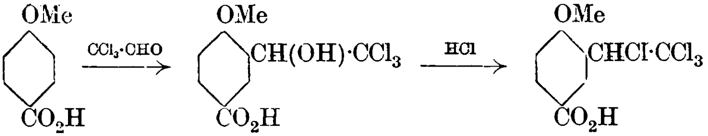
CCCLXXXIII.—*The Condensation of Chloral with Anisic Acid, with* p-*Nitroanisole, and with* 2 : 6-*Dichloroquinol.*

By Frederick Daniel Chattaway and Fernando Calvet.

Many phenols substituted in the para-position readily condense with chloral under the influence of concentrated sulphuric acid and form derivatives of 1 : 3-benzdioxin (Chattaway, J., 1926, 2720; Chattaway and Calvet, J., 1927, 685; this vol., p. 1088; Chattaway and Morris, J., 1927, 2083).

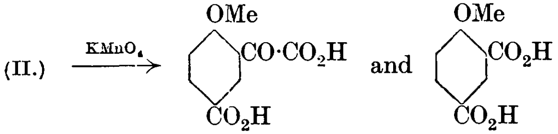
When, however, the formation of the heterocyclic benzdioxin ring is prevented by replacement of the phenolic hydroxyl by an alkyloxy-group, only one molecule of chloral reacts and a single βββ-trichloro-α-hydroxyethyl group, $\cdot CH(OH)\cdot CCl_3$, is introduced into the nucleus in a position ortho to the alkyloxy-group. For example, anisic acid condenses thus to form 5-*carboxy*-2-*methoxy*-1-βββ-*trichloro*-α-*hydroxyethylbenzene* (I).

This compound can be isolated during the first stages of the action. If, however, this be prolonged for many days, hydrogen chloride, which is slowly produced by the decomposition of some small amount of the chloral, replaces the α-hydroxyl group by a chlorine atom and the final product is 5-*carboxy*-2-*methoxy*-1-αβββ-*tetrachloroethylbenzene* (II).



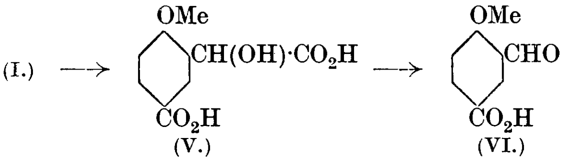
(I.) (II.)

Its constitution has been established by oxidising it with an alkaline solution of potassium permanganate; it then yields a mixture of 5-*carboxy*-2-*methoxyphenylglyoxylic acid* (III), which gives a very well-defined *phenylhydrazone*, and 4-*methoxy*iso*phthalic acid* (IV), which on hydrolysis of its methoxy-group yields 4-hydroxy*iso*-phthalic acid.

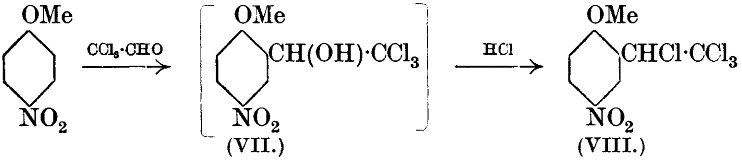


(III.) (IV.)

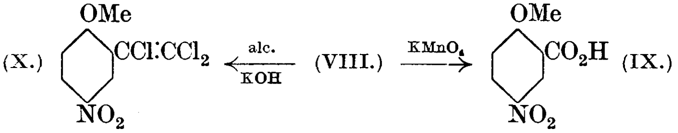
5-Carboxy-2-methoxy-1-βββ-trichloro-α-hydroxyethylbenzene (I), which melts about 73° higher than the corresponding 2-ethoxyderivative (Chattaway and Calvet, J., 1927, 689), is a comparatively stable substance, the methoxy-group not being easily hydrolysed. When the substance is heated with concentrated sulphuric acid on a water-bath, hydrogen chloride is liberated and 4-*methoxy*iso*phthalaldehydic acid* (VI) is formed, probably by elimination of formic acid from the 5-carboxy-2-methoxymandelic acid (V) which must be the first product of the hydrolysis.



p-Nitroanisole condenses with chloral in a similar manner in presence of concentrated sulphuric acid. When the action is prolonged, 5-*nitro*-2-*methoxy*-1-αβββ-*tetrachloroethylbenzene* is formed (VIII). The intermediate product of the action, 5-nitro-2-methoxy-1-βββ-trichloro-α-hydroxyethylbenzene (VII), has not actually been isolated; but its formation is certain, since when the solution of *p*-nitroanisole and chloral in concentrated sulphuric acid is saturated at the beginning with hydrogen chloride the final product is formed much more rapidly and completely than when the necessary hydrogen chloride is formed by the comparatively slow decomposition of the chloral.

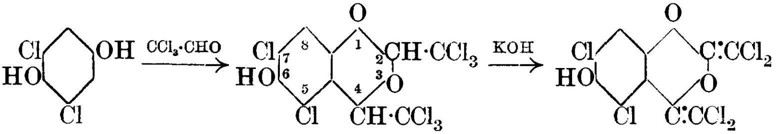


The constitution of the final condensation product was established by oxidising it with potassium permanganate in acetone solution; it then yielded 5-nitro-2-methoxybenzoic acid (IX), identical with the product obtained by nitration of *o*-methoxybenzoic acid. When acted upon by boiling alcoholic potash, it lost one molecule of hydrogen chloride and yielded αββ-*trichloro*-5-*nitro*-2-*methoxystyrene* (X).



It has been shown (*loc. cit.*) that, although many substituents in a position ortho to the phenolic hydroxyl hinder the formation of a benzdioxin ring, they have little or no effect when in a meta-position. Condensation also proceeds in the usual manner when both meta-positions are thus occupied. For example, 2 : 6-dichloroquinol, in which both positions meta to one of the two hydroxyls are occupied by chlorine atoms, condenses readily, under the influence of concentrated sulphuric acid, with two molecules of chloral, yielding 5 : 7-*dichloro*-6-*hydroxy*-2 : 4-*bistrichloromethyl*-1 : 3-*benzdioxin* (XI), only the hydroxyl group which has both the adjacent *o*-positions unoccupied taking an active part in the reaction.

The heterocyclic dioxin ring of this condensation product shows unusual resistance to the action of alcoholic potash, which only removes a molecule of hydrogen chloride from each of the side chains and forms 5 : 7-*dichloro*-6-*hydroxy*-2 : 4-*bisdichloromethylene*-1 : 3-*benzdioxin* (XII).



(XI.) (XII.)

The benzdioxin ring in 6-amino-2 : 4-bistrichloromethyl-1 : 3-benzdioxin behaves similarly (see this vol., p. 1089).

EXPERIMENTAL.

5-*Carboxy*-2-*methoxy*-1-ββ*β*-*trichloro*-α-*hydroxyethylbenzene* (I).—A solution of 40 g. (1 mol.) of anisic acid and 50 g. (1·2 mols.) of chloral hydrate in 400 c.c. of concentrated sulphuric acid was kept at the ordinary temperature for 10 hours and then poured into 2000 c.c. of water containing ice. A viscid mass separated which, after being heated with water, broke up into a mass of needle-shaped crystals; these were recrystallised from alcohol and from chloroform-light petroleum. 5-*Carboxy*-2-*methoxy*-1-βββ-*trichloro*-α-*hydroxyethylbenzene* is sparingly soluble in benzene and chloroform, practically insoluble in light petroleum, and easily soluble in boiling acetic acid and alcohol, from which it slowly separates as highly refractive, short prisms, m. p. 198—199° (Found: C, 39·9; H, 3·2; Cl, 35·8. $C_{10}H_9O_4Cl_3$ requires C, 40·1; H, 3·0; Cl, 35·6%).

5-*Carboxy*-2-*methoxy*-1-αβββ-*tetrachloroethylbenzene* (II).—(1) *By condensation of anisic acid and chloral in presence of concentrated sulphuric acid.* A solution of 50 g. of anisic acid and 60 g. of chloral hydrate in 500 c.c. of concentrated sulphuric acid was kept at the ordinary temperature for 8 days, hydrogen chloride being gradually formed in considerable quantity. When the clear resulting liquid was poured into 3000 c.c. of water 5-*carboxy*-2-*methoxy*-1-αβββ-*tetra*-

chloroethylbenzene separated as a voluminous white solid; this, after being washed with hot water, crystallised from alcohol in colourless needles (50 g.), m. p. 247—249° (Found: C, 37·85; H, 2·45; Cl, 44·65; *M*, 331. $C_{10}H_8O_3Cl_4$ requires C, 37·8; H, 2·5; Cl, 44·7%; *M*, 318). The substance is sparingly soluble in boiling water, moderately easily soluble in boiling benzene, chloroform, and light petroleum, and easily soluble in boiling alcohol and in aqueous alkalis.

(2) *By the action of hydrogen chloride upon* 5-*carboxy*-2-*methoxy*-1-ββℬ-*trichloro*-α *hydroxyethylbenzene*. A solution of 2 g. of the trichloro-compound in 20 c.c. of concentrated sulphuric acid was saturated with dry hydrogen chloride, kept at the ordinary temperature for 1 day, and then poured into 50 c.c. of water containing ice. The solid which separated was recrystallised from alcohol; it melted at 247—249° and was identical in every respect with the substance described in (1).

Action of Concentrated Sulphuric Acid on 5-*Carboxy*-2-*methoxy*-1-βββ-*trichloro*-α-*hydroxyethylbenzene*.—A solution of 10 g. of the trichloro-compound in 100 c.c. of concentrated sulphuric acid was heated on a water-bath for 45 minutes until hydrogen chloride ceased to be evolved. It was then cooled and poured into 500 c.c. of water containing ice. The 4-*methoxy*iso*phthalaldehydic acid* (VI) that separated (yield, 4·5 g.) crystallised from alcohol in very small, colourless plates, m. p. 244—245° (Found: C, 59·5; H, 4·7. $C_9H_8O_4$ requires C, 60·1; H, 4·45%). When heated with 2 : 4-dichlorophenylhydrazine it yielded the 2 : 4-*dichlorophenylhydrazone*, which crystallised from alcohol in very small, pale yellow needles, m. p. 303—305° (decomp.) (Found: Cl, 20·85. $C_{15}H_{12}O_3N_2Cl_2$ requires Cl, 20·9%).

Oxidation of 5-*Carboxy*-2-*methoxy*-1-αβββ-*tetrachloroethylbenzene*. *Isolation of* 4-*Methoxy*iso*phthalic Acid* (IV) *and* 5-*Carboxy*-2-*methoxyphenylglyoxylic Acid* (III).—5-Carboxy-2-methoxy-1-αβββ-tetrachloroethylbenzene (15 g.) was dissolved in 300 c.c. of boiling water containing an excess of sodium carbonate, and about 30 g. of finely powdered potassium permanganate were added gradually until it was no longer decolorised on continued boiling. The manganese dioxide was filtered off, and the colourless filtrate made acid with hydrochloric acid; 4-*methoxy*iso*phthalic acid* (4·5 g.) then separated. It was several times recrystallised successively from acetic acid, dilute alcohol, and finally from boiling water, from which it separated in minute colourless needles, m. p. 275—276° (Found: C, 55·0; H, 4·3. $C_9H_8O_5$ requires C, 55·1; H, 4·1%).

When heated for 5—10 minutes with hydriodic acid (b. p. 127°), it gave 4-hydroxy*iso*phthalic acid, m. p. 310°.

The aqueous acid mother-liquor from which the 4-methoxy*iso*phthalic acid had separated was repeatedly extracted with ether. Evaporation of the ether left *5-carboxy-2-methoxyphenylglyoxylic acid* as a crystalline, colourless solid; this was easily soluble in boiling acetic acid, from which it separated in small colourless prisms, m. p. 254—255° (Found: C, 53·3; H, 3·8. $C_{10}H_8O_6$ requires C, 53·6; H, 3·6%).

It reacts with hydrazines to form sparingly soluble hydrazones. The *phenylhydrazone* separates from boiling alcohol in pale yellow, microscopic prisms, m. p. 231° (decomp.) (Found: C, 61·0; H, 4·6; N, 8·9. $C_{16}H_{14}O_5N_2$ requires C, 61·2; H, 4·5; N, 8·9%).

5-Nitro-2-methoxy-1-αβββ-tetrachloroethylbenzene (VIII).—A solution of 50 g. of *p*-nitroanisole (1 mol.) and 60 g. of chloral hydrate (1·1 mols.) in 450 c.c. of concentrated sulphuric acid was kept at the ordinary temperature, hydrogen chloride being slowly liberated. Crystals of *5-nitro-2-methoxy-1-αβββ-tetrachloroethylbenzene*, which began to appear after 10 to 12 days, were separated after 4 weeks, well washed with water, and recrystallised from alcohol (yield, 33 g.). The substance is insoluble in water, very sparingly soluble in light petroleum, and easily soluble in boiling acetone, benzene, and alcohol, from which it separates in slightly yellow needles, m. p. 131—132° (Found: N, 4·4; Cl, 44·4; *M*, cryoscopic in benzene, 340. $C_9H_7O_3NCl_4$ requires N, 4·4; Cl, 44·5%; *M*, 319).

When the condensation of chloral with *p*-nitroanisole was carried out in concentrated sulphuric acid saturated with hydrogen chloride, separation of the product began on the third day and was practically complete by the eighth day.

Action of Potassium Hydroxide on 5-Nitro-2-methoxy-1-αβββ-tetrachloroethylbenzene: Formation of αββ-Trichloro-5-nitro-2-methoxystyrene (X).—The tetrachloro-compound (2 g.) was heated for a short time with 25 c.c. of a mixture of equal parts of alcohol and a 50% aqueous solution of potassium hydroxide. As the reaction proceeded, *αββ-trichloro-5-nitro-2-methoxystyrene* separated as an oil, which solidified on cooling and then crystallised from alcohol in pale yellow, shining plates, m. p. 94—95° (Found: N, 4·9; Cl, 37·6. $C_9H_6O_3NCl_3$ requires N, 4·95; Cl, 37·7%).

Oxidation of 5-Nitro-2-methoxy-1-αβββ-tetrachloroethylbenzene to 5-Nitro-2-methoxybenzoic Acid (IX).—Potassium permanganate (30 g.) was added during 48 hours to 5 g. of 5-nitro-2-methoxy-1-αβββ-tetrachloroethylbenzene dissolved in 100 c.c. of boiling acetone. After 48 hours' boiling, the solid formed was separated from the cooled liquid and extracted with 100 c.c. of alcohol. Partial evaporation of the extract gave needles of potassium 5-nitro-2-methoxybenzoate, from which the acid. m. p. 161°, was obtained (Found:

C, 48·85; H, 3·4; N, 7·7. Calc. for $C_8H_7O_5N$: C, 48·7; H, 3·5; N, 7·1%), identical with a specimen prepared by the method of Simonsen and Rau (J., 1917, **111**, 228).

5:7-*Dichloro*-6-*hydroxy*-2:4-*bistrichloromethyl*-1:3-*benzdioxin* (XI).—To a solution in 250 c.c. of concentrated sulphuric acid of 25 g. (1 mol.) of 2:6-dichloroquinol, obtained by oxidising 2:4:6-trichlorophenol with cold fuming nitric acid and reducing the 2:6-dichlorobenzoquinone formed by sulphur dioxide, 48 g. of chloral hydrate were added. The mixture was well shaken for ½ hour and kept for 3 days at the ordinary temperature. Ice was then added and 5:7-*dichloro*-6-*hydroxy*-2:4-*bistrichloromethyl*-1:3-*benzdioxin*, which separated as a viscid, colourless mass, was well washed with water and repeatedly crystallised from alcohol (yield, 41 g.). It was easily soluble in boiling alcohol, chloroform, and benzene and sparingly soluble in light petroleum and separated from these solvents in small, glistening, colourless plates, m. p. 114—115° (Found: C, 26·15; H, 1·0; Cl, 62·1. $C_{10}H_4O_3Cl_8$ requires C, 26·05; H, 0·85; Cl, 62·2%). It dissolved in aqueous alkalis and gave a greenish-brown colour with a solution of ferric chloride.

The phenolic hydroxyl group is easily acetylated when the compound is heated for a short time with acetyl chloride or acetic anhydride containing a drop of sulphuric acid. 5:7-*Dichloro*-6-*acetoxy*-2:4-*bistrichloromethyl*-1:3-*benzdioxin* crystallises from boiling alcohol, in which it is moderately easily soluble, in small, colourless prisms, m. p. 179—180° (Found: Cl, 57·2. $C_{12}H_6O_4Cl_8$ requires Cl, 57·0%).

5:7-*Dichloro*-6-*hydroxy*-2:4-*bisdichloromethylene*-1:3-*benzdioxin* (XII).—To a boiling solution of 5 g. of potassium hydroxide (9 mols.) in 50 c.c. of alcohol, 4·5 g. of 5:7-dichloro-6-hydroxy-2:4-bistrichloromethyl-1:3-benzdioxin (1 mol.) were added and the mixture was boiled under reflux for 15 minutes; 50 c.c. of hot water were then added and the alcohol was distilled off in a current of steam. From the cooled, acidified liquid, 5:7-*dichloro*-6-*hydroxy*-2:4-*bisdichloromethylene*-1:3-*benzdioxin* separated. It is easily soluble in boiling alcohol, chloroform, and carbon tetrachloride, from which it separates in small, compact, colourless crystals, m. p. 137—138° (Found: Cl, 55·5. $C_{10}H_2O_3Cl_6$ requires Cl, 55·6%). When dissolved in carbon tetrachloride, it does not combine with bromine at the ordinary temperature.

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