CIII.—*The Condensation of* p-*Hydroxybenzoic Acid with Chloral.*

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It has recently been shown (J., 1926, 2720) that *p*-nitrophenol reacts with chloral in presence of concentrated sulphuric acid in a complicated and unexpected way, the final product being anhydro-

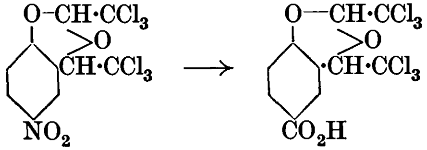
5-nitro-2-βββ-trichloro-α-hydroxyethoxy-1-βββ-trichloro-α-hydroxyethylbenzene (I), the constitution of which was shown by its yielding 5-nitro-2-ethoxyphenylglycollic acid on treatment with alcoholic potash.

In similar circumstances, chloral reacts equally readily with *p*-hydroxybenzoic acid, giving a very stable and well-crystallised product, 2 mols. of the aldehyde condensing with 1 mol. of the acid, with loss of a molecule of water :

$$C_7H_6O_3 + 2CCl_3{\cdot}CHO - H_2O = C_{11}H_6O_4Cl_6.$$

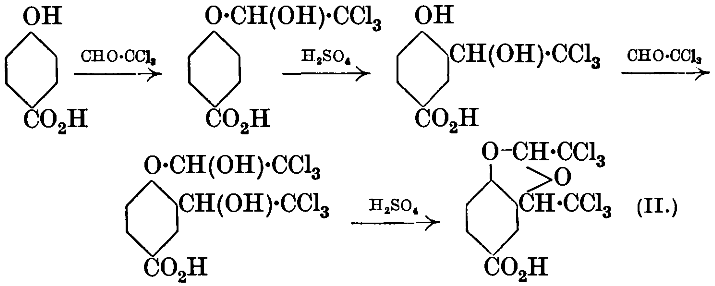
The constitution (II) of the compound formed is similar to that of the condensation product (I) yielded by *p*-nitrophenol, since it can also be formed from the latter by replacement of the nitro-group by carboxyl through the amino- and the cyano-group.

(I.)



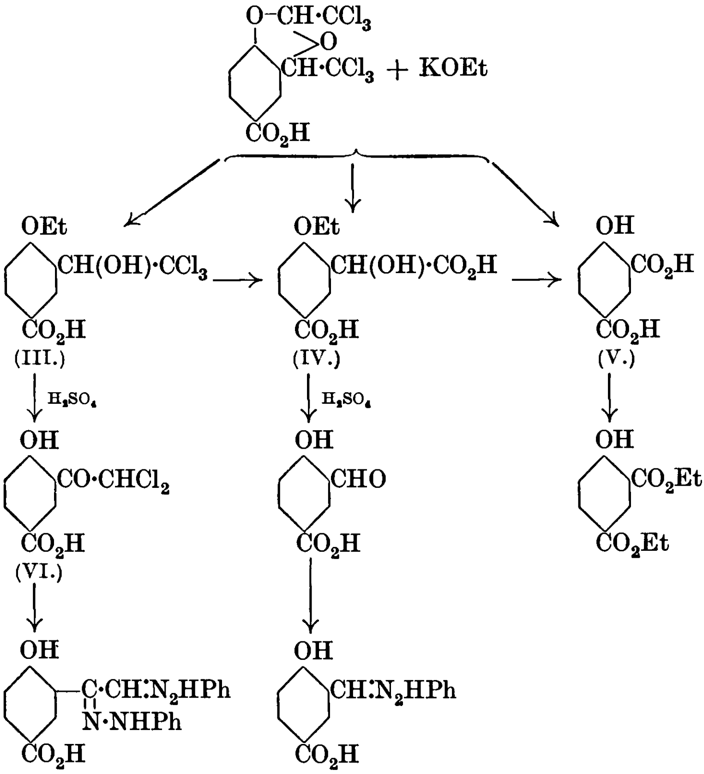
(II.)

Since in the formation of the compound from chloral and *p*-hydroxybenzoic acid the carboxyl group remains unaffected, a condensation with the phenolic hydroxyl must first occur and be followed by intramolecular rearrangement. The hydroxyl group being thus re-formed, a second condensation of the same type must occur and be succeeded by elimination of water, thus,



the final product being *anhydro-5-carboxy-2-βββ-trichloro-α-hydroxyethoxy-1-βββ-trichloro-α-hydroxyethylbenzene.*

Its constitution is confirmed by its behaviour with alcoholic potash, with which it yields a mixture of 5-*carboxy*-2-*ethoxy*-1-βββ-*trichloro-α-hydroxyethylbenzene* (III), 5-*carboxy*-2-*ethoxyphenylglycollic acid* (IV), and 2-*hydroxy*-1 : 5-iso*phthalic acid* (V). These compounds were identified as shown in the following scheme :



Experimental.

Preparation of Anhydro-5-carboxy-2-ββββ-trichloro-α-hydroxyethoxy-1-βββ-trichloro-α-hydroxyethylbenzene (II).—(a) *By condensation of* p-*hydroxybenzoic acid and chloral.* A solution of 50 g. of *p*-hydroxybenzoic acid (1 mol.) and 150 g. of chloral hydrate (3 mols.) in 500 c.c. of concentrated sulphuric acid was kept at the ordinary temperature, with frequent shaking, for 3 days. The liquid had then become a pulp owing to the separation of the condensation product mixed with metachloral formed by the action of sulphuric acid upon the excess of chloral present (Byasson, *Compt. rend.*, 1880, **91**, 1071). The whole was poured into about 3 litres of water containing ice, and the solid which separated was filtered off and dried on the water-bath. The condensation product was extracted in a Soxhlet apparatus with ether, in which metachloral is insoluble. The ethereal solution was dried, the ether distilled off, and the condensation product obtained by crystallising the colourless, crystalline residue (yield, 46 g.) three times from ether–light petroleum.

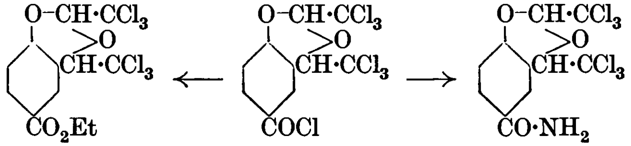
It is insoluble in water but moderately easily soluble in hot alkaline solutions. It dissolves easily in the ordinary organic solvents such as ether, alcohol, benzene, and acetic acid and separates from any of these in colourless needles, m. p. 225·5—226·5° (Found : C, 32·1; H, 1·6; Cl, 51·4. $C_{11}H_6O_4Cl_6$ requires C, 31·8; H, 1·4; Cl, 51·3%).

(b) *From the corresponding* 5-*nitro-compound* (I) *through the* 5-*amino- and* 5-*cyano-derivatives.* Anhydro-5-amino-2-βββ-trichloro-α-hydroxyethoxy-1-βββ-trichloro-α-hydroxyethylbenzene (10 g.), obtained by reduction of the corresponding nitro-compound (I) (J., 1926, 2725), was suspended in a mixture of 40 c.c. of concentrated hydrochloric acid and 180 c.c. of water and diazotised by adding, during 2 hours, the requisite amount of sodium nitrite dissolved in 30 c.c. of water, the temperature being kept at — 5° to — 10°. The diazotised solution was poured slowly into a concentrated solution of 40 g. of copper sulphate and 50 g. of potassium cyanide in about 100 c.c. of water kept at 45—50°. (If the temperature is allowed to rise above this limit, a considerable amount of tarry matter is formed.) The *nitrile*, which separated on cooling as a microcrystalline mass, was extracted with ether. A yield of 2·1 g. was obtained.

Anhydro-5-*cyano*-2-βββ-*trichloro*-α-*hydroxyethoxy*-1-βββ-*trichloro*-α-*hydroxyethylbenzene* is an odourless solid which is not volatile in steam. It is insoluble in water, sparingly soluble in low-boiling petroleum, and easily soluble in boiling ether and alcohol. It is best recrystallised from ether–light petroleum, from which it separates in colourless needles, m. p. 159·5—160·5° (Found : Cl, 53·95. $C_{11}H_5O_2NCl_6$ requires Cl, 53·8%).

The nitrile was easily hydrolysed to the corresponding acid (II) by heating it for a short time with somewhat dilute sulphuric acid. A mixture of 1·3 g. of the nitrile, 30 c.c. of water, and 45 c.c. of concentrated sulphuric acid was heated to gentle boiling for about 20 minutes. On cooling and diluting the solution with water, the acid separated as a microcrystalline solid. It crystallised from warm ether–light petroleum in colourless needles (yield, 1 g.), m. p. 226°, identical with those obtained in method (a) (Found : Cl, 51·1%).

The Ethyl Ester, Acid Chloride, and Amide of Anhydro-5-*carboxy*-2-βββ-*trichloro*-α-*hydroxyethoxy*-1-βββ-*trichloro*-α-*hydroxyethylbenzene.*



—The *ethyl* ester was prepared by saturating a cooled and concentrated alcoholic solution of the acid with dry hydrogen chloride and heating it in a sealed tube for some hours. The ester separated in colourless crystals on cooling. It was recrystallised from hot alcohol, in which it was moderately easily soluble and from which it separated in small, colourless, rhombic plates, m. p. 100·5—101·5° (Found : Cl, 48·3. $C_{13}H_{10}O_4Cl_6$ requires Cl, 48·1%).

The ester was also obtained by boiling the acid chloride, described below, with alcohol.

The *acid chloride* was obtained by gently heating the acid with an excess of phosphorus pentachloride and pouring the mixture over ice. It is very easily soluble in ether and very sparingly soluble in petroleum. It separates from ether–light petroleum in colourless, compact crystals, m. p. 98—102° (Found : Cl, 56·5. $C_{11}H_5O_3Cl_7$ requires Cl, 57·3%).

The *amide*, obtained by gently heating the acid chloride with a mixture of equal parts of strong ammonia solution and alcohol, was easily soluble in boiling alcohol, from which it separated in long, colourless prisms, m. p. 195·5—197° (Found : Cl, 51·2; N, 3·2. $C_{11}H_7O_3NCl_6$ requires Cl, 51·4; N, 3·4%).

*Action of Alcoholic Potassium Hydroxide upon Anhydro-*5-*carboxy-*2-βββ-*trichloro-α-hydroxyethoxy*-1-βββ-*trichloro-α-hydroxyethylbenzene.* — *Isolation of* 5-*carboxy*-2-*ethoxy*-1-βββ-*trichloro-α-hydroxyethylbenzene* (III). 20 G. of the acid (1 mol.) were added gradually to a hot solution of 48 g. of potassium hydroxide (18 mols.) in 200 c.c. of alcohol, and the mixture was gently boiled for ½ hour. Boiling water (200 c.c.) was added, and the alcohol distilled in steam. The dark red solution thus obtained deposited, on cooling, the potassium salt of 5-carboxy-2-ethoxy-1-βββ-trichloro-α-hydroxyethylbenzene in colourless, thin, flaky plates. These were filtered off and treated with dilute hydrochloric acid. The *acid*, isolated by means of ether and obtained as a crystalline, colourless mass, separated from warm ether–light petroleum in small, compact crystals (yield, 8·1 g.), m. p. 124—126° (Found : C, 41·9; H, 3·5; Cl, 33·8. $C_{11}H_{11}O_4Cl_3$ requires C, 42·15; H, 3·6; Cl, 33·9%).

It is very sparingly soluble in water or petroleum and easily soluble in ether or alcohol. It forms with alkalis colourless salts which are sparingly soluble in water.

Identification of 2-*hydroxy*-1 : 5-iso*phthalic acid* (V). The dark red mother-liquor from the preceding potassium salt was acidified with hydrochloric acid. The acid set free, which in part crystallised, was extracted with ether. Partial evaporation of the ether and addition of a little light petroleum gave 3·2 g. of a microcrystalline product, consisting mainly of 2-hydroxy-1 : 5-*iso*phthalic acid. As it was difficult to separate this acid in a pure condition, it was identified by conversion into its *ethyl* ester. This, after two crystallisations from methyl alcohol, melted sharply at 52·5° (Found : C, 60·2; H, 6·1. $C_{12}H_{14}O_5$ requires C, 60·4; H, 5·9%).

Identification of 5-carboxy-2-ethoxyphenylglycollic acid (IV). On allowing the ethereal mother-liquor from which the 2-hydroxy-1 : 5-*iso*phthalic acid had separated to evaporate spontaneously, an acid crystallised in colourless, silky needles, but in too small quantity to admit of complete purification. It was shown to be mainly 5-carboxy-2-ethoxyphenylglycollic acid in the following way. A solution of the acid (1·6 g.) in 3 c.c. of concentrated sulphuric acid was heated on a water-bath for 10 minutes, cooled, and poured into water. The product, isolated by means of ether, was a brown, crystalline solid which sublimed in colourless needles; these softened at 235°, melted at 244°, and agreed in properties with 5-carboxy-2-hydroxybenzaldehyde (Tiemann and Reimer, *Ber.*, 1876, 9, 1274). It dissolved easily in hot water, and the solution gave a yellow colour with sodium hydroxide and a dark red colour with ferric chloride. It reacted with semicarbazide, yielding a well-crystallised semicarbazone.

The *phenylhydrazone*, which separated as a yellow solid when phenylhydrazine was added to a hot aqueous solution of the aldehyde, crystallised from boiling alcohol, in which it was moderately easily soluble, in yellow needles, m. p. 257—258° (decomp.) (Found : N, 10·2. $C_{14}H_{12}O_3N_2$ requires N, 10·9%).

An alcoholic solution of the hydrazone is acid to litmus and gives a strong orange coloration with ferric chloride.

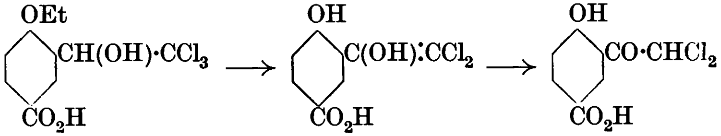
Oxidation of 5-Carboxy-2-ethoxyphenylglycollic Acid (IV) *to 2-Hydroxy-*1 : 5-iso*phthalic Acid* (V) *by Alkaline Potassium Permanganate.*—When the aqueous alkaline solution of the products of the action of potassium ethoxide upon anhydro-5-carboxy-2-βββ-trichloro-α-hydroxyethoxy-1-βββ-trichloro-α-hydroxyethylbenzene, obtained by diluting the mixture and distilling off the alcohol, was boiled and treated with a dilute aqueous solution of potassium permanganate until the colour of this was no longer discharged, a yellow solution was obtained. This was filtered from manganese dioxide, concentrated, and acidified with sulphuric acid. Ether then extracted 2-hydroxy-1 : 5-*iso*phthalic acid, from which the well-characterised ethyl ester was prepared.

The action of alcoholic potash upon the condensation product of *p*-hydroxybenzoic acid and chloral therefore takes place in the three stages (III ⟶ IV ⟶ V) shown on p. 687.

The action of alcoholic potash upon anhydro-5-carboxy-2-βββ-trichloro-α-hydroxyethoxy-1-βββ-trichloro-α-hydroxyethyl-benzene is much less violent than its action upon the analogously constituted 5-nitro-compound, owing to the greater stability of the first product, 5-carboxy-2-ethoxy-1-βββ-trichloro-α-hydroxyethylbenzene, which reacts with alcoholic potash sufficiently slowly to admit of its isolation as above described.

*Action of Sulphuric Acid upon 5-Carboxy-2-ethoxy-*1-βββ-*trichloro-α-hydroxyethylbenzene* (III) *and Formation of ωω-Dichloro-5-carboxy-2-hydroxyacetophenone* (VI).—A mixture of 10 g. of 5-carboxy-2-ethoxy-1-βββ-trichloro-α-hydroxyethylbenzene and 100 c.c. of concentrated sulphuric acid was heated for 10 minutes on a water-bath; hydrogen chloride was then liberated. After cooling, the dark brown solution was poured into 500 c.c. of water, and the product, *ωω-dichloro-5-carboxy-2-hydroxyacetophenone*, which was mainly deposited as a colourless solid, was extracted with ether. On evaporation of the ether, a well-crystallised product was left which was moderately easily soluble in water and easily soluble in alcohol. It separated from a mixture of these solvents in thin, unctuous plates, m. p. 163—166°. When powdered, it is extremely irritating and causes violent sneezing (Found: C, 43·4; H, 2·7; Cl, 28·45. $C_9H_6O_4Cl_2$ requires C, 43·4; H, 2·4; Cl, 28·5%).

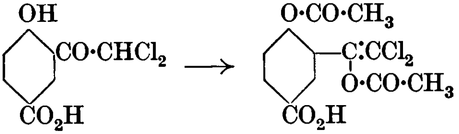
The compound must be formed by the elimination of hydrogen chloride under the influence of sulphuric acid followed by an intramolecular rearrangement thus:



ωω-Dichloro-5-carboxy-2-hydroxyacetophenone yields an *osazone* and a well-crystallised semicarbazone.

The osazone was obtained by gently boiling a slight excess of phenylhydrazine with a fairly concentrated alcoholic solution of the acetophenone. It separated as a yellow, crystalline mass and was recrystallised from boiling alcohol, in which it was moderately easily soluble, and from which it separated in canary-yellow needles, m. p. 243·5° (Found: N, 15·1. $C_{21}H_{18}O_3N_4$ requires N, 15·0%).

Acetyl Derivative of ωω-Dichloro-5-carboxy-2-hydroxyacetophenone.



—2 G. of the dichloro-acetophenone and 1 g. of anhydrous sodium acetate were added to 20 c.c. of acetic anhydride and heated gradually on an oil-bath. The liquid was allowed to boil gently for a few seconds, cooled, and poured into water; the viscid mass thus obtained was recrystallised from alcohol, from which it separated in colourless needles, m. p. 194—196° (Found : Cl, 21·5; C, 46·5; H, 3·1. $C_{13}H_{10}O_6Cl_2$ requires Cl, 21·3; C, 46·8; H, 3·0%).

Preparation of 5-Carboxy-2-hydroxyacetophenone, by Reduction of ωω-Dichloro-5-carboxy-2-hydroxyacetophenone (VI).—2 G. of ωω-dichloro-5-carboxy-2-hydroxyacetophenone and 25 c.c. of hydriodic acid (b. p. 126°) were heated to 115—120° for a short time. Reduction occurred very easily, free iodine was liberated, and on cooling the liquid 5-*carboxy-2-hydroxyacetophenone* crystallised out. It was recrystallised from dilute alcohol, from which it separates in colourless, shining plates, m. p. 246—247° (Found : C, 59·9; H, 4·4. $C_9H_8O_4$ requires C, 60·0; H, 4·4%).

It is sparingly soluble in water and easily soluble in alcohol. Its aqueous solution gives a cherry-red coloration with ferric chloride.

It yields a well-characterised *phenylhydrazone* when its concentrated alcoholic solution is heated with a slight excess of phenylhydrazine. This is sparingly soluble in alcohol, from which it separates in long, pale-yellow needles, m. p. 286° (Found : N, 10·2. $C_{15}H_{14}O_3N_2$ requires N, 10·4%).

*The Action of Hydriodic Acid on 5-Carboxy-2-ethoxy-*1-ββ*β-tri-chloro-α-hydroxyethylbenzene* (III).—2·7 G. of the substance were boiled gently for a short time with 25 c.c. of hydriodic acid (b. p. 126°). Iodine was liberated and, on cooling, 5-carboxy-2-hydroxyacetophenone crystallised out. After being recrystallised from dilute alcohol, it was obtained in shining plates, identical with those obtained by reduction of ωω-dichloro-5-carboxy-2-hydroxyacetophenone, and giving the same phenylhydrazone with phenylhydrazine.

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