H_7As:AsC_7H_7$, *Ber.*, 1913, **46**, 1742.

[3] Ehrlich and Karrer, *loc. cit.*

CHAPTER VIII

LUARGOL

Co-ordination Compounds of Aromatic Arsenicals

THE arsenoaryl compounds exhibit considerable residual affinity, and in this respect resemble the aliphatic tertiary arsines which long ago were shown by Cahours and Gal (p. 42) to give rise to co-ordination compounds with the chlorides of platinum, palladium, and gold.

In the course of his researches on salvarsan, Ehrlich was led to examine the interaction of this drug and various metallic salts, with the result that he discovered a new series of co-ordination compounds in which one or two molecular proportions of the metallic salt enter into such intimate combination with the arsenoaryl derivative that the metal is held in the new complex in a non-ionisable condition, whereby many of its ordinary analytical (ionic) interactions become masked.

This interaction is a very general one ; it is manifested not only by all arsenoaryls whether substituted in the nucleus or not, but is also exhibited by organic arsenious oxides and arsines.[1]

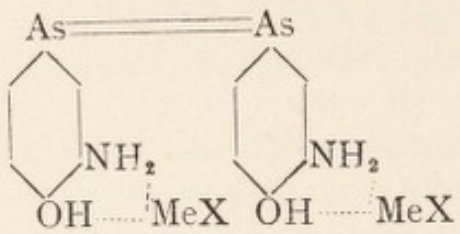
On the other hand, this combination occurs with the salts of copper, silver, gold, mercury, palladium, iridium, ruthenium, and osmium. The tendency for aromatic arsenious oxides, RAsO, to form these co-ordination compounds with metallic salts is less pronounced than in the case of arsenobenzene and its derivatives. In the oxides the residual affinity of the arsenic is less effective, and appears also to be greatly influenced by the substituents of the aromatic nucleus. With the primary arsines, such as 4-amino-3-hydroxyphenylarsine, for example, the residual affinity is very strong ; but so also is the tendency for these

[1] Even quinquevalent arsenic exhibits a capacity for forming co-ordinated compounds with such associating groups as MoO_4 or Mo_2O_7. Rosenheim and Bulecki, *Ber.*, 1913, **46**, 539.

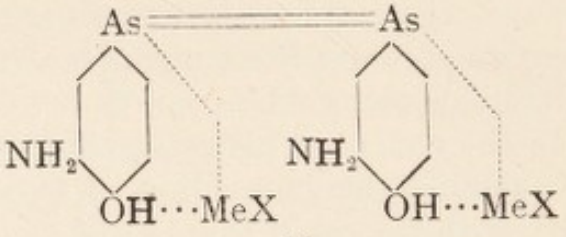
arsines to act as reducing agents. The metallic co-ordination compounds are produced momentarily, but the metal is forthwith precipitated by the reducing action of the organic arsine.

On account of their therapeutic importance, it is chiefly the co-ordination compounds of salvarsan which have been studied, but similar products have been obtained from other arsenoaryls, and even from arsenobenzene itself. These facts throw light on the constitution of the arsenical co-ordination complexes.

If these products were peculiar to salvarsan and its analogues, there would be some justification for the view that the substituent groups OH and NH_2 were more or less responsible for these combinations. The following formulæ indicate two ways in which this influence of the substituents might be manifested. Residual affinity as distinct from principal valency is represented conventionally in the formulæ by dotted lines.



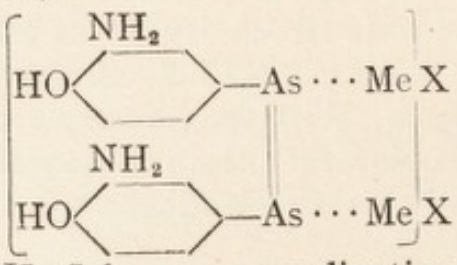
I.



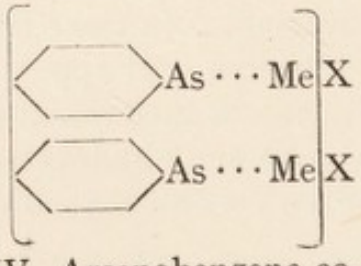
II.

In the first arrangement the substituents alone are involved in the co-ordination complex, but this constitution is not convincing, inasmuch as it does not explain the non-formation of similar additive compounds from the metallic salts, MeX, and aminophenylarsinic acids, $AsO_3H_2 \cdot C_6H_3(NH_2) \cdot OH$.

The second configuration suggests the intervention of the unsaturated arsenic atoms, but does not indicate the formation of co-ordination compounds from unsubstituted arsenobenzene, This fact is, however, taken into account in the third alternative, in which the co-ordination is represented as taking place entirely between the unsaturated arsenic atoms and the metallic salts (2 mols.).



II. Salvarsan co-ordination compounds.



IV. Arsenobenzene co-ordination compounds.

This formulation suggests a maximum of two molecules of metallic salt to each molecular proportion of arsenoaryl (= 2 atoms of As). The experimental results show, however, that complexes exist with only one molecular proportion of the metallic salt, in which, therefore, according to the foregoing view, the residual affinity of only one arsenic atom is saturated.

$$\left[\begin{array}{l} \text{R·As}\cdots\text{Me} \\ \quad\| \\ \text{R·As}\cdots\cdots \end{array}\right]\text{X}$$

Arseno-compounds containing even a smaller proportion of the metallic salt have been recognised, notably the important drug " Luargol."

The discovery of these arsenoaryl metallic compounds was first made known publicly by Ehrlich at the International Congress of Medicine held in London in 1913, although his earliest patent application was dated July, 1912. A fuller communication on the subject in collaboration with Karrer was published posthumously in 1915.[1]

Shortly after Ehrlich's earliest communication, Danysz, working independently, noticed the formation of a metallic complex from salvarsan and silver nitrate. His earliest note on this observation was published in 1913, and a fuller account of the co-ordination compounds of salvarsan with silver chloride, bromide, and iodide was given in 1914.[2]

As an illustration of the great tendency which exists to form these co-ordination complexes from the arsenoaryls and salts of the noble metals, it may be mentioned that when the latter are present during reduction of the generating arylarsinic acids, the noble metals are not precipitated by the reducing agent, but are found in the co-ordination complex at the close of the reduction.

The experimental difficulties in the way of studying these salvarsan metallic complexes are considerable. The products show little tendency to crystallise, and their solubility is not very, different from that of the generating arseno-compound. The copper compounds were found to be most readily separated.

[1] Ehrlich and Karrer, *Ber.*, 1915, **48**, 1634.

[2] Danysz, *Compt. rend.*, 1913, **157**, 644; 1914, **158**, 199.

Copper Derivatives.

1. $C_{12}H_{12}O_2N_2As,2HCl,CuCl_2$:—Salvarsan (100 grams) in 1600 c.c. of methyl alcohol and 16 c.c. of saturated alcoholic hydrochloric acid is treated with 35·8 grams of crystallised copper chloride ($CuCl_2,2H_2O$) in 400 c.c. of methyl alcohol. The copper derivative separates, the mixture is poured into 8 litres of ether, and the brick-red precipitate washed and dried *in vacuo*. The whole operation is conducted preferably in an atmosphere of carbon dioxide or nitrogen.

This copper derivative is a reddish to orange-yellow powder, moderately soluble in water, more readily in glycerol or glycol. It dissolves in 2*N*-sodium hydroxide without precipitation of copper hydroxide until the liquid is heated for some time.

The compound is strongly toxic to trypanosomes. When tried on mice infected with *Trypanosoma brucei* the ratio of healing dose to the lethal dose is only 15 per 1,000. This substance has also given promising results in various human diseases.[1]

2. $C_{12}H_{12}O_2N_2As_2,2HCl,2CuCl_2$:—This copper derivative is prepared as in the preceding experiment, but the amount of copper salt is doubled. The great tendency which exists to form these salvarsan co-ordination compounds is illustrated in a striking manner by an alternative method of preparation. Sodium 3-amino-4-hydroxyphenylarsinate and copper chloride are dissolved in water in molecular proportions and reduced at 50° with alkaline hydrosulphite. Reduction of arsinic acid to arseno-compound and formation of the co-ordination complex proceed concurrently, and yellowish-brown flocculæ of the copper compound are precipitated. The product is very soluble in dilute hydrochloric acid or aqueous sodium hydroxide.

Silver Derivatives.

1. $C_{12}H_{12}O_2N_2As_2,2HCl,2AgNO_3$:—A brown, flocculent precipitate produced by pouring into ether the reddish-brown solution obtained by mixing methyl-alcoholic solutions of salvarsan and silver nitrate. It is easily soluble in water, aqueous sodium hydroxide, or methyl alcohol. The silver present is not

[1] *Arch. Schiffs- und Tropenhygiene*, **17**, 845; **18**, 743; *Münchener med. Wochenschrift*, 1914, **61**, 1; 1915, **62**, 147, 149.

precipitated by chlorides. Sodium chloride throws down a brownish-yellow precipitate moderately soluble in water.

$$\begin{matrix} R\cdot As \cdots AgNO_3 \\ \| \\ R\cdot As \cdots AgNO_3 \end{matrix} \xrightarrow{2NaCl} \begin{matrix} R\cdot As \cdots AgCl \\ \| \\ R\cdot As \cdots AgCl \end{matrix} + 2NaNO_3$$

A compound with only one $AgNO_3$ is similarly prepared.

Mercury Derivatives.—(1) With $HgCl_2$: yellow, granular powder from methyl alcohol. Decomposed by water or aqueous sodium hydroxide with separation of metallic mercury.

(2) The mercuric iodide compound is more stable than the preceding; it dissolves readily in water.

Gold Derivatives.—Compounds are formed with one and two molecular proportions of gold chloride. These brownish-yellow powders are easily soluble in water, alcohol, or aqueous alkalis. Addition of more than two molecular proportions of gold chloride to an aqueous solution of the compound with $2AuCl_3$ determines the sudden precipitation of all the gold present in the metallic state.

$$\begin{matrix} R\cdot As,AuCl_3 \\ \| \\ R\cdot As,AuCl_3 \end{matrix} + 2/3AuCl_3 + 6H_2O = 2R\cdot AsO_3H_2 + 8HCl + 2\ 2/3\ Au.$$

The platinum and palladium compounds are brown powders soluble in water.

Arsenobenzene in pyridine gives, with aqueous silver nitrate, a deep brown solution from which ether-alcohol precipitates a black co-ordination compound. The copper compound, a reddish-brown, insoluble powder, is obtained by adding hypophosphorous acid to a solution of copper chloride and phenylarsinic acid.[1]

Section I.—Co-ordination Compounds of Arsenobenzene and its Derivatives.[2]

Arsenobenzene and Silver Nitrate.—Arsenobenzene in pyridine and concentrated aqueous silver nitrate in molecular proportions give a brownish-black solution from which ether-alcohol precipitates the black product which is insoluble in water.

Arsenophenylglycine and Auric Chloride.—A dilute solution of auric chloride (0·25 gram) is added slowly to 1·5 grams of arseno-

[1] Ehrlich and Karrer, *Ber.*, 1915, **48**, 1644.

[2] M. L. and B., D.R.-P., 268220, 268221, 270253, 270256, 270257, 270258, 270259.

phenylglycine in water. The additive compound, which is precipitated by alcohol-ether, is a greyish-yellow powder easily soluble in water or aqueous alkalis ; it retains the gold very tenaciously.

4 : 4′-*Dihydroxyarsenobenzene and Auric Chloride.*—Molecular proportions of these substances are mixed in sufficient aqueous caustic soda to dissolve the arseno-compound, which is precipitated by alcohol-ether as a brownish-black powder readily soluble in water.

3 : 4 : 3′ : 4′-*Tetramino-arsenobenzene*-N-*methylenesulphinate and Cupric Chloride.*—The additive compound is a yellowish-red powder soluble in alkalis.

Co-ordination Compounds of Arylarsenical Derivatives and the Metals.[1]

On mixing the salts of gold or the platinoid metals with solutions of salvarsan dihydrochloride, soluble co-ordination compounds are produced, in which the metal is no longer precipitated by electrolytes such as acids, bases or salts. The solutions of these co-ordination compounds are more stable than those of salvarsan itself. These compounds are quite different from the product of the interaction of gold chloride and sodium *p*-arsanilate.[2]

Introduced into the animal organism, these co-ordination compounds combine the haptophoric capacity of the arseno-compound and the specific physiological reaction of the metal.

Salvarsan-Gold Compound.—To 5 c.c. of 5 per cent. aqueous solution of salvarsan dihydrochloride are added 2 c.c. of 10 per cent. gold chloride. A clear dark brown solution is obtained of acid reaction ; it gives no precipitate of auric hydroxide with alkali. The alkaline solution does not give a precipitate of gold when reduced with formaldehyde or sodium hydrosulphite.

A similar co-ordination compound is prepared by adding 2 c.c. of 5 per cent. sodium aurate to 5 c.c. of an aqueous 5 per cent. solution of disodium salvarsan.

The salvarsan-gold compound can be obtained solid by concentrating the solution *in vacuo* or by precipitation with alcohol-ether or alcohol-acetone.

Two varieties of *salvarsan-platinum compound* are obtained as in the following examples.

[1] M. L. and B., D.R.-P., 268220; *cf.* Eng. P., 1247/1914.

[2] D.R.-P., 206343.

a. 3 c.c. of 10 per cent. aqueous platinic chloride to 5 c.c. of 5 per cent. salvarsan dihydrochloride.

b. 2 c.c. of 10 per cent. platinic chloride rendered alkaline with sodium hydroxide to 5 c.c. of 5 per cent. disodium salvarsan.

Co-ordination Compounds of Salvarsan.

1. *With Mercuric Chloride.*[1]—Molecular proportions of salvarsan dihydrochloride and mercuric chloride are dissolved in methyl alcohol, the solution of the arsenical reagent slightly acidified with methyl-alcoholic hydrochloric acid and mixed with mercuric solution. The colour changes from light yellow to deep orange, and ether precipitates the compound as a pale yellow powder readily soluble in glycerin, ethylene glycol, methyl alcohol, or acidified potassium iodide solution. It is decomposed by water, especially on warming.

2. *With Silver Nitrate.*—i. On mixing methyl-alcoholic solutions of salvarsan dihydrochloride and silver nitrate in molecular proportions the mixture assumes a reddish-brown colour, and ether precipitates the product as a brownish-yellow powder, very soluble in water, methyl alcohol, or glycerin. The silver present is a non-ionisable condition and is not eliminated by reducing agents.

ii. A dark brown product, obtained as in the preceding experiment by using two molecular proportions of silver nitrate, dissolves in water with an intense reddish-brown colour.

3. *With Silver Nitrate and Auric Chloride.*—Silver nitrate and auric chloride in molecular proportions and dissolved in methyl alcohol are added successively to a methyl-alcoholic solution of salvarsan dihydrochloride. Ether precipitates the triple compound as a brownish-red powder, easily soluble in water, glycerin, or other hydroxylic solvents.

4. *With Cuprous or Cupric Chloride.*—i. A methyl-alcoholic solution of salvarsan hydrochloride (1 mol.) is added to cuprous chloride (1 mol.) dissolved in methyl-alcoholic hydrochloric acid, the product being precipitated by ether. It is a brick-red powder easily soluble in water.

ii. A methyl-alcoholic solution of salvarsan hydrochloride, slightly acidified, is added to hydrated cupric chloride dissolved in the same solvent. The solution becomes brownish-red and the co-ordinated compound begins to crystallise, the precipita-

[1] M. L. and B., D.R.-P., 270253.

tion being completed with ether. The orange-yellow product is readily soluble in water, glycerin, or ethylene glycol. In the cold, aqueous alkalis do not precipitate copper hydroxide; only on warming is the copper eliminated as oxide.

An alternative mode of preparation of these co-ordination compounds of salvarsan is to mix the generator of this organic arsenical with the metallic salt before adding the reducing agent.[1]

With Cupric Chloride.—i. 3-Amino-4-hydroxyphenylarsinic acid (10 grams) and hydrated cupric chloride (3·64 grams) in 100 c.c. of water and 43 c. of 2*N*-hydrochloric acid are treated successively at 50° with sodium hydrosulphite (50 grams) in 150 c.c. of water and 43 c.c. of 2*N*-caustic soda. The brownish-red precipitate is readily soluble in dilute hydrochloric acid or caustic soda.

ii. 3-Amino-4-hydroxyphenylarsenious oxide (2 mols.) and cupric chloride (1 mol.) are dissolved in hydrochloric acid and the arsenical compound reduced with stannous chloride. The hydrochloride of the copper additive compound is precipitated.

3. *With Auric Chloride.*—3-Amino-4-hydroxyphenylarsenious oxide hydrochloride (2 mols.) and auric chloride (1 mol.) in aqueous solution are treated with sodium hydrosulphite, when the auric chloride additive compound of 3:3′-diamino-4:4′-dihydroxyarsenobenzene is obtained as a golden-yellow precipitate.

4. *With Platinic Chloride.*—As in the foregoing experiment the additive compound of platinic chloride and salvarsan separates at once as a yellowish-brown precipitate readily soluble in pyridine or in *N*-hydrochloric acid.

Co-ordination Compounds of Neosalvarsan.[2]

1. *With Cupric Chloride.*—Sodium 3:3′-diamino-4:4′-dihydroxy-arsenobenzene-*N*-methylenesulphinate (3 parts) and hydrated cupric chloride, $CuCl_2,2H_2O$ (0·7 part), are mixed in strong aqueous solutions and the additive compound precipitated as a yellow, voluminous powder on adding the mixed solution to ether-alcohol. In the cold the product no longer gives the reaction of copper, the combination being broken up only on boiling.

2. *With Silver Nitrate.*—The product, a black powder, is precipitated by ether-alcohol from an aqueous solution of its generators, which are mixed in molecular proportions. The

[1] M. L. and B., D.R.-P., 270258. [2] M. L. and B., D.R.-P., 268221.

aqueous solution of this silver compound is markedly fluorescent.

3. *With Gold Chloride.*—The generators are mixed in molecular proportions and the very soluble brownish-red product is precipitated from its aqueous solution with ether-alcohol.

4. *With Platinic Chloride.*—The brown product from molecular proportions of platinic chloride and neosalvarsan is readily soluble in water and is precipitated therefrom by ether-alcohol

Section II.—Luargol: "102" of Danysz's Series.

3 : 3'-Diamino-4 : 4'-dihydroxyarsenobenzene-silver-bromide-antimonyl Sulphate, $[C_{12}H_{12}O_2N_2As_2]_2,AgBr,SbO(H_2SO_4)_2$.—The importance of the combinations of salvarsan and metallic salts was first made public by Ehrlich on the 8th August, 1913, at the International Medical Congress held in London. On the 20th October of the same year Danysz described the therapeutic and antiseptic effects of salvarsan silver derivatives, one of these being a combination of the organic arsenical with silver nitrate.[1] Subsequently he described a method of making the corresponding silver halide combinations which consisted in adding drop by drop a solution of the silver halide in potassium cyanide to a solution of salvarsan. A precipitate forms, which dissolves to a dark limpid solution, hydrogen cyanide being evolved. In this way one molecule of silver halide can be combined with one molecule of salvarsan. If precipitation occurs before this proportion is reached, hydrochloric acid is added. Finally, the complex product is precipitated by sulphuric acid in the form of its sparingly soluble sulphate, which can be freed from potassium cyanide and chloride. The product is an orange-yellow to dark brown powder, dissolving in water rendered alkaline by soda. The chlorine derivative is less active than the iodine and bromine compounds. The toxicity of the bromo-compound is equal to that of salvarsan, whereas its sterilising power *in vitro* or *in vivo* is much greater.

The bromide combinations are much more active than those with silver chloride or nitrate and less toxic than the iodide compounds.

Even though the mercury, gold, and platinum combinations are a little more active than those of silver, they are less stable and relatively more toxic.

Continuing his researches, Danysz found that a triple combina-

[1] *Compt. rend.*, 1913, **157**, 644; 1914, **158**, 199.

tion could be produced of salvarsan, silver bromide, and tervalent antimony having the above empirical formula.

It has been found that antimony compounds have a beneficial effect in refractory cases of trypanosomiasis and in arsenic-resisting cases of syphilis. In " Luargol " the antiseptic properties of salvarsan are increased by the co-ordinated silver bromide, and these are reinforced by the specific action of the antimony.

The drug has the following percentage composition :— C, 19·84 ; Ag, 7·40 ; Br, 5·52 ; As, 20·60 ; Sb, 8·19 ; S, 8·87.[1]

Luargol is very efficacious in experimental cases of *Trypanosoma surra* and *Tr. gambiense ;* the ratio of maximum tolerated to trypanocidal dose is 80 or 100 : 1, whereas with salvarsan it is 10 : 1. In sleeping sickness luargol is stated to be ten times as active as salvarsan. Very promising results have been obtained in a large number of cases of human syphilis.[2]

Luargol is insoluble in water and is rendered soluble by the addition of caustic soda (0·4 gram NaOH to 1·0 gram luargol). The solution thus prepared should be injected intravenously ; ill-effects are produced by subcutaneous exhibition. The substance and its solutions are comparatively stable, and the alkaline preparation can be heated for two to three hours without losing its efficacy.

Section III.—Co-ordination Compounds of Aromatic Polyarsenides.[3]

The polyarsenical compound (3 grams) described on page 270, which probably has the constitution

$$\begin{array}{l} As{:}As{\cdot}C_6H_3(OH){\cdot}NH_2 \\ \quad\vdots \\ As{:}As{\cdot}C_6H_3(OH){\cdot}NH_2, \end{array}$$

is dissolved in methyl alcohol containing hydrochloric acid (D = 1·12) and treated with one or other of the following reagents :—

1. *Cuprous chloride* (1 gram) in methyl-alcoholic hydrochloric acid, the additive compound being precipitated from the dark red solution by ether. The product is soluble in water to a solution from which sulphuric acid precipitates a sparingly

[1] Danysz, *Compt. rend.*, 1914, **159**, 452.

[2] Renault, Fournier, and Guénot, *Compt. rend.*, 1915, **161**, 685. Dalimier and Lévy-Franchel, *ibid.*, 1916, **162**, 440.

[3] M. L. and B., D.R.-P., 270256.

soluble sulphate. The copper present is not precipitated by caustic alkali.

2. *Mercuric chloride* (2·7 grams) in methyl alcohol. An orange precipitate separates and the deposition is completed by ether. The product is not soluble in water or methyl alcohol and is blackened by caustic soda.

3. *Silver Nitrate* (0·85 gram).—The brown product is readily soluble in methyl alcohol or water and is precipitated by ether. It does not give the ionic reactions of silver.

Cupric Chloride.—The hydrated chloride, $CuCl_2,2H_2O$, (1·7 grams) in methyl alcohol (5 c.c.) and arsenious chloride (1·8 grams) are added successively to 3-amino-4-hydroxy-phenyl-arsenious oxide (2 grams) in 10 c.c. of alcohol, and this solution added to a well-cooled solution of stannous chloride (5 grams) in 20 c.c. of hydrochloric acid (D 1·19) and 20 c.c. of glacial acetic acid. The hydrochloride of the copper additive compound of the foregoing polyarsenide is precipitated as a brown powder, soluble in water or aqueous alkalis.[1]

Other Co-ordination Compounds of Organic Arsenicals :—

I. *Aliphatic Series.*

1. Cacodyl oxide compounds (*v.* p. 13).
2. Metallic thiocacodylates (*v.* p. 16).
3. Trialkylarsine compounds (*v.* p. 42).

II. *Aromatic Series.*

1. Copper salvarsan (*v.* p. 228).
2. Compounds of the primary arylarsines (*v.* p. 263, 264).
3. Compounds of the aryl arseno-phosphides and -antimonides (*v.* p. 272, 274).

Application of Drugs containing Tervalent Arsenic.

Even the barest summary of the voluminous literature which has developed round the medical application of organic arsenical compounds would be quite beyond the scope of this treatise. Moreover, much of the subject matter is still in the controversial stage. It seems, however, definitely established that compounds containing tervalent arsenic are far more efficacious against

[1] M. L. and B., D.R.-P., 270258.

pathogenic protozoa than the corresponding derivatives of quinquevalent arsenic and, in efficacious doses, are much less toxic and dangerous to the host of these organisms.

Atoxyl, which was originally stated to be forty times less toxic than potassium arsenite (Fowler's solution), was at first extensively used in psoriasis, anæmia, syphilis, sarcoma, elephantiasis, relapsing fever, malaria, tuberculosis, and trypanosomiasis, but its poisonous effects are cumulative, leading to disturbance of vision and later complete blindness through optic atrophy. The toxic action on the kidneys, though delayed, showed eventually the effect of arsenic on these organs.

Ehrlich's investigations were directed to the production of an arsenical drug in which the ratio of curative dose to toxic dose should be as small as possible and in any case less than one-third. The most promising results were obtained successively with sodium arsenophenyl-*p*-glycinate (" 418 ") and with 3:3′-diamino-4:4′-dihydroxyarsenobenzene dihydrochloride (" 606 "). The latter drug came nearest to Ehrlich's ideal of " *Therapia sterilisans magna*," the extermination of all the parasites at " one fell swoop." This procedure would have the great practical advantage of killing off the specific pathogenic germs before successive generations of these organisms had acquired an immunity to smaller doses. This ideal of a single curative dose has not been realised in practice, although the effect of salvarsan and allied drugs is extremely rapid and well marked, even after very few repetitions.

Among the drugs containing quinquevalent arsenic which for a time had a vogue in the treatment of sleeping sickness, syphilis, and relapsing fever may be mentioned Arsacetin (sodium acetyl-*p*-arsanilate), Orsudan (sodium acetyl-2-aminotolyl-5-arsinate), and Pectine (sodium benzenesulphonyl-*p*-arsanilate). These drugs were less toxic than atoxyl, and their solutions, unlike those of atoxyl, could be sterilised by boiling or even by heating under pressure at 130°, without the occurrence of destructive hydrolysis leading to the production of poisonous arsenic acid.

As the result of exhaustive trials on animals and numerous clinical tests, medical practice has now concentrated on the use of salvarsan and its modern substitutes.

In Great Britain salvarsan, also sold as kharsivan and arsenobillon, and neosalvarsan, also purveyed as neokharsivan and novarsenobillon, are approved by the Local Government Board

for issue under the Public Health (Venereal Diseases) Regulations, 1916, provided that none of these drugs shall be offered for sale until the preparations have been examined and passed by a committee of experts appointed by the Board of Trade.

The two drugs are very similar in curative action, and not only have they a specific action in all stages of syphilis, but they are also beneficial in other diseases due to spirillosæ. Favourable results are obtained in recurrent fever, frambœsia (yaws, pian), filaria, malaria, plague, leprosy, Vincent's angina, and pernicious anæmia. Amongst diseases of animals, salvarsan and neosalvarsan exercise a specific influence in the pleuro-pneumonia of horses, in African glanders (lymphangitis epizootica), and in anthrax.

These drugs are administered by injection either intravenously, intramuscularly (into the gluteal muscles), or subcutaneously (into the tissues adjoining bases of shoulder blades), and intrarectal injection has also been employed. The prevailing method is that of intravenous injection, a procedure which is far more readily carried out with neosalvarsan than with salvarsan. It is for this reason that the former drug, which dissolves in water to a neutral sŏlution ready immediately for injection, is rapidly gaining in popular favour. This tendency is brought out in a remarkable manner by the following summary, which indicates the practice of the French Military Medical Service.

The following table shows that in nearly 95,000 intravenous injections, 77 per cent. of these applications were made with neosalvarsan either used as such or employed under the synonym of novarsenobillon. About 9·7 per cent. of the cases were treated with salvarsan (arsenobillon). Galyl, the complex phosphamate of salvarsan discovered by Mouneyrat, was used in 9·2 per cent. of the cases, the technique adopted being similar to that employed with neosalvarsan.

Nearly 4 per cent. of the injections were made with luargol, the salvarsan co-ordination compound with silver bromide and antimony oxide introduced by Danysz. This drug, like salvarsan, needs before injection a preliminary treatment with caustic soda.

The report is a striking testimony alike to the vast scale on which organic arsenical drugs are now employed, and to the comparative freedom from untoward ill-effects arising from their exhibition.

The Intravenous Injection of Organo-arsenical Compounds.

[*A summary of 95,000 intravenous injections of arsenical compounds performed by the French Military Medical Service during the first two years of the war.*]

In August, 1916, the French Under-Secretary of State for Military Hygiene addressed a circular to the various military commands asking for detailed information as to the number, results, etc., of the intravenous injections of arsenical compounds performed during the first two years of the war. The replies were summarised by M. Paul Ravaut and his report was published in the November, 1916, issue of the "Archives de Médecine et de Pharmacie Militaire."

The total number of medical officers who had performed personally injections of the nature specified was 185, and their reports dealt with 94,762 injections. The preparations used were :

Novarsenobillon	in 37,352 cases.
Neosalvarsan	,, 35,826 ,,
Salvarsan and arsenobillon ..	,, 9,215 ,,
Galyl	,, 8,846 ,,
Luargol	,, 3,523 ,,

No fatal case was reported among the 94,762 injections and comparatively few serious accidents. These may be summarised as follows :—

	Nov-arseno.	Neosal-varsan.	Salvarsan and Arseno.	Galyl.	Luargol.
Transient coma	—	1	—	—	—
Epileptiform crisis and delirium	—	1	—	—	—
Grave nitritoid crises ..	—	—	—	4	—
Meningeal reaction ..	—	2	—	—	—
Facial paralysis	—	2	—	—	—
Epileptic crisis	—	1	—	1	—
Albuminaria	2	4	1	3	1
Icterus	7	8	1	2	2
Acute dermatitis	—	—	—	—	1
Total	9	19	2	10	4
Percentage	0·025	0·051	0·021	0·113	0·113

Of the less important incidents recorded the following is an analysis :—

	Nov-arseno.	Neosal-varsan.	Salvarsan and Arseno.	Galyl.	Luargol.
Mild nitritoid crises ..	9	11	5	Frequent	—
Herxheimer reaction (cutaneous)	1	5	—	2	—
Vertigo and cephalalgia ..	8	15	3	Frequent	—
Erythema, pruritus and urticaria	7	13	2	4	4
Oedema of the face	6	4	—	—	—
Vomiting and diarrhœa ..		16 cases not analysed.			

Although the list of accidents and incidents appears long, it should be considered only in conjunction with the large number of injections performed.

The following conclusions are cited from M. Ravaut's report :—

A. All medical officers except two recognise the efficacy and necessity of the employment of intravenous injections of arsenical compounds in the treatment of syphilis. Their principal reasons are :—

1. Rapid superficial healing and cicatrisation of contagious lesions attained much more rapidly than with mercury. It is claimed that a rapid cure can be effected with two or three injections, but that it is insufficient, for, under such conditions, relapses are almost constant.

2. Many doctors report the rapid cicatrisation of lesions under the influence of arsenic which have resisted treatment with mercury ; some patients, on the point of being discharged, have been able to return to duty as the result of an arsenical treatment.

3. If the established rules are followed, the employment of the remedy is without danger. " Treatment by arsenical compounds is much less dangerous than intensive mercurial treatment and infinitely more efficacious."

B. Almost all the doctors insist on the necessity of associating arsenic and mercury in the treatment of syphilis, the two remedies being complementary.

C. The technique generally employed is that of concentrated injections. The question of the water to be employed is satisfactorily settled—for sterilised water, even when not fresh, and boiled water are used impartially and without inconvenient results.

D. To prevent or to treat vaso-dilatory accidents and nitritoid crises numerous doctors record the good effects of adrenaline (by the mouth : 30 drops of a 1 in 1000 solution ; hypodermically : 1 c.c. of the same solution).

E. General criticism of the various arsenical compounds employed :—

Novarsenobillon.—Preferred to all others. All find it at least equal to neosalvarsan and sometimes superior. The incidents attendant on injection appear less frequent.

Neosalvarsan.—Very good.

Arsenobillon and Salvarsan.—Are considered very active. Have only been used in default of the preceding—the injection of which is much simpler and more rapid. One doctor only has used them systematically.

Galyl.—Very active according to some. Complaint is made of irregularities in quality, of variations in solubility, and of the frequency of small accidents following on injection. Owing to this last fact, a dose of 0·2 gram has rarely been exceeded, and this has diminished the efficacy of the treatment.

Luargol.—An arsenobenzol reinforced with silver and antimony. Some doctors find it extremely active. Complaint is made that it has given rise to indurations of the veins of the arm in consequence of too high a content of caustic soda in the solvent.

The foregoing report, which certainly does not show bias in favour of arsenical drugs of French origin against those of German manufacture, has for this reason been selected as an epitome of existing medical practice and testimony in regard to the utility of organo-arsenical medicaments.

CHAPTER IX

Aromatic Antimonials

Part I.

Aromatic Stibines and their Immediate Derivatives.

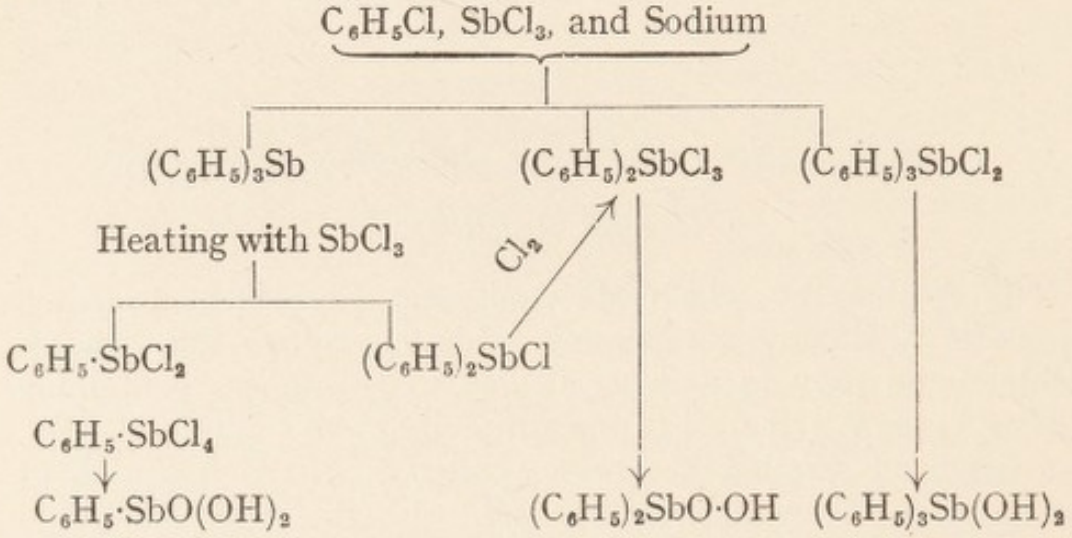
General Reactions.

The method by which Michaelis and Reese first prepared aromatic antimony compounds leads chiefly to the triarylstibines and only in a lesser degree to substances containing two aryl groups attached to one antimony atom. More recently, the Grignard reaction has been applied to the preparation of aromatic antimony derivatives, and, with the magnesium aryl bromides or iodides, only tertiary stibines and their halide derivatives have been isolated. Certain aryl-antimony derivatives containing amino-groups such as the antimony analogues of atoxyl and salvarsan are prepared by special methods based on the discovery made by the Chemische Fabrik von Heyden that antimonial groups can be introduced into the aromatic nucleus through the agency of the diazo-reaction (*v.* Part II.). The processes due to Michaelis are illustrated by the following diagram (I., p. 294), which is drawn up with special reference to the phenyl compounds.

The method of synthesis is analogous to that employed by Michaelis for the arsenic compounds. The sodium process is available, but the reaction is considerably complicated by the greater tendency possessed by antimony of passing from the triadic to the pentadic condition. When antimony trichloride and chlorobenzene are heated in benzene solution with sodium for 24 hours the products are triphenylstibine, triphenylstibine dichloride, and diphenylstibine trichloride. Triphenylstibine dichloride can be converted into triphenylstibine sulphide, a

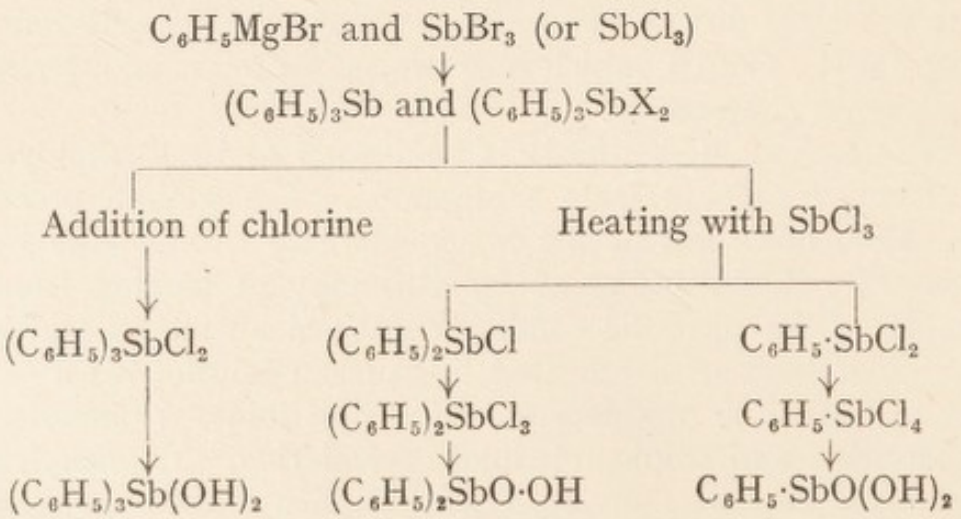
substance which has been used in skin diseases under the name of "*sulphoform.*" Triphenylstibine when heated under pressure with antimony trichloride yields phenylstibine dichloride, and thus the primary, secondary, and tertiary series of aromatic antimony derivatives are obtainable from the products of the sodium condensation. This method was generalised so that aromatic antimony compounds were synthesised containing tolyl, anisyl, and phenetyl groups.

I.—Sodium Method.



The Grignard reaction gives rise mainly to triphenylstibine or its dihalide derivatives, but the following diagram shows how the diphenyl and monophenyl series of antimony compounds are obtainable from the tertiary stibine.

II.—Grignard Reaction for Aryl Antimony Compounds.



Antimony Analogues of Atoxyl and Salvarsan.

Before referring to organo-antimony derivatives of therapeutic interest it should be pointed out that salts of antimonyl tartaric acid have figured largely in recent researches on the treatment of diseases of protozoal origin. Lithium antimonyl tartrate has been extensively used by Dr. Plimmer in his investigations on sleeping sickness. Potassium ammonium antimonyl tartrate has been introduced, under the name of antiluetin, by Tsuzuki,[1] and the use of sodium antimonyl tartrate and aniline antimonyl tartrate [2] has also been suggested. Dr. Martindale has prepared a 10 per cent. solution of antimonious oxide in glycerin. This preparation (*injectio antimonii oxidi*), which probably contains a glyceryl antimonite, is diluted to a definite strength with water; it has been tried with promising results by intramuscular and intravenous injections in trypanosomiasis, kala azar, and other tropical diseases.[3] Sodium antimony dithioglycinate, $CO_2Na{\cdot}CH_2{\cdot}S{\cdot}Sb{\cdot}S{\cdot}CH_2{\cdot}CO{\cdot}O$, and the triamide of antimony trithioglycine, $Sb[S{\cdot}CH_2{\cdot}CO{\cdot}NH_2]_3$, when injected into animals, have afforded protection from trypanosomes.[4]

Although the therapeutic application of organic derivatives of antimony has not hitherto reached the prominence attained by the arsenical compounds, yet great advances have been made in the synthesis of the aromatic antimonials, and, in most cases, the antimony analogues of the important aromatic arsenical drugs have been prepared. The modern improvements which have facilitated the production of aryl-antimony derivatives are twofold. First, we have the application of the Grignard reaction to the production of triphenylstibine and its homologues (*Ber.*, 1904, **36**, 4620; *Chem. Soc. Trans.*, 1911, **99**, 2290), a process which is also applicable to the synthesis of tertiary aromatic arsines. As regards the antimony compounds, the writer in collaboration with Miss Micklethwait showed how it was possible to pass from triphenylstibine to the primary and secondary series by heating the base with antimony trichloride

[1] *Deutsch. Med. Wochensch.*, 1913, p. 947.

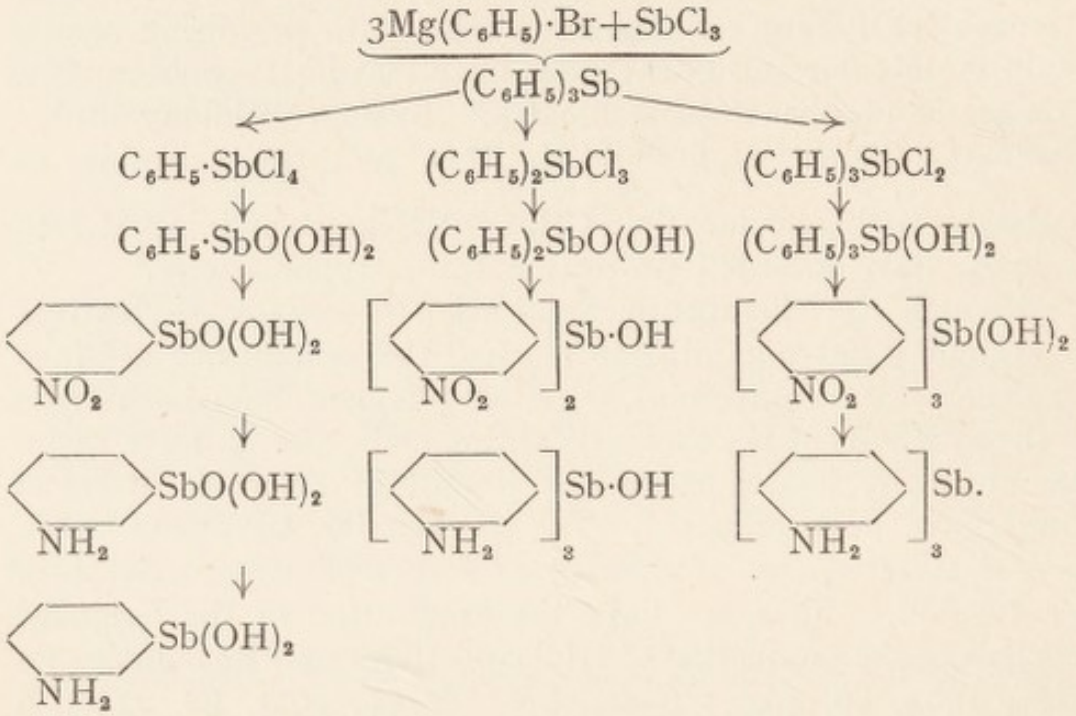
[2] *Pharm. Zeit.*, 1909, **54**, 919.

[3] American leishmaniasis has been cured in many instances by subcutaneous, intramuscular, and intravenous administration of this preparation, which keeps well and does not produce the general effects or local irritation of tartar emetic.—*Lancet*, Sept. 1, 1917, p. 355.

[4] *J. Pharm.*, 1910, **144**, 101.

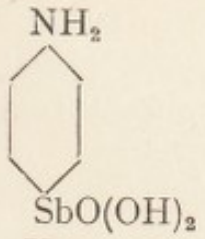
when both phenylstibine dichloride and diphenylstibine chloride were produced.

The following diagram shows how these initial products were converted successively into stibinic acids, nitrostibinic acids, and the reduction products of the latter. These experiments demonstrated that the stibinic groups induce substitution in the meta-position. Accordingly the reduced products, two of which were obtained independently by P. May, all contained their amino-groups in the meta-position with respect to antimony. These bases and their salts are characterised by their irritating action on the mucous membrane of the nose and throat; they have a slight trypanocidal action, but are very irritant when administered subcutaneously. (Plimmer, Fry, and Ranken, *Proc. Roy. Soc.*, 1911, **83**B, 144.)



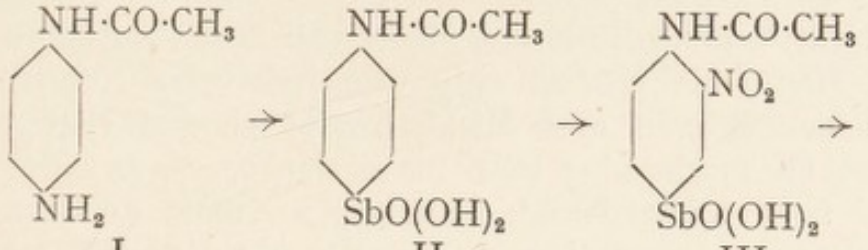
The second recent improvement in the synthesis of aromatic antimony compounds was the discovery made by the Chemische Fabrik von Heyden that antimony groups could be introduced into the aromatic nucleus through the agency of the diazo-reaction. This discovery led first to the synthesis of antimony atoxyl, and more recently to that of the antimony analogue of salvarsan.

Acetyl-*p*-phenylenediamine (I.) when diazotised and treated in alkaline solution with antimony trichloride becomes converted into acetyl-*p*-aminophenylstibinic acid (II.). This product on hydrolysis yields *p*-aminophenylstibinic acid (IIA),

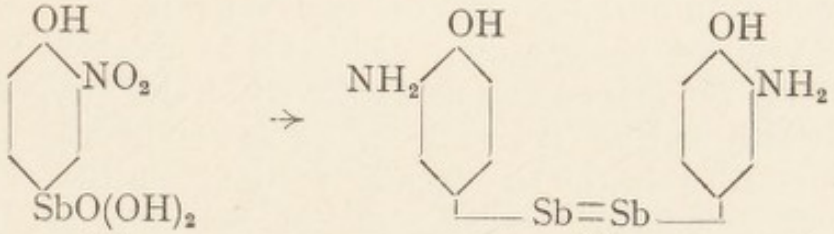


IIA.

the sodium salt of which is the analogue of atoxyl (D.R.-P., 270488).



I. II. III.



IV. V.

The acetylated derivative gave, on nitration, the compound (III.), and this substance, when boiled with caustic alkalis, underwent hydrolysis, a hydroxyl group replacing the acetylamino-complex; 3-nitro-4-hydroxyphenylstibinic acid (IV.) when reduced with alkaline hydrosulphite gave rise to the unstable 3 : 3′-diamino-4 : 4′-dihydroxystibinobenzene (V.), obtained as a reddish-brown precipitate readily soluble in acids or alkalis, and becoming white by aerial oxidation (Fabr. Heyden, D.R.-P., 268451).

The diazo-process for obtaining aromatic stibinic acids is a general one, and remarkably complex antimony derivatives can be synthesised.[1]

[1] Fabr. Heyden, D.R.-P., 254421, 261825, 268451, 269205, 269206.

Section I.—Aryl Derivatives containing One Aromatic Group attached to One Antimony Atom.

1. *Primary Phenylantimony Compounds.*

The starting point in the preparation of these primary antimonials is the tertiary stibine, which is heated with antimony chloride and xylene in a sealed tube for 48 hours at 240°.

By fractionating the products of this reaction Hasenbäumer[1] isolated phenylstibine dichloride, whereas Michaelis and Günther[2] obtained from this process only diphenylstibine chloride in small yield. Morgan and Micklethwait[3] showed that both compounds are produced so that this method serves as a starting point for both primary and secondary aromatic antimonials. The simultaneous production of these two compounds has more recently been confirmed by Grüttner and Wiernik.[4]

The best yield of phenylstibine dichloride is obtained when triphenylstibine (30 grams) and antimony trichloride (40 grams) are heated with xylene (18 c.c.) for 75 hours at 240–245°, when about 70 per cent. of the organic product consists of the dichloride, the remainder consisting of diphenylstibine chloride. A larger excess of antimony chloride does not increase the yield of the phenyl compound. The reactions occurring are to be represented as follows, the former being the more rapid and effective.

i. $Sb(C_6H_5)_3 + SbCl_3 = Sb(C_6H_5)Cl_2 + Sb(C_6H_5)_2Cl$.

ii. $Sb(C_6H_5)_2Cl + SbCl_3 = 2Sb(C_6H_5)Cl_2$.

Phenylstibine dichloride,[5] $C_6H_5 \cdot SbCl_2$, colourless crystals ; m.p. 58° ; b.p. 290°, is very soluble in cold alcohol, benzene, ether, or light petroleum. In the cold it has only a faint odour, but on warming this becomes very pungent and attacks the mucous membrane

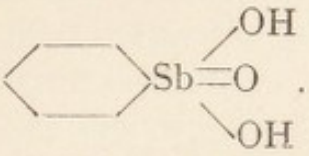
Phenyldimethylstibine, $C_6H_5 \cdot Sb(CH_3)_2$, colourless, mobile liquid ; b.p. 112°/16–18 mm. in CO_2 ; D_4^{20} 1·4490, $n_D^{19\cdot5}$ 1·5983, is prepared by the Grignard reaction with magnesium methyl bromide in ethereal solution on crude phenylstibine dichloride. It forms *methiodide* and *ethiodide,* colourless needles, decomposing at 235° and 150°, and dihalogen compounds, *dichloride, dibromide,* and *di-iodide,* m.p.'s 128°, 112–113°, 98·5–99°.

[1] *Ber.*, 1898, **31**, 2910.
[2] *Ber.*, 1911, **44**, 2316.
[3] *Chem. Soc. Trans.*, 1911, **99**, 2288.
[4] *Ber.*, 1915, **48**, 1749, 1759.
[5] Hasenbäumer, *Ber.*, 1898, **31**, 2912.

Phenyldiethylstibine, $C_6H_5 \cdot Sb(C_2H_5)_2$, colourless liquid; b.p. 128°/16–18 mm. in CO_2, D_4^{24} 1·3487, $n_D^{21\cdot8}$ 1·5903, fuming and sometimes taking fire in air, prepared as above by the Grignard reaction. *Methiodide* formed less readily than in the preceding example; no ethiodide; *dichloride* and *dibromide* both oily; *di-iodide* (m.p. 88·5–89°).[1]

Phenylstibine oxide, $C_6H_5 \cdot SbO$, crystalline, m.p. 150°, disagreeable odour, prepared by the action of aqueous sodium carbonate on the foregoing chloride.

Phenylstibine sulphide, $C_6H_5 \cdot SbS$, crystalline, m.p. 65°, produced by dissolving the oxide or chloride in alcoholic ammonia and passing in sulphuretted hydrogen, the liquid being then acidified.

Phenylstibinic Acid, 

—*Phenylstibinic chloride*, $C_6H_5 \cdot SbCl_4$, hygroscopic, crystalline mass, obtained by saturating with chlorine an ethereal solution of phenylstibine chloride. Hydrolysed by water into *phenylstibinic acid*, $C_6H_5 \cdot SbO(OH)_2$, white, amorphous powder, decomposing above 200°, insoluble in water, but dissolving in ammonia, caustic and carbonated alkalis, and in glacial acetic acid. The alkali salts are easily soluble, crystalline substances; the ammonium salt is somewhat unstable; the barium salt,

$$[C_6H_5 \cdot SbO(OH) \cdot O]_2Ba,$$

is a white precipitate.

Salts of the Arylstibinic Acids with Neutral Reaction.

The alkali salts of the arylstibinic acids were described by Hasenbäumer (*loc. cit.*) as easily hydrolysable substances; the ammonium salts he assumed to be incapable of existence. This matter was examined further by the Chemische Fabrik von Heyden,[2] which succeeded in preparing soluble neutral alkali salts and also the corresponding ammonium compounds.

The alkali salts having the composition $\bar{A}r \cdot SbO(OH) \cdot OM$ or $\bar{A}rSbO(OM)_2$ give an alkaline reaction in aqueous solution, but stable soluble salts with neutral reaction can be prepared containing less than one molecular proportion of alkali to a

[1] Grüttner and Wiernik, *Ber.*, 1915, **48**, 1759.
[2] D.R.-P., 267083.

molecular proportion of stibinic acid. A similar sparingly soluble ammonium salt can be obtained by heating an ammoniacal solution of the aromatic stibinic acid.

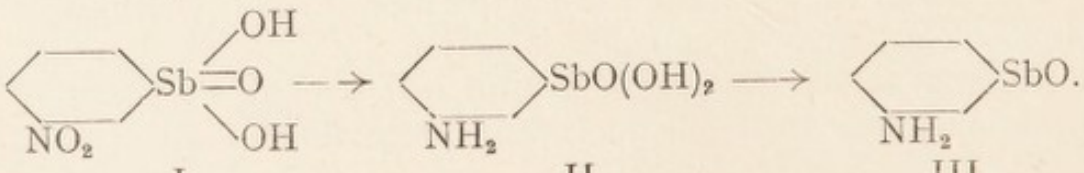
Phenylstibinic acid (2·5 grams) suspended in 25 c.c. of water is dissolved by the addition of *N*-sodium hydroxide (10 c.c.). The alkali salt is precipitated from the filtered solution on the addition of 20 per cent. sodium hydroxide and washed with salt solution until a neutral reaction is obtained. The residue dissolves to a stable neutral solution. A similar quantity of phenylstibinic acid is dissolved in 30 c.c. of *N*-sodium hydroxide and the excess of alkali neutralised with *N*-sulphuric acid (litmus indicator). The turbid solution is heated on the water-bath, filtered, and the filtrate evaporated to dryness. The residue is freed from sodium sulphate by extraction with methyl alcohol. This alcoholic extract when evaporated to dryness gives a soluble neutral salt containing one atomic proportion of sodium to three molecular proportions of phenylstibinic acid.

Acetyl-p-*aminophenylstibinic acid* (*v.* p. 315) gives a soluble neutral sodium salt containing the same atomic proportion of sodium obtained by dissolving the free acid in aqueous sodium hydroxide, saturating the solution with carbon dioxide, filtering, neutralising with acetic acid, filtering again, and precipitating the alkali salt with sodium sulphate. The alkali salt, freed from inorganic impurities by dissolving in methyl alcohol, is obtained by concentrating the alcoholic extract. The product contains water of crystallisation.

A soluble neutral salt of *p*-aminophenylstibinic acid is prepared by dissolving the acid in excess of aqueous sodium hydroxide, neutralising with acetic acid, and precipitating the product with alcohol.

The existence of these neutral soluble alkali salts containing less than one atomic proportion of alkali metal to each molecular proportion of acid has been observed in the case of the arylstibinic acids but not in that of the arylphosphinic or arylarsinic acids. These alkali salts are suitable for therapeutic injections.

m-*Nitrophenylstibinic acid* (I.).



I. II. III.

—Phenylstibinic acid is nitrated with a mixture of 12 parts of nitric acid (D 1·5) and 4 parts of concentrated sulphuric acid, the temperature ranging from 40° to 55°. The solution poured on to ice gives a yellow precipitate consisting in part of basic nitrates. This product is dissolved in *N*-sodium hydroxide and the nitro-acid precipitated with acetic or hydrochloric acid. The compound, which is not very crystallisable, has no melting point below 290°. When heated with phosphorus pentabromide and chloroform at 100–110° it is decomposed, yielding 1-bromo-3-nitrobenzene (70 per cent. of theory).[1]

When reduced with zinc and ammonium chloride in alcohol and with stannous chloride *m*-nitrophenylstibinic acid yields successively *m*-aminophenylstibinic acid (II.) and *m*-aminophenylstibine oxide (III.). The hydrochloride of the former amine has the following composition:

$$HCl,NH_2\cdot C_6H_4\cdot SbOCl_2.$$[2]

2. *Tolyl Series.*

p-*Tolylstibine chloride*,[3] $CH_3\cdot C_6H_5\cdot SbCl_2$, crystalline, m.p. 93·5°, b.p. above 360°, is obtained by heating tri-*p*-tolylstibine (10 grams) and antimony trichloride (12 grams) with xylene at 245° for 48 hours. It is very soluble in the ordinary organic solvents and is best obtained crystalline by distillation.

This dichloride forms the oxide, sulphide, and tetrachloride, the last of these hydrolysing readily to p-*tolylstibinic acid*,

$$CH_3\cdot C_6H_4\cdot SbO(OH)_2,$$

a white, amorphous powder.

Section II.—Diarylantimony Derivatives.

1. *Phenyl Series.*

Diphenylstibine chloride, $(C_6H_5)_2SbCl$, is the by-product obtained by heating together at 240–250° triphenylstibine and antimony trichloride in the presence of dry xylene. The oily product, after drying and removing the xylene, is fractionated

[1] Morgan and Micklethwait, *Chem. Soc. Trans.*, 1911, **99**, 2296; *cf.* Fabr. Heyden, D.R.-P., 287709.

[2] Morgan and Micklethwait, *Chem. Soc. Proc.*, 1912, **28**, 20; *cf.* P. May, *ibid.*, p. 5, and *Chem. Soc. Trans.*, 1912, **101**, 1033.

[3] Hasenbäumer, *Ber.*, 1898, **31**, 2914.

under 5–7 mm. pressure into two portions, the lower boiling at 160–200° and the higher at 200–240°. The higher fraction solidifies on cooling and gives colourless crystals of diphenylstibine chloride (m.p. 68°). When treated with chlorine in dry ether this substance yields diphenylstibine trichloride, which, after crystallisation from hydrochloric acid, melts at 176°.[1]

Diphenylmethylstibine,[2] $(C_6H_5)_2Sb{\cdot}CH_3$, colourless, viscous oil, b.p. 174–177°/16–18 mm. in CO_2; D_4^{20} 1·2134; n_D^{20} 1·6021, oxidising in air but not fuming. Prepared from crude diphenylstibine chloride and magnesium methyl bromide. *Chloride*, $(C_6H_5)_2Sb(CH_3)Cl_2$, colourless prisms, m.p. 144°; *bromide*, m.p. 148°.

Diphenylethylstibine,[3] $(C_6H_5)_2Sb{\cdot}C_2H_5$, colourless, viscous oil, b.p. 190–192°/16–18 mm. in CO_2; $D_4^{19·5}$ 1·3541, $n_D^{20·5}$ 1·6309; crystalline *dichloride* and *dibromide*, m.p.'s 163–164° and 158°.

Diphenylstibine trichloride,[4] $(C_6H_5)_2SbCl_3$, lustrous, colourless needles containing $1H_2O$, m.p. 180°. This substance is a by-product in the interaction of antimony trichloride (48 grams), chlorobenzene (48 grams), and sodium (20 grams). The two chloro-compounds are dissolved in 150–200 c.c. of dry benzene and added to the sodium previously granulated by melting and shaking under boiling toluene. If the reaction does not occur spontaneously, it is started by cautiously warming the mixture. After 24 hours the filtered solution is evaporated, the oily residue mixed with alcoholic hydrochloric acid, and dissolved in the minimum amount of boiling alcohol. On cooling the greater part of the triphenylstibine dichloride separates, and the mother liquor, concentrated, yields impure diphenylstibine trichloride, which is purified by extraction with hot dilute hydrochloric acid, leaving undissolved triphenylstibine dichloride; the yield of diphenylstibine trichloride is about 11 to 16 per cent. of the weight of antimony trichloride. On treatment with alcoholic silver nitrate the trichloride yields a basic nitrate, crystallising in lustrous, colourless needles, decomposing at 206°.[5]

Diphenylstibine trichloride is a by-product of the interaction of antimony trichloride and mercury diphenyl in xylene at 130°, the main product being triphenylstibine dichloride.[6]

[1] Morgan and Micklethwait, *Chem. Soc. Trans.*, 1911, **99**, 2295.

[2] Grüttner and Wiernik, *Ber.*, 1915, **48**, 1759; Lettermann, *Inaug. Diss.*, Rostock, 1911. [3] *Ibid.*

[4] Michaelis and Reese, *Annalen*, 1886, **233**, 58; Morgan and Micklethwait, *Chem. Soc. Trans.*, 1911, **99**, 2293. [5] *Ibid.*

[6] Hasenbäumer, *Ber.*, 1898, **31**, 2911.

Diphenylstibinic acid, $(C_6H_5)_2SbO{\cdot}OH$, white powder decomposing above 250°. Its behaviour towards alkalis depends on the mode of preparation from diphenylstibine trichloride.

1. When dissolved in alcohol and treated with dilute ammonia, the trichloride gives a granular precipitate of diphenylstibinic acid insoluble in ammonia or sodium carbonate.[1]

2. The trichloride dissolved in aqueous sodium hydroxide and the solution acidified with acetic acid gives a diphenylstibinic acid readily soluble in ammonia or sodium carbonate. The two preparations are probably differently hydrated forms of diphenylstibinic acid, the less soluble form being possibly the meta-compound, $(C_6H_5)_2SbO{\cdot}OH$, whilst the more soluble product may be an ortho- or a pyro-compound.[2]

With hydrochloric acid, diphenylstibinic acid is reconverted into diphenylstibinic chloride.

Di-m-*nitrodiphenylstibinic acid* (I.).

I. II.

—This dinitro compound is obtainable by the nitration of diphenylstibinic acid, but it is preferably prepared by nitrating the basic nitrate of this acid, produced by treating diphenylstibine trichloride in alcoholic solution with silver nitrate. This basic nitrate, crystallising in clusters of lustrous, colourless needles (decomposing at 200°), is added to nitric acid (D 1·5) mixed with 4 volumes of concentrated sulphuric acid, the temperature being maintained at 40° and then raised to 55°. The clear solution poured on to ice gives a pale yellow product, which is dissolved in *N*-sodium hydroxide, reprecipitated by acetic or hydrochloric acid, and crystallised from glacial acetic acid. The dinitrostibinic acid separates in radiating clusters of flattened needles, decomposing indefinitely at 212°. It is insoluble in water, alcohol, or benzene; its alkali salts are soluble to an orange-yellow solution. The other metallic salts are very sparingly soluble. When heated at 130–160° with phosphorus pentabromide alone or with bromine, this dinitrostibinic acid loses antimony and 1-bromo-3-nitrobenzene is produced.[3]

Di-m-*aminodiphenylhydroxystibine* (II.), a colourless, caseous

[1] Michaelis and Reese, *Annalen*, 1886, **233**, 59.

[2] Morgan and Micklethwait, *Chem. Soc. Trans.*, 1911, **99**, 2296.

[3] *Ibid.*, 2294.

mass melting indefinitely at 76–80°, is precipitated from acid solution by ammonia and turns brown on exposure to air. It is produced from the preceding compound by reduction with tin and hydrochloric acid or zinc and ammonium chloride. The *hydrochloride*, $ClSb(C_6H_4{\cdot}NH_2)_2,2HCl$, crystallises from acidified water in very soluble, colourless needles. This base and its salts have an irritating action on the mucous membrane of the throat and nose which is even more intense than that noticed with tri-*m*-aminophenylstibine and its hydrochloride.[1]

Section III.—Triarylantimony Derivatives.

1. *Phenyl Series.*

Triphenylstibine, $(C_6H_5)_3Sb$, colourless, triclinic plates, m.p. 48° (51°), b.p. 231–232°/16–18 mm., above 360°/760 mm. (with partial decomposition); D 1·4998/12°.[2]

Preparation—1. Sodium method.[3] Redistilled antimony trichloride (40 grams) and chlorobenzene (40 grams) are dissolved in about 4 volumes of dry benzene and treated with sodium (50 grams) in a reflux apparatus. A vigorous reaction sets in, after which the mixture is heated to boiling and filtered from unattacked sodium, the filtrate being then distilled to remove benzene. The residue, which speedily solidifies, consists mainly of triphenylstibine together with diphenylstibine trichloride and triphenylstibine dichloride and some triphenylstibine oxide produced by the action of moisture. The triphenylstibine is best purified through its dichloride. The mixture of antimony compounds is treated with alcoholic hydrochloric acid in which diphenylstibine trichloride dissolves. The residue, freed from alcohol, is treated with sufficient light petroleum to dissolve the stibine, and chlorine is introduced so long as a precipitate is produced. The triphenylstibine dichloride is recrystallised from alcohol dissolved in alcoholic ammonia and reduced with a rapid stream of sulphuretted hydrogen; heat is generated, and the liquid becomes dark red from the formation of ammonium polysulphide. On cooling, triphenylstibine separates and is recrystallised from light petroleum.

2. Grignard reaction. A 10 per cent. benzene solution containing 18 grams of antimony trichloride is added slowly to the

[1] Morgan and Micklethwait, *Chem. Soc. Proc.*, 1912, **28**, 20.

[2] Ghira, *Gazzetta*, 1894, **24**, [i], 317.

[3] Michaelis and Reese, *Annalen*, 1886, **233**, 45.

Grignard reagent prepared from 50 grams of bromobenzene and 7·2 grams of powdered magnesium suspended in dry ether; the mixture is then boiled for six hours and distilled in steam to remove benzene and bromobenzene. The fusible organic residue is freed from diphenyl by extraction with small quantities of cold alcohol, and the undissolved triphenylstibine crystallised from hot alcohol. Yield nearly quantitative.[1]

The condensation can be carried out entirely in ethereal solution, but the yield is less.[2]

Triphenylstibine can be purified through its sulphide (p. 306). One hundred grams of triphenylstibine sulphide dissolved in 450 c.c. of absolute alcohol and 50 c.c. of benzene are heated on the water-bath with finely-divided copper ("Naturkupfer C") or with iron powder; the filtered solution yields from 80 to 90 per cent. of pure triphenylstibine (m.p. 51°).[3]

Unlike triethylstibine, this aromatic stibine does not decompose strong hydrochloric acid; it removes chlorine from cupric and ferric chlorides, however, becoming triphenylstibine dichloride and forming the lower chlorides of the metals. It differs from triphenyl-phosphine and -arsine in not combining with mercuric chloride. On the contrary, it is decomposed by this salt, yielding phenyl-mercuric chloride and antimony trichloride. With chlorine and bromine it combines additively to form triphenylstibine dichloride and dibromide. Triphenylstibine dissolves in fuming nitric acid with a vigorous reaction, and triphenylstibine nitrate crystallises out on cooling.

Methyl iodide decomposes triphenylstibine, giving trimethylstibine di-iodide, iodobenzene, and ethane. Zinc dimethyl decomposes the stibine, giving toluene, antimony, and zinc.

When heated with arsenic, antimony is eliminated with the production of triphenylarsine.

Triphenylstibine dichloride, $(C_6H_5)_3SbCl_2$, colourless needles, m.p. 143°, a by-product of the interaction between antimony chloride, chlorobenzene, and sodium, is also prepared by chlorinating triphenylstibine or by the interaction of antimony trichloride and mercury diphenyl in dry xylene at 130°.[4] It is not affected by water, differing in this respect from the easily hydrolysed

[1] Morgan and Micklethwait, *Chem. Soc. Trans.*, 1911, **99**, 2290.

[2] Pfeiffer, *Ber.*, 1904, **37**, 4621; *cf.* Carré, *Bull. Soc. chim.*, 1913, [iv], **13**, 102.

[3] Kaufmann, *Ber.*, 1908, **41**, 2762; D.R.-P., 240316.

[4] Hasenbäumer, *Ber.*, 1898, **31**, 2911.

triphenylarsine dichloride. It is slowly attacked by aqueous alkalis, and more readily hydrolysed by alcoholic alkalis.

Triphenylstibine dibromide,[1] $(C_6H_5)_3SbBr_2$, colourless, flattened needles from glacial acetic acid, m.p. 216°; it is sparingly soluble in the volatile organic solvents.

Triphenylstibine di-iodide, $(C_6H_5)_3SbI_2$, lustrous, yellowish-white plates from petroleum-benzene, m.p. 153°.

Triphenylstibine dihydroxide, $(C_6H_5)_3Sb(OH)_2$, white powder, m.p. 212°, insoluble in ether or petroleum, dissolving readily in alcohol or glacial acetic acid; prepared by adding triphenylstibine dibromide to warm alcoholic potash.

Triphenylstibine dinitrate,[2] $(C_6H_5)_3Sb(O{\cdot}NO_2)_2$, colourless leaflets from nitric acid, insoluble in water, m.p. 156° (with decomposition).

Triphenylstibine hydroxynitrate,[3] $(C_6H_5)_3Sb(OH){\cdot}NO_3$, lustrous, colourless leaflets from boiling water, softening at 220°, m.p. 224–225°; prepared by treating triphenylstibine dichloride with alcoholic silver nitrate. This hydroxynitrate is reduced completely into triphenylstibine and ammonia on treatment with Devarda's alloy in presence of alkali.

Triphenylstibine hydroxysulphate, $[(C_6H_5)_3Sb(OH)]_2{\cdot}SO_4$, m.p. 252°, colourless, nodular crystals, obtained by using aqueous silver sulphate in the foregoing preparation.

Triphenylstibine hydroxychloride, $(C_6H_5)_3Sb(OH){\cdot}Cl$, transparent, colourless spicules from benzene, m.p. 218°, produced by adding an alcoholic solution of triphenylstibine dichloride to a large volume of boiling water, and evaporating the solution to the crystallising point. This compound and the preceding hydroxysulphate when sulphonated with about 10 parts of fuming sulphuric acid (20 per cent. SO_3) at 100° yield a *trisulphonic* acid which, when isolated from its barium salt by sulphuric acid, is obtained on evaporation as a brittle, yellow mass resembling amber and approximating in composition to the formula

$$(HO)_2Sb(C_6H_4{\cdot}SO_3H)_3,3H_2O.$$[4]

Triphenylstibine sulphide, "Sulphoform," $(C_6H_5)_3SbS$, white needles, m.p. 119–120°, is obtained by passing sulphuretted hydrogen cautiously into a solution of triphenylstibine chloride or bromide in alcoholic ammonia. When a faint yellow coloration is produced, which disappears on shaking, the sulphide separ-

[1] Michaelis and Reese, *Annalen*, 1886, **233**, 49, 50. [2] *Ibid.*

[3] Morgan, Micklethwait, and Whitby, *Chem. Soc. Trans.*, 1910, **97**, 36.

[4] Morgan and Micklethwait, *ibid.*, 1911, **99**, 2297.

ates in colourless crystals (yield 80 per cent.). For triphenylstibine chloride the solution needs to be boiling, but for the bromide the reaction takes place at the ordinary temperature. Prolonged treatment with hydrogen sulphide leads to an intense yellowish-red solution from which only triphenylstibine and sulphur can be obtained. The sulphide dissolves readily in benzene, chloroform, or glacial acetic acid, less easily in alcohol, and is very slightly soluble in ether. It is insoluble in alcoholic sulphuretted hydrogen or ammonia, but in alcoholic ammonium sulphide it dissolves to a red solution which on prolonged heating gives sulphur and triphenylstibine. This sulphide, introduced into pharmacy as "Sulphoform," has a curative action in eczema, seborrhœa, and similar skin troubles. Triphenylstibine sulphide can be used as a convenient source of triphenylstibine, for when dissolved in alcohol-benzene and boiled for one to four hours in a reflux apparatus with "Naturkupfer C" or with iron powder and a little ferric chloride the sulphur is removed by the metal, and the yield of triphenylstibine is 80–90 per cent.[1]

Tri-m-*nitrotriphenylstibinic acid* (I.),

I. II.

—This trinitro-acid is produced by the nitration of triphenylstibine hydroxynitrate (p. 306), 3 grams of this nitrate being added to 25 c.c. of nitric acid (D 1·5) and 6 c.c. of concentrated sulphuric acid maintained at 40° and afterwards at 55°. After two hours the cooled solution is poured on to ice, the precipitated nitro-compound dissolved in *N*-sodium hydroxide, reprecipitated by acid, and crystallised from glacial acetic acid. The trinitro-compound separates in pale yellow leaflets, decomposing indefinitely from 170° to 191°. Its alkali salts are soluble to brownish-orange solutions; the other metallic salts dissolve only sparingly in water. Dry sodium tri-*m*-nitrotriphenylstibinate, heated with phosphorus pentabromide, bromine, and triethylamine in chloroform solution at 130–150°, yields 1-bromo-3-nitrobenzene.

Tri-m-*aminotriphenylstibine* (II.), colourless crystals from glacial acetic acid, decomposing indefinitely at 80°, sparingly

[1] Kaufmann, D.R.-P., 223694, 240316; *Ber.*, 1908, **41**, 2762; Michaelis and Reese, *Annalen*, 1886, **233**, 44.

soluble in water or the volatile organic solvents, is prepared by adding the preceding trinitro-compound to a suspension of zinc dust in alcohol containing ammonium chloride. After half an hour the solution is filtered into ice-cold water. The precipitated base dissolved in dilute hydrochloric acid is set free by ammonia. The crystalline *hydrochloride*, $Sb(C_6H_4{\cdot}NH_2,HCl)_3$, is readily soluble in alcohol or water, but is precipitated from the latter by strong hydrochloric acid.

The base and its salts, either in the solid state or in hot solution, have a curious pungent odour and cause violent fits of sneezing. The hydrochloride has a certain degree of trypanocidal power, but when injected subcutaneously it is very irritant, causing ulceration at the point of injection.[1]

Tri-p-*anisylstibine*,[2] $Sb(C_6H_4{\cdot}OCH_3)_3$, well-defined, colourless rhombohedra, m.p. 180·5–181°, dissolving readily in chloroform, benzene, or toluene, but less soluble in alcohol, ether, ethyl acetate, glacial acetic acid, or carbon bisulphide, is prepared by the following methods :—

1. Sodium antimonide (150 grams), obtained by adding 40 grams of sodium gradually to antimony (360 grams) heated to redness in a Hessian crucible, is powdered and treated with *p*-bromoanisole (100 grams) in a reflux apparatus heated for one hour at 217° and then 24 hours at 150–160°. The warm product, extracted at 70° with a mixture of benzene and chloroform, is filtered from finely-divided antimony, and distilled first alone and then in steam. The residue extracted with chloroform yields a solution from which the stibine crystallises on adding benzene. About 10 per cent. of this product is obtained, calculated on the weight of *p*-bromoanisole. This method can be employed for other aromatic stibines, but it offers no advantages over the sodium method.

2. Sodium (thrice the calculated quantity) is added in thin slices to freshly distilled antimony trichloride (80·8 grams) and *p*-bromoanisole (200 grams) in 800 c.c. of benzene. A vigorous reaction sets in, and after 24 hours the mixture is heated to boiling with addition of 10–15 grams of sodium. The benzene solution is distilled in steam to remove *p*-bromoanisole. The residue dissolved in benzene-chloroform yields tri-*p*-anisylstibine, 68 grams being obtained from 200 grams of *p*-bromoanisole. This stibine is decomposed by boiling

[1] Morgan and Micklethwait, *Chem. Soc. Trans.*, 1911, **99**, 2292.

[2] Löloff, *Ber.*, 1897, **30**, 2834.

concentrated hydrochloric acid into anisole and antimony trichloride.

The *mercurichloride*, $(CH_3{\cdot}O{\cdot}C_6H_4)_3Sb,HgCl_2$, white, crystalline precipitate from alcohol, sintering at 235–240°, decomposing at 285°. Prolonged boiling with alcohol gives rise to *p*-anisylmercuric chloride, $CH_3{\cdot}O{\cdot}C_6H_4{\cdot}HgCl$ (m.p. 239°).

Tri-p-*anisylstibine dichloride*, $(CH_3{\cdot}O{\cdot}C_6H_4)_3SbCl_2$, is best prepared by adding alcoholic cupric chloride to a chloroform-alcohol solution of tri-*p*-anisylstibine so long as cuprous chloride is precipitated. The filtrate yields the dichloride, which separates from chloroform-petroleum in white crystals, m.p. 116–117°. The *dibromide*, a white, crystalline product, m.p. 123°, is obtained by mixing bromine and the stibine in chloroform. This compound and the chloride combine with benzene to form derivatives $(CH_3{\cdot}O{\cdot}C_6H_4)_3SbX_2,C_6H_6$, which lose benzene at 81–83°.

Tri-p-*anisylstibine di-iodide*, yellow leaflets, m.p. 116°, produced from its generators in dry chloroform ; the *dinitrate* results from the interaction of the dibromide and silver nitrate in alcoholic solution ; it decomposes at 217°.

Tri-p-*anisylstibine oxide*, $(CH_3{\cdot}O{\cdot}C_6H_4)_3SbO$, crystalline crusts from alcohol, m.p. 191°, produced by the action of alkalis on the foregoing dihalides, preferably the bromide.

In this series the passage from tertiary to secondary aromatic antimonials is effected in the following manner by means of chlorine.

Tetrachlorodi-p-*anisylstibine trichloride*,

$$(CH_3{\cdot}O{\cdot}C_6H_2Cl_2)_2SbCl_3,$$

colourless crystals, m.p. 184°, is soluble in the organic media excepting petroleum. It is produced by passing chlorine into tri-*p*-anisylstibine (1 part) in 15 parts of dry chloroform. The solution is allowed to evaporate in a dry atmosphere and the residue is taken up with benzene, when the trichloride separates on concentration. The mother liquor on treatment with light petroleum yields a by-product, trichloro-*p*-anisole (m.p. 60–61°). These compounds are produced by the chlorination of the three *p*-anisyl groups, followed by the elimination of one of these in the form of trichloro-*p*-anisole.

Tetrachlorodi-p-*anisylstibine acid*, $(CH_3{\cdot}O{\cdot}C_6H_2Cl_2)_2SbO{\cdot}OH$, a voluminous, white precipitate, m.p. 228–229°, insoluble in the ordinary organic media, soluble in dilute caustic soda to the

sodium salt and in alcoholic hydrochloric acid as the trichloride, is produced by treating the preceding trichloride dissolved in ether with aqueous alcohol.

Tri-p-*phenetylstibine*, $(C_2H_5{\cdot}O{\cdot}C_6H_4)_3Sb$, warty aggregates of acicular prisms, m.p. 82–83°, is obtained by substituting *p*-bromophenetole for *p*-bromoanisole in the preparation of tri-*p*-anisylstibine (p. 308), but, being more soluble than the latter in all ordinary organic media, the yield is less. This stibine is hydrolysed into phenetole and antimony trichloride by hot concentrated hydrochloric acid. The *mercurichloride*, softening at 205–210° and decomposing at 225°, the *dichloride*, m.p. 84°, the *dibromide*, a felted mass of needles, m.p. 110–111°, the *di-iodide* prismatic, crystals, m.p. 121–122°, and the *dinitrate*, crystalline crusts, m.p. 151–152°, decomposing at 170°, are all prepared in accordance with methods already described above for the tri-*p*-anisyl compounds.

2. *Tolyl Series.*

$$3CH_3{\cdot}C_6H_4Br + SbBr_3 + 6Na = (CH_3{\cdot}C_6H_4)_3Sb + 6NaBr.$$

Tri-o-*tolylstibine*,[1] $(CH_3{\cdot}C_6H_4)_3Sb$, colourless, transparent, lustrous crystals from alcohol, m.p. 79–80°, prepared by adding sodium (50 grams) to antimony tribromide (36 grams) and *o*-bromotoluene (51 grams) dissolved in about 200–300 c.c. of benzene. The reaction proceeds spontaneously, and after 4–5 days the benzene is removed and the residue extracted with light petroleum. If *o*-bromotoluene[2] containing a small amount of *p*-bromotoluene is employed, a small amount of di-*o*-tolyl-*p*-tolylstibine separates in tufts of colourless, acicular crystals on concentrating the petroleum extract. The tri-*o*-tolyl-isomeride remains in the mother liquor and is best obtained through its dibromide produced by adding an ethereal solution of bromine. Fractionation of this crude dibromide gives two compounds, one melting at 185–186° (more soluble), and a less soluble isomeride (m.p. 209°); the latter when reduced with sulphuretted hydrogen in alcoholic ammonia yields pure tri-*o*-tolylstibine, which is very soluble in chloroform, benzene, or ether, and less so in alcohol.

The *mercurichloride*, $(CH_3{\cdot}C_6H_4)_3Sb,HgCl_2$, silky leaflets,

[1] Michaelis and Genzken, *Annalen*, 1887, **242**, 176.

[2] Longuinine, *Ber.*, 1871, **4**, 516.

softening at 125°, decomposing at 135°, obtained from alcoholic solutions of its generators, is a very stable substance, and does not yield *o*-tolylmercurichloride even at 250°.

Tri-o-*tolylstibine dichloride*, $(CH_3 \cdot C_6H_4)_3SbCl_2$, colourless needles, m.p. 178–179°, is made by passing chlorine into an ethereal solution of the stibine; the *dibromide*, colourless, lustrous crystals, m.p. 209–210°, and the *di-iodide*, yellowish-white crystals, m.p. 174–175°, are similarly prepared.

Tri-o-*tolylstibine oxide*, $(CH_3 \cdot C_6H_4)_3SbO$, white, amorphous powder, m.p. about 220°, is prepared by the action of alcoholic potash on the dichloride, the latter being regenerated on treating the oxide with hydrochloric acid.

Di-o-*tolyl*-p-*tolylstibine*, $(CH_3 \cdot C_6H_4)_3Sb$, acicular crystals, m.p. 112–113°, the by-product found in the tri-*o*-tolylstibine condensation when *p*-bromotoluene is present, yields a *dibromide*, m.p. 185–186°, and a *mercurichloride*, separating from alcohol in colourless needles, m.p. 164–165°.

Tri-m-*tolylstibine*,[1] $(CH_3 \cdot C_6H_4)_3Sb$, fan-shaped clusters of colourless crystals from alcohol, m.p. 67–68° (D 1·3957/15·7°), is prepared by condensing antimony bromide and *m*-bromotoluene[2] with sodium in benzene as in the case of the ortho-isomeride, the yield being 65 per cent. of the calculated amount. The *mercurichloride*, $(CH_3 \cdot C_6H_4)_3Sb,HgCl_2$, softens at 100° and decomposes at 140°. When boiled with alcohol it is decomposed, yielding *m*-tolylmercuric chloride.

Tri-m-*tolylstibine dichloride*, $(CH_3 \cdot C_6H_4)_3SbCl_2$, colourless needles, m.p. 137–138°, much more soluble in ether than its *o*- and *p*-isomerides, is prepared by direct addition of its generators; the *dibromide* and *di-iodide* form colourless crystals melting respectively at 113° and 138–139°.

Tri-m-*tolylstibine oxide*, yellowish-white, amorphous powder, softening at 186° and becoming transparent at 210°, is obtained by the action of alcoholic potash on the bromide; dissolved in glacial acetic acid, it yields a *basic acetate*, $(C_7H_7)_3Sb(OH)\bar{A}c$.

Tri-m-*tolylstibine sulphide*, lustrous, acicular crystals, m.p. 162–163°, readily obtained from the dichloride by the action of alcoholic ammonium sulphide.

Tri-p-*tolylstibine*,[3] $(CH_3 \cdot C_6H_4)_3Sb$, well-defined, colourless,

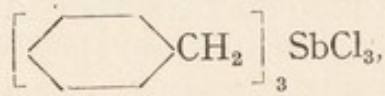
[1] Michaelis and Genzken, *loc. cit.*, p. 184.
[2] Wroblewski, *Annalen*, 1873, **168**, 153.
[3] Michaelis and Genzken, *loc. cit.*, p. 167.

transparent rhombohedra from ether, m.p. 127–128°, D 1·35448/15·6°, is prepared by adding sodium (50 grams, thrice the calculated amount) to antimony tribromide (36 grams) and *p*-bromotoluene (51 grams) in about 4 volumes of dry benzene. After two to three days the filtered solution is concentrated, when the crude product crystallises (yield 63 per cent.). Unlike triphenylstibine, which is decomposed by mercuric chloride into antimony trichloride and phenylmercuric chloride, tri-*p*-tolylstibine forms a *mercurichloride*, $(CH_3 \cdot C_6H_4)_3Sb,HgCl_2$, a white precipitate from alcoholic solutions of its generators; it crystallises from ether in nacreous needles and leaflets, softening at 165°, decomposing at 175°. When boiled with alcohol, this additive compound decomposes, yielding *p*-tolylmercuric chloride. The tri-*p*-tolylstibine halides are produced by combining their generators in ethereal solutions; they form colourless, lustrous crystals, the *dichloride*, *dibromide*, and *di-iodide* melting respectively at 156–157°, 233–234°, and 182–183°; a *hydroxy-iodide* formed by partial hydrolysis of the di-iodide melts at 218–219°.

Tri-p-*tolylstibine oxide*, $(CH_3 \cdot C_6H_4)_3SbO$, white, amorphous powder, m.p. 220°, produced by the action of alcoholic potash on the preceding dihalides, is soluble in the ordinary organic media, but insoluble in water. When dissolved in glacial acetic acid it yields a crystalline *basic acetate*, $(C_7H_7)_3Sb(OH) \cdot \bar{A}c$, m.p. 168–169°.

Tri-*p*-tolylstibine [1] is readily obtained by the Grignard reaction; *p*-bromotoluene (20 grams), magnesium (3 grams), and antimony tribromide (14 grams) being employed in ethereal solution. The stibine separating from the ethereal solution is crystallised from methyl alcohol.

Tribenzylstibine dichloride,[2]



m.p. 105–108°, lustrous, colourless crystals from alcohol, prepared through the Grignard reaction with benzyl chloride and antimony trichloride. When hydrolysed by weak alkalis, the dichloride yields *tribenzylstibine oxide*, $(C_6H_5CH_2)_3SbO$, which decomposes indefinitely at 240°.

[1] Pfeiffer, *Ber.*, 1904, **37**, 4621.

[2] Morgan and Micklethwait, *Chem. Soc. Proc.*, 1912, **28**, 69.

Part II

The Diazo-synthesis of Arylantimony Derivatives.

Section IV.—Aromatic Stibinic Acids.

The preparation of aromatic stibinic acids was greatly facilitated in 1911 when the Chemische Fabrik von Heyden made the remarkable discovery that the stibinic group could be introduced into aromatic nuclei through the agency of the diazo-reaction.[1]

Preparation of Phenylstibinic Acid from Aniline.—The base (1 gram-mol.) dissolved in 1 litre of water containing sulphuric acid (1·5 gram-mols.) is diazotised with a solution of sodium nitrite (1 mol.). A solution of 600 grams of sodium hydroxide in 3 litres of water is added to aqueous antimony trichloride prepared by dissolving antimony trioxide (0·5 mol.) in 764 grams of hydrochloric acid (D 1·123). The solution, which is rapidly cooled to 0° when a portion of the sodium antimonite separates, is then treated with the diazonium solution, the mixture being vigorously stirred. The evolution of nitrogen is favourably influenced by the preliminary addition of copper paste. After several hours the excess of sodium hydroxide is almost neutralised with dilute sulphuric acid, and phenylstibinic acid is precipitated from the filtrate by the addition of hydrochloric acid. The crude product is purified from antimony trioxide by dissolving 100 grams in 250 grams of hydrochloric acid (D 1·123) and by saturating the hot solution with dry ammonium chloride. *Phenylstibinic oxychloride* separates in well-defined leaflets and is washed with a saturated solution of ammonium chloride in hydrochloric acid and dissolved in a slight excess of dilute aqueous sodium carbonate. The purified phenylstibinic acid is precipitated by adding dilute hydrochloric acid to the slightly alkaline filtrate.

Phenylstibinic acid thus obtained through the diazo-reaction differs in a few particulars from the substance prepared by Hasenbäumer.[2]

[1] Fabr. Heyden, D.R.-P., 254421.

[2] *Ber.*, 1898, **31**, 2913; *Inaug. Dissert.*, Rostock, 1898.

Phenylstibinic Acid,

	Hasenbäumer's Acid.	*Chemische Fabrik von Heyden's Acid.*
Free Acid	Amorphous, decomposed at 200°.	Amorphous, remaining unchanged at 250°.
Combination with Ammonia	Dissolving in ammonia, but the combination decomposed on heating. No ammonium salt.	Dissolving in ammonia; crystalline ammonium salt isolated.
Combination with Alkalis	No well defined sodium salt.	Easily soluble in aqueous sodium hydroxide or carbonate. Sodium salt precipitated on addition of sodium chloride.

Phenylstibinic acid, as was to be expected, is entirely different in its properties from phenylphosphinic and phenylarsinic acids, the latter being well crystallisable compounds, easily soluble in water. These differences are similar to those between antimonic acid and phosphoric and arsenic acids.

Phenylstibinic acid can also be prepared through the diazotisation of aniline antimonious chloride. Sodium nitrite (71 grams) is added to a solution of aniline (93 grams) and antimony trichloride (220 grams) in hydrochloric acid (850 grams, D 1·123) and 1 litre of water. To the cooled solution are added, with vigorous stirring, 400 grams of sodium hydroxide dissolved in 10 litres of water. After a short time nitrogen is evolved, and phenylstibinic acid is extracted from the product as in the foregoing process.[1]

Antimony trichloride[2] forms, with diazonium chlorides, additive compounds which are only very sparingly soluble in the ordinary solvents. These products can be employed in the diazo-synthesis of aromatic derivatives of antimony.

p-*Hydroxyphenylstibinic Acid*, $HO{\cdot}C_6H_4{\cdot}SbO(OH)_2$.—The diazo-solution from 109 grams of *p*-aminophenol, 147 grams of sulphuric acid, 1 litre of water, and 71 grams of sodium nitrite is added, with stirring, to the sodium antimonite mixture obtained as in the foregoing condensation. The mixture is saturated with carbon dioxide and filtered repeatedly to remove antimony trioxide. The filtrate is saturated with sodium chloride and

[1] Fabr. Heyden, D.R.-P., 261825; addition to D.R.-P., 254421.

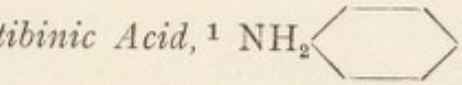
[2] P. May, *Chem. Soc. Trans.*, 1912, **101**, 1037.

p-hydroxyphenylstibinic acid precipitated by dilute sulphuric acid.

p-Hydroxyphenylstibinic acid, although sparingly soluble in cold, dissolves more readily in hot water or in aqueous methyl alcohol. It dissolves readily in ammonia solution, and the ammonium salt is precipitated on adding ammonium chloride.

Preparation of p-*Aminophenylstibinic Acid* (p-*Stibanilic Acid*).—This substance, the antimony analogue of *p*-arsanilic acid, is obtained by the following reactions. Acetyl-*p*-phenylenediamine (1 gram-mol.) added to well-cooled sulphuric acid (1·5 gram-mol.) in 1 litre of water is diazotised with sodium nitrite (1 mol.) and the solution added to the cooled mixture of sodium antimonite. The decomposition being completed, the solution is almost neutralised with dilute sulphuric acid and the remainder of the caustic alkali removed by saturating with carbon dioxide. The unaltered antimony trioxide is filtered off, the filtrate saturated with sodium chloride, and the precipitated sodium acetyl-*p*-aminophenylstibinate freed from sodium chloride by dissolving in methyl alcohol and concentrating the solution. This sodium salt is readily soluble in water to a neutral solution, but is less soluble in excess of alkali.

Acetyl-p-*aminophenylstibinic acid* is sparingly soluble in water or dilute acids; it dissolves readily in ammonia or in alkali hydroxides and carbonates. The acetyl group is readily removed by hydrolytic agents.

4-*Aminophenylstibinic Acid*,[1]  .

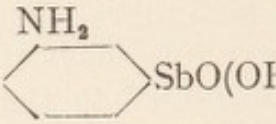
—Acetyl-4-aminobenzene-1-stibinic acid (50 parts) is heated for some hours with 5 per cent. aqueous sodium hydroxide (500 parts) until a diluted sample gives, with acid, a precipitate, immediately re-dissolving in excess of this reagent. 4-Aminophenylstibinic acid is then precipitated from the alkaline solution by dilute acetic acid. The sodium salt is deposited on adding alcohol to a solution of the acid in aqueous sodium hydroxide; it is easily soluble in water.

4-Aminophenylstibinic acid is practically insoluble in the ordinary organic media; it is readily soluble in dilute acids or alkalis. The acid itself tends to decompose, but its sodium salt is more stable; when, however, the latter is warmed with potassium iodide and dilute sulphuric acid, antimony is eliminated and *p*-iodoaniline is produced.

[1] Fabr. Heyden, D.R.-P., 270488.

4-Aminophenylstibinic acid is readily soluble in acids or alkalis ; it condenses with aldehydes, and yields a red azo-derivative on successive diazotisation and coupling with alkaline-β-naphthol. The *o*-hydroxybenzylidene derivative is obtained by its interaction with salicylaldehyde in presence of excess of acetic acid.[1]

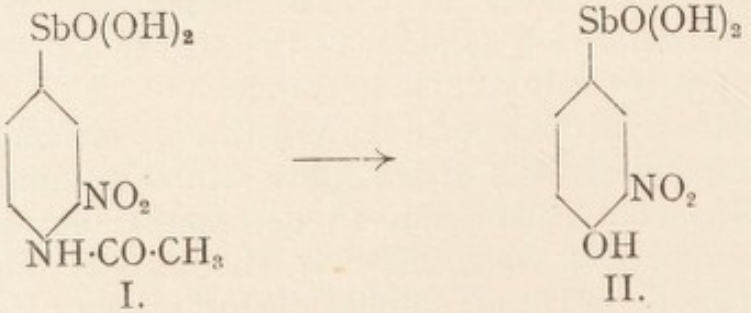
Sodium p-*aminophenylstibinate* (or p-*stibanilate*) is the antimonial analogue of the arsenical drug atoxyl (sodium *p*-arsanilate) ; it has been recommended as a curative and protective agent in diseases of protozoal origin.

3-*Aminophenyl*-1-*stibinic Acid*,  .

—3-Nitrophenyl-1-stibinic acid (15 parts, *cf.* pp. 296 and 300) is mixed with stannous chloride (48 parts) and added to 130 parts of alcoholic hydrochloric acid (37 per cent. hydrogen chloride). The mixture becomes rapidly warm, the reagents pass into solution, and colourless leaflets of m-*aminophenylstibinous chloride hydrochloride* separate until the solution sets to a stiff paste of crystals, which is washed with alcoholic hydrochloric acid. The salt is purified by crystallisation from dilute methyl alcohol containing hydrochloric acid ; it melts and decomposes at 215° (*v.* p. 301).

3-Aminophenyl-1-stibinic acid is obtained by treating the foregoing chloride hydrochloride successively with sodium hydroxide, hydrogen peroxide, and a slight excess of acetic acid ; it is a white powder decomposing on heating without definite melting point and is insoluble in the ordinary organic media, dissolving, however, readily in dilute alkalis and acids. The addition to these solutions of excess of hydrochloric acid leads to the precipitation of well-defined crystals of the oxychloride hydrochloride, $SbOCl_2 \cdot C_6H_4 \cdot NH_2,HCl$.

3-*Nitro*-4-*acetylaminophenyl*-1-*stibinic acid* [2] (I.).



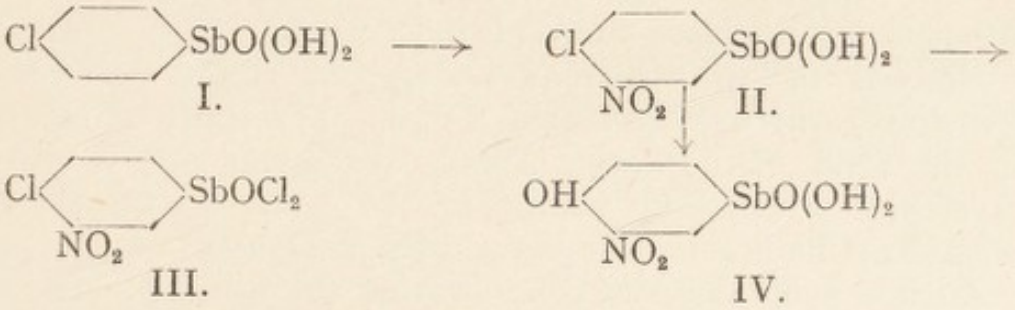
I. II.

[1] Fabr. Heyden, D.R.-P., 254421.
[2] Fabr. Heyden, D.R.-P., 259875, 287709.

—Anhydrous sodium 4-acetylaminophenylstibinate (113 grams), obtained by drying the hydrated salt at 110°, is dissolved in glacial acetic acid (300 grams). To the cooled solution (—10° to —2°) are added successively 800 grams of concentrated sulphuric acid and a mixture of nitric acid (25·4 grams, D 1·515) and sulphuric acid (100 grams) ; the mixture is stirred throughout this operation and cooled below 0°. After stirring for several hours the solution is poured into ice-water, the yellowish-brown 3-nitro-4-acetylaminophenyl-1-stibinic acid washed with water and dried. This acid, which is readily soluble in ammonia and in alkali hydroxides or carbonates, is reprecipitated from alkaline solutions with acids, and decomposes on heating without definite melting point.

3-*Nitro*-4-*hydroxyphenyl*-1-*stibinic acid* (II.) is produced by boiling the preceding compound (35 grams) with aqueous potassium hydroxide (300 grams, D 1·30) until all the ammonia has been evolved ; it is precipitated by adding dilute sulphuric acid to the alkaline solution. The dried acid, a brown powder, insoluble in water and the ordinary organic solvents excepting glacial acetic acid, has no melting point, but intumesces on heating ; it is readily soluble in aqueous alkalis and ammonia. This acid is also obtainable from *p*-chloroaniline by the following series of operations.[1]

p-*Chlorophenylstibinic acid* (I.).



Antimony trichloride [2] (84 grams) dissolved in 110 grams of hydrochloric acid (D 1·123) and 50 grams of water is added to a diazo-solution obtained by adding sodium nitrite (29 grams) to *p*-chloroaniline (50 grams) dissolved in hydrochloric acid (250 grams, D 1·123) and water (150 grams). The bulky, yellow precipitate is washed with dilute hydrochloric acid and suspended in 1½ litres of water to which sodium hydroxide

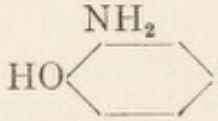
[1] Fabr. Heyden, D.R.-P., 261825 ; addition to D.R.-P., 254421.

[2] P. May, *Chem. Soc. Trans.*, 1912, **101**, 1037.

solution (150 grams, D 1·47) is added. After the slow evolution of nitrogen is ended the insoluble residue is extracted repeatedly with warm dilute sodium hydroxide and the combined filtrates are acidified. The precipitated *p*-chlorophenylstibinic acid is dried and dissolved in warm hydrochloric acid (110 grams, D 1·123). After adding animal charcoal the filtered solution is saturated with solid ammonium chloride, when *p*-chlorophenylstibinic oxychloride, $Cl{\cdot}C_6H_4{\cdot}SbOCl_2$, is precipitated, and washed with hydrochloric acid (D 1·123) saturated with ammonium chloride to remove inorganic antimony compounds. *p*-Chlorophenylstibinic acid is obtained in a state of purity by dissolving the oxychloride in dilute sodium hydroxide and precipitating the acid from the filtrate with dilute hydrochloric acid. The dried, colourless acid dissolves in alcohol, benzene, chloroform, or carbon bisulphide and is obtained therefrom in a crystalline form which decomposes on heating without melting.

p-Chlorophenylstibinic acid when nitrated according to the process outlined on p. 317 is converted into 4-*chloro*-3-*nitrophenyl*-1-*stibinic acid* (II.), a slightly coloured powder which has no definite melting point, but decomposes violently on heating; it is easily soluble in warm alcohol, but separates therefrom in an amorphous condition on evaporation. On dissolving this compound in concentrated hydrochloric acid and on adding ammonium chloride there separates, on cooling, long needles of the oxychloride (III.), which are hydrolysed by water regenerating 4-chloro-3-nitrophenyl-1-stibinic acid. Alkaline hydrolysis of the chloronitro-compound leads to 3-*nitro*-4-*hydroxyphenyl*-1-*stibinic* acid (IV., p. 317), which is obtained in the form of the easily soluble potassium salt, a scarlet, crystalline powder, by boiling for ten hours 4-chloro-3-nitrophenyl-1-stibinic acid (163 grams) with 300 grams of 50 per cent. potassium hydroxide and concentrating the solution. The free acid, a yellowish powder, is precipitated by acid from an aqueous solution of the potassium salt.[1]

3-*Amino*-4-*hydroxyphenyl*-1-*stibinic acid*,



—3-Nitro-4-hydroxyphenyl-1-stibinic acid (30·8 parts)[2] dissolved in 160 parts of water containing 4 parts of sodium hydroxide

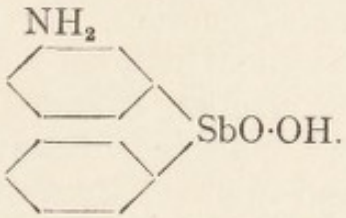
[1] Fabr. Heyden, D.R.-P., 262236. [2] D.R.-P., 259575, 262296.

is reduced with anhydrous sodium hydrosulphite (65 parts) in a solution of sodium hydroxide (2 parts) and in 200 parts of water. As the red solution loses its colour a white precipitate separates. The mixture being continually cooled, the excess of sodium hydrosulphite is decomposed by a current of air and the reduction product collected.

3-Amino-4-hydroxyphenyl-1-stibinic acid is unstable and darkens even in a dried condition. On heating it decomposes without melting. In water and the ordinary organic media it is insoluble, but nevertheless it dissolves readily in alkalis, ammonia, or acids. Its amino-group is diazotisable, and the diazo-compound couples with alkaline resorcinol and other phenols. The sodium salt, which is easily soluble in water, is precipitated therefrom on the addition of alcohol.

3-Amino-4-hydroxyphenyl-1-stibinic acid is also obtained from 3-nitro-4-hydroxyphenyl-1-stibinic acid by reduction in aqueous solution with sodium amalgam.[1]

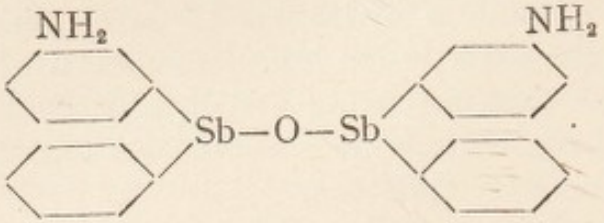
m-*Aminodiphenylstibinic acid*,



—*m*-Aminophenylstibinous chloride hydrochloride (320 parts, *v.* page 316) is dissolved in water (1500 parts) containing 280 parts of sodium hydroxide and mixed in the cold with the diazo-solution obtained in the usual way from aniline (93 parts), hydrochloric acid (660 parts, D 1·085), water (400 parts), and sodium nitrite (71 parts). After the vigorous evolution of nitrogen has subsided *m*-aminodiphenylstibinic acid is precipitated by adding acetic acid. The slightly coloured product is readily soluble either in aqueous alkalis or acids; it is purified by dissolving in alkali and by adding to the solution excess of strong hydrochloric acid when *m*-aminodiphenylstibinic acid hydrochloride is precipitated. The dried hydrochloride (43 parts) is dissolved in warm methyl alcohol (300 parts) and the solution saturated with sulphur dioxide at a temperature not exceeding 26°. After some hours hydrochloric acid (20 parts D 1·123) and water (100 parts) are successively added and the precipitated by-products removed by filtration.

[1] Fabr. Heyden, D.R.-P., 270488.

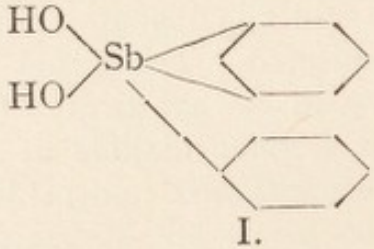
Bis-m-*aminodiphenylstibinous oxide*,



—The filtrate from the reduction is cooled with ice and cautiously rendered alkaline, when bis-*m*-aminodiphenylstibinous oxide is obtained as a caseous, slightly coloured precipitate sintering at about 70°, reducing Fehling's solution, and having a powerful irritating action on the mucous membrane of the nose. This oxide is insoluble in aqueous alkalis.[1]

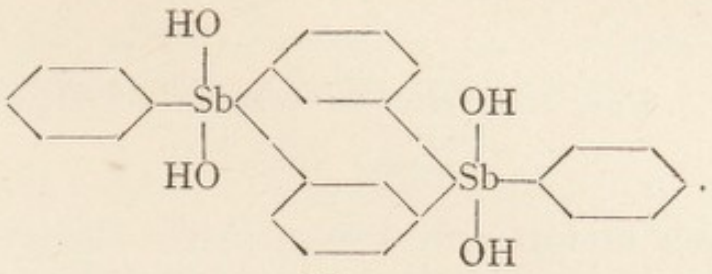
Phenyl-m-*phenylenestibinic acid*.[2]

m-Aminodiphenylstibinous oxide (6 parts) is dissolved in methyl alcohol containing 21·7 parts of hydrochloric acid (D 1·084) diluted with water and treated with sodium nitrite (1·42 parts) in aqueous solution. On neutralising the acid solution with aqueous sodium hydroxide, an evolution of nitrogen sets in, and after the reaction is ended, the liquid is acidified and the crude product collected, dissolved in warm alcoholic hydrochloric acid, reprecipitated by water, and extracted with ether. The organic stibinic acid is removed from the ethereal extract by dilute aqueous sodium hydroxide and precipitated from the alkaline solution by ammonium chloride. In the dried condition this acid is a light brown powder decomposing on heating without definite melting point ; it is only sparingly soluble in aqueous alkalis, but dissolves readily in warm glacial acetic acid. The constitution ascribed to this acid by the Chemische Fabrik von Heyden is indicated by formula I., although the properties and mode of preparation of the substance are not inconsistent with the dimeric configuration II.



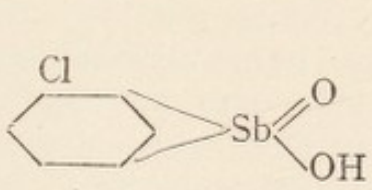
I.

[1] Fabr. Heyden, D.R.-P., 269206; addition to D.R.-P., 268451.
[2] Fabr. Heyden, D.R.-P., 269205; addition to D.R.-P., 254421.

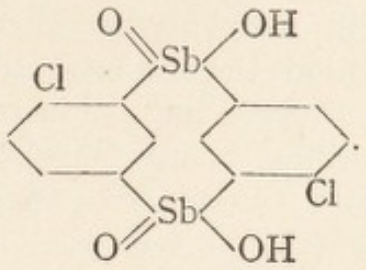


II.

Chloro-m-*phenylenestibinic acid,*



or



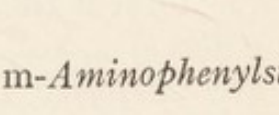
I. II.

—*m*-Amino-*p*-chlorophenylstibinous chloride (32 parts), prepared by the reduction of *p*-chloro-*m*-nitrophenylstibinic acid, is dissolved in 400 parts of water containing 133 parts of hydrochloric acid (D 1·084) and converted into its sparingly soluble diazo-compound by the addition of 7·3 parts of sodium nitrite. Sodium hydroxide solution (250 parts, D 1·19) is added to the mixture after cooling the latter with ice and stirring is continued until the evolution of nitrogen has subsided. The solution is then filtered and the crude product precipitated by adding hydrochloric acid. The dried precipitate is dissolved in warm alcoholic hydrochloric acid with the addition of animal charcoal and reprecipitated after cooling by dilution with water. Chloro-*m*-phenylenestibinic acid is further purified by dissolving in aqueous alkali and reprecipitating with acid ; it is thus obtained as a brown powder having no reducing action on Tollens's silver solution. The acid is insoluble in the majority of organic media ; it dissolves in aqueous alkali slowly in the cold and more rapidly on warming. On heating it decomposes without exhibiting any definite melting point.

Section V.—Mono-aryl Derivatives containing Tervalent Antimony.

1. *Aromatic Stibinoxides.*[1]

Previously to 1911 only two aromatic stibino-oxides were known, namely, phenylstibinoxide and *p*-tolylstibinoxide (Hasenbäumer, *Ber.*, 1898, **31**, 2912, 2914), obtained by hydrolysis from the corresponding chlorides, $R{\cdot}SbCl_2$. But at this date the Chemische Fabrik von Heyden discovered that under suitable reducing conditions the aromatic stibinic acids can be converted either into the corresponding stibinous oxides or into compounds containing the stibino-group –Sb=Sb–. Stannous chloride is employed to prepare the oxides, whereas sodium hydrosulphite is a convenient agent for reducing the stibine oxides or stibinic acids to the stibino-compounds. If nitro-groups are present in the aromatic stibinic acid, these can, by a suitable choice of reducing agent, be either reduced or left unchanged. Although it was previously known that the reduction of arsenic acids led to arseno-oxides and arseno-derivatives containing the group –As=As– (*Ber.*, 1911, **43**, 917), yet it was not to be expected that stibinic acids would behave similarly. In many instances organic antimony compounds react differently from the corresponding arsenic derivatives. Antimony is more readily removed from the aromatic nucleus, thus benzoyl chloride withdraws antimony from triaminotriphenylstibine, whereas triaminotriphenylarsine readily yields the tribenzoyl derivative.[2] Michaelis[3] in his comparative studies noted the difference between the aromatic derivatives of antimony and those of phosphorus and arsenic.

m-*Aminophenylstibine oxide*, 

m-Nitrophenylstibinic acid (15 parts) prepared by nitrating phenylstibinic acid with nitric–sulphuric acids is thoroughly mixed with stannous chloride (48 parts) and treated with 130 parts of alcoholic hydrochloric acid (37 per cent. HCl). The mixture becomes considerably warmer, the reagents pass into solution, and a separation of colourless leaflets sets in until a

[1] Fabr. Heyden, D.R.-P., 268451.

[2] Günther, *Inaug. Dissert.*, Rostock, 1904, p. 13; *Annalen*, 1902, **321**, 184.

[3] *Annalen*, 1886, **233**, 39.

solid crystalline magma is produced. These crystals, consisting of m-*aminophenylstibinous chloride hydrochloride*,

$$HCl,NH_2\cdot C_6H_4\cdot SbCl_2,$$

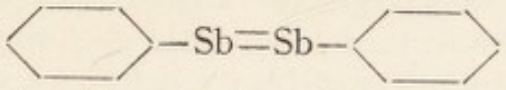
are obtained in a yield of 90 per cent. of the calculated amount, a similar proportion being furnished by the reduction carried out in concentrated aqueous hydrochloric acid, but by this method the product is contaminated with coloured impurities. This salt is fairly soluble in water or methyl alcohol, less so in ethyl alcohol, and insoluble in acetone, ether, or benzene. When crystallised from aqueous methyl alcohol containing hydrochloric acid it melts at 215°.

m-Aminophenylstibine oxide is obtained as a gelatinous precipitate by hydrolysing the hydrochloride with aqueous sodium hydroxide (3 mols.) ; it is washed with salt solution and methyl alcohol. The oxide is soluble in acids, and its crystalline sulphate is precipitated by alcohol. Like phenylstibine oxide, this compound has an intensely irritating action on the mucous membrane. With neutral or alkaline hydrogen peroxide *m*-aminophenylstibine oxide is oxidised to m-*aminophenylstibinic acid*, a white, amphoteric substance soluble in alkalis or in acids. The crystalline hydrochloride,

$$HCl,NH_2\cdot C_6H_4\cdot SbO(OH)_2,$$

separates on the addition of excess of hydrochloric acid.[1]

2. *Stibinoaryl Derivatives.*

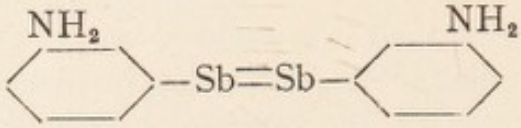
Stibinobenzene,[2]  .

—An aqueous solution of sodium hydrosulphite (10 parts) is added, with stirring, to the solution of phenylstibinic acid (5 parts) in the calculated amount of aqueous sodium hydroxide, and the mixture warmed to 30° and stirred for several hours. A yellow precipitate, which rapidly forms, becomes by the end of the reduction yellowish-brown. The dried crude product is freed from less soluble impurities containing sulphur by boiling in a reflux apparatus with a mixture of equal parts of alcohol and benzene containing copper powder. After distilling off these solvents from the filtered solution, the stibinobenzene separates as a pale yellow powder, insoluble in water, but readily soluble in glacial acetic acid and crystallising from

[1] D.R.-P., 268451.

[2] Fabr. Heyden, D.R.-P., 268451.

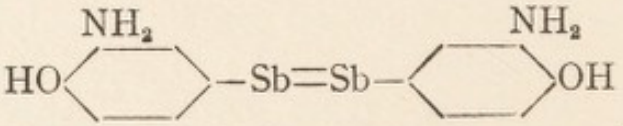
chloroform. On treatment with oxidising agents, such as hydrogen peroxide in glacial acetic acid, stibinobenzene is reconverted into phenylstibinic acid.

3 : 3′-*Diaminostibinobenzene*, 

—A filtered solution of sodium hydrosulphite (100 parts), magnesium chloride (50 parts), and 10 per cent. sodium hydroxide (100 parts) in 1000 parts of water is added to *m*-aminophenylstibinous chloride-hydrochloride dissolved in 2000 parts of water containing 64 parts of sodium hydroxide. A yellow precipitate slowly separates, and after several hours, or more rapidly by gently warming, a stiff orange-yellow paste is obtained, which on account of its insolubility can be washed with water or aqueous alkalis. When dissolved in glacial acetic acid the clear solution becomes rapidly brown ; mineral acids such as dilute hydrochloric acid produce a far-reaching decomposition, the yellow compound becoming brown and finally black with partial separation of elemental antimony. The stibino-compound is purified by dissolving in tartaric acid and precipitating with alcohol.

3 : 3′-Diaminostibinobenzene can also be prepared by adding a saturated solution of sodium hypophosphite (70 parts) to 32 parts of *m*-aminophenylstibinous chloride hydrochloride dissolved in 1000 parts of water ; the excess of reducing agent serves to fix the mineral acid, which would otherwise decompose the reduction product. The course of the reaction is manifested by a yellow coloration changing to brown. The solution is heated rapidly nearly to boiling, and the reduction product precipitated in yellowish-brown flakes by the addition of ammoniacal ice-water. This reduction may also be effected in methyl alcohol.

3 : 3′-*Diamino*-4-4′-*dihydroxystibinobenzene*.[1]



3-Nitro-4-hydroxyphenylstibinic acid (31 parts) dissolved in 500 parts of water and 6 parts of sodium hydroxide is mixed with a solution of anhydrous sodium hydrosulphite (200 parts)

[1] Fabr. Heyden, D.R.-P, 268451.

in water (400 parts) and sodium hydroxide (17 parts). The red solution slowly becomes decolorised and a precipitate appears which redissolves on adding more sodium hydroxide. After several hours' warming at 40°, 3 : 3′-diamino-4 : 4′-dihydroxystibinobenzene begins to separate as a reddish-brown precipitate, and when completely deposited is collected in the entire absence of air. The product is easily soluble in aqueous alkalis or acids; the latter, especially hydrochloric acid, however, speedily produce a further change. The hydroxyl group is identified by means of ferric chloride and the amino-group through the diazo-reaction and subsequent coupling.

3 : 3′-Diamino-4 : 4′-dihydroxystibinobenzene is easily acylated; it readily condenses with aldehydes. Alkaline hydrogen peroxide oxidises it with loss of colour to 3-amino-4-hydroxystibinic acid.

This substance, in the form of its dihydrochloride, is of exceptional interest as being the antimonial analogue of the important arsenical drug salvarsan.

Application of Organic Compounds of Antimony.

Reference has already been made to the use of antimony compounds containing the antimonyl group, SbO, in the treatment of trypanosomiasis and allied diseases. These compounds are not truly organo-antimonials in the sense in which this expression is used throughout this monograph. For although they contain both antimony and carbon, these elements are not directly attached to one another, but are united through the intermediary of oxygen.

The promising results obtained by Plimmer, Fry, Ranken and others[1] in the treatment of sleeping sickness and yaws both with antimony salts, such as lithium antimonyl tartrate, and even with the finely divided metalloid itself, have led to trials of various organo-antimony derivatives. The effect of these products is promising, but so far nothing of specific effect has been discovered to equal the arsenical drugs of the salvarsan and neosalvarsan types.

Sodium acetyl-*p*-aminophenylstibinate (*Stibacetin*) has been tried with success in rendering mice immune against various strains of trypanosomes; the dose required to do this was $\frac{1}{10}$th

[1] *Proc. Roy. Soc.*, 1909, **81**, *B*, 334; 1910, **83**, *B*, 140; *Nature*, 1913, **90**, 662.

the lethal amount. Smaller quantities of the drug led to strains of trypanosomes resistant to antimony.[1]

Uhlenhuth has reported on the effect of stibacetin on experimental tumours of rats and mice, the results being comparable with those obtained with the arsenical analogue, arsacetin.[2]

Complete immunity to trypanosomes in rats, dogs, and rabbits was obtained by injecting the animals at the time of inoculation with sodium antimony dithioglycinate or the triamide of antimony trithioglycine (*v.* p. 295). Protection was also afforded by injecting with the dithioglycinate twenty-four hours after inoculation. In these compounds the antimony is united to carbon only through the intermediary of sulphur. Sulphoform, the sulphide of triphenylstibine, is another sulphurised antimonial which has been employed medicinally; this substance being used as a remedy in various skin diseases (*cf.* p. 306.)

The amino-derivatives of triphenylstibine oxide and of diphenylarsinic and monophenylarsinic acids are active against trypanosomes, but they are irritant when introduced subcutaneously.

[1] Lange, *Zeitsch. Immunitäts Forschungen Referate*, 1912, **4**, 6; *cf.* Hügel, *Deutsche Medizinische Wochenschrift*, 1913, **50**.

[2] *Medizinische Klinik*, 1912, 37.

CHAPTER X

Miscellaneous Organic Derivatives of Arsenic and Antimony

Section I.—Hydroaromatic Derivatives of Arsenic and Antimony.

Although the aliphatic and aromatic derivatives of these metalloids have been studied very extensively, scarcely any attention has been directed to the possibilities of combining arsenic and antimony with saturated cyclic radicals.

The condensation of camphor (in the form of its sodium derivative) with the trichlorides of phosphorus, arsenic, and antimony has been investigated by the writer in collaboration with F. M. G. Micklethwait and W. R. Moore. Sodium camphor[1] suspended in toluene condenses vigorously with arsenious chloride, and the mixture when added to water yields a mixture of two acidic substances; one is *dicamphorylarsinic acid*, and the other, an uncrystallisable material, is *tricamphorylarsinic acid*. A third substance having the composition of tribornylarsine was also obtained, but in quantities too small for detailed examination.[2]

With antimony trichloride the reaction goes somewhat differently; only one main product is obtained, namely *tricamphorylstibinic chloride*, which is slowly resolved by water into tricamphorylstibinic acid, a very unstable compound decomposed by dilute aqueous sodium hydroxide or even by boiling water.

For purposes of comparison the condensation was repeated with phosphorus trichloride, and in this instance also only one product was isolated, dicamphorylphosphinic acid.[3]

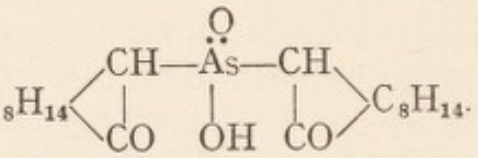
[1] Haller, *Compt. rend.*, 1891, **112**, 1490; 1892, **113**, 22; *cf.* Forster, *Chem. Soc. Trans.*, 1901, **79**, 957.

[2] Morgan and Micklethwait, *Chem. Soc. Trans.*, 1908, **93**, 2146; 1909, **95**, 1476.

[3] Morgan and Moore, *Chem. Soc. Trans.*, 1910, **97**, 1699.

Condensation Products from Sodium Camphor and the Trichlorides of the Phosphorus Group.

Products.	Phosphorus trichloride.	Arsenic trichloride.	Antimony trichloride.
Dicamphoryl derivatives.	$(C_{10}H_{15}O)_2PO{\cdot}OH$, dicamphorylphosphinic acid, stable in concentrated aqueous alkali hydroxides; decomposed by fused alkali hydroxides.	$(C_{10}H_{15}O)_2AsO{\cdot}OH$, dicamphorylarsinic acid, stable in hot dilute aqueous alkali hydroxides; decomposed by very strong solutions of these alkalis.	—
Tricamphoryl derivatives.	—	$(C_{10}H_{15}O)_3As(OH)_2$, tricamphorylarsinic acid, is as stable towards alkalis as the above dicamphoryl derivative.	$(C_{10}H_{15}O)_3SbCl_2$, tricamphorylstibinic chloride, slowly resolved by water into $(C_{10}H_{15}O)_3Sb(OH)_2$, tricamphorylstibinic acid, very unstable, decomposed by dilute aqueous sodium hydroxide and even by boiling water.

Dicamphorylarsinic Acid, C_8H_{14}  C_8H_{14}.

—Camphor (75 grams) dissolved in warm toluene (200 c.c.) is converted into sodium camphor by adding 7·5 grams of sodium. The precipitated sodium derivative suspended in 200 c.c. of fresh toluene is treated slowly with arsenious chloride (38 grams) diluted with twice its bulk of toluene. Considerable heat is generated; the mixture acquires a jelly-like consistence and gradually assumes a deep crimson hue. This colour slowly fades and the mixture regains its fluidity until it consists of a yellow mobile solution with a pulverulent precipitate of sodium chloride. After one hour the mixture is heated at 90–100°, and then poured into water and extracted with hot aqueous sodium hydroxide. The alkaline extract, acidified, gives a brownish-white precipitate of crude dicamphorylarsinic acid, the yield being about 10 per cent. on the weight of camphor taken. Crystallisation from benzene gives colourless crystals. Further purification gives highly refractive, obliquely truncated

prisms, melting with decomposition at 266°, $[\alpha]_D^{20} + 186{\cdot}6°$. Dicamphorylarsinic acid is almost insoluble in water or petroleum ; it dissolves more readily in benzene and is freely soluble in chloroform or alcohol.

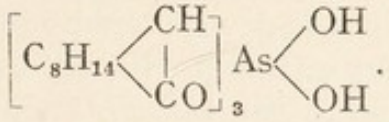
The salts of the alkali metals and ammonium are extremely soluble in water or alcohol. The calcium, strontium, barium, nickel, and cobalt salts are not precipitated in aqueous solutions ; the ferric, mercuric, and cupric salts are almost insoluble in water.

Silver dicamphorylarsinate, $(C_{10}H_{15}O)_2AsO{\cdot}OAg$, a white, sparingly soluble precipitate from sodium dicamphorylarsinate and silver nitrate, is amorphous at first, but slowly becomes crystalline.

Cadmium dicamphorylarsinate, $[(C_{10}H_{15}O)_2AsO_2]_2Cd$, separates as a sparingly soluble, white, crystalline compound on mixing strong aqueous solutions of cadmium chloride and potassium dicamphorylarsinate.

From aqueous solutions of its salts, dicamphorylarsinic acid is set free by acetic acid, but only a very slight precipitate is produced by carbonic acid. Dicamphorylarsinic acid does not yield an oxime on treatment with hydroxylamine in hot aqueous or alcoholic solutions.

Dicamphorylarsinic oxychloride, $(C_{10}H_{15}O)_2AsO{\cdot}Cl$, obtained by the interaction of potassium dicamphorylarsinate and phosphorus pentachloride, separates from chloroform and benzene in colourless crystals melting at 158° : it is very sensitive to moisture, and is rapidly decomposed on exposure to the atmosphere ; its specific rotation, taken in dry chloroform, gave $[\alpha]_D + 106°$.

Tricamphorylarsinic Acid,  .

—Sodium camphor and arsenious chloride are condensed in dry toluene in the manner indicated in the preceding experiment, and the product extracted repeatedly with aqueous sodium hydroxide. After precipitation with mineral acid, the acidic products are extracted with small quantities of benzene until a residue is obtained consisting of crude dicamphorylarsinic acid ; the benzene extracts also yield small quantities of this substance. The final brown mother liquors are evaporated to dryness, the residue dissolved in dilute aqueous sodium hydroxide, and the solution boiled with animal charcoal and concentrated

to the crystallising point. The crystals, which consist of sodium dicamphorylarsinate, are removed, the solution acidified, and the viscid precipitate again subjected to the treatment with benzene and sodium hydroxide to remove further quantities of dicamphorylarsinic acid. The precipitate finally obtained is a brown uncrystallisable solid, softening at 110° and melting indefinitely at 130°. This acid dissolves in water containing a small amount of alcohol; it is extremely soluble in benzene, alcohol, or acetic acid, separating in a viscid condition from its concentrated solutions in these solvents. The *silver* salt, is a greyish-white precipitate obtained by double decomposition with ammonium tricamphorylarsinate and silver nitrate.

Tricamphorylstibinic Chloride,[1] $\left[C_9H_{14}\begin{matrix}CH\\|\\CO\end{matrix}\right]_3Sb\begin{matrix}Cl\\Cl\end{matrix}$.

—On adding a toluene solution of antimony trichloride to sodium camphor suspended in the same medium, considerable heat is generated and a bulky precipitate is produced. The mixture warmed on the water-bath and left for a few days is then treated with water, when a white precipitate of antimony oxide separates. The toluene filtrate is distilled in steam, and the residue extracted with benzene. From the concentrated benzene extract the chloride separates in colourless, ice-like crystals, this separation being promoted by the addition of light petroleum. When recrystallised from benzene, the product melts and decomposes at 244°, although when rapidly heated it sometimes remains unchanged at 247–248°: $[\alpha]_D^{20°}=367{\cdot}3°$ (in chloroform).

Tricamphorylstibinic chloride dissolves only sparingly in alcohol and is insoluble in water. In acid solutions it is fairly stable, and may be boiled with 2*N*-hydrochloric acid without decomposition. On warming with 2*N*-sodium hydroxide, the chloride is readily hydrolysed into antimonic and hydrochloric acids and camphor. Destructive hydrolysis occurs on warming the chloride with aqueous sodium hydrogen carbonate or dilute ammonia. A similar decomposition is effected by alcoholic silver nitrate.

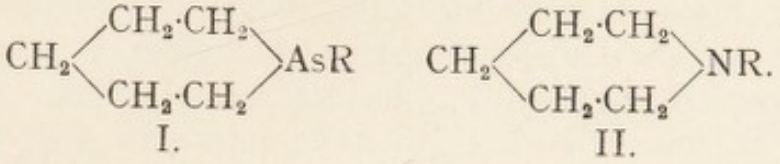
Section II.—Heterocyclic Rings containing Arsenic and Antimony.

Although certain arsenostilbene derivatives are regarded by Karrer as containing two doubly-linked arsenic atoms in an

[1] Morgan, Micklethwait, and Whitby, *Chem. Soc. Trans.*, 1910, **97**, 35.

eight-membered ring (p. 240), it was not until 1915 that analogues of piperidine were synthesised in which the nitrogen is replaced by phosphorus, arsenic, antimony, and bismuth.

In this year Grüttner and Wiernik obtained phenyl*cyclo*pentamethylenearsine and phenyl*cyclo*pentamethylenestibine. This discovery was followed in 1916 by the preparation of even simpler cyclic derivatives of arsenic when Zappi obtained methyl*cyclo*pentamethylenearsine. The general formula for these arsenical analogues (I.) of *N*-substituted piperidines (II.) is as follows :

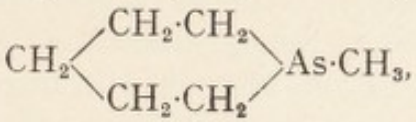


I. II.

On account of the analogy exhibited by the foregoing formulæ, Zappi suggests that the names arsedine and arsepedine should be employed for the arsenical analogues of pyridine and piperidine respectively.

The general method of preparation is through the agency of the Grignard reaction.

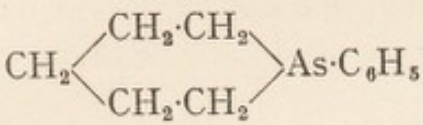
1-*Methylarsepedine* (*Methyl*cyclo*pentamethylenearsine*),



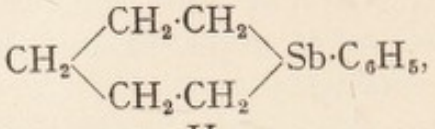
colourless liquid having an odour of mustard oil ; D 1·218/18° ; b.p. 156°/760 mm., 76°/36 mm., 65°/20–22 mm. ; volatile in steam. It is prepared by adding methylarsenious chloride to the magnesium derivative of αε-dichloropentane. It behaves as an unsaturated compound, becoming oxidised in air to a colourless *oxide*, $C_5H_{10}AsCH_3{:}O$, soluble in alkaline solution. The methiodide, $C_5H_{10}As(CH_3)_2I$, white, crystalline solid, m.p. 290°, decomposes on heating into methyl iodide and 1-methylarsepedine. With moist silver oxide the methiodide gives the strongly alkaline *hydroxide*, $C_5H_{10}As(CH_3)_2{\cdot}OH$. 1-Methylarsepedine combines additively with the halogens yielding dihalogen derivatives, $C_5H_{10}As(CH_3)(Hal)_2$. The dichloro- and dibromo-compounds are hygroscopic substances ; the di-iodo-derivative is a yellow powder decomposing at 120°. 1-Methylarsepedine furnishes a platinichloride and picrate (yellow compounds, m.p. 163° and 258°).[1]

[1] Zappi, *Bull. Soc. chim.*, 1916, [iv], **19**, 151, 290.

1-*Phenylarsepedine* (*Phenyl*cyclo*pentamethylenearsine*, I.),



I.



II.

colourless, viscous oil of unpleasant odour; D_4^{20} 1·2480; $n_D^{21\cdot4}$ 1·5944; b.p. 153–154°/18–20 mm. (in carbon dioxide).

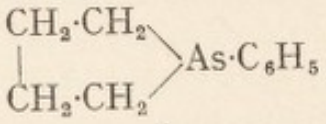
Phenylarsenious chloride is added to the magnesium compound of αε-dibromo- (or dichloro-) pentane in ethereal solution. A poorer yield of 1-phenylarsepedine is obtained through Michaelis's method by the interaction of phenylarsenious chloride, dibromo- (or dichloro-) pentane, and sodium in ether. The *dichloride*, $C_5H_{10}As(C_6H_5)Cl_2$, hygroscopic leaflets, melts at 138–139°; the following are characteristic derivatives:—*mercurichloride*, needles, m.p. 201·5–202°; *methiodide*, colourless leaflets, m.p. 179·5°; n-*butiodide*, m.p. 140°.

1-p-*Tolylarsepedine*, $C_5H_{10}\cdot As\cdot C_6H_4\cdot CH_3$, prepared with *p*-tolylarsenious chloride by the Grignard reaction, has the following characteristics: colourless oil, D_4^{20} 1·2174; n_D^{20} 1·5948; b.p. 162–163°/20 mm. (in carbon dioxide); *dichloride*, m.p. 134°; mercurichloride, m.p. 175°.

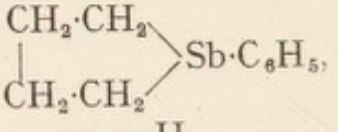
*Phenyl*cyclo*pentamethylenestibine* (II.), prepared by the general method from phenylstibine chloride, has the following characteristics: colourless, viscous oil, unpleasant odour, b.p. 169–171°/18–20 mm. (in carbon dioxide); D_4^{20} 1·4966; $n_D^{22\cdot4}$ 1·6203. Exposed to air it slowly oxidises to *phenyl*cyclo*pentamethylenestibine oxide*, $C_5H_{10}\cdot Sb(C_6H_5){:}O$, colourless powder unfused at 280°; *dichloride*, m.p. 141–142°.

The pyrrolidine analogues containing arsenic and antimony have also been prepared by the Grignard reaction, using αδ-dibromobutane.

*Phenyl*cyclo*tetramethylenearsine* (I.),



I.



II.

colourless, mobile oil, odour not unpleasant; b.p. 128·5°/15–16 mm.; D_4^{17} 1·2824; n_D^{17} 1·6768: prepared by adding phenylarsenious chloride to the magnesium compound of αδ-dibromobutane in ethereal solution. It is very unsaturated, giving the following additive compounds: —*dichloride*, hygroscopic crystals, m.p.

120·5°; *mercurichloride*, leaflets, m.p. 160–162°; *methiodide*, m.p. 135–136°; and higher alkyl iodides.

*Phenyl*cyclo*tetramethylenestibine* (II.), prepared by the Grignard reaction, using phenylstibine chloride; colourless oil, unpleasant odour, b.p. 156–158°/20–22 mm.; n_D^{23} 1·6313; *dichloride* and *dibromide*, birefringent crystals, m.p. 150° and 149°.[1]

Section III.—Arsenical Derivatives containing Heterocyclic Nuclei.

Arsenic Compounds of the Quinoline Series.[2]

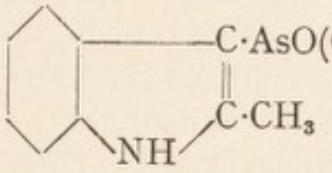
Quinoline, 8-hydroxyquinoline, and tetrahydroquinoline when treated with arsenious chloride in ethyl acetate yielded respectively the additive compounds $C_9H_7N,AsCl_3$, m.p. 138°; $C_9H_7NO,AsCl_3$, m.p. 168°; and $C_9H_{11}N,AsCl_3$, m.p. 134°.

The introduction of arsenic into the ring was not effected either by the action of aluminium chloride or by Béchamp's reaction. Skraup's reaction carried out on *p*-arsanilic acid led merely to quinoline. Knorr's reaction with ethyl acetoacetate on *p*-arsanilic acid did not give an arsenical product.

The reaction of Döbner and Miller furnished *quinaldinearsinic acid*, $CH_3{\cdot}C_9H_6N{\cdot}AsO_3H_2$, although only in poor yield, by mixing *p*-arsanilic acid (6 grams) with 21 c.c. of acetaldehyde and allowing the excess of the latter to evaporate over sulphuric acid. Fuming hydrobromic acid (48 c.c. of D 1·49) was added to the mixture, when a yellow, crystalline material separated which was washed with water dissolved in alcohol and reprecipitated with water. The yellow arsinic acid begins to decompose at 140° and chars at 170°. Reduced with sodium and ethyl alcohol it yields *quinaldinearsenious oxide*, $CH_3{\cdot}C_9H_5N{\cdot}AsO$, a flocculent precipitate from alcohol-acetic acid, decomposing at 120°.

Arsinic Acids of Indole Series.[3]

Methylindolearsinic Acid (*Methylketolearsinic Acid*),



colourless needles, m.p. 180–182°, prepared by adding methyl-

[1] Grüttner, Wiernik, and Krause, *Ber.*, 1915, **48**, 1473; 1916, **49**, 437

[2] Fränkel and Löwy, *Ber.*, 1913, **46**, 2546.

[3] C. F. Boehringer and Söhne, D.R.-P., 240793.

ketole (13 parts) to anhydrous arsenic acid (28·4 parts) in 6 parts of hot water. The product freed from arsenic acid with water was dissolved in aqueous caustic soda and reprecipitated by hydrochloric acid. This arsinic acid is easily soluble in alcohol or glacial acetic acid.

Sodium salt, $C_9H_9O_3NAsNa,2\frac{1}{2}H_2O$, readily soluble in water, decomposing at 225–235°; quinine salt,

$$C_{20}H_{24}O_2N_2,C_9H_{10}O_3NAs,2H_2O,$$

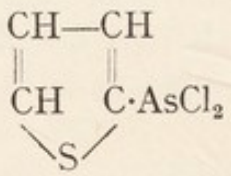
m.p. 170–172°, easily soluble in methyl or ethyl alcohol, precipitated therefrom by water in colourless needles; insoluble in ether or chloroform. Chloro-derivative, m.p. 185–186° (decomposed).

α-Naphthindolearsinic acid, crystals.—α-Naphthindole (4 parts) in 40 parts of toluene heated in a reflux apparatus with anhydrous arsinic acid (6·4 parts) in 5 parts of absolute alcohol: the toluene is removed by distillation, the residue, after extraction with alcohol, dissolved in aqueous caustic soda and reprecipitated by acid.

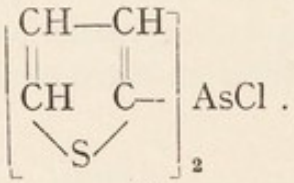
Arsenical Derivatives of Thiophen.

The general methods of Béchamp and Bart are not readily applicable to the thiophen series, and the arsenical derivatives of this heterocyclic sulphur compound are preferably prepared from the mercury derivatives which are easily obtained from thiophen and its homologues.

Thienylarsenious Chloride (I.),



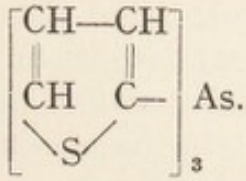
I.



II.

—Arsenious chloride (130 grams) is added to powdered mercuridithienyl, the mixture being cooled during addition. The dark brown filtrate from mercuric chloride is fractionated in hydrogen under a pressure of 11 mm. The fraction 116–130° on further rectification gives the dichloride boiling at 118–122° (11 mm.) as a light brown liquid with unpleasant odour.

Dithienylarsenious chloride (II.) is obtained from fraction 150–194°/11 mm. by further rectification as a brown liquid, b.p. 219–232°/13 mm.

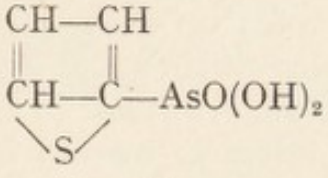
Trithienylarsine, 

—The portions of the foregoing distillations boiling over 190° were concentrated and finally distilled with the aid of a Gaede pump. The arsine is a pale yellowish-green, viscous liquid, almost inodorous, b.p. 199–200·5°/0·5 mm.[1]

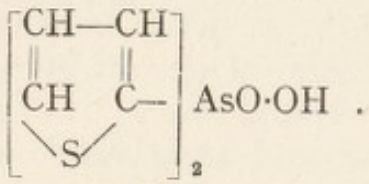
When thiophene-2-mercurichloride and arsenious chloride are heated in toluene for a prolonged period the chief product is dithienylarsenious chloride.

This synthetic process based on the use of organo-mercurials, which is an extension of one of Michaelis's general methods for arylarsenicals,[2] was first employed by C. Finzi, who oxidised the chloro-compounds directly to arsinic acids.

Thiophen-2-arsinic Acid (*Thienyl-2-arsinic Acid, I.*)



I.



II.

—Mercury 2 : 2′-dithienyl or preferably thiophen-2-mercurichloride (white plates, m.p. 183°), prepared by adding a cold saturated solution of mercuric chloride and 30 per cent. aqueous sodium acetate to thiophen dissolved in alcohol, is treated with freshly distilled arsenious chloride, the mixture being finally warmed on the water-bath. The product filtered from mercuric chloride is treated successively with aqueous caustic soda and hydrogen peroxide. Inorganic arsenic is separated partly by crystallising out sodium arsenate and partly by precipitation with barium chloride. The filtrate freed from barium with sulphuric acid is evaporated to dryness, sodium chloride rendered insoluble by concentrated hydrochloric acid, and the final mother liquor evaporated over quicklime. The residue, consisting of a mixture of two arsinic acids, is dissolved in absolute alcohol, decolorised with animal charcoal, and converted into sodium salts. *Sodium thiophen-2-arsinate,* $C_4H_3S{\cdot}AsO_3HNa$, separates in transparent, colourless, non-deliquescent, rhombic scales, very soluble in water.

[1] Steinkopf (with Bauermeister), *Annalen*, 1917, **413**, 331.

[2] Michaelis, *Annalen*, 1880, **201**, 196; 1902, **320**, 272; *cf.* pp. 62, 72.

Thiophen-2-arsinic acid[1] is fairly soluble in water or alcohol and forms colourless needles, m.p. 135·5°. At 105–108° it is converted into *thiophen-2-arsinic anhydride*.

Sulphurous acid, in the presence of a trace of hydriodic acid, reduces this arsinic acid to *thienyl-2-arsenious oxide*, a white substance insoluble in water but dissolving in concentrated aqueous caustic alkali. Further reduction with alkali hydrosulphite leads to *arsenothiophene*, $C_4H_3S{\cdot}As{:}As{\cdot}C_4H_3S$. Salts of thiophene-2-arsinic acid:—*Magnesium* salt, colourless mammillated crystals, on boiling a solution of the acid with magnesia mixture; *barium* salt, $(C_4H_3S{\cdot}AsO_3H)_2Ba$, white crystals, prepared by treating the acid successively with baryta water and carbon dioxide; the filtered solution yields the salt on concentration; *silver* salt, $C_4H_3S{\cdot}As{\cdot}O_3Ag_2$, white, amorphous precipitate.

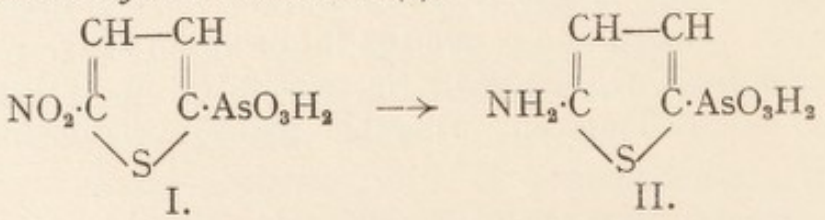
2 : 2′-*Dithienylarsinic Acid* (II.).—The alcoholic mother liquor from sodium thiophen-2-arsinate in the foregoing preparation is distilled to dryness. The residue, taken up with water and dilute hydrochloric acid, gives 2 : 2′-dithienylarsinic acid, sparingly soluble in cold water; it dissolves in alcohol, but not in ether or benzene, and separates from boiling water in minute needles, m.p. 172°.

With magnesia mixture it does not yield a precipitate either in the cold or on boiling, a property distinguishing this secondary arsinic acid from arsenic acid or from primary arsinic acids.

2 : 2′-Dithienylarsinic acid is obtained in better yield by heating thiophen-2-arsenious chloride with thiophen-2-mercurichloride in sealed tubes.

The following nitro-compounds are obtained from the two thienylarsinic acids. Although the orientation of the nitro-group is not determined with certainty, it is inferred from analogy with other reactions in the thiophen series that the nitro-group takes up the remaining ortho-position with respect to sulphur.

4-*Nitrothienyl-2-arsinic acid* (I),



[1] Finzi, *Gazzetta*, 1915, **45**, [ii], 286.

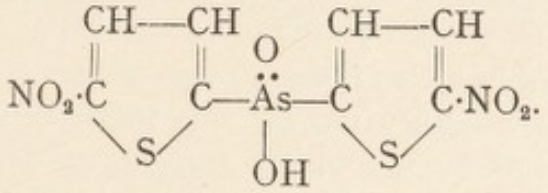
—Thiophen-2-arsinic acid is added to a cooled mixture of fuming nitric and concentrated sulphuric acids, the nitrous fumes being removed by a current of air. The nitro-compound precipitated by the cautious addition of cold water (40–50 per cent.) is crystallised from boiling water ; it forms slightly yellow prisms melting and passing into its anhydride at 194°.

4-Aminothienyl-2-arsinic acid (II.) is produced by reducing the preceding nitro-compound in methyl-alcoholic solution with sodium amalgam. The alcohol is removed by distillation, the residue acidified with excess of hydrochloric acid, and filtered from sodium chloride and tarry impurity. Sodium acetate added to the filtrate precipitates the aminoarsinic acid, crystallising in yellowish leaflets, m.p. 194°, sparingly soluble in organic solvents, water, or methyl alcohol ; its *hydrochloride,*

$$HCl,NH_2{\cdot}C_4H_2S{\cdot}AsO_3H_2,$$

soluble in water or alcohol, separates in dendritic forms like ice crystals on glass ; *acetyl* derivative, colourless prisms from water, decomposing at 134°.

4 : 4′-Dinitrodithienyl-2-arsinic Acid,



—This dinitro-acid (decomposing at 287°), prepared by nitrating dithienyl-2-arsinic acid, is precipitated by diluting the mixed nitric-sulphuric acids with water and purified through its sodium salt.[1]

Section IV.—Arsenical Esters and Arsenical Lipoid and Protein Combinations.

1. *Arsenical Esters.*

Esters of Arsenious and Arsenic Acids.

Although the esters of arsenious and arsenic acids are not organo-arsenical compounds in the sense implied in this treatise they are of utility in organic synthesis.

Methyl and *ethyl arsenate,*[2] R_3AsO_4, are produced by heating

[1] Finzi and Furlotti, *Gazzetta*, 1915, **45**, [ii], 290.
[2] J. M. Crafts, *J. Pharm.*, 1871, [iv], **13**, 242.

well-dried silver arsenate suspended in ether with methyl or ethyl iodide at 100° :

Me ester, b.p. 128–130°/60 mm. D 1·5591/14·5°.
Et ester, b.p. 148–150°/60 mm. D 1·3264/0°.

Ethyl arsenite.—Three methods of preparation.

(1) Arsenious oxide with ethyl silicate at 200° in sealed tubes, SiO_2 deposited.

(2) Ethyl iodide with Ag_2HAsO_3 at 150°, yields less than with arsenate.

(3) Preferable method : $3NaO{\cdot}C_2H_5 + AsBr_3 = 3NaBr + As(O{\cdot}C_2H_5)_3$ in alcoholic solution. Ammonia is introduced to precipitate $AsBr_3xNH_3$, the ethereal filtrate fractionated.

Me ester, $As(O{\cdot}CH_3)_3$, b.p. 128–129°. D 1·428.
Et ester, $As(O{\cdot}C_2H_5)_3$, b.p. 165–166°. D 1·224/4°.
Am ester, $As(O{\cdot}C_5H_{11})_3$, b.p. 288° and 193–194°/60 mm.

The alkyl arsenites are produced by heating crystallised arsenious oxide with various alcohols in a reflux apparatus so that the alcohol and water vapour circulate over calcium carbide. The water is eliminated and the dried alcohol drops back on the oxide. In this way good yields of the esters are obtained. The method is available for the phenyl ester.[1]

An ingenious modification of this method is due to Lang, Mackey, and Gortner, in which anhydrous copper sulphate is used in the reflux apparatus as the dehydrant. Good yields are obtained in most instances.

	%		%
Me ester	33·8	Trimethylcarbinyl ester	54·27
Et ,, ...	4·5	Amyl ester	54·00
Pr ,, ...	56·75	*iso*Amyl ester	58·62
iso-Butyl ester ..	56·25		

The phenyl ester made by this method is a yellow, viscous liquid freezing at 31°, b.p. 305/30 mm.; D 1·59. The tolyl and naphthyl esters are producible by this method : *resorcinyl arsenite*, $(C_6H_4O_2)_3As_2$, is an amber liquid, m.p. 24°, D 1·9, decomposed by water,[2] soluble in alcohol.

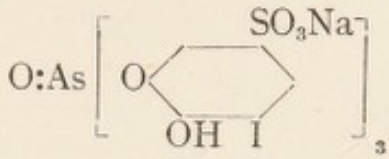
Mixed anhydrides of arsenious oxide [3] :—

Acetyl arsenite, $As[O{\cdot}CO{\cdot}CH_3]_3$, colourless needles, m.p. 82° ; b.p. 165–170°/31 mm.; soluble in chloroform or ethyl acetate,

[1] Auger, *Compt. rend.*, 1906, **143**, 968.
[2] *Chem. Soc. Trans.*, 1908, **93**, 1364 ; *Chem. Soc. Proc.*, 1909, **25**, 199.
[3] Pictet and Bon, *Bull. Soc. chim.*, 1905, [iii], **33**, 1139.

decomposed by water or alcohols. When fused with benzoic acid it yields *benzoyl arsenite*. $As[O{\cdot}CO{\cdot}C_6H_5]_3$, white, crystalline mass ; m.p. 155° ; soluble in anhydrous solvents except petroleum.

The complex monoiodo-arsenical ester



is prepared by heating at 100° silver arsenate (10 parts) with 29 parts of sodium 2 : 6-di-iodophenol-4-sulphonate in 300 parts of water.[1]

The hexamethylenetetramine compound of arsenic acid,

$$(C_6H_{12}N_4)_3(H_3AsO_4)_2,$$

is precipitated on mixing saturated alcoholic solutions of its generators. It is much less toxic than arsenic acid.[2]

The iron salts of arsenitartaric and arsenicitric acid have been recommended for use in therapeutics.[3]

2. *Arsenical Compounds of the Unsaturated (Acetylenoid) Higher Fatty Acids—Elarson.*

Good clinical results have been obtained in anæmia with the strontium salt of an arsenical additive compound of behenolic acid containing As = 13 and Cl = 6 per cent. The salt has been introduced into pharmacy under the name of "*Elarson.*"[4]

The acids of the acetylene series have the property of combining with trihalides of phosphorus and arsenic, and when the more complex acids are employed the products are fatty (lipoid) materials absorbable in the alimentary canal ; they still possess acidic properties, yielding soluble alkali salts and insoluble calcium and strontium salts.

Stearolic acid and arsenious chloride ($1\frac{1}{2}$ parts) are heated at 140°, the product is dissolved in ether, shaken with water to remove excess of arsenic compounds, the ethereal solution concentrated, rendered alkaline, and the clear solution acidified. The precipitated fatty mass is redissolved in ether and the solution dried with calcium chloride and evaporated.

Similar products are obtainable from behenolic acid and

[1] Wolffenstein, D.R.-P., 239073.

[2] Bossi, *Giorn. Farm. Chim.*, 1911, **60**, reprint. [3] D.R.-P., 208711.

[4] E. Fischer and Klemperer, *Therapie der Gegenwart*, 1913, Jan.

arsenious bromide, phosphorus trichloride and phosphorus tribromide, and from stearolic acid and phosphorus trichloride.[1]

Alternative methods of production consist in treating behenolic acid with arsenious oxide, anhydrous copper, or magnesium sulphate and leading in dry hydrogen chloride or bromide at 140°.[2]

The acetylenoid acids can be mixed with arsenious oxide and treated slowly with thionyl chloride or heated with arsenic or phosphorus and sulphuryl chloride, the temperature being raised to 140–145°.[3]

The esters of the chloroarsinosoacetylenoid acids are therapeutically valuable, being soluble in lipoid substances and devoid of acid reaction.

Methyl behenolate reacts similarly with arsenious chloride at 135° and yields on ethereal extraction *methyl chloroarsinosobehenolate* as a brown oil ; the *ethyl* ester has similar properties. Behenolic anhydride, from behenolic acid and phosgene in pyridine, condenses with arsenious chloride at 140° and yields a brown solid, *chloroarsinosobehenolic anhydride.*

Chloroarsinosobehenolic acid and thionyl chloride undergo a vigorous interaction, and the product, a complex acid chloride, condenses with aniline to yield *chloroarsinosobehenolanilide.*[4]

The iron salts of these arsenical and phosphorus acids are of utility and are made by adding alcoholic ferric chloride or basic ferric acetate to alcoholic solutions of the arsinoso-compound.[5]

The chemical nature of these substances was worked out by Fischer[6] in the case of the behenolic acid derivatives, as this material was more amenable than the products from stearolic and phenylpropiolic acids. The unsaturated aliphatic acids containing triple (acetylene) linkings combine with arsenious chloride to give an additive compound containing the group I.

I. II.

As the result of treatment with alkali during the process of separation the chlorine atoms attached to arsenic are removed

[1] Heinemann, D.R.-P., 257641. E. Fischer, U.S. P., 1082509, 1082510 ; Eng. P., 18732/1912, 10378, 10379/1913 ; Fr. P., 449014.

[2] Heinemann, D.R.-P., 268829.

[3] Heinemann, D.R.-P., 271159.

[4] D.R.-P., 273219.

[5] Heinemann, D.R.-P., 271158.

[6] E. Fischer, *Annalen*, 1914, **403**, 109.

and replaced by oxygen, giving rise to a compound containing the group II. To these products Fischer gives the name of chloroarsinoso-compound.

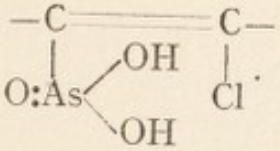
Chloroarsinosobehenolic acid, $C_{22}H_{40}O_3AsCl$, is prepared from pure behenolic acid and arsenious chloride (1·25 parts) heated at 140° for six hours, when the mixture is subsequently shaken with water and ether. The ethereal solution is treated successively with cold *N*-caustic potash and dilute hydrochloric acid. The preparation still contains behenolic acid, which crystallises out on cooling. The final product containing about 86 per cent. of the chloroarsinoso-compound is a light brownish-red oil insoluble in water, but dissolving easily in alcohol, ether, benzene, chloroform, or olive oil. The alkali salts are soluble, and a carefully neutralised solution of the potassium salt has been used in intravenous injections.

Strontium chloroarsinosobehenolate, "Elarson," $(C_{22}H_{39}O_3AsCl)_2Sr$, is an amorphous, colourless precipitate obtained by adding an alcoholic solution of the chloroarsinoso-acid to a methyl-alcoholic solution of strontium chloride saturated with gaseous ammonia. It is very sparingly soluble in alcohol, ether, or olive oil.

Methyl chlorobehenolarsinic acid ester, $C_{23}H_{44}O_5AsCl$:—Chloroarsinosobehenolic acid, is converted into its methyl ester by heating with sulphuric acid and methyl alcohol. The methyl ester is treated with bromine in carbon disulphide solution; the solution is diluted with ether and shaken with water. The crude ester is converted into its strontium salt, $(C_{23}H_{43}O_5AsCl)_2Sr$, and set free with acid.

This acid ester is hydrolysed by methyl-alcoholic potash to the dibasic *chlorobehenolarsinic acid*, which is purified through its strontium salt, $C_{23}H_{40}O_5AsClSr$.

In these arsinic acid derivatives produced from chloroarsinosobehenolic acid by the oxidising action of bromine the following arsenical group is probably present.



In these compounds the arsenic is much more firmly held to the carbon than in the chloroarsinoso-derivatives which are decomposed into arsenious and behenolic acids by warming on the water-bath with dilute alkali.

Arsenical Esters containing Complex Open Chain Radicals.[1]

Dibromobehenic acid (12 grams), obtained by brominating erucic acid, is heated gradually with 7·4 grams of silver arsenate; the reaction occurs between 125° and 170°; 1·5 grams of the arsenate are added and silver bromide is removed quantitatively.

Lecithin (50 grams) is converted into bromolecithin by 10 grams of bromine and the product heated in toluene with the equivalent amount of silver arsenate. After filtering from silver bromide, the toluene is distilled off *in vacuo*, and the residue contains the organic arsenical ester.

3. *Protein Combinations containing Arsenic.*

Insoluble combinations containing firmly attached arsenic are produced by dissolving albumin from white of egg (100 grams) in acetic anhydride at 137°, cooling the solution, and adding phosphoric anhydride (200 grams). The mixture is then treated with arsenious chloride (50 grams), the excess of inorganic reagents subsequently decomposed by water, and the resulting phosphoric and arsenious acids removed from the protein precipitate by washing with water. The preliminary solution in acetic anhydride may be omitted. The product, an amorphous, brown mass, contains 0·6 per cent. of arsenic and 0·8 per cent. of phosphoric oxide; it is insoluble in water, dilute acids, or organic media, but is soluble in dilute aqueous alkalis. It fails to give the ordinary analytical reactions of arsenic with sulphuretted hydrogen or ammonium phosphomolybdate. A similar product is obtained by adding successively sulphur trioxide (200 grams) and arsenious chloride (100 grams) slowly to well-cooled white of egg (1200 grams). The mixture is washed with water till free from sulphuric and arsenious acids.[2]

The product dried at 150° is a yellowish-brown powder insoluble in water or dilute acids, but dissolving in dilute aqueous alkalis; its alkaline solution is not coagulated on warming. The percentages of arsenic and added sulphur trioxide are 0·6 and 0·3 per cent. respectively. Similar products are obtained from casein, plant albumin, glue, peptones, and albumoses;

[1] Wolffenstein, D.R.-P., 239073. [2] Gnezda, D.R.-P., 201370.

they all contain arsenic in a firmly combined form in which its analytical reactions are masked.[1]

An arsenical preparation insoluble in the gastric juices is obtained by adding arsenious chloride diluted with alcohol to gliadin or glutenin suspended in alcohol at the ordinary temperature and stirred for six hours. The alcohol is removed *in vacuo* and after polymerisation the product washed with absolute alcohol. This arsenical albumin is soluble in hot water and contains about 4·33 per cent. of arsenic.[2]

Soluble stable combinations of salvarsan base and protein substances have been produced by the interaction of salvarsan and the alkali salts of lysalbic and protoalbic acids, nucleic acid or casein. The insoluble additive product is dissolved in alkali hydroxide and the alkali salt precipitated by alcohol-ether or obtained solid by evaporating *in vacuo*.[3]

Colloidal iron arsenate-albumose preparations[4] have been suggested for use in therapeutics.

[1] *Cf.* D.R.-P., 104496, 135306, 135307. [2] Kloffer, D.R.-P., 214717.
[3] Dering, D.R.-P., 261542.
[4] Kalle, D.R.-P., *Anmeldung* 23394/Kl 12 *p*.

APPENDIX

Estimation of Arsenic in Organic Compounds.

RECENT developments in the investigation of organic derivatives of arsenic have brought into prominence the problem of estimating this element when directly combined with carbon. The following methods have been adopted for destroying the organic matter in these substances :

(1) Combustion of the substance mixed with soda-lime by heating in a stream of air or oxygen ; the residue is dissolved in hydrochloric or nitric acid, the arsenic then precipitated as sulphide, and finally converted into magnesium pyroarsenate.[1]

(2) Oxidation of the organic arsenic derivative by fusion with sodium peroxide, the arsenic being estimated gravimetrically as pyroarsenate.[2]

(3) Destruction of the organic matter with nitric acid containing magnesium nitrate, when a final ignition leads to the formation of magnesium arsenate.[3]

(4) The substance is carefully mixed with its own weight of potassium nitrate, oxidised with nitric acid. The mixture evaporated to dryness, extracted with acetic acid, and treated successively with sodium acetate and standard uranium acetate solution (1 c.c. = 0·0053 As)$_4$.[4]

Exception has been taken to the sodium peroxide method on the ground that at the high temperature produced by the oxidation some loss of volatile arsenic compounds may result. But with due care in mixing and heating the reagents the loss becomes almost inappreciable, even when the oxidation is violent and the substance employed somewhat volatile.

The chief difficulty arises at a later stage in the precipitation of magnesium ammonium arsenate in the presence of the large

[1] La Coste and Michaelis, *Annalen*, 1880, **201**, 224.
[2] Pringsheim, *Amer. Chem. J.*, 1904, **31**, 386.
[3] Monthulé, *Ann. Chim. anal.*, 1904, **9**, 308.
[4] Martindale, *Extra Pharmacopoeia*, 1915, II. 27.

excess of alkali salt produced from the sodium peroxide. The results obtained are almost uniformly too high, even when measured quantities of "magnesia mixture" and the other reagents are employed. Satisfactory values are obtained by redissolving the magnesium ammonium arsenate and reprecipitating it with ammonia, but this procedure renders the analysis very long and tedious, as the two precipitations each require considerable time for their completion.

The arsenic may be removed by rendering acid with hydrochloric acid and distilling. But the process is lengthy owing to the unavoidably large bulk of solution to be distilled with a ferrous salt in a current of hydrogen chloride.[1]

Iodimetric method of Little, Cahen, and Morgan.

A quicker method giving satisfactory results is based on a volumetric process due to Gooch and Browning.[2]

The reaction involved may be sufficiently indicated by the following equation :

$$As_2O_5 + 4HI \rightleftharpoons As_2O_3 + 2H_2O + 2I_2,$$

these authors having shown that the change takes place quantitatively from left to right, when the liberated iodine is removed by boiling. The arsenious oxide is then titrated with standard iodine in the usual way.

Procedure.[3]

The finely powdered substance (0·2 to 0·3 gram) is mixed in a nickel crucible with 10 to 15 grams of sodium peroxide and sodium carbonate in equal proportions, a portion of these reagents being spread over the mixture to prevent loss by projection. A gentle heat is applied for about fifteen minutes, and the fusion completed by raising the temperature to dull redness for five minutes. With careful mixing and heating, the oxidation generally takes place without fuming or detonation.

The contents of the crucible are extracted with water and rinsed into a 450 c.c. conical flask. From 25 to 31 c.c. of sul-

[1] Morgan, *Chem. Soc. Trans.*, 1904, **85**, 1001.

[2] *Amer. J. Sci.*, 1890, [iii], **11**, 66.

[3] Little, Cahen, and Morgan, *Chem. Soc. Trans.*, 1909, **95**, 1478; *cf.* Warunis, *Chem. Zeit.*, 1912, **31**, 1205; Böhrisch and Küschner, *Pharm. Zentr.-h.* 1911, **52**, 1365.

phuric acid (1 : 1) are added cautiously, and, if necessary, the solution is boiled down to 100 c.c., when 1 gram of potassium iodide is introduced, and the liquid further concentrated to 40 c.c. A few drops of dilute sulphurous acid are added to destroy the last traces of iodine, and the bright green solution is diluted considerably with hot water and saturated with hydrogen sulphide. The arsenious sulphide is collected, washed about three times with hot water, dissolved off the filter with 20 c.c. of *N*/2-sodium hydroxide, and the filtrate returned to the conical flask, where it is treated with 30 c.c. of hydrogen peroxide (20 vols.), the excess of this reagent being destroyed by heating on the water-bath for ten minutes. After the frothing has subsided, a few drops of phenolphthalein are added, followed by 11 c.c. of sulphuric acid (1 : 1), this quantity giving 10 c.c. in excess. One gram of potassium iodide is now added to the liquid, which should have a volume of 100 c.c., and the solution concentrated to 40 c.c., when its pale yellow colour is removed by a few drops of dilute sulphurous acid. Cold water is quickly added, and the diluted solution neutralised with 2*N*-sodium hydroxide and just acidified with sulphuric acid. The requisite amount of 11 per cent. sodium phosphate (see Note 3) is added, and the arsenite solution titrated with standard iodine and starch in the usual way.

Notes on the Method.

1. A gravimetric estimation may be effected by proceeding as far as the oxidation of the sulphide with alkaline hydrogen peroxide and then precipitating as magnesium ammonium arsenate by Austin's method.[1]

2. The manipulation might be simplified by estimating directly, by Gooch and Browning's method, the arsenate in the filtered aqueous extract of the fused mass. The filtration of nickel hydroxide and carbonate is, however, extremely tedious, and this modification of the process does not lead to greater rapidity or accuracy. The precipitate may be rendered more amenable by oxidation to nickelic hydroxide with the aid of bromine, but the results obtained in the titration are not satisfactory.

3. The titration may be carried out in the presence of sodium hydrogen carbonate, but the addition of disodium hydrogen

[1] *Zeitsch. anorg. Chem.*, 1900, **23**, 146.

phosphate, which has been advocated by E. W. Washburn,[1] is preferable. The volume of 11 per cent. sodium phosphate added should be equal to the number of c.c. of $N/10$-iodine required in the titration.

4. This method gives trustworthy results with all the commercial arsenical derivatives, whether containing triadic or pentadic arsenic.

Iodimetric method of Ewins.

A method of estimating arsenic in organic tissues, devised by Norton and Koch,[2] has been successfully utilised in the estimation of the metalloid in its organic derivatives.[3] The principle is essentially that of Kjeldahl's method of the determination of nitrogen adapted to the estimation of arsenic (or antimony).

In a comparatively simple and rapid method of determining arsenic in salvarsan and neosalvarsan described by Lehmann,[4] the substance is completely oxidised by means of permanganate and concentrated sulphuric acid, the product further treated with hydrogen peroxide, and the arsenic finally estimated volumetrically by the amount of iodine liberated from an acid solution containing potassium iodide. The method is rapid (one to one and a half hours for the estimation), and gives accurate results with the compounds mentioned and certain closely allied derivatives provided adequate precautions are taken to ensure the complete elimination of excess of hydrogen peroxide (merely boiling is insufficient). In certain cases, however, the method entirely fails, owing to the fact that preliminary treatment with potassium permanganate and sulphuric acid does not bring about complete oxidation. Benzarsinic acid and dimethyl- and diethyl-benzarsinic acids are especially resistant to this treatment. The method of Norton and Koch is applicable to such compounds, and quite satisfactory results have been obtained with arsenic derivatives of widely differing constitution. The method requires only the simplest apparatus and materials, needs very little attention, and is applicable to all but very volatile arsenic derivatives. Essentially it consists in the moist combustion of the organic compounds

[1] *J. Amer. Chem. Soc.*, 1908, **30**, 31.
[2] *Ibid.*, 1905, **27**, 1247.
[3] Ewins, *Chem. Soc. Trans.*, 1916, **109**, 1356.
[4] *Apoth. Zeit.*, 1912, **27**, 545.

by means of concentrated sulphuric acid ; the arsenic present is converted into arsenious acid, which is finally estimated volumetrically by means of iodine in the usual manner.

Procedure.

A small quantity of the substance (0·1 to 0·2 gram) is washed into a long-necked Kjeldahl flask of about 300 c.c. capacity. Ten grams of potassium sulphate and 0·2 to 0·3 gram of starch are then added. Any solid adhering to the neck of the flask is washed in with a little water. Twenty c.c. of concentrated sulphuric acid are next cautiously added, and the flask is then placed on a wire gauze over a Bunsen flame. As soon as the contents of the flask begin to froth the flame is lowered somewhat until the frothing diminishes, which generally happens within about ten to fifteen minutes from the commencement of heating. The flame is then again turned on full, and heating continued until the liquid becomes colourless or of a very pale yellow tint. The flask is shaken once or twice during the heating in order to wash down any material adhering to the walls. The time required for the complete combustion of the material is usually about four hours, but during the greater part of this time the flask may safely be left without attention.

The contents of the flask are next allowed to cool, and then washed quantitatively into a flat-bottomed flask of about 350 c.c. capacity. A solution of sodium hydroxide (10–12*N*) is then added from a burette until the solution is just distinctly alkaline to litmus.

The flask and its contents are then cooled to about 30–40°, and a few drops of concentrated sulphuric acid added until the solution is again distinctly acid. A saturated solution of sodium hydrogen carbonate is next added from a burette until the solution becomes distinctly alkaline and an excess of 5–10 c.c. of the reagent is present.

To this solution is now added 2 c.c. of a 1 per cent. solution of starch, and the arsenious acid present is titrated by means of a *N*/20-solution of iodine. Towards the end of the titration the solution usually develops a reddish-violet tint, which fades perceptibly on keeping. The end-point, however, is only reached when the solution acquires the characteristic deep blue colour given by free iodine in the presence of starch. This blue colour, moreover, shows no tendency to fade on keeping.

From the amount of iodine required, the percentage of arsenic present is easily calculated. One c.c. of *N*/20-iodine ≡ 0·001875 gram of arsenic.

The Pharmacopœia Germanica oxidises 0·2 gram of the arsenic compound with 10 c.c. of concentrated sulphuric acid and 1 c.c. of fuming nitric acid in a long-necked 100 c.c. Jena flask. After boiling for one hour the cooled mixture is treated with 50 c.c. of water and evaporated, this procedure being repeated. To the cold solution are added successively 10 c.c. of water and 2 grams of potassium iodide in 5 c.c. of water, sufficient water being added to dissolve the precipitate. After thirty minutes the iodine is titrated (without an indicator) with *N*/10 sodium thiosulphate : 1 c.c. ≡ 0·003748 gram of arsenic.

Analysis of very Volatile Arsenicals.

Gaseous and very volatile arsenical compounds such as methylarsine and phenylarsine are analysed as follows by Palmer and Dehn.[1]

The carbon and hydrogen are estimated by combustion in a long tube packed with lead chromate and copper oxide, the burning being conducted in a current of oxygen. For the arsenic estimation a similar tube is employed packed with pure zinc oxide. The contents are dissolved in acid, the arsenic precipitated as arsenious sulphide, oxidised to arsenic acid, and reprecipitated as magnesium ammonium arsenate and weighed as pyroarsenate.

Separation of Arsenic Acid from p*-Arsanilic Acid and its Derivatives.*

Sufficient hydrochloric acid is added to decompose the alkali salt of the organic arsinic acid. The substituted arsanilic acids are usually precipitated completely from the cooled acid solution, and the arsenic acid remaining in the filtrate is then thrown down as magnesium ammonium arsenate and weighed as pyroarsenate.

p-Arsanilic acid itself is not, however, precipitated completely in the foregoing circumstances. The soluble portion is converted into its azo-resorcinol derivative, which is precipitated almost completely, the last trace of colour being removed by animal charcoal.[2]

[1] *Ber.*, 1901, **34**, 3597.

[2] Schmitz, *Ber.*, 1914, **47**, 364.

Estimation of Antimony in Organic Compounds.

In the combustion of organic antimony derivatives Landolt employed a mixture of warm copper oxide with 4–5 per cent. of potassium chlorate which was kept dried over concentrated sulphuric acid. The estimation of carbon and hydrogen in an organic antimonial is effected satisfactorily with oxygen in a lead chromate combustion tube when the antimony is fixed as lead antimonate.

The antimony is estimated by heating with a mixture of sodium peroxide and sodium carbonate as in the fusion method for arsenic in its organic derivatives. The fused mass is rendered slightly acid either with hydrochloric acid alone or mixed with phosphoric acid, and the antimony is precipitated by sulphuretted hydrogen from the boiling solution in the form of the black, crystalline, anhydrous antimonious sulphide. This precipitate is collected in a broad Soxhlet tube so arranged that it can be heated to 280–300° by a ring burner. The Soxhlet tube is fitted with a glass stopper carrying a thermometer and furnished with a side tube through which carbon dioxide is passed during the heating in order to exclude air from the sulphide.[1] By this procedure the antimony can be determined gravimetrically as trisulphide.

Antimony when present in aromatic stibines and their derivatives is estimated by burning the substance with oxygen in a narrow tube containing lime and soda-lime, dissolving out the contents of the tube with hydrochloric acid, and precipitating the antimony as trisulphide. This substance is oxidised and weighed as Sb_2O_4.[2]

[1] Cahen and Morgan, *Analyst*, 1909, **34**, 3.

[2] Michaelis and Reese, *Annalen*, 1886, **233**, 46; Löloff, *Ber.*, 1897, **30**, 2835.

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INDEX OF AUTHORS' NAMES

INDEX OF SUBJECTS

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Emeritus Professor of General Chemistry in the Imperial College of Science and Technology, South Kensington; and formerly Principal of the Government Laboratory, London.

INTRODUCTION

DURING the last four or five decades the Applications of Chemistry have experienced an extraordinary development, and there is scarcely an industry that has not benefited, directly or indirectly, from this expansion. Indeed, the Science trenches in greater or less degree upon all departments of human activity. Practically every division of Natural Science has now been linked up with it in the common service of mankind. So ceaseless and rapid is this expansion that the recondite knowledge of one generation becomes a part of the technology of the next. Thus the conceptions of chemical dynamics of one decade become translated into the current practice of its successor; the doctrines concerning chemical structure and constitution of one period form the basis of large-scale synthetical processes of another; an obscure phenomenon like Catalysis is found to be capable of widespread application in manufacturing operations of the most diverse character.

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will afford examples of the application of recent knowledge to modern manufacturing procedure. As regards their scope, it should be stated the books are not intended to cover the whole ground of the technology of the matters to which they relate. They are not concerned with the technical *minutiæ* of manufacture except in so far as these may be necessary to elucidate some point of principle. In some cases, where the subjects touch the actual frontiers of progress, knowledge is so very recent and its application so very tentative that both are almost certain to experience profound modification sooner or later. This, of course, is inevitable. But even so such books have more than an ephemeral interest. They are valuable as indicating new and only partially occupied territory; and as illustrating the vast potentiality of fruitful conceptions and the worth of general principles which have shown themselves capable of useful service.

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