

LXX.—*The Action of Phosphorus Pentachloride on the Methylene Ethers of Catechol Derivatives. Part IV. Derivatives of Dihydroxyphenyl-acetic, -glycollic, and -glyoxylic Acids.*

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DERIVATIVES of ethylcatechol have recently received much attention on account of their relationship to epinephrine (adrenaline); certain cyclic carbonates and methylene ethers belonging to this class were described a short time ago by one of us (*Trans.*, 1908, **93**, 2081), and the same and closely related derivatives have been obtained simultaneously by Pauly (*Ber.*, 1908, **41**, 4151) and by Böttcher (*Ber.*, 1909, **42**, 253). The latter author claims to have accomplished a new synthesis of the active principle of the suprarenal gland—a claim the validity of which has been questioned by Pauly (*Ber.*, 1909, **42**, 484), not without reason.

While working at this subject we were induced to prepare other

substances containing the complex $\text{HO} \begin{array}{c} \text{HO} \\ \diagdown \quad \diagup \\ \text{---} \text{---} \text{---} \\ \diagup \quad \diagdown \end{array} \text{CH(OH) \cdot C}$ in order to compare their solubility in water with that of epinephrine, which, strangely enough for a substance of this type, is insoluble in water. In particular we attempted the preparation of the methylamide of 3:4-dihydroxymandelic acid, $\text{C}_6\text{H}_3(\text{OH})_2 \cdot \text{CH(OH) \cdot CO \cdot NH \cdot CH}_3$; we found this substance to be very soluble in water, and were unable to obtain it in the pure state. As was to be expected, it was physiologically inert, and it could not be reduced to a physiologically active base.

The above amide was prepared from the corresponding ethyl ester, which we isolated in a pure crystalline condition. It is readily soluble in water or alcohol, and dihydroxymandelic acid itself is extremely soluble, in contrast to epinephrine.

The starting point of our experiments was the observation that, although 3:4-methylenedioxymandelic acid itself can only be prepared in small quantities by the method given by Lorenz (*Ber.*, 1881, **14**, 793), a good yield of the corresponding ethyl ester is directly obtainable from piperonalcyanohydrin. From this ester we prepared the acid, and from the latter by phosphorus pentachloride the acid chloride, $\text{CCl}_2 \cdot \text{O}_2 \cdot \text{C}_6\text{H}_3 \cdot \text{CHCl} \cdot \text{COCl}$, which could be easily purified by distillation. By treatment with formic acid, the cyclic carbonate of 3:4-dihydroxyphenylchloroacetic acid, $\text{CO} \cdot \text{O}_2 \cdot \text{C}_6\text{H}_3 \cdot \text{CHCl} \cdot \text{CO}_2\text{H}$, re-

sulted, which, on boiling with water, was converted into 3:4-dihydroxymandelic acid.

The ethyl ester could not be readily prepared from the acid; in order to obtain it, we utilised an observation, that when ethyl 3:4-methylenedioxymandelate is heated with only three molecular proportions of phosphorus pentachloride at comparatively low temperatures, scarcely any acid chloride is formed, the ester grouping remaining intact. In this way we obtained, by a series of reactions analogous to those already described, ethyl 3:4-dihydroxymandelate in a pure condition. Like homoprotocatechuic acid, this ester contains three hydroxyl groups, is readily soluble in water, and but sparingly so in boiling xylene; 3:4-dihydroxymandelic acid contains four hydroxyl groups, is quite insoluble in boiling xylene, and extremely soluble in water.

In some of our experiments with phosphorus pentachloride (as well as with thionyl chloride) at a higher temperature (180—200°), we observed the partial conversion of the derivatives of dihydroxyphenylchloroacetic acid into derivatives of dihydroxyphenyldichloroacetic acid; whilst the former could be converted into derivatives of dihydroxyphenylglycollic acid, the latter ultimately yielded dihydroxyphenylglyoxylic acid, $C_6H_3(OH)_2 \cdot CO \cdot CO_2H$. The methylene ether of this acid had been previously obtained by the oxidation of safrole; we prepared it more conveniently by oxidising the corresponding hydroxy-acid. Its methylamide, $CH_2 : O_2 : C_6H_3 \cdot CO \cdot CO \cdot NH \cdot CH_3$, was also obtained by condensing piperonyl chloride with methyl isocyanide.

The formation of derivatives of phenyldichloroacetic acid from those of phenylmonochloroacetic acid by means of phosphorus pentachloride, referred to above, is quite analogous to the oxidation of piperonyloin (a benzoin derivative) to dicarbonyltetraoxybenzil, previously described by us (*Trans.*, 1908, **93**, 736) as the result of the action of thionyl chloride; in either case the grouping $CH(OH) \cdot CO$ is oxidised to $CCl_2 \cdot CO$.

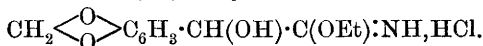
We may here review the conditions under which the various chlorine atoms introduced by phosphorus pentachloride (and thionylchloride) are eliminated from the compounds described in this and in previous papers. The chlorine atoms in the methylene group, and in aliphatic carboxyl groups, are the most labile, and are removed by formic acid without boiling, and by exposure to moist air in the cold. The chlorine atom in 3:4-carbonyldioxybenzoyl chloride is somewhat more stable, and is only removed by boiling with formic acid for a short time (*Trans.*, 1908, **93**, 568).

Next in order of stability come apparently the pair of chlorine atoms in an aldehyde group, as in 3:4-carbonyldioxybenzylidene chloride, which require boiling with formic acid for some time (Pauly,

Ber., 1907, **40**, 3096). The removal of the two chlorine atoms, which gives rise to a diketone (*Trans.*, 1908, **93**, 737) or a ketonic acid (the present paper), is only accomplished slowly by prolonged boiling with formic acid. Finally, the single chlorine atom replacing an alcoholic hydroxyl group (*Trans.*, 1908, **93**, 2084, and the present paper) is quite resistant to boiling formic acid, and has to be eliminated by water.

EXPERIMENTAL.

3 : 4-*Methylenedioxyphenylhydroxyacetimino-ethylether Hydrochloride*,



Piperonal (20 grams) is melted, and a concentrated solution of sodium hydrogen sulphite (15 grams) in warm water is stirred in. The additive compound which separates out is collected, washed, and made into a thick paste with a little water. A cold aqueous saturated solution of potassium cyanide (10 grams) is then added; on stirring, the bisulphite compound dissolves completely, and the piperonalcyanohydrin separates as a colourless liquid, which soon becomes pink. It is dissolved in ether, the ethereal solution is filtered, and dried. After the addition of rather more than one molecular proportion of alcohol, the solution is saturated with hydrogen chloride at a temperature below 10°. On standing for a short time, the solution is transformed into a mass of crystals. After draining and washing with dry ether, the pure hydrochloride is obtained. It melts and decomposes at 118—119°. Yield = 60 per cent. of the theoretical:

0.2067 gave 0.1104 AgCl. Cl = 13.3.

$\text{C}_{11}\text{H}_{14}\text{O}_3\text{NCl}$ requires Cl = 13.7 per cent.

Ethyl 3 : 4-Methylenedioxymandelate, $\text{CH}_2 \begin{array}{c} \diagup \text{O} \diagdown \\ \diagdown \text{O} \diagup \end{array} \text{C}_6\text{H}_3 \cdot \text{CH}(\text{OH}) \cdot \text{CO}_2\text{Et}.$

The hydrochloride described above is warmed with water. The ester separates as an oil which solidifies on cooling. When crystallised from xylene it forms white needles melting at 72° and boiling at 179—181°/8 mm., 197°/15 mm. The yield is almost quantitative:

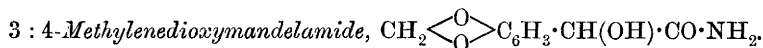
0.1631 gave 0.3499 CO_2 and 0.0786 H_2O . C = 58.5; H = 5.4.

$\text{C}_{11}\text{H}_{12}\text{O}_5$ requires C = 58.9; H = 5.4 per cent.

3 : 4-*Methylenedioxymandelic Acid*, $\text{CH}_2 \begin{array}{c} \diagup \text{O} \diagdown \\ \diagdown \text{O} \diagup \end{array} \text{C}_6\text{H}_3 \cdot \text{CH}(\text{OH}) \cdot \text{CO}_2\text{H}.$

Ten grams of the above ester were boiled for three hours with 10 grams of potassium hydroxide dissolved in 100 c.c. of 90 per cent.

alcohol. The resulting solution was nearly neutralised with hydrochloric acid and filtered from precipitated potassium chloride. The filtrate was evaporated to dryness, and the residue dissolved in a little water. On acidification, the acid separated out and, after recrystallisation from dilute alcohol, formed colourless, hexagonal plates, melting at 162°. Yield, 80—90 per cent. The acid is only very sparingly soluble in benzene. We are unable to confirm Lorenz's statement that the substance is very unstable; his substance cannot have been pure, as he gives the melting point 152—153°: Garelli gives 156°.

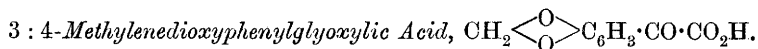


This substance was prepared by leaving the ester in contact with a large excess of concentrated aqueous ammonia, when it was gradually transformed into glistening, rhombic plates, which, after recrystallisation from a mixture of ethyl acetate and alcohol, melted sharply at 140°. The amide is readily soluble in hot water:

0.2196 gave 14.2 c.c. N₂ (moist) at 25° and 764 mm. N = 7.3.

C₉H₉O₄N requires N = 7.2 per cent.

The reduction of this amide to a base was attempted without success.

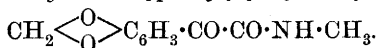


This acid has been previously obtained by Ciamician and Silber (*Ber.*, 1890, 23, 1165) by oxidation of *isosafrole*, but the yield is very small. We failed to obtain it from 3 : 4-methylenedioxymandelic acid by oxidation with potassium dichromate and sulphuric acid, but with alkaline permanganate a small yield of the ketonic acid was obtainable.

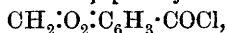
Five grams of methylenedioxymandelic acid were dissolved in 150 c.c. of water by means of a slight excess of sodium carbonate, and 10 grams of finely-powdered potassium permanganate were gradually added to the boiling solution. After removal of the manganese dioxide by filtration, the solution was acidified, and the acid, which separated out somewhat slowly, was crystallised from benzene, in which it is fairly soluble. It forms yellow needles melting at 148° if the benzene of crystallisation has been driven off by previous heating at 100°. Yield, 10—20 per cent.

This acid was also obtained from its methylamide (by hydrolysis with sodium hydroxide), and then formed long, yellow needles, m. p. 148—149°. The methylamide was prepared by a different method, as follows:

3 : 4-Methylenedioxyphenylglyoxylmethylamide,



Equimolecular proportions of piperonyl chloride,

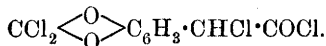


and methyl isocyanide were heated to 90° for fifteen minutes, when the odour of the latter substance had disappeared. The resulting syrup was dissolved in chloroform, and benzene was added until no more tarry precipitate was formed. On passing steam through the yellow filtrate, a little piperonylic acid separated, and then, on cooling, a yellow oil appeared which soon solidified. After recrystallisation from very dilute sodium carbonate solution, it formed pale yellow leaflets, m. p. 112° :

0.1962 gave 11.2 c.c. N₂ (moist) at 9° and 742 mm. N = 6.70.

C₁₀H₉O₄N requires N = 6.76 per cent.

3 : 4-Dichloromethylenedioxyphenylchloroacetyl Chloride,



Methylenedioxymandelic acid (5 grams) was heated with four molecular proportions of phosphorus pentachloride (21.5 grams) under a reflux condenser to 180° for five hours. On distillation, phosphorus trichloride and phosphoryl chloride first passed over, and then a colourless liquid boiling constantly at 167/10 mm., the yield of which amounted to 80 per cent. of the theory :

0.1808 gave 0.2405 CO₂ and 0.0242 H₂O. C = 36.3 ; H = 1.5.

0.1815 „ 0.3430 AgCl. Cl = 46.7.

C₉H₄O₃Cl₄ requires C = 35.8 ; H = 1.3 ; Cl = 47.0 per cent.

3 : 4-Carbonyldioxyphenylchloroacetic Acid, CO $\begin{array}{c} \diagup \text{O} \\ \diagdown \text{O} \end{array}$ C₆H₃ · CHCl · CO₂H.

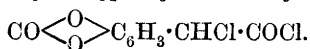
The acid chloride described above reacts violently with cold formic acid ; the reaction is completed by boiling for a short time, and then a crystalline solid separates out if the solution is moderately concentrated. After recrystallisation from formic acid, the substance formed short, broad prisms melting at 144° :

0.1828 gave 0.3159 CO₂ and 0.0366 H₂O. C = 47.1 ; H = 2.2.

0.2041 „ 0.1310 AgCl. Cl = 15.9.

C₉H₅O₅Cl requires C = 47.3 ; H = 2.2 ; Cl = 15.5 per cent.

3 : 4-Carbonyldioxyphenylchloroacetyl Chloride,



This substance was obtained by heating the above acid (1.5 grams) with thionyl chloride (15 c.c.) on the water-bath for one and a-half hours. On distillation, the chloride boiled at 185—186°/9 mm. :

0.2102 gave 0.2458 AgCl. Cl = 28.9.

$\text{C}_9\text{H}_4\text{O}_4\text{Cl}_2$ requires Cl = 28.7 per cent.

The substance was treated in benzene solution with equimolecular proportions of various bases, but no crystalline product could be isolated.

3 : 4-Dihydroxymandelic Acid, $\text{C}_6\text{H}_3(\text{OH})_2 \cdot \text{CH}(\text{OH}) \cdot \text{CO}_2\text{H}$.

By warming carbonyldioxyphenylchloroacetic acid in aqueous-acetone solution on the water-bath in the presence of powdered marble, and subsequent evaporation, this acid is obtained as an amorphous, pale yellow solid, which is extremely soluble in water, alcohol, acetone, ether, or ethyl acetate, but not at all in boiling benzene or xylene. When a concentrated alcoholic solution is dropped into a large quantity of boiling xylene, the whole of the acid is at once precipitated. In spite of many attempts, we have been unable to crystallise the acid or any of its salts; the only crystalline derivative obtained was the ethyl ester described below.

A specimen purified by precipitation from alcoholic solution by benzene, and still containing a little calcium salt, was analysed, and gave, after subtracting the ash :

Found, C = 53.0 ; H = 5.9.

$\text{C}_8\text{H}_8\text{O}_5$ requires C = 52.2 ; H = 4.35 per cent.

The acid thus obtained was a white, amorphous powder, and was very unstable. Its aqueous solution darkens on exposure to light and air, instantly reduces ammoniacal silver nitrate solution, and is coloured an intense green by ferric chloride. The brucine salt of the acid separated as an amorphous precipitate on mixing alcoholic solutions of the two constituents; the quinine salt is, on the other hand, readily soluble in alcohol. Neither salt could be crystallised.

Ethyl 3 : 4-Dihydroxymandelate, $\text{C}_6\text{H}_3(\text{OH})_2 \cdot \text{CH}(\text{OH}) \cdot \text{CO}_2\text{Et}$.

Ethyl methylenedioxy mandelate (20 grams) was heated under a reflux condenser with three molecular proportions (55.8 grams) of phosphorus pentachloride to 160° for three hours. On distillation, a

fraction boiling at 184—187°/10 mm. and weighing 19.5 grams was collected :

0.1406 gave 0.1980 AgCl. Cl = 34.8.

$C_{11}H_9O_4Cl_3$ requires Cl = 34.2 per cent.

The chlorine content and reactions of this distillate showed it to be somewhat impure *ethyl 3:4-dichloromethylenedioxyphenylchloroacetate*, $CCl_2 \cdot O_2 \cdot C_6H_3 \cdot CHCl \cdot CO_2 \cdot C_2H_5$; the ester grouping had remained intact. The distillate reacted violently with cold formic acid, and after distillation, 11.5 grams, boiling at 197—201°/10 mm., were collected :

0.2363 gave 0.1407 AgCl. Cl = 14.8.

$C_{11}H_9O_5Cl$ requires Cl = 13.8 per cent.

The latter substance was therefore a somewhat impure cyclic carbonate, corresponding with the first-named substance. The theoretical yield is 14 grams; the deficiency was partly due to the presence of a little acid chloride in the first distillate, which was subsequently converted by formic acid into the non-volatile acid. The second distillate, boiling at 197—201°/10 mm., consisted therefore of *ethyl 3:4-carbonyldioxyphenylchloroacetate* contaminated with a slight proportion of a substance containing more chlorine, probably the corresponding carbonyldioxyphenyldichloroacetate.

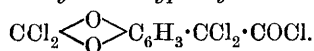
Six grams of the last-mentioned distillate were dissolved in 100 c.c. of acetone, and water was added until the solution became slightly turbid. Rather less than the calculated amount of marble was added; the solution was then boiled on the water-bath for two to three hours, after which time a turbidity was no longer produced on dilution with water. After concentration in a vacuum to 10 c.c., a pink, crystalline solid slowly separated; yield of the crude product = 70 per cent. of the theory.

Ethyl 3:4-dihydroxymandelate, which was thus obtained, is very soluble in water, but only slightly so in boiling xylene, from which it separates in white crystals melting at 152—153° :

0.1596 gave 0.3323 CO_2 and 0.0863 H_2O . C = 56.8; H = 6.0.

$C_{10}H_{12}O_5$ requires C = 56.7; H = 5.7 per cent.

3:4-Dichloromethylenedioxyphenyldichloroacetyl Chloride,

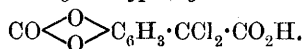


Methylenedioxyphenylglyoxylic acid (5 grams) was heated with four molecular proportions of phosphorus pentachloride (21.6 grams) to 160° for three hours. On distillation, 5 grams of a liquid boiling at 172—187°/8 mm. were obtained; the fraction 185—187°/8 mm. was analysed :

0.1632 gave 0.3456 AgCl. Cl = 52.4.

$C_9H_3O_3Cl_5$ requires Cl = 52.7 per cent.

3 : 4-Carbonyldioxyphenyldichloroacetic Acid,



On treatment of the whole distillate with formic acid and boiling for half a minute, a white, crystalline solid separated, which was obtained pure by recrystallisation from benzene and melted at 152—153°:

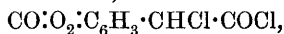
0.1762 gave 0.2656 CO₂ and 0.0267 H₂O. C = 41.1 ; H = 1.7.

0.1592 „ 0.1712 AgCl. Cl = 26.6.

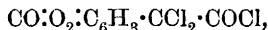
$C_9H_4O_5Cl_2$ requires C = 41.1 ; H = 1.5 ; Cl = 27.0 per cent.

The same acid was obtained direct from ethyl methylenedioxy-mandelate by the prolonged action of a large excess of thionyl chloride at a high temperature. Two grams of this ester were heated with 8 c.c. of thionyl chloride to 200° for ten hours. The excess of thionyl chloride was distilled off, and the residue then boiled at 190—225°/14 mm. On exposure to moist air in a shallow dish, the distillate partly crystallised, and after pressing on a porous plate and recrystallisation from benzene, 0.3 gram of an acid was obtained, melting at 152° and identical with 3 : 4-carbonyldioxyphenyldichloroacetic acid already described.

The primary result of the action of thionyl chloride on the ester was doubtless the formation of ethyl 3 : 4-carbonyldioxyphenylethylchloroacetate, $CO:O_2:C_6H_3 \cdot CHCl \cdot CO_2Et$, boiling at 197—201°/10 mm., described above. Two further reactions then took place; in one the ester grouping was attacked, so that the acid chloride,



already described b. p. 185—186°/9 mm., was formed. Finally, this was oxidised by thionyl chloride to the acid chloride,



which in moist air yielded the acid $CO:O_2:C_6H_3 \cdot CCl_2 \cdot CO_2H$. A similarly complex distillate was obtained by the prolonged action of phosphorus pentachloride on ethyl methylenedioxy-mandelate at 190—200°.

Thus the fraction 170—175°/10 mm. contained Cl = 40.3; the fraction 178—184°/9 mm., Cl = 40.8; $CCl_2:O_2:C_6H_3 \cdot CHCl \cdot COCl$ requires Cl = 47.0; $CCl_2:O_2:C_6H_3 \cdot CHCl \cdot CO_2Et$ requires Cl = 34.2, and $CCl_2:O_2:C_6H_3 \cdot CCl_2 \cdot CO_2Et$ requires Cl = 42.5 per cent.

As has been pointed out above, the two additional reactions scarcely take place with phosphorus pentachloride at a lower temperature, so that the reaction product then consists almost wholly of the ester, $CCl_2:O_2:C_6H_3 \cdot CHCl \cdot CO_2Et$.

3:4-Dihydroxyphenylglyoxylic Acid, $C_6H_3(OH)_2 \cdot CO \cdot CO_2H$.

This acid is readily obtained by boiling the cyclic carbonate of the corresponding dichloroacetic acid with water. The latter acid gradually dissolves, and the solution becomes yellow, carbon dioxide being evolved. On cooling, a well-crystallised solid separated, which, on recrystallisation from a mixture of ethyl acetate and petroleum (b. p. 80—90°), formed yellow needles melting at 159°. The substance retained one molecule of water of crystallisation, which it did not lose in a vacuum over sulphuric acid at the laboratory temperature; the water is, however, given off under atmospheric pressure at 100°, the substance becoming more deeply yellow.

For analysis the substance was dried by the former method:

0.0965 gave 0.1689 CO_2 and 0.0359 H_2O . C = 47.7; H = 4.1.

0.0299 lost 0.0026 H_2O at 100°. H_2O = 8.7.

$C_8H_6O_5, H_2O$ requires C = 48.0; H = 4.0; H_2O = 9.0 per cent.

3:4-Dihydroxyphenylglyoxylic acid is readily soluble in water, although much less than the corresponding hydroxy-acid (3:4-dihydroxymandelic acid, described above). The solution in water and in alcohol is coloured intensely green by ferric chloride, the coloration becoming pink on the addition of alkali.

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