153. *Interaction of* p-*Cresol and other Phenols with Chloral and its Hydrate.*

By Michael P. Balfe and William C. Webber.

In the course of an investigation which we have had to discontinue before completion, compounds of type (I) have been prepared from phenol and *p*-cresol by interaction with chloral. (II, X = Me) was prepared by Pauly and Schanz (*Ber.*, 1923, **56**, 979) from *p*-cresol and chloral hydrate; an improved preparation is now described. Acetylated derivatives of (II), (III), (IV), and (V), all of which are primarily derived from *p*-cresol and chloral or chloral hydrate, are described.

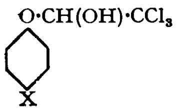
Phenols which contain electron-attracting *p*-substituents do not yield compounds of these types, but give only benzdioxin derivatives (VII) on reaction with chloral (Chattaway *et al.*, J., 1927, 685, 2013; 1928, 1088). The mechanism of this reaction is discussed.

Equimolecular proportions of *p*-cresol and chloral react at room temperature, yielding a moderately stable p-*tolyl ether* (I, X = Me); the reaction is accelerated by a trace of anhydrous potassium carbonate. A less stable *phenyl ether* (I, X = H) can also be prepared, but under these conditions chloral does not react with *o*- or *m*-cresol, *p*-nitrophenol or *p*-hydroxybenzoic acid.

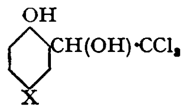
We find that (II, X = Me) is best prepared by repeated saturation of a melt of *p*-cresol and chloral hydrate with hydrogen chloride. Its diacetyl derivative was described by Meldrum and Lonkar (*J. Univ. Bombay*, **1937**, 116) and we have now obtained a *monoacetyl* derivative. Though this gives colorations (fugitive on heating) with ferric chloride solution, this reaction is not always diagnostic of phenolic groups (*e.g.*, acetoacetic ester and lactic acid give colorations, but thymol does not; see also the discussion on this point by Raschig, *Z. angew. Chem.*, 1907, **20**, 206). We conclude that the phenolic group is acetylated, because the compound is insoluble in cold aqueous sodium hydroxide, and gives the monoacetyl derivative of (III, X = Me) by interaction with *p*-cresol.

On addition of concentrated sulphuric acid to an equimolecular mixture of (II, X = Me) and *p*-cresol in acetic acid solution, much resinification and sulphonation occur, but three derivatives can be isolated. These are the above-mentioned monoacetyl derivatives of (II) and of (III) and a diacetyl derivative of (IV). We have not determined which of the two possible diacetyl derivatives of (IV) we have obtained, but the composition of the substance is indicated by its conversion into the *triacetyl* derivative of (IV).

On treatment with aqueous potassium hydroxide (3 mols.), (II, X = Me) yields a *substance* $C_{18}H_{15}O_4Cl_3$, m.p. 184°. It is insoluble in cold aqueous sodium hydroxide, and on acetylation yields a substance $C_{22}H_{19}O_6Cl_3$; we therefore suggest that its constitution is (V) (the isomers of which are less probable), the acetylation product being a *diacetate*. Meldrum and Lonkar (*loc. cit.*) obtained a substance, m. p. 182°, of the same chlorine content as (V) by treating (II, X = Me) with sodium hydroxide (10 mols.). They concluded that it was (VI) with one molecule of ethyl alcohol of crystallisation. Our compound does not contain ethyl alcohol, but whether that obtained by Meldrum and Lonkar's method is identical with it, or is its precursor, cannot be stated, since we have not repeated the experiment by their method.



(I.)



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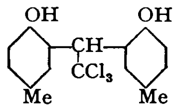

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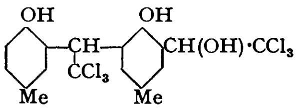

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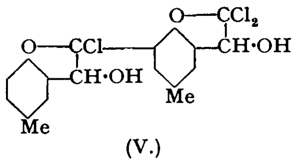
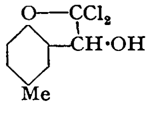
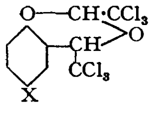


(V.)



(VI.)



(VII.)

The formation of (II) from *p*-cresol is slow, and when X is electron-attracting (NO_2, CO_2H), this reaction does not occur under the conditions which we used. Thus neither (I) nor (II) can be obtained from phenols which contain an electron-attracting *p*-substituent, yet both modes of reaction must occur during the formation of the benzdioxin derivative (VII) from such phenols and chloral in the presence of sulphuric acid (Chattaway *et al.*, *loc. cit.*). This reaction probably occurs in the following stages: (i) the chloral is converted into a kationic entity, the reactivity of which overcomes the deactivating effect of the *p*-substituent in the phenol, and an intermediate of type (II) is formed; (ii) ionisation of the phenol, repressed by the sulphuric acid, is now assisted by the second electron-attracting substituent. A small equilibrium proportion of phenoxide * molecules, substituted both as in (I) and as in (II), can therefore exist; these are immediately converted into (VII) by the sulphuric acid and the process therefore goes to completion. This scheme differs slightly from that suggested by Chattaway (J., 1926, 2720), but his initial stage, formation of (I), followed by rearrangement to (II), appears to be ruled out by the fact that a compound of type (II) can be obtained from anisic acid (Chattaway and Calvet, J., 1928, 1088).

In the course of this work, we have observed the separation of a compound of chloral and sulphuric acid, from mixtures of chloral or its hydrate and sulphuric acid in somewhat narrow ranges of composition and of strength of acid. Its composition probably corresponds to $CCl_3\cdot CH(OH)\cdot O\cdot SO_2\cdot OH,1\frac{1}{2}H_2O$, resembling chloral hydrochloride (Vorländer, *Annalen*, 1905, **341**, 21). This substance may be the alkyl hydrogen sulphate corresponding to the sodium salt described by Kerp and Bauer (*Chem. Ztg.*, 1907, **31**, 970).

EXPERIMENTAL.

p-Tolyl βββ-Trichloro-α-hydroxyethyl Ether (I, X = Me).—Powdered anhydrous potassium carbonate (0·5 g.) was added during 1½ minutes to a solution of *p*-cresol (10·8 g.; 1 mol.) in a mixture of chloral (14·8 g.; 1 mol.) and chloroform (5 c.c.). After 3 minutes the mixture had crystallised. The solid was collected, washed with 100 c.c. of light petroleum (b. p. 60—80°) containing 5% of benzene, and recrystallised from methylene chloride (15 c.c.) at 0°, giving the *ether* (I, X = Me) (9 g., 35% yield) in large, thick, regular, hexagonal plates, m. p. 46—47° (Found: C, 42·2; H, 3·5. $C_9H_9O_2Cl_3$ requires C, 42·2; H, 3·5%). When anhydrous sodium acetate (5 g.) was used instead of potassium carbonate, the yield was 6 g. The crystalline compound was unchanged after storage in the absence of moisture for 2 years, and 10 g. of the compound, mixed with 0·2 g. of potassium carbonate, 0·2 g. of magnesium carbonate, or 0·5 g. of anhydrous potassium acetate, were unchanged after 27 months. It was also recovered unchanged after storage in solution in benzene or chloroform for 2 years. It could not be recovered from solution in methyl or ethyl alcohol or acetone. On fractional distillation 20 g. of the compound yielded 11·2 g. of chloral (b. p. 97—98°) and 0·3 g. of chloral hydrate. Its chloral content was determined by decomposition with standard potassium hydroxide and back-titration of the excess of alkali: 0·2968 g. neutralised 9·7 c.c. of 0·8602*N*-alkali; hence chloral content = 57·4% ($C_9H_9O_2Cl_3$ requires 57·7%).

Phenyl βββ-trichloro-α-hydroxyethyl ether (I, X = H), prepared by the same method, chloral (29·6 g.; 1 mol.) and phenol (18·8 g.; 1 mol.) being used with anhydrous potassium carbonate (1 g.), formed large, colourless, rhombic plates, m. p. 15—18° (yield 3·6 g., 7·5%), chloral content 60% ($C_8H_7O_2Cl_3$ requires 63·7%). The analysis and m. p. range reflect the lesser stability of the compound, which decomposes more readily in solution than the *p*-tolyl ether.

*3-βββ-Trichloro-α-hydroxyethyl-*p*-cresol* (II, X = Me).—Hydrogen chloride was bubbled intermittently through a melt of chloral hydrate (33·1 g.; 1 mol.) and *p*-cresol (21·6 g.; 1 mol.) with occasional shaking. The crystals which separated were removed after approximately 6-day intervals, three crops (18, 10, and 7 g.; total yield, 35%) being obtained; no by-products could be isolated from the mother-liquors. A similar result was obtained when chloral was used instead of its hydrate.

(I, X = Me) is converted into (II) when it is stored in an atmosphere of hydrogen chloride for several months, or kept in solution in the presence of potassium carbonate; this change probably occurs *via* dissociation of (I) into its components, rather than ionic rearrangement, since it is retarded by addition of *p*-cresol.

The compound (II, X = Me) crystallises from much boiling water or from light petroleum (b. p. 60—80°) containing 10% of benzene in colourless needles, m. p. 147·5° (Found: Cl, 41·7. Calc. for $C_9H_9O_2Cl_3$: Cl, 41·9%), very soluble in ethyl alcohol and acetic acid, less soluble in ether, chloroform or benzene. It gives a deep magenta coloration with concentrated sulphuric acid; with ferric chloride solution, a dark blue colour in 40% aqueous ethyl alcohol and a deep green coloration in 30% aqueous methyl alcohol. On simultaneous hydrolysis and oxidation with potassium dichromate (Jeneff's method) it yields 5-methylsalicylaldehyde, m. p. 55°, in 10% yield (Found: C, 70·6; H, 5·9. Calc. for $C_8H_8O_2$: C, 70·6; H, 5·9%) (Tiemann and Schotten, *Ber.*, 1878, **11**, 773, give m. p. 56°).

The diacetyl derivative (acetic anhydride–sodium acetate) has m. p. 104·5° (Meldrum and Lonkar, *loc. cit.*, gave m. p. 106°) and crystallises in clusters of colourless monoclinic columns from acetic acid and as slender columns from aqueous alcohol (Found: Cl, 31·5. Calc. for $C_{13}H_{13}O_4Cl_3$: Cl, 31·4%). The *monoacetyl* derivative was obtained by saturating a solution of (II) (2 g.) in glacial acetic acid (30 c.c.) with hydrogen chloride and after 24 hours pouring it into water; recrystallised from light petroleum (b. p. 60—80°) containing 10% of benzene, the monoacetate formed colourless needles, m. p. 168° (yield, 66%) (Found: C, 44·2; H, 4·0; Cl, 35·6. $C_{11}H_{11}O_3Cl_3$ requires C, 44·4; H, 3·7; Cl, 35·8%).

Monoacetyl Derivative of (III, X = Me).—To a solution of 14·8 g. (1 mol.) of the monoacetyl derivative of (II, X = Me) and 5·4 g. (1 mol.) of *p*-cresol in 250 c.c. of glacial acetic acid, 180 g. of 99% sulphuric acid were added, with stirring, at a rate to maintain the temperature at 50°. The clear solution was poured into 1 l. of water, and the precipitate washed with much water, then recrystallised three times from aqueous alcohol. The resulting *monoacetate* of (III, X = Me) had m. p. 198°. Yield, 4·5 g. (23%) (Found: C, 55·7; H, 4·3; Cl, 27·6. $C_{18}H_{17}O_3Cl_3$ requires C, 55·8; H, 4·4; Cl, 27·5%). On boiling with acetic anhydride and sodium acetate, it gave the *diacetyl* derivative of (III), m. p. 162° (Found: Cl, 24·4. $C_{20}H_{19}O_4Cl_3$ requires Cl, 24·7%). In a similar experiment using 12·8 g. (1 mol.) of (II) and 7·5 g. (1 mol.) of *p*-tolyl acetate, 11% of the monoacetyl derivative of (III) and 10% of its diacetyl derivative were obtained.

Interaction of (II, X = Me) *and* p-*Cresol in Acetic Acid Solution in Presence of Sulphuric Acid.*—Below 20°, only slow sulphonation and above 60°, condensation to uncrystallisable derivatives, occurred. Between 50° and 60°, small amounts of crystallisable derivatives were formed; *e.g.*, to 12·8 g. of (II, X = Me) and 5·4 g. of *p*-cresol (1 mol.) in 300 c.c. of glacial acetic acid, 180 g. of 99% sulphuric acid were added, the temperature being kept at 60°. The cooled mixture was poured into 1 l. of water, and the precipitate washed with much water, dried, washed with 50 c.c. of light

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* The formation of these hemi-acetals is a reversible process, and involves ionisation of the hydroxyl group. Like that of the other compounds (acetals and *gem*-diols) of the general formula $R'\cdot CH(OR'')\cdot OR'''$, their stability increases with increasing electron attraction in R′, and decreases with increasing electron-release from OR″ and with increasing electron attraction (anionic stability) in OR‴

petroleum (b. p. 60—80°), and recrystallised from aqueous alcohol, being separated into the monoacetyl derivative of (II, X = Me) (2·1 g.), the monoacetyl derivative of (III) (0·5 g.), and a diacetyl derivative of (IV) (approx. 0·1 g.), m. p. 200°.

Interaction of (II, X = Me) *and* p-*Cresol in Nitrobenzene Solution in Presence of Sulphuric Acid.*—To 12·8 g. of (II, X = Me) and 10·8 g. (2 mols.) of *p*-cresol in 60 c.c. of nitrobenzene, 18 g. of 99% sulphuric acid in 20 c.c. of nitrobenzene were added, the temperature being kept at 15°. The mixture was then poured into water, steam-distilled to remove *p*-cresol and nitrobenzene, and evaporated to dryness, leaving a resinous mass (15·6 g.). Higher temperature, higher proportions of sulphuric acid, or use of undiluted sulphuric acid, produced only water-soluble sulphonation products (*p*-cresolsulphonic acid was isolated as its ammonium salt). Use of 90% sulphuric acid produced no reaction.

A similar resinous product was obtained in experiments as above with (II, X = Me), without *p*-cresol. These resinous products were dissolved in glacial acetic acid and saturated with hydrogen chloride. From the gum which separated, after lixiviation with methyl alcohol and repeated crystallisation from ethyl alcohol, a *diacetyl* derivative of (IV) was obtained (approx. 1 g.), in nodular clusters of colourless needles, m. p. 200° (slight decomp.) (Found : C, 45·7; H, 3·5; Cl, 36·8. $C_{22}H_{20}O_5Cl_6$ requires C, 45·7; H, 3·5; Cl, 36·9%).

This diacetyl derivative (on acetylation with acetic anhydride) and the above resinous products (on boiling with acetic anhydride and sodium acetate) gave the *triacetyl* derivative of (IV), crystallising from ethyl alcohol in short colourless prisms, m. p. 178° (Found : C, 46·5; H, 3·7; Cl, 34·2. $C_{24}H_{22}O_6Cl_6$ requires C, 46·5; H, 3·5; Cl, 34·4%). The resinous products gave a 6% yield of triacetate.

Action of Potassium Hydroxide on (II, X = Me).—To a solution of 12·8 g. of (II, X = Me) in 50 c.c. of water containing 2·8 g. (1 mol.) of potassium hydroxide at 16°, 100 c.c. of water containing 5·6 g. of potassium hydroxide were added slowly, with stirring. The orange-red precipitate was twice recrystallised from benzene, finally from aqueous alcohol (yield, 0·8 g.). This *substance*, m. p. 184°, is insoluble in aqueous alkali, indicating that it is not highly hydroxylated, and its analysis (Found : C, 54·0; H, 3·8; Cl, 26·5. $C_{18}H_{15}O_4Cl_3$ requires C, 53·8; H, 3·7; Cl, 26·5%) corresponds with formula (V). On boiling with acetic anhydride and sodium acetate, it yields a *diacetate*, crystallising from ethyl alcohol in clusters of colourless rhombs, m. p. 133° (Found : C, 54·6; H, 4·0; Cl, 22·0. $C_{22}H_{19}O_6Cl_3$ requires C, 54·4; H, 3·9; Cl, 21·9%).

Chloral Hydrogen Sulphate.—Chloral hydrate (16·55 g. portions) was stirred with sulphuric acid (100 g.) of various strengths for 6 hours, and the crystalline mass which formed the upper layer was collected after 2 days. From acid of 77% strength or lower, no crystals separated (except a deposit of unchanged chloral hydrate); the maximum yield (22 g.) was obtained with 79·8% acid, and higher strengths of acid gave lower yields (16 g. at 81·2% strength). At any given acid strength between 78·5 and 80·5% there is an optimum ratio of chloral to acid. Thus from 49·65 g. of chloral and 78·5% acid, the maximum yield (48 g.) was obtained with 500 g. of the acid; chloral (44·24 g.) gave 62 g. of the crude substance on mixing with 300 g. of 77·0% acid. The substance absorbed moisture when exposed to air, yielding chloral hydrate and sulphuric acid, and on heating decomposed, chloral and sulphuric acid separating in two layers.

The substance separates in a pulpy mass of small needles. Between 16° and 22°, it appears to be in equilibrium with acid of composition $H_2SO_4,1\frac{1}{2}H_2O$. Accurate analysis is impossible, as it decomposes when washed to remove adhering acid. An attempt was made roughly to estimate its composition by determining the sulphate (as barium sulphate) and the chloral + sulphuric acid (titration with sodium hydroxide) in the filtrate from a known weight of the substance obtained from known amounts of chloral hydrate and sulphuric acid. The composition of the solid corresponded to $CCl_3{\cdot}CH(OH){\cdot}SO_3{\cdot}OH,1\frac{1}{2}H_2O$ + 21·2% of $H_2SO_4,1\frac{1}{2}H_2O$. Since the solid could not be freed from surplus acid, the result suggests that it contains chloral and sulphuric acid in equimolecular proportion.

Thanks are due to Dr. J. Kenyon, F.R.S., for his interest in this work.

BATTERSEA POLYTECHNIC, LONDON, S.W. 11. [*Received, September 1st*, 1942.]