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No. 4

PREPARATION OF ACID PHENYLIC SALTS OF DIBASIC ACIDS.

BY

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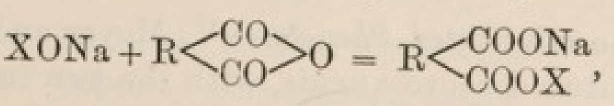
Preparation of Acid Phenylic Salts of Dibasic Acids.

By Samuel Barnett Schryver, D.Sc., Ph.D.

It has long been known that anhydrides of dibasic organic acids, on treatment with alcohols or with alcoholic solutions of sodium alcoholates, are readily converted into the acid alkylic salts or their corresponding sodium compounds. Under certain conditions, which will be specified, sodium derivatives of phenols are capable of forming sodium phenylic salts by interaction with the anhydrides of dibasic organic acids, in accordance with the general equation :



$$XONa + R\begin{matrix}\diagup CO \diagdown \\ \diagdown CO \diagup\end{matrix}O = R\begin{matrix}\diagup COONa \\ \diagdown COOX\end{matrix},$$

where X is the phenylic residue, and R the residue of a dibasic acid (compare Walker, Trans., 1892, **41**, 1089). The reaction must be carried out in the presence of a liquid which is incapable of acting chemically either on the sodium salt or the anhydride, and xylene was employed in most cases, as it can be heated on a water-bath without the necessity of using a condenser ; several other hydrocarbons are, however, equally suitable.

The sodium salt is very conveniently prepared in most cases by the direct action of sodium on a solution of the phenol in the solvent in which the reaction is to be carried out. The reaction generally takes place immediately on adding the anhydride to the sodium salt, and often with the evolution of a considerable amount of heat ; on cooling, the sodium phenylic salt separates, generally in a gelatinous form, and can be extracted with water. From the aqueous solution thus obtained, the acid salt can be precipitated by the addition of mineral acids.

The reaction is also applicable to substituted phenols, but of these there are two classes at present known, which will not react with anhydrides in the way just described.

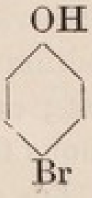
(a) *The Ortho- and Para-nitrophenols.*—Whereas metanitrophenol acts on camphoric anhydride with ease, the ortho- and para-derivatives do not react with it, even when the mixture is heated to 180°.

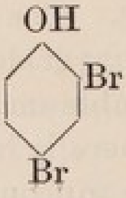
Several instances have been pointed out recently in which the meta-compound acts quite differently from both the ortho- and para-derivatives. Lobry de Bruyn (*Rec. Trav. Chem.*, 1894, **13**, 101) has shown that whereas ortho- and para-dinitrobenzene are readily converted into ethoxynitrobenzenes by the action of alcohol, the meta-compound does not react with alcoholic ammonia, even at 250°. Menschutkin (*Ber.*, 1897, **30**, 2968) shows further that meta-nitrobromobenzene will not react with dipropylamine, although both the ortho- and para-derivatives form condensation products with it with relative ease. On the other hand, metatoluidine acts on allylic bromide more readily than either the ortho- or para-compound, the relative rates of reaction being 54 for the ortho-, 445 for the meta-, and 96 for the para-derivative.

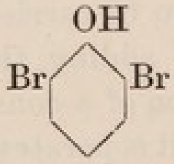
It will be noted that in the two cases where a metanitro-compound does not react, the strongly negative nitro-group causes the other substituted group or element to resist the action of a basic substance (alcoholic ammonia or propylamine). The converse is observed, however, in the action of nitrophenols on anhydrides, and whilst the nitro-group protects the hydroxyl radicle in the ortho- or para-position, metanitrophenol readily reacts with a substance of acidic character.

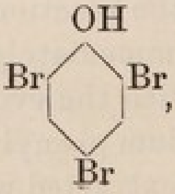
(b) *The Diortho-substituted Phenols.*—V. Meyer and his pupils have shown that substituted benzoic acids, with the two substituent groups in the ortho-position relatively to the carboxylic group, are incapable of forming alkyl salts when treated with an alcohol and hydrochloric acid (V. Meyer and Sudborough, *Ber.*, 1894, **27**, 510, 512, 1580, 3146); benzamides derived from such acids, moreover, appear to be hydrolysed with very great difficulty (Sudborough, Trans., 1895, **65**, 603). The sodium salts of diortho-substituted phenols will not condense with anhydrides.

This law has been confirmed by an investigation of the reactions of the following bromophenols with camphoric anhydride :









as it was observed that, whereas the sodium salt of the first two compounds readily underwent condensation, yielding the well crystallised bromophenyl hydrogen camphorates on acidification, the other two bromophenols did not react even at 180°.

The analogy between these facts and those observed by V. Meyer and his pupils on the etherification of substituted benzoic acids is certainly striking. The general law, however, has only been tested by the reactions of the bromo-substitution products, as pressure of other work has prevented me from following this subject further. It must therefore be left an open question whether the non-reactivity of the diortho-substituted products is to be ascribed to the stereochemical influence of the substituent groups (V. Meyer), or to the proximity of the hydroxyl radicle to two other groups of strongly negative character; in other words, whether it is due to a dynamic or a static cause.

In the action of camphoric anhydride on sodium derivatives of phenols, only one acid phenylic salt was obtained in each case, except in that of metanitrophenyl camphorate, which was formed in very small quantity; the crystalline compounds seemed homogeneous, and melted sharply, frequent recrystallisation failing to alter the melting point to any appreciable extent. No mixtures corresponding to the allo- or ortho-monomethylic salts were obtained (Braunschweig, *Ber.*, 1892, **25**, 1806; Walker, Trans., 1892, **41**, 1089).

Several of the products described in the following work may find applications for therapeutic purposes.

EXPERIMENTAL.

I. *Action of Anhydrides on the Sodium Derivatives of simple Phenols, or Ethers of polyhydric Phenols.*

Phenyl Hydrogen Camphorate, $COOH\cdot C_8H_{14}\cdot COO\cdot C_6H_5$.—Sodium, in wire or small pieces, was added to a molecular proportion of pure phenol dissolved in ten times its weight of xylene, and the mixture warmed to about 90°; the sodium dissolved, and the sodium phenate which is formed separated as a white powder. As soon as this action was completed, a molecular equivalent of camphoric anhydride was added to the solution while still warm, and the mixture vigorously shaken; the sodium phenate dissolved almost immediately, and after a short time sodium phenyl camphorate separated in a gelatinous form. The mixture was vigorously shaken with water, equal in volume to that of the xylene, to dissolve the sodium salt, and on acidifying, phenyl hydrogen camphorate separated as an oil. This was taken up with ether, the ethereal solution dried over calcium chloride, and after distilling off the ether, the residue was left in a vacuum for a few days, when the light yellow oil commenced to solidify, forming hard clusters of radiating needles, which can be separated only with some difficulty from the sides of the crystallising basin. After drying on a porous plate and recrystallising from a mixture of chloroform and light petroleum, they melted sharply at 100°.

0·1086 gave 0·2768 CO_2 and 0·0709 H_2O. C = 69·51 ; H = 7·25.
$C_{16}H_{20}O_4$ requires C = 69·56 ; H = 7·25 per cent.

Thymyl Hydrogen Succinate, $COOH\cdot CH_2\cdot CH_2\cdot COO\cdot C_{10}H_{13}$.—Thymol dissolved in xylene was treated with metallic sodium, the same relative quantities being used as in the preparation of sodium phenate. The sodium derivative of thymol is readily soluble in xylene, and since the solution darkens very rapidly—as a result, probably, of oxidation—the anhydride should be added as soon as the sodium has dissolved ; the dark colour of the solution then disappears, and the sodium thymyl succinate separates in the form of a light yellow, gelatinous mass. It is extracted with water, and the acid salt, precipitated from the aqueous solution, separates as an oil which very readily solidifies, forming a mass of granular crystals. For analysis, it was twice recrystallised from a mixture of chloroform and light petroleum, from which it separated in aggregates of well-defined crystals melting at 121—122°.

0·1145 gave 0·2809 CO_2 and 0·0780 H_2O. C = 66·89 ; H = 7·56.
$C_{14}H_{18}O_4$ requires C = 67·20 ; H = 7·20 per cent.

Thymyl Hydrogen Phthalate, $COOH\cdot C_6H_4\cdot COO\cdot C_{10}H_{13}$.—This compound, prepared in exactly the same way as the corresponding succinate, is precipitated from the solution of the sodium salt as an oil which readily solidifies ; it forms aggregates of well-defined crystals when precipitated from an ethereal solution by light petroleum, and the specimen analysed was twice recrystallised in this way.

0·1267 gave 0·3371 CO_2 and 0·0669 H_2O. C = 72·55 ; H = 5·82.
$C_{18}H_{18}O_4$ requires C = 72·47 ; H = 6·04 per cent.

Thymyl Hydrogen Camphorate, $COOH\cdot C_8H_{14}\cdot COO\cdot C_{10}H_{13}$.—This salt, prepared by a similar method from camphoric anhydride, is precipitated by mineral acids from the solution of its sodium salt as an oil which often does not solidify for several days ; it then forms an indistinct, light yellow mass, which is readily soluble in ether, chloroform, and light petroleum. The specimen analysed was twice recrystallised from the last named solvent, from which it separated in the form of hard, nodular masses melting at 89°. It has a slight local anæsthetic action, producing a feeling of numbness when placed on the back of the tongue.

0·1172 gave 0·3119 CO_2 and 0·900 H_2O. C = 72·58 ; H = 8·52.
$C_{20}H_{28}O_4$ requires C = 72·28 ; H = 8·43 per cent.

The sodium salt of this compound, like the other sodium thymyl salts, is very readily hydrolysed by warm water; the acid salts, on the other hand, are fairly stable.

Guaiacyl Hydrogen Camphorate, $COOH\cdot C_8H_{14}\cdot COO\cdot C_6H_4\cdot OCH_3$.—Guaiacol, dissolved in ten times its weight of xylene, is heated at about 90° with a molecular proportion of sodium, either in wire or small slices; the sodium derivative thus formed is fairly readily soluble in warm, although sparingly so in cold xylene. As soon as the sodium has dissolved, camphoric anhydride (1 mol.) is added to the solution while still warm, and an immediate reaction takes place, sodium guaiacyl camphorate separating after a short time as a white, somewhat gelatinous mass. This is extracted with water, and, on acidifying, guaiacyl hydrogen camphorate separates as an oil, which begins to crystallise almost immediately and after a short time forms a hard, granular mass which can be readily pounded in a mortar. The camphorate analysed was twice recrystallised from a mixture of chloroform and light petroleum, from which it separated in white, glistening needles melting at 112°. It is very soluble in acetone or alcohol, the concentrated solution in the latter forming a thick syrup.

0·1018 gave 0·2476 CO_2 and 0·0675 H_2O. $C=66·33$; $H=7·46$.
$C_{17}H_{22}O_5$ requires $C=66·61$; $H=7·13$ per cent.

4·2064 substance dissolved in alcohol required for complete neutralisation 13·9 c.c. (calculated 13·5 c.c.) of N-soda, with phenolphthalein as indicator. The neutral solution thus prepared, after dilution with water, gave the following reactions:

$AgNO_3$. White precipitate, rapidly darkening.
$HgCl_2$. White, gelatinous precipitate.
$FeCl_3$. Buff-coloured precipitate, rapidly turning grey.
$CuSO_4$. Bright green precipitate.
$ZnCl_2$. White precipitate.
$Bi(NO_3)_3$. White precipitate.

Normal guaiacyl camphorate, $C_8H_{14}(COO\cdot C_6H_3\cdot OCH_3)_2$, was prepared by warming the acid salt with a molecular equivalent of phosphorus pentachloride, adding a molecular equivalent of guaiacol, and heating on the water-bath until only small quantities of hydrogen chloride were evolved; the product was then poured into ice-water. The normal salt, which at first separated as an oil, but solidified after a short time, was then recrystallised once or twice from hot alcohol, in which it is readily soluble, although only sparingly so in the cold. The specimen analysed was crystallised finally from a mixture of chloroform and light petroleum, and was obtained in stellate clusters of thin, white needles which melted at 124°.

0·1231 gave 0·3162 CO_2 and 0·0800 H_2O. C = 70·05; H = 6·58.
$C_{24}H_{28}O_6$ requires C = 69·90; H = 6·79 per cent.

Guaiacyl Hydrogen Succinate, $COOH·CH_2·CH_2·COO·C_6H_4·OCH_3$.—Owing to the readiness with which the sodium salt undergoes hydrolysis, the following method was adopted for its preparation; benzene was used instead of xylene, and the sodium guaiacyl succinate was collected, pressed, dried, powdered, and thrown in small quantities at a time into 10 per cent. sulphuric acid on which a layer of ether floated. The acid salt thus formed was immediately taken up by the ether, and remained only for a very short time in contact with the water. After evaporating the ether and leaving the residue in a vacuum for some days, a mass of crystals was obtained, which was dried on a porous plate and then dissolved in ether; the ethereal solution, after filtration from a small quantity of sparingly soluble matter, was mixed with sufficient light petroleum to precipitate only a portion of the substance, as the first fraction was likely to contain small quantities of succinic acid. The crystalline residue, obtained by evaporating the filtrate, was dissolved in chloroform, to which light petroleum was then added, the succinate separating in beautiful, stellate aggregates of needles which melted at 75°.

0·1070 gave 0·2301 CO_2 and 0·0504 H_2O. C = 58·65; H = 5·23.
$C_{11}H_{12}O_5$ requires C = 58·93; H = 5·35 per cent.

Carvacryl Hydrogen Camphorate.—Sodium dissolves in a warm solution of carvacrol in xylene, and the sodium derivative crystallises on cooling. Carvacrol hydrogen camphorate prepared in the usual way forms a syrup, which does not crystallise even when surrounded by a cooling mixture.

Eugenyl Hydrogen Camphorate, $COOH·C_8H_{14}·COO·C_9H_8·OCH_3$.—Sodium dissolves readily in a mixture of a hydrocarbon and eugenol, forming a dark coloured solution. The eugenyl hydrogen camphorate, when isolated in the ordinary way, is a dark coloured mass which can be purified by boiling its solution in benzene with animal charcoal, and finally recrystallising from benzene and light petroleum. It melts at 115·5°.

0·4856 gram was equivalent to 13·9 c.c. N/10 sulphuric acid (calculated 14·0 c.c.) when titrated in alcoholic solution with barium hydroxide, using phenolphthalein as indicator.

β-Naphthyl Hydrogen Camphorate, $COOH·C_8H_{14}·COO·C_{10}H_7$.—Sodium dissolves with some difficulty in a solution of β-naphthol in xylene, and the sodium salt thus formed has a somewhat dark colour. It reacts readily, however, with camphoric anhydride, and the β-naphthyl hydrogen camphorate can be isolated easily, but is obtained pure only with difficulty, as it is somewhat strongly coloured when first precipitated. In order to recrystallise it, light petroleum is added to its solution in chloroform until a permanent turbidity is produced; more light petroleum is then poured carefully over this mixture, so as to form a layer on the top and as it slowly diffuses through the heavier underlying liquid, the naphthyl camphorate separates in radiating clumps of light pink crystals which melt at 121—122°.

0·4644 gram corresponds to 14·1 N/10 sulphuric acid (calculated 14·0 c.c.) when neutralised with barium hydroxide in alcoholic solution, using phenolphthalein as indicator.

II. *Action of Anhydrides on Substituted Phenols.*

In the reactions described under this heading, camphoric anhydride was used, for the following reasons:

(*a*) Its solubility in xylene, in which all the reactions were carried out: hence the greater ease with which it reacts, compared with other anhydrides.

(*b*) The relatively greater stability of the camphorates as compared with the succinates and other acid salts investigated: hence the greater ease in isolating the products of reaction.

Salyl Hydrogen Camphorate.—Sodium dissolves in a warm solution of salol (phenyl salicylate) in xylene, forming a white derivative which readily reacts with camphoric anhydride; the product is a thick syrup which does not crystallise on long standing, even when surrounded by a freezing mixture.

Nitrophenols and Camphoric Anhydride.—The sodium orthonitrophenate for these experiments was made, partly by the direct action of sodium on a warm solution of the phenol in xylene and partly by dissolving the phenol in alcohol, adding the theoretical quantity of sodium ethoxide in alcohol, and precipitating the red sodium salt thus formed by ether. The sodium derivative of the paranitrophenol was prepared by the former, that of the meta-derivative by the latter method. Neither the ortho- nor the para-derivative reacted with camphoric anhydride, even after prolonged heating at 180°; the metanitro-compound, however, entered into reaction with it fairly readily.

Metanitrophenyl hydrogen camphorate, $COOH{\cdot}C_8H_{14}{\cdot}COO{\cdot}C_6H_4{\cdot}NO_2$.—This salt was obtained when camphoric anhydride was dissolved in ten times its weight of xylene, the solution heated on a water-bath, and the solid metanitrophenol added, with continual stirring; after a time, the red compound dissolved, and, on cooling, the nitrophenyl camphorate separated in the form of a light yellow, gelatinous mass. The acid camphorate, isolated in the usual way, completely solidified after some time. It was insoluble in light petroleum and only slightly soluble in chloroform, but dissolved readily in warm benzene, from which it was precipitated by light petroleum. It commenced to melt at 115°, although it was not completely fused until some degrees higher. Possibly the substance was a mixture of the allo- and ortho-compounds.

0·2243 gave 8·6 c.c. moist nitrogen at 15° and 767 mm. N = 4·4.

$C_{16}H_{19}NO_6$ requires N = 4·3 per cent.

Succinic anhydride heated with the sodium derivative of orthonitrophenol also gave no reaction. Probably the method just described may be generally applied to nitrophenols to distinguish the meta- from the ortho- and para-compounds.

Action of Camphoric Anhydride on Sodium Bromophenates.

Parabromophenyl Hydrogen Camphorate, $COOH\cdot C_8H_{14}\cdot COO\cdot C_6H_4Br$.—Sodium readily dissolves in a warm solution of parabromophenol in xylene, forming a white derivative; this goes into solution on adding camphoric anhydride, and the mixture deposits sodium bromophenyl camphorate on standing. On acidifying the aqueous solution of this salt with mineral acids, the acid separates almost immediately in a crystalline form. It is very readily soluble in chloroform, and when precipitated from solution in this solvent by light petroleum, separates in radiating masses of hard, thick needles, which are not perfectly white and melt at 111°.

0·2421 gave 0·1303 AgBr. Br = 22·9.

$C_{16}H_{19}BrO_4$ requires Br = 22·6 per cent.

2:4-*Dibromophenyl Hydrogen Camphorate*, $COOH\cdot C_8H_{14}\cdot COO\cdot C_6H_3Br_2$.—2 : 4-Dibromophenol was prepared by the action of bromine on a solution of phenol in carbon bisulphide in the presence of small quantities of aluminium chloride. The carbon bisulphide solution of the bromophenol thus formed was washed, first with water, then with dilute alkali, and dried; after removing the carbon bisulphide by evaporation, the residue was fractionally distilled in a vacuum.

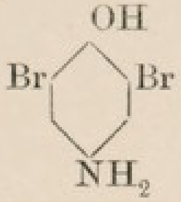
From the pure dibromo-compound thus obtained, 2 : 4-dibromophenyl hydrogen camphorate was prepared in exactly the same way as the corresponding monobromo-derivative. It very readily crystallises, and is easily soluble in hot, although somewhat sparingly in cold, chloroform, and separates in the form of dendritic masses of small crystals melting at 173°.

0·1711 gave 0·1467 AgBr. Br = 36·5.

$C_{16}H_{18}Br_2O_4$ requires Br = 36·8 per cent.

Action of Camphoric Anhydride on Sodium 2 : 6-Dibromophenate.

2 : 6-Dibromophenol was obtained in small quantity by distilling tetrabromophenolphthalein with concentrated sulphuric acid (Baeyer, *Annalen*, 1880, **202**, 138); the yield, however, was extremely small. It was finally prepared from Fischer and Hepp's diorthobromamidophenol (*Ber.*, 1888, **21**, 674).



This was dissolved in four times its weight of alcohol, and to the solution rather more than the theoretical quantity of ethylic nitrite was added in 16 per cent. alcoholic solution; after some time, the whole was dropped gradually into an equal bulk of boiling alcohol, and kept in the state of constant ebullition for about one hour. The alcohol was then distilled off, and the residual oil distilled in steam. The dibromophenol thus obtained, being somewhat coloured, was purified by fractional distillation in a vacuum, and then had a constant boiling point not far removed from that of the 2 : 4-dibromo-compound.

2 : 6-Dibromophenol did not react with camphoric anhydride, either when treated under the same conditions as the 2 : 4-bromo-compound, or when the mixture was heated in sealed tubes at 150°.

The 2 : 4 : 6-tribromophenol was prepared in the usual way, and recrystallised several times from aqueous alcohol. It reacted with the anhydride neither at the temperature of a water-bath nor at 180° in sealed tubes.

Action of Camphoric Anhydride on Sodium Nitrosophenates.

Sodium derivatives were made from nitrosophenol and nitrosothymol by the action of sodium ethoxide on the alcoholic solutions and precipitation by ether. The sodium derivative of nitrosothymol prepared in this way did not separate immediately but only after some little time; it crystallised in dichroic golden plates reflecting a green light, and when dried in mass formed a brick-red powder.

When warmed with a 10 per cent. solution of camphoric anhydride in xylene on a water-bath, the sodium derivative of nitrosophenol charred before any reaction occurred. A similar result was obtained with nitrosothymol, although the latter, when left for a long time with a more dilute solution of the anhydride in xylene, partially disappeared, forming a white sodium salt which was not further investigated.

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