

Derivatives of Hydroxybenzoic Acids.

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Chloral has been condensed with certain aromatic acids, *viz.*, *m*-hydroxybenzoic acid and its alkyl derivatives (Fritsch, *Annalen*, 1897, 296, 344). Subsequently Meldrum and Alimchandani studied condensations with gallic acid (*J. Chem. Soc.*, 1920, 117, 964) and cresotic acids (*J. Indian Chem. Soc.*, 1925, 2, 9). The condensation products in most of these cases were phthalides.

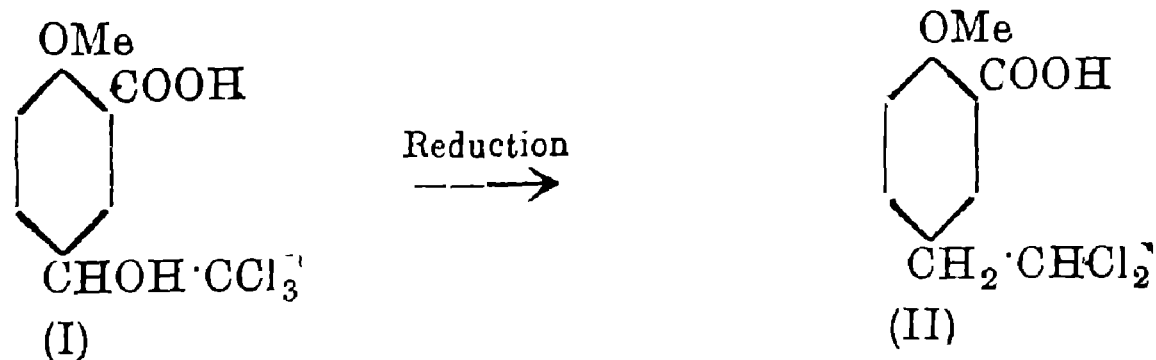
The present work deals with the condensation of chloral with *o*-, *m*-, and *p*-methoxybenzoic acids and *p*-hydroxybenzoic acid. It was undertaken with a view to study the properties of the condensation products and of the $\text{CHOH}\cdot\text{CCl}_3$ group.

One molecule of *o*-methoxybenzoic acid was condensed with one molecule of chloral in presence of sulphuric acid to 2-methoxy-5- $\alpha\alpha$ -trichloro- β -hydroxyethylbenzoic acid (I).

Several unsuccessful attempts were made to oxidise (I) to a ke-tonic acid by (i) Fenton's reagent, (ii) dilute and concentrated nitric acid, and (iii) alkaline potassium permanganate solution. With the first two reagents the substance was recovered unchanged, but with alkaline permanganate 4-methoxyisophthalic acid (m. p. 265°) was obtained, thus fixing the position of the chloral group.

Attempts were made to hydrolyse the $\text{CHOH}\cdot\text{CCl}_3$ group using various strengths of sodium hydroxide, potassium hydroxide and barium hydroxide solutions, but the yields were poor. The period of heating on a water-bath was varied from 3 hours to 7 days and finally the mixture was heated at 110° , 120° , 130° and 140° ; granular crystals were obtained, m. p. 263° , the melting point was lowered by admixture with 4-methoxyisophthalic acid. The equivalent agreed with the formula $\text{OMe}\cdot\text{C}_6\text{H}_3\cdot\text{COOH}\cdot\text{CHOH}\cdot\text{COOH}$.

The compound (I) on reduction with zinc and glacial acetic acid (*cf.* Meldrum and Alimchandani, *J. Indian Chem. Soc.*, 1925, 2, 9) gave 2-methoxy-5- $\alpha\alpha$ -dichloroethylbenzoic acid (II).



On fusion with sodium hydroxide (II) gave 4-methoxy-5-carboxy-phenylacetaldehyde, while on oxidation with fuming nitric acid it gave 4-methoxyisophthalic acid.

The condensation products of *m*-hydroxy- and *m*-methoxybenzoic acids and chloral were respectively 5-hydroxy- and 5-methoxytrichloromethylphthalides which were reduced to 3-hydroxy- and 3-methoxy-6- α -dichloroethylbenzoic acids. The latter was further reduced by sodium amalgam to 3-methoxy-6-ethylbenzoic acid.

The condensation product of *p*-methoxybenzoic acid and chloral was reduced to 3- $\alpha\alpha\alpha$ -trichloro- β -hydroxyethyl-4-methoxybenzoic acid which was reduced to 3- $\alpha\alpha$ -dichloroethyl-4-methoxybenzoic acid.

It is thus evident that an additional carboxyl group can be inserted in a certain aromatic acid by condensing that acid with chloral and then by oxidation. It is also possible to insert a dichloroethyl group by suitable reduction of $\text{CHOH}\cdot\text{CCl}_3$ group.

EXPERIMENTAL.

The three hydroxybenzoic acids were methylated according to the method of Meldrum and Shah (*J. Chem. Soc.*, 1923, 123, 1991; Graebe, *Annalen*, 1905, 349, 249).

o-Methoxybenzoic acid (30 g.), chloral (40 g.) and sulphuric acid (75 c.c.) were mixed and kept for 48 hours. On dilution a resinous product was obtained which when crystallised from glacial acetic acid gave 2-methoxy-5- $\alpha\alpha\alpha$ -trichloro- β -hydroxyethylbenzoic acid (I). It crystallised in small needles, m. p. 216° , yield 15 g. It is soluble in alcohol, acetone, chloroform and insoluble in ether and benzene. (Found: Cl, 35.5; Equiv., 302.6. $\text{C}_{10}\text{H}_9\text{O}_4\text{Cl}_3$ requires Cl, 35.5 per cent. Equiv., 299.5).

The potassium salt was obtained as plates. (Found: K, 12.0. $\text{C}_{10}\text{H}_8\text{O}_4\text{Cl}_3\text{K}$ requires K, 11.6 per cent).

The barium salt was obtained by adding barium acetate solution to a neutral solution of the ammonium salt as small needles. (Found: Ba, 17.9; H_2O , 7.0. $\text{C}_{20}\text{H}_{16}\text{O}_8\text{Cl}_6\text{Ba}$, H_2O requires Ba, 17.4; H_2O , 6.8 per cent).

The calcium salt was crystallised from hot water as granules. (Found: Ca, 5.2; H_2O , 14.6. $\text{C}_{20}\text{H}_{16}\text{O}_8\text{Cl}_6\text{Ca}$, $6\text{H}_2\text{O}$ requires Ca, 5.4; H_2O , 14.5 per cent).

The acetyl derivative was obtained as granular crystals, m. p. 143° . (Found: Cl, 31.2 per cent. Equiv., 341.4).

The methyl ester was prepared by refluxing the acid (10 g.), methyl alcohol (35 g.) and dry hydrochloric acid gas (3 g.) on a water-bath for 5 hours. It was crystallised from methyl alcohol in plates, m. p. 145°. (Found: Cl, 33.6. $C_{11}H_{11}O_3Cl_3$ requires Cl, 33.9 per cent).

The ethyl ester crystallised from ethyl alcohol in needles, m. p. 157°. (Found: Cl, 32.2. $C_{12}H_{13}O_3Cl_3$ requires Cl, 32.4 per cent).

The amide.—Methyl ester (5 g.) ammonia (d 0.88, 120 c.c.) and absolute alcohol (50 c.c.) were shaken for 40 hours when the amide precipitated as a fine powder. It crystallised in tiny needles from alcohol, m. p. 241°. (Found: Cl, 35.3. $C_{10}H_{10}NCl_3$ requires Cl, 35.7 per cent).

2-Methoxy-5-aaa-trichloro- β -chloroethylbenzoic acid.—The acid (2 g.) was heated with thionyl chloride (1.5 g.) at 60° for 4 hours and the acid chloride thus obtained was hydrolysed and crystallised in needles from glacial acetic acid, m. p. 132°. (Found: Cl, 44.3; Equiv., 317.9. $C_{10}H_8O_3Cl_4$ requires Cl, 44.6 per cent. Equiv., 317.9).

The anilide was prepared by pouring the acid chloride mixture, obtained above, into aniline. The anilide crystallised in needles from alcohol, m. p. 154°. (Found: Cl, 36.2. $C_{16}H_{13}O_2NCl_4$ requires Cl, 36.1 per cent).

The p-toluidide, prepared by adding the acid chloride mixture to p-toluidine in pyridine, crystallised in small plates from alcohol, m. p. 184°. (Found: Cl, 34.6. $C_{17}H_{15}O_2NCl_4$ requires Cl, 34.8 per cent).

Oxidation of (I).—The acid (5 g.) was dissolved in potassium hydroxide (4 g. in 50 c.c. water) and potassium permanganate (4 g. in 50 c.c. water) was gradually added. Sulphur dioxide was passed through the solution after 48 hours and the filtrate was concentrated and acidified when 4-methoxyisophthalic acid was obtained, m. p. 265° (Jacobsen, *Ber.*, 1878, 11, 899; Schall, *Ber.*, 1879, 12, 828). (Found: Equiv., 98.9. $C_9H_8O_5$ requires Equiv., 98.0). The calcium salt crystallised in needles from hot water. (Found: Ca, 14.9; H_2O , 13.2. $C_9H_6O_5Ca, 2H_2O$ requires Ca, 14.8; H_2O , 13.3 per cent).

Hydrolysis of (I).—The acid (5 g.) was heated with potassium hydroxide (4 g. in 23 c.c. water) at 100° for 6-8 hours. The filtrate was acidified with dilute hydrochloric acid when 4-methoxy-5-carboxy-phenylglycollic acid was obtained in poor yield. The product collected

from several experiments was crystallised from glacial acetic acid, m. p. 263° . (Found: Equiv., 112.7. $C_{10}H_{10}O_6$ requires Equiv., 113.0).

Reduction of (I): Formation of 2-methoxy-5- α -dichloroethylbenzoic acid (II).—The acid (15 g.) was reduced in glacial acetic acid (80 c.c.) solution using zinc dust (8 g.) and the mixture was stirred for 3 hours. The product obtained on diluting the filtrate crystallised in needles from glacial acetic acid, m. p. 127° , yield 69%. (Found: Cl, 28.3; Equiv., 250. $C_{10}H_{10}O_3Cl_2$ requires Cl, 28.5 per cent. Equiv., 249).

The methyl ester crystallised in small needles, m.p. 57° . The above ester was also prepared by reducing the corresponding ester of (I). (Found: Cl, 26.7. $C_{11}H_{12}O_3Cl_2$ requires Cl, 26.9 per cent).

The amide was prepared similarly to the amide of (I). It crystallised in needles from alcohol, m. p. 147° . It was also prepared by reducing the corresponding amide of (I). (Found: Cl, 28.3. $C_{10}H_{10}O_2NCl_2$ requires Cl, 28.6 per cent).

The anilide.—The acid chloride mixture obtained by treating (II) with thionyl chloride was added to aniline. It crystallised in needles from alcohol, m. p. 105° . (Found: Cl, 22.0. $C_{16}H_{15}O_2Cl_2$ requires Cl, 21.9 per cent).

The p-toluidide was obtained as small brown plates, m. p. 115° . (Found: Cl, 20.8. $C_{17}H_{17}O_2NCl_2$ requires Cl, 21.0 per cent).

Hydrolysis of the methoxy group of (II).—5 G. of (II) were treated with hydroiodic acid (20 c.c.) at 125° and 2-hydroxy-5- α -dichloroethylbenzoic acid crystallised from acetic acid, m. p. 166° . (Found: Cl, 29.9; Equiv., 234.3. $C_9H_8O_3Cl_2$ requires Cl, 30.2 per cent. Equiv., 235.0).

Fusion of (II) with alkali: Isolation of 3-carboxy-4-methoxyphenylacetaldehyde.—3 G. of (II) were heated at 165° for $\frac{1}{2}$ hour with powdered sodium hydroxide (2 g.) in water (2 c.c.) The filtrate on acidification gave the aldehyde, which was crystallised from acetic acid, m.p. 165° . (Found: Equiv., 210.4. $C_{10}H_{10}O_4, H_2O$ requires Equiv., 212.1).

The potassium salt contains one and a half molecule of water. (Found: K, 15.0; H_2O , 10.1. $C_{10}H_9O_4K, \frac{1}{2}H_2O$ requires K, 15.1; H_2O , 10.4 per cent).

Oxidation of (II).—5 G. of (II) were dissolved in fuming nitric acid and kept at 100° for 1 hour. It was cooled and diluted when 5-methoxyisophthalic acid was obtained, m. p. 265° .

3-Hydroxy-6-aa-dichloroethylbenzoic acid was prepared by the reduction of 5 g. of 5-hydroxytrichloromethylphthalide (condensation product of *m*-hydroxybenzoic acid with chloral. Fritsch, *loc. cit.*) with zinc dust (3 g.) and glacial acetic acid (30 c.c.). It crystallised in needles from dilute acetic acid, m. p. 194°. (Found: Cl, 30.2. $C_9H_7O_3Cl_2$ requires Cl, 30.2 per cent).

3-Methoxy-6-aa-dichloroethylbenzoic acid (III) was prepared by the reduction of 5-methoxytrichloromethylphthalide (condensation product of *m*-methoxybenzoic acid with chloral, m.p. 135°) with zinc and acetic acid. It crystallised in needles from acetic acid, m. p. 165°, yield 7.4 g. (Found: Cl, 28.6; Equiv., 250. $C_{10}H_{10}O_3Cl_2$ requires Cl, 28.5 per cent. Equiv., 249).

The sodium salt was obtained as small needles. (Found: Na, 8.6. $C_{10}H_9O_3Cl_2Na$ requires Na, 8.5 per cent).

The methyl ester was obtained by refluxing (III) (3 g.) in methyl alcohol (25 c.c.) containing dry hydrochloric acid (2 g.) for 5 hours. It crystallised in needles from alcohol, m. p. 88°. (Found: Cl, 26.8. $C_{11}H_{12}O_3Cl_2$ requires Cl, 27.0 per cent).

The ethyl ester crystallised in needles from alcohol, m. p. 64°. (Found: Cl, 25.5. $C_{12}H_{14}O_3Cl_2$ requires Cl, 25.6 per cent).

The anilide.—2G. of (III) and thionyl chloride (1.5 g.) were heated at 60° for 4 hours and the mixture was added to aniline. It crystallised in needles from alcohol, m. p. 118°. (Found: Cl, 21.6. $C_{16}H_{15}O_2NCl_2$ requires Cl, 21.9 per cent).

Further reduction of (III): Isolation of 3-methoxy-6-ethylbenzoic acid.—5 G. of (III) were further reduced by sodium amalgam. A current of carbon dioxide was passed into the solution to keep it neutral. The substance obtained on acidifying was crystallised from chloroform to remove a compound containing chlorine, which is present in a small quantity, and it was finally crystallised from alcohol as granules, m. p. 87°. (Found: Equiv., 190.5. $C_{10}H_{12}O_3$ requires Equiv., 190.1).

3-aaa-Trichloro-β-hydroxyethyl-4-methoxybenzoic acid.—Anisic acid (40 g.) and chloral (55 g.) were kept for 72 hours in presence of sulphuric acid (80 c.c.) The acid obtained on dilution was crystallised thrice from acetone as granules; shrinks at 161° and melts at 275°. (Found: Cl, 35.5; Equiv., 300.6. $C_{10}H_9O_4Cl_3$ requires Cl, 35.5 per cent. Equiv., 299.5).

3-aa-Dichloroethyl-4-methoxybenzoic acid.—The above acid (10 g.) was reduced by zinc dust (6 g.) and acetic acid (70 c.c.). It separated from glacial acetic acid or 50% alcohol in granules. It is soluble in acetone, shrinks at 210° and melts at 221°. (Found: Cl, 28·3; Equiv., 250·5. $C_{10}H_{10}O_3Cl_2$ requires Cl, 28·5 per cent. Equiv., 249).

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