CXXXVIII.—*The Condensation of Chloral with Substituted Phenols.*

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Phenols have been found to condense with aldehydes in three characteristic ways :

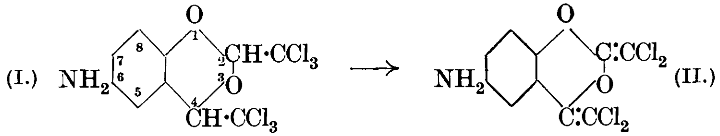
(1) The phenol (1 mol.) unites with the aldehyde (1 mol.), the condensation being of the aldol type.

(2) The phenol (2 mols.) reacts with the aldehyde (1 mol.), water (1 mol.) being eliminated and a dihydroxy-derivative of diphenylmethane or closely related hydrocarbon produced.

(3) The aldehyde (2 mols.) condenses with the phenol (1 mol.), subsequent elimination of water leading to the formation of a heterocyclic compound. For example, chloral reacts thus with *p*-nitrophenol (Chattaway, J., 1926, 2720), *p*-hydroxybenzoic acid (Chattaway and Calvet, J., 1927, 685), and phenol-*p*-sulphonic acid (Chattaway and Morris, J., 1927, 2013) in presence of concentrated sulphuric acid, yielding derivatives of 1 : 3-benzdioxin.

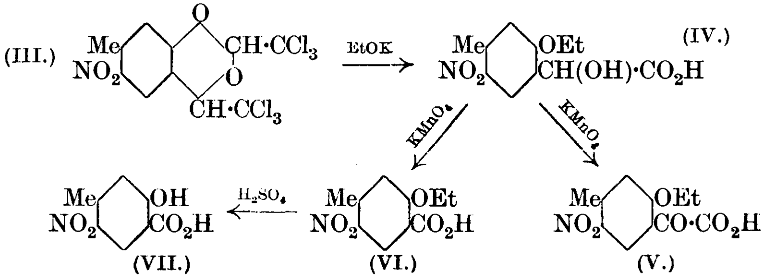
Several other *p*-substituted phenols react with chloral in a similar way. For example, *p*-aminophenol in presence of concentrated sulphuric acid readily gives 6-amino-2 : 4-bistrichloromethyl-1 : 3-benzdioxin (I), identical with the reduction product from 6-nitro-2 : 4-bistrichloromethylbenzdioxin (Chattaway, J., 1926, 2722, 2725, where the two substances are named as derivatives of ethylbenzene).

The action of alcoholic potash does not break this compound down so completely as it does the similarly constituted 6-nitro- and 6-carboxy-compounds, two molecules only of hydrogen chloride being eliminated and 6-*amino*-2 : 4-*bisdichloromethylene*-1 : 3-*benzdioxin* (II) formed.



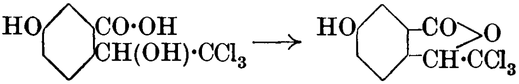
Azophenols also react similarly; for example, *p*-tolueneazophenol yields 6-p-*tolueneazo*-2 : 4-*bistrichloromethyl*-1 : 3-*benzdioxin* (formula as I), the constitution of which has been established by reducing it in alcoholic solution with stannous chloride to *p*-toluidine and 6-amino-2 : 4-bistrichloromethylbenzdioxin (I).

o-Nitro-*m*-cresol condenses similarly with chloral in presence of concentrated sulphuric acid and forms 6-*nitro*-7-*methyl*-2 : 4-*bis-trichloromethyl*-1 : 3-*benzdioxin* (III), showing that the presence of a methyl group in a position meta to the phenolic hydroxyl does not interfere with the reaction. The constitution of this compound is shown by its behaviour with alcoholic potash : 5-*nitro*-2-*ethoxy*-4-*methylmandelic acid* (IV) is formed, which on oxidation by potassium permanganate yields a mixture of 5-*nitro*-2-*ethoxy*-p-*tolylglyoxylic acid* (V) and 6-*nitro*-3-*ethoxy*-p-*toluic acid* (VI); the latter on hydrolysis of the ethoxy-group yields 6-nitro-3-hydroxy-*p*-toluic acid (VII) identical with the product obtained by the nitration of 3-hydroxy-*p*-toluic acid :



Salicylic acid and both *o*- and *m*-nitrophenol, where the position para to the hydroxyl group is open, also condense with chloral in presence of concentrated sulphuric acid, possibly by the introduction of a $-CH(OH)\cdot CCl_3$ group in the vacant para-position, but in each case a viscid and resin-like uncrystallisable product has been obtained.

That the $-CH(OH)\cdot CCl_3$ group enters the unoccupied para-position in these reactions is rendered more probable by the circumstance that when the adjacent meta-position is occupied by a group with which it can react, well-crystallised condensation products are formed; *e.g.*, *m*-hydroxybenzoic acid gives 5-hydroxytrichloromethylphthalide (Fritsch, *Annalen*, 1897, **296**, 344).



Even by using a large excess of chloral (2 mols.) it has been found impossible to introduce another $-CH(OH)\cdot CCl_3$ group into the molecule, the reason probably being that its introduction is such a slow process that before any recognisable amount has been introduced the chloral itself polymerises to metachloral under the influence of the sulphuric acid.

5-Nitrosalicylic acid, *p*-nitro-*o*-cresol, and 2 : 4-dinitrophenol, in all of which one position ortho to the hydroxyl group is occupied, do not condense with chloral in presence of concentrated sulphuric acid. This may be due to the steric hindrance of the substituents ortho to the phenolic group preventing the addition which probably precedes the entrance of the $-CH(OH)\cdot CCl_3$ group into the nucleus.

EXPERIMENTAL.

6-*Amino*-2 : 4-*bistrichloromethyl*-1 : 3-*benzdioxin* (I).—To a solution of 70 g. of *p*-aminophenol hydrochloride in 800 c.c. of concentrated sulphuric acid, cooled with ice-water, 250 g. of chloral hydrate were added. The mixture was well shaken for ½ hour and, after 3 days, poured into 2500 c.c. of water containing ice. The brown solid that separated was recrystallised (yield, 98 g.) from much boiling water, in which it was sparingly soluble, and was then washed with a little alcohol, which dissolved a small quantity of adhering tarry matter. The residual mixture of 6-amino-2 : 4-bistrichloromethylbenzdioxin sulphate and *p*-aminophenol-*o*-sulphonic acid was finely powdered and poured into 100 c.c. of water, to which a solution of sodium hydroxide was added until an alkaline reaction was obtained; the sodium aminophenolsulphonate remained in solution. The precipitated condensation product

(45 g.), after being recrystallised from alcohol, melted at 174·5° and proved to be identical with the amino-compound obtained by reduction of 6-nitro-2 : 4-bistrichloromethylbenzdioxin (Chattaway, *loc. cit.*), giving the same acetyl derivative, m. p. 206°. Its identity with the latter compound was further established by converting it into the corresponding 6-carboxylic acid by replacing the amino-group by carboxyl, through the cyano-derivative.

From the alkaline solution, on acidification with acetic acid, *p*-aminophenol-*o*-sulphonic acid crystallised in very small needles, which were recrystallised from water (8·5 g.) (Found : C, 38·6; H, 3·7; N, 7·6; S, 16·6. Calc. for $C_6H_7O_4NS$: C, 38·1; H, 3·7; N, 7·4; S, 16·9%) (compare Post, *Annalen*, 1880, **205**, 49).

7-*Bromo*-6-*amino*-2 : 4-*bistrichloromethyl*-1 : 3-*benzdioxin*.—The base (4·2 g.) and bromine (30 c.c. of a solution of 160 g. per litre) were boiled in glacial acetic acid for a few seconds. (Longer heating causes further bromination.) The *monobromo*-compound, which crystallised on cooling, was obtained, after several crystallisations from alcohol, in well-formed, colourless needles, m. p. 171—173° (yield, 2 g.). It is insoluble in light petroleum, but fairly readily soluble in ether, alcohol and acetic acid (Found : Cl, 46·3; Br, 17·4. $C_{10}H_6O_2NCl_6Br$ requires Cl, 45·8; Br, 17·2%).

The monobromo-compound yielded an *acetyl* derivative when it was boiled for 10 minutes with a mixture of acetic anhydride and acetyl chloride. The product was twice recrystallised from boiling alcohol, in which it was moderately easily soluble, and from which it separated in small, colourless plates, m. p. 231—232·5° (Found : Cl, 42·8; Br, 16·1. $C_{12}H_8O_3NCl_6Br$ requires Cl, 42·2; Br, 15·8%).

6-*Amino*-2 : 4-*bisdichloromethylene*-1 : 3-*benzdioxin* (II).—The finely powdered base (I) (30 g.) was slowly added to a boiling solution of 80 g. of potassium hydroxide in 400 c.c. of alcohol and further boiled for $\frac{1}{2}$ hour. To the boiling liquid 400 c.c. of hot water were added and the alcohol was distilled off in steam. On cooling, the heavy oily product solidified. After being recrystallised three times from hot alcohol (yield, 17 g.) it was obtained in small, colourless needles, m. p. 113—117°. It is easily soluble in alcohol, ether, chloroform, carbon tetrachloride, and carbon disulphide (Found : C, 37·8; H, 1·4; N, 4·5; Cl, 45·2. $C_{10}H_5O_2NCl_4$ requires C, 38·3; H, 1·6; N, 4·5; Cl, 45·4%). It can be kept for a considerable time without change, though after some months it becomes tarry. When dissolved in carbon tetrachloride it combines directly with bromine without evolution of hydrogen bromide and thus appears to be an unsaturated compound.

When added to acetic anhydride containing a drop of concentrated sulphuric acid, it readily formed an *acetyl* derivative, which crystallised from dilute, boiling alcohol in microscopical needles, m. p. 191—194° (Found : Cl, 40·0. $C_{12}H_7O_3NCl_4$ requires Cl, 40·0%).

6-p-*Tolueneazo*-2 : 4-*bistrichloromethyl*-1 : 3-*benzdioxin* (formula as I).—A solution of 20 g. of *p*-tolueneazophenol and 40 g. of chloral hydrate in 300 c.c. of concentrated sulphuric acid was kept for 3 days with frequent shaking, a small quantity of the condensation product separating, and was then poured into 1000 c.c. of cold water. The red product dissolved readily in boiling alcohol, and separated in reddish-yellow needles (10 g.), m. p. 152—153°. It is easily soluble in ether, alcohol, and acetic acid (Found : Cl, 43·4; N, 5·7. $C_{17}H_{12}O_2N_2Cl_6$ requires Cl, 43·5; N, 5·7%).

Reduction. 4 G. of the finely powdered substance and 10 g. of stannous chloride were added to 100 c.c. of alcohol, and the liquid was boiled under reflux for 5 minutes, its colour being totally discharged. The liquid was made slightly acid with dilute hydrochloric acid, the alcohol distilled off in steam, and the aqueous liquid cooled and extracted with ether. The extract was concentrated to a small volume and steam-distilled; *p*-toluidine came over, and was identified by means of its acetyl derivative.

The solid remaining in the flask, after being recrystallised from alcohol, was identified as 6-amino-2 : 4-bistrichloromethylbenzdioxin, giving the already described acetyl derivative. The yield was 2·3 g.

5-*Hydroxytrichloromethylphthalide*.—When a solution of 13 g. (1 mol.) of *m*-hydroxybenzoic acid and 33 g. (2 mols.) of chloral hydrate in 100 c.c. of concentrated sulphuric acid was kept for 2 days, the condensation product crystallised in fine needles, mixed with metachloral. The liquid was poured into 500 c.c. of ice-water and the phthalide which separated was extracted with hot alcohol and recrystallised several times from this solvent; m. p. 199—200° (compare Fritsch, *loc. cit.*) (Found : Cl, 39·8. Calc. for $C_9H_5O_3Cl_3$: Cl, 39·75%).

6-*Nitro*-7-*methyl*-2 : 4-*bistrichloromethyl*-1 : 3-*benzdioxin* (III).—The condensation was effected as in the preceding case (19 g. of *p*-nitro-*m*-cresol [1 mol.]; 41 g. of chloral hydrate [2 mols.]; 200 c.c. of concentrated sulphuric acid; 800 g. of crushed ice). The solid that separated was washed with a few c.c. of boiling alcohol, which removed a little tar, and crystallised several times from alcohol (animal charcoal), being obtained in very slightly yellow needles, m. p. 148—150° (Found : Cl, 49·8. $C_{11}H_7O_4NCl_6$ requires Cl, 49·5%).

5-*Nitro*-2-*ethoxy*-4-*methylmandelic Acid* (IV).—10 G. of finely powdered 6-nitro-7-methyl-2 : 4-bistrichloromethylbenzdioxin were added to a cooled solution of 14 g. of potassium hydroxide (9 mols.) in 100 c.c. of alcohol. The reaction proceeds with evolution of heat, and the temperature must not be allowed to rise. The liquid was boiled for just 3 minutes on the water-bath, 100 c.c. of hot water were added, and after partial neutralisation with dilute hydrochloric acid, the alcohol was distilled off in steam. On allowing the aqueous liquid to cool (and after separating by filtration a considerable amount of tarry matter which came down first) 5-*nitro*-2-*ethoxy*-4-*methylmandelic acid* was obtained as a voluminous mass of very small needles (3·2 g.). After being recrystallised three times from water, it melted at 155°. It is very soluble in boiling water and alcohol, moderately easily soluble in ether, but insoluble in low-boiling petroleum (Found : C, 51·6; H, 5·3; N, 5·5. $C_{11}H_{13}O_6N$ requires C, 51·8; H, 5·1; N, 5·5%).

Preparation of 5-*Nitro*-2-*ethoxy*-p-*tolylglyoxylic Acid* (V) *and* 6-*Nitro*-3-*ethoxy*-p-*toluic Acid* (VI).—An alkaline solution of 5 g. of the mandelic acid in sodium carbonate was heated on the water-bath, and 11 g. of potassium permanganate were slowly added, the colour of which was discharged after 10 minutes' heating. The filtrate from the manganese dioxide (which was washed with hot water), on cooling, was made acid with dilute hydrochloric acid; the product which then crystallised (1·9 g.) was a mixture of very small prisms and minute needles. The latter dissolved in boiling benzene (30 c.c.), and on cooling, the solution deposited 6-*nitro*-3-*ethoxy*-p-*toluic acid* (VI), m. p. 166° after twice crystallising from water (yield, 0·7 g.). It is easily soluble in ether and benzene but insoluble in low-boiling petroleum (Found : C, 53·6; H, 4·8; N, 6·3. $C_{10}H_{11}O_5N$ requires C, 53·3; H, 4·9; N, 6·2%).

The prisms (1 g.) left undissolved by the boiling benzene crystallised from boiling water in colourless plates, m. p. 194°. From its analysis and the fact that it gives a well-defined phenylhydrazone the substance is shown to be 5-*nitro*-2-*ethoxy*-p-*tolylglyoxylic acid* (V) (Found : C, 52·5; H, 4·4; N, 5·6. $C_{11}H_{11}O_5N$ requires C, 52·2; H, 4·3; N, 5·5%).

The *phenylhydrazone* separated in yellow needles when an alcoholic solution of the ketonic acid was boiled for 15 minutes with a small excess of phenylhydrazine. After crystallising three times from alcohol, in which it was easily soluble, it melted at 199° (Found : N, 12·3. $C_{17}H_{17}O_5N_3$ requires N, 12·2%).

Hydrolysis of the Ethoxy-group of 6-*Nitro*-3-*ethoxy*-p-*toluic Acid*.—A solution of 0·5 g. of the acid in 5 c.c. of concentrated sulphuric acid was heated for 3 hours on a water-bath and poured into 30 c.c. of water. The 6-nitro-3-hydroxy-*p*-toluic acid (VII) that separated, after being recrystallised from a few c.c. of water, was obtained in very slightly yellow needles (0·25 g.), m. p. 225°, identical with the acid described below (Found : N, 7·3. Calc. for $C_8H_7O_5N$: N, 7·1%).

The Nitration of 3-*Hydroxy*-p-*toluic Acid*.—We have not been able to obtain a fully nitrated product by Borsche and Berkhout's method (*Annalen*, 1903, **330**, 101). The following method is satisfactory.

To a vigorously stirred suspension of 10 g. of 3-hydroxy-*p*-toluic acid in 50 c.c. of glacial acetic acid, a mixture of 10 c.c. of nitric acid (*d* 1·5) and 10 c.c. of acetic acid was added. The temperature rose to about 60—70°, and the toluic acid dissolved completely. After cooling, the whole was poured into 400 c.c. of cold water, and the solid which separated was recrystallised from boiling water (yield, 5 g.). The nitrohydroxy-*p*-toluic acid (VII) was thus obtained in very pale yellowish needles, m. p. 225°, melting somewhat higher than the product described by Borsche and Berkhout (Found : N, 7·2%).

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