712. *Organic Fluoro-compounds. Part V.* ω-Trihalogenoacetophenones.*

By W. B. Whalley.

The first portion of this communication describes novel syntheses of 2 : 6-dihydroxy-4-methoxyacetophenone (III), 2-methylphloroglucinol 5-methyl ether (VI), 4-hydroxy-2 : 6-dimethoxyacetophenone (VIII; R = Ac), 4-hydroxy-2 : 6-dimethoxybenzoic acid (VIII; R = CO_2H), and of several derivatives, by the application and extension of the work reported in Part IV.* The Hoesch synthesis with trichloromethyl cyanide and 4-hydroxy-3-methylcoumarone (XIII; R = H) furnished 4-hydroxy-3-methyl-2-trichloroacetylcoumarone (XIII; R = CO·CCl_3) whilst trifluoromethyl and trichloromethyl cyanides and 2-methylphloroglucinol 1-methyl ether gave rise to the ketones (XI; R = CF_3) and (XI; R = CCl_3), respectively. 2-Methylphloroglucinol 1 : 5-dimethyl ether (XII; R = H) similarly furnished the ketones (XII; R = CO·CF_3) and (XII; R = CO·CCl_3).

The theoretical implications of the bright colour and the reactions of the ω-trichloro- and ω-trifluoro-polyhydroxyacetophenones and their derivatives are discussed.

The new and improved method for the preparation of 2 : 6-dihydroxy-4-methoxybenzaldehyde recently described (Part IV *) has been extended to provide an easy synthesis of the hitherto difficultly accessible 2 : 6-dihydroxy-4-methoxyacetophenone (III) (Sonn and Bulow, *Ber.*, 1925, **58**, 1691). The application of the Hoesch reaction with methyl cyanide to ω-trichloro-2 : 4-dihydroxy-6-methoxyacetophenone (I; R = CCl_3) (Part IV, *loc. cit.*) was not successful, but by the substitution of the methyl ester (I; R = OMe) the keto-ester (II) was obtained in moderate yield. The production of the keto-ester (II) from (I; R = OMe) by *C*-acetylation by using acetic anhydride in the presence of boron trifluoride proceeded quantitatively, as did the formation of (IV; R = CCl_3) from (I; R = CCl_3) by the same method. The alkaline hydrolysis of (II) or (IV; R = CCl_3) readily furnished 2 : 6-dihydroxy-4-methoxyacetophenone (III) in quantitative yield. The structures allocated to (II) and (IV; R = CCl_3) follow from the production of (III) by hydrolysis, and are further confirmed by the reduction of (IV; R = CCl_3) with zinc dust and acetic acid to the diketone (IV; R = Me), identical with an authentic specimen kindly provided by Dr. F. M. Dean of this Department (Dean and Robertson, forthcoming publication).

The Clemmensen reduction of (V; R = CHO) (Part IV, *loc. cit.*) readily gave rise in high yield to methyl 2 : 4-dihydroxy-6-methoxy-3-methylbenzoate (V; R = Me), which was converted by alkaline hydrolysis into 2-methylphloroglucinol 5-methyl ether (VI) (cf. Curd and Robertson, *J.*, 1933, 437; Robertson and Whalley, *J.*, in the press). The application of the Gattermann aldehyde synthesis to (V; R = Me) furnished methyl 5-formyl-2 : 4-dihydroxy-6-methoxy-3-methylbenzoate (VII).

The interaction of phloroglucinol dimethyl ether and trichloromethyl cyanide gave rise exclusively to the ketone (VIII; R = CO·CCl_3), unaccompanied by detectable quantities of the second possible isomeride (IX; R = CCl_3). The absence of the second ketone is remarkable in view of the well-established production of the two possible isomerides with a variety of other cyanides (Canter, Curd, and Robertson, *J.*, 1931, 1245). Phloroglucinol dimethyl ether and trifluoromethyl cyanide behaved normally and furnished a mixture of the isomeric ketones (VIII; R = CO·CF_3), and (IX; R = CF_3) which were readily separable by steam-distillation.

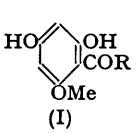
* Part IV, *J.*, 1951, 665.

Alkaline hydrolysis of (VIII; R = CO·CCl_3) furnished the acid (VIII; R = CO_2H), whilst Clemmensen reduction (Part IV, *loc. cit.*) readily gave rise to 2-ethylphloroglucinol 1 : 3-dimethyl ether (VIII; R = Et), thus providing a rapid and convenient means of access to these two compounds.

Reduction of ω-trichloro-4-hydroxy-2 : 6-dimethoxyacetophenone (VIII; R = CO·CCl_3) with zinc dust in acetic acid furnished 4-hydroxy-2 : 6-dimethoxyacetophenone (VIII; R = Ac) in high yield, thus providing an alternative route to this compound and obviating its separation from the isomeric ketone which is a necessary concomitant of the usual synthesis (Canter, Curd, and Robertson, *loc. cit.*).

In view of the propensity of the trichloroacetyl group for substitution in the *para*-position to a phenolic hydroxyl group, as indicated by the production of (VIII; R = CO·CCl_3) and of ω-trichloro-4-hydroxy-2-methoxyacetophenone (Part IV, *loc. cit.*), the application of the Hoesch synthesis with trichloromethyl and trifluoromethyl cyanides to 2-methylphloroglucinol 1-methyl ether and 2-methylphloroglucinol 1 : 5-dimethyl ether seemed of interest. With trichloromethyl cyanide and methylphloroglucinol 5-methyl ether substitution occurred in the normal position only with the production in low yield of ω-trichloro-2 : 6-dihydroxy-4-methoxy-3-methylacetophenone (XI; R = CCl_3). No trace of the second, expected isomeride could be detected. This is in accordance with the well-established behaviour of 2-methylphloroglucinol 1-methyl ether under the normal conditions of the Hoesch synthesis (compare Curd and Robertson, *J.*, 1933, 1173). The orientation of (XI; R = CCl_3) is established by the ready conversion into methyl 2 : 6-dihydroxy-4-methoxy-3-methylbenzoate (XI; R = OMe) under the conditions described in Part IV (*loc. cit.*).

Trifluoromethyl cyanide and 2-methylphloroglucinol 1-methyl ether gave rise to a good yield of only one isomeride, which by analogy with the corresponding derivative from trichloromethyl cyanide is represented by (XI; R = CF_3).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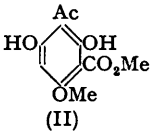
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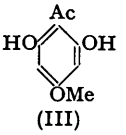
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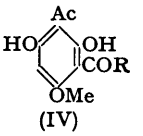
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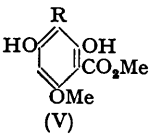
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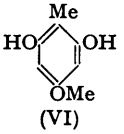
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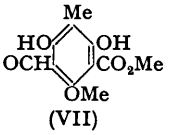
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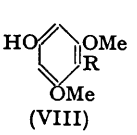
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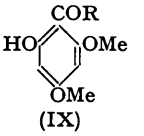
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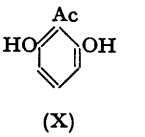
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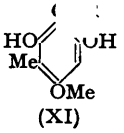
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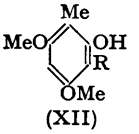
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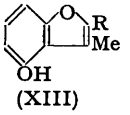
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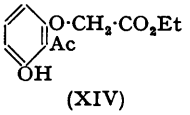
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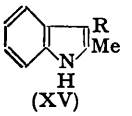

(XV)

In accordance with the previously observed behaviour of 2-methylphloroglucinol 1 : 5-dimethyl ether (Curd and Robertson, *loc. cit.*), trifluoromethyl and trichloromethyl cyanides with this phenol gave only the ketones (XII; R = CO·CF_3) and (XII; R = CO·CCl_3), respectively, the orientations of which were established by the ferric reactions in alcohol and by hydrolysis to the acid (XII; R = CO_2H). The trichloromethyl ketone (XII; R = CO·CCl_3) was obtained in small yield.

In view of the interesting implications, which are discussed more fully later, of the colours exhibited by the ω-trichloro- and ω-trifluoro-acetophenones, the preparation of 4-hydroxy-3-methyl-2-trichloroacetylcoumarone (XIII; R = CO·CCl_3) was carried out. The condensation of 2-acetylresorcinol (X) with ethyl bromoacetate readily furnished the phenoxy-ester (XIV) which was converted by the standard procedure into the coumarones (XIII; R = H) and (XIII; R = CO_2Et). The application of the Hoesch synthesis with trichloromethyl cyanide to (XIII; R = H) gave rise to (XIII; R = CO·CCl_3), but the reaction did not proceed as readily as in the case of the isomeric 6-hydroxy-4-methylcoumarone (Part IV, *loc. cit.*). This is not surprising in view of the well-recognised inactivity to this type of substitution of the 2-position of the resorcinol system, and the α-position of (XIII; R = H) is equivalent to the 2-position. Direct conversion of (XIII; R = CO·CCl_3) into (XIII; R = CO_2Et) (Part IV,

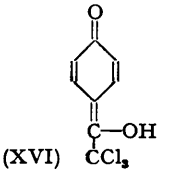
loc. cit.) gave rise to a product identical with that obtained by the direct cyclisation of (XIV) with sodium ethoxide, thus establishing the orientation of (XIII; R = $CO{\cdot}CCl_3$).

The ready conversion of 2-methyl-3-trichloroacetylindole (XV; R = $CO{\cdot}CCl_3$) into the corresponding methyl ester (XV; R = CO_2Me) is also reported and discussed later.

Discussion.

Several points concerning the chemistry of the ω-trichloro- and ω-trifluoropolyhydroxymethyl ketones described in this and the previous part (Part IV, *loc. cit.*) merit further discussion.

These compounds are often yellow and even brilliant yellow in colour and, in view of the non-chromophoric properties of the appropriate aromatic moieties and of the trichloroacetyl and trifluoroacetyl groups, the colour would seem to be ascribable to the presence of a quinonoid structure (*ortho* or *para*) of type (XVI), similar to that suggested by Hunsberger and Amstutz (*J. Amer. Chem. Soc.*, 1948, **70**, 671) to account for the properties of the electronically similar hydroxyphenylglyoxylic acids (compare Ralph and Robertson, *J.*, 1950, 3380). The driving force behind this change is presumably the very strong electrophilic nature of the trihalogenomethyl group which is more readily exerted in the quinonoid form. Further, the presence of the *ortho-para* directing hydroxyl and methoxyl groupings would be expected to enhance the stability of these quinonoid structures (compare Gomberg and West, *J. Amer. Chem. Soc.*, 1912, **34**, 1529). The solutions of these trihalogeno-ketones in alkali always have an intense



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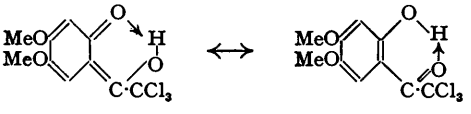
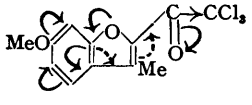


(XVII) (XVIII)



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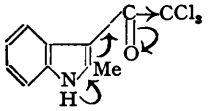

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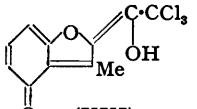
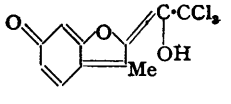


(XXI)



(XXII)

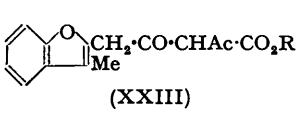
yellow colour presumably because the salts formed are those of the appropriate enol. The lack of normal carbonyl reactivity in the trihalogenoacetyl systems is due partially at least to this quinonoid system (compare the behaviour of the phenylglyoxylic acids), a view which is supported by the fact that there have now been prepared, albeit with difficulty, the 2 : 4-dinitrophenylhydrazones of ω-trifluoro-2 : 4-dimethoxyacetophenone and of 6-methoxy-2-trifluoroacetylcoumarone (Part IV, *loc. cit.*). The enolic hydroxyl group together with the quinonoid carbonyl in compounds of types (XVI), (XVII), and (XXII) constitute aromatic vinylogues of the carboxylic acid system, thus satisfactorily explaining the lack of normal activity of the quinonoid carbonyl group and the acidity of the enolic hydroxyl, a property which is enhanced by the electrophilic trihalogenomethyl residue. The very intense yellow colour of the ω-trihalogeno-*o*-hydroxyacetophenones is undoubtedly due to resonance between the two canonical structures of types (XVII) and (XVIII) producing resonance stabilisation of the *ortho*-quinonoid form with a consequent deepening of colour (compare Johnson, "Modern Electronic Concepts of Valence," Vol. II, p. 1870, of "Organic Chemistry" 2nd edn., Wiley, New York, 1943, edited by Gilman).

The bright yellow colours of 4- and 6-hydroxy-2-trihalogenoacetylcoumarones together with the deep orange colour produced in alcoholic sodium acetate solution, and the lack of colour exhibited by the 7-methoxy-2-trihalogenoacetylcoumarones (Part IV, *loc. cit.*) are indicative of the structures (XXI) and (XXII) for the hydroxy-compounds. By analogy with the resonance structures types (XVII) and (XVIII) allocated to the *o*-hydroxy-ω-trihalogenoacetophenones, the *p*-hydroxy-ketones and the benzofuranones (XXI) and (XXII) may be more accurately represented by the resonance structures types (XXIV) and (XXV) respectively, rather than as tautomers.* However, we prefer not to make a definite decision on this point at the moment. The case of transformation of the benzofuran system into this quinonoid type provides an interesting comparison with the cyclisation of 2-substituted

* We are indebted to one of the referees for emphasing this point.

coumarones of type (XXIII) to usnolic acids (Foster, Robertson, and Healey, *J.*, 1939, 1594) where related quinonoid intermediates may constitute the transition stage.

The work of Fischer and his co-workers (*inter alia*, *Ber.*, 1931, **64**, 240, 2636) has clearly shown that the hydrolytic fission of ω-trichloro-ketones (the haloform reaction) is catalysed by hydroxyl ions. The conversion of polyhydroxy-ω-trichloroacetophenones, 2-trichloroacetylcoumarones, and of 2-methyl-3-trichloroacetylindole into the corresponding methyl (and sometimes ethyl) esters in high yield (Part IV, *loc. cit.*, and the present paper) in the presence of methanol (or ethanol) containing a trace of aqueous potassium hydroxide is likewise catalytic. This simple reaction, which has not been previously described, although the conversion of ω-trichloroacetophenone into methyl benzoate in the presence of aqueous methanolic potassium hydroxide has been reported (Houben, *Ber.*, 1931, **64**, 2645), failed with 4-hydroxy-2-methoxy- and 4-hydroxy-ω-trichloro-2 : 6-dimethoxyacetophenone but proceeded with every ω-trichloro-*o*-hydroxyacetophenone examined.



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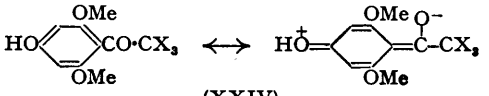

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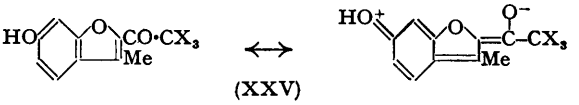
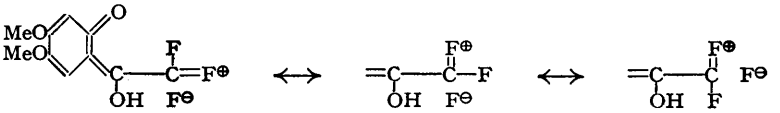


(XXV)

The ready conversion of 6-methoxy-2-trichloroacetylcoumarone (XIX), 4-hydroxy-2-trichloroacetylcoumarone (XIII; R = $CO{\cdot}CCl_3$), and of 2-methyl-3-trichloroacetylindole (XX) into the corresponding methyl (and ethyl) carboxylic ester may be due to the favourable electromeric displacements initiated by the hetero-atoms.

The stability towards alkali of the ω-trifluoropolyhydroxyacetophenones (compare Part IV, *loc. cit.*) is in sharp contrast to the great facility with which the corresponding trichloro-ketones undergo the haloform reaction. The insolubility of the fully methylated ω-trifluoromethyl ketones no doubt increases the resistance to hydrolysis (compare Aston *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 1413) but this cannot be a factor influencing the stability of the hydroxy-compounds. We suggest that this stability is a consequence of the very high percentage of double bond character exhibited by the carbon–fluorine bond in the $>CF_2$ and $-CF_3$ residues (compare Pauling, "The Nature of the Chemical Bond," p. 235, Cornell University Press, 1948), and that this phenomenon influences the polar nature, and also the normal length of the carbon–carbon bond joining the trifluoromethyl carbon to the adjacent carbon atom (compare, *e.g.*, the abnormal Cl–C distance in trifluoromethyl chloride) with a reduction of the susceptibility of this carbon–carbon bond to heterolytic fission, *i.e.* to nucleophilic attack by the hydroxyl ion.

Further, resonance between the various possible structures, such as types (XXVI), (XXVII), and (XXVIII), will contribute additional stability to the molecule.*



(XXVI) (XXVII) (XXVIII)

This decreased reactivity towards nucleophilic displacement reactions also provides an explanation for the failure of the ω-trifluoroacetophenones to undergo conversion into carboxylic esters in a manner similar to the ω-trichloroacetophenones (Part IV, *loc. cit.*).

* The much greater stability towards decarboxylation of trifluoroacetic acid compared with trichloroacetic acid (Auerbach, Verhoek, and Henne, *J. Amer. Chem. Soc.*, 1950, **72**, 299) is also rationalised by the application of this theory. The three additional resonance forms for the trifluoroacetate ion enhance the resistance of the carbon–carbon bond to the heterolytic fission which occurs during decarboxylation :

$$CF_3{\cdot}CO_2^{\ominus} \longrightarrow CF_3^{\ominus} + CO_2$$

(Auerbach, Verhoek, and Henne, *loc. cit.*; Johnson and Moelwyn-Hughes, *Proc. Roy. Soc.*, 1940, *A*, **175**, 118).

Similarly, as might be predicted, trifluoroacetaldehyde apparently undergoes the haloform reaction only " with strong aqueous bases " (Shechter and Conrad, *J. Amer. Chem. Soc.*, 1950, **72**, 3372).

Experimental.

2 : 6-*Dihydroxy-4-methoxyacetophenone* (III).—(*a*) A solution of methyl 2 : 4-dihydroxy-6-methoxybenzoate (Part IV, *loc. cit.*) (1·7 g.) in ether (100 ml.) containing zinc chloride (4 g.), methyl cyanide (10 ml.), and aluminium chloride (2 g.) was saturated at 5° with hydrogen chloride. 24 Hours later the semicrystalline ketimine salt was separated and dissolved in water (50 ml.), and the solution heated on the steam-bath for 20 minutes. The crystalline mass which separated from the cooled hydrolysate was collected and repeatedly recrystallised from methanol giving methyl 3-acetyl-2 : 4-dihydroxy-6-methoxybenzoate in long, slender needles, m. p. 170°, identical with the product from method (*b*).

When a solution of the previous partially purified keto-ester (1 g.) in water (15 ml.) containing potassium hydroxide (2 g.) was refluxed for 30 minutes, cooled, and acidified, 2 : 6-dihydroxy-4-methoxyacetophenone (0·6 g.) separated, m. p. 136°. Crystallisation from aqueous methanol gave the product in almost colourless needles, m. p. 137° (Found : C, 59·4; H, 5·3. Calc. for $C_9H_{10}O_4$: C, 59·3; H, 5·5%). Sonn and Bulow (*loc. cit.*) give m. p. 136°.

(*b*) A mixture of methyl 2 : 4-dihydroxy-6-methoxybenzoate (2·2 g.), acetic anhydride (0·7 g., 1·1 mol.), and acetic acid (15 ml.) was saturated with boron trifluoride (without cooling), whereupon the initially clear solution solidified to a yellow crystalline mass. Water (50 ml.) was then added and the suspended solid collected, washed with water, and dissolved in methanol (15 ml.), and the solution heated to boiling. The crystalline mass which separated on the addition of water was purified from a large volume of methanol to give *methyl 3-acetyl-2 : 4-dihydroxy-6-methoxybenzoate* (2·2 g.) in long, slender needles, m. p. 170° (Found : C, 55·1; H, 5·0. $C_{11}H_{12}O_6$ requires C, 55·0; H, 5·0%). Hydrolysis of this keto-ester as in (*a*) furnished a quantitative yield of 2 : 6-dihydroxy-4-methoxyacetophenone in needles.

(*c*) A mixture of ω-trichloro-2 : 6-dihydroxy-4-methoxyacetophenone (2 g.), acetic anhydride (0·7 g., 1 mol.), and acetic acid (5 ml.) was saturated with boron trifluoride (without cooling). The product was isolated as described in (*b*) and purified from aqueous methanol to give 2 : 6-*dihydroxy-4-methoxy-3-trichloroacetylacetophenone* (2·2 g.) in fawn-coloured needles, m. p. 115° (Found : C, 39·4; H, 3·5. $C_{11}H_9O_5Cl_3$ requires C, 40·3; H, 2·8%). Hydrolysis of this compound as described in (*a*) gave a quantitative yield of 2 : 6-dihydroxy-4-methoxyacetophenone in pink needles.

When a solution of the diketone (0·5 g.) in methanol (7 ml.) containing 1 drop of 60% potassium hydroxide solution was refluxed for 5 minutes and the product isolated in the normal way a quantitative yield of methyl 3-acetyl-2 : 4-dihydroxy-6-methoxybenzoate was obtained, identical with the compounds prepared by methods (*a*) and (*b*).

A suspension of the foregoing diketone in 2N-sodium hydrogen carbonate, containing a few drops of methanol, was warmed gently on the steam-bath whereupon a vigorous reaction occurred with the production of a clear solution and the evolution of chloroform. Isolation of the product and its purification from aqueous acetone furnished a quantitative yield of 3-*acetyl-2 : 4-dihydroxy-6-methoxybenzoic acid*, m. p. 182° (decomp.) (Found : C, 53·1; H, 4·4. $C_{10}H_{10}O_6$ requires C, 53·1; H, 4·4%).

The reduction of 2 : 6-dihydroxy-4-methoxy-3-trichloroacetylacetophenone (0·5 g.) with zinc dust (1 g.) and acetic acid (5 ml.) on the steam-bath during 3 minutes furnished a quantitative yield of 3-acetyl-2 : 6-dihydroxy-4-methoxyacetophenone, m. p. 105°, identical with an authentic specimen.

Methyl 5-Formyl-2 : 4-dihydroxy-6-methoxy-3-methylbenzoate (VII).—Methyl 3-formyl-2 : 4-dihydroxy-6-methoxybenzoate was prepared by the following modification of the method previously described (Part IV, *loc. cit.*). A suspension of methyl 2 : 4-dihydroxy-6-methoxybenzoate (2·2 g.) in ether (120 ml.) containing zinc cyanide (1·5 g.) and hydrogen cyanide (10 ml.) was saturated with hydrogen chloride, and the product isolated as previously described to give the aldehyde (2 g.).

A suspension of the aldehydo-ester (2 g.) in methanol (40 ml.) was added in several portions, during 5 minutes, to concentrated hydrochloric acid (20 ml.) and water (10 ml.) containing amalgamated zinc (15 g.), and the mixture warmed gently for 5 minutes more, when the reaction with aqueous 2 : 4-dinitrophenylhydrazine sulphate was negative. The hot clear solution was decanted from the amalgam and combined with further alcohol washings of the reducing agent, and the total liquors diluted with water; the product rapidly separated as a crystalline solid. Purification from aqueous methanol gave *methyl 2 : 4-dihydroxy-6-methoxy-3-methylbenzoate* (1·6 g.) in rosettes of stout prisms, m. p. 202°, exhibiting a violet ferric reaction in alcohol (Found : C, 57·2; H, 6·2. $C_{10}H_{12}O_5$ requires C, 56·6; H, 5·7%).

When a solution of the ester (1 g.) in water (7 ml.) containing potassium hydroxide (1 g.) was refluxed for 30 minutes in an atmosphere of nitrogen and the product isolated with ether, 2-methylphloroglucinol 5-methyl ether (0·65 g.) was obtained as an almost colourless crystalline mass, m. p. 124°. Robertson and Curd (*loc. cit.*) record m. p. 124°. The m. p. of a mixture with an authentic specimen of the isomeric 1-methyl ether was about 80°.

A solution of methyl 2 : 4-dihydroxy-6-methoxy-3-methylbenzoate (0·75 g.) in ether (100 ml.), containing zinc cyanide (0·5 g.) and hydrogen cyanide (5 ml.), was saturated with hydrogen chloride, and 24 hours later a solution in water (50 ml.) of the crystalline aldimine complex was hydrolysed on the steam-bath for 10 minutes. The crystalline aldehydo-ester separated from the cooled hydrolysate and was recrystallised from methyl alcohol giving *methyl 5-formyl-2 : 4-dihydroxy-6-methoxy-3-methylbenzoate* (0·6 g.) in long, slender prisms, m. p. 122°, giving a brown-violet ferric reaction in alcohol (Found : C, 55·7; H, 5·1. $C_{11}H_{12}O_6$ requires C, 55·0; H, 5·0%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in orange prisms, m. p. 262—263° (decomp.) (Found : N, 13·5. $C_{17}H_{16}O_9N_4$ requires N, 13·3%).

ω-Trichloro-4-hydroxy-2 : 6-dimethoxyacetophenone (VIII; R = CO·CCl_3).—A solution of phloroglucinol dimethyl ether (5 g.) in ether (100 ml.) containing zinc chloride (5 g.) and trichloromethyl cyanide (10 g.) was saturated with hydrogen chloride at 5°, and a pale yellow crystalline solid separated. 24 Hours later the isolated complex was hydrolysed and crystallised from benzene giving *ω-trichloro-4-hydroxy-2 : 6-dimethoxyacetophenone* in pale yellow, massive prisms (3·7 g.), m. p. 117° (Found: C, 40·7; H, 3·4; Cl, 35·7. $C_{10}H_9O_4Cl_3$ requires C, 40·1; H, 3·0; Cl, 35·6%). Neither the purified nor the crude ketone gave a ferric reaction. Solution in warm 2N-sodium hydroxide rapidly gave a quantitative yield of 4-hydroxy-2 : 6-dimethoxybenzoic acid, m. p. 201° (decomp.) (Fischer and Pfeffer, *Annalen*, 1912, **389**, 211, record m. p. 175°) (Found: C, 54·4; H, 5·7. Calc. for $C_9H_{10}O_5$: C, 54·4; H, 5·1%).

A solution of the foregoing ketone (1 g.) in methanol was added to hydrochloric acid (5 ml.) and water (5 ml.) containing amalgamated zinc (5 g.). Reduction was completed at 50—60° in 5 minutes. Addition of water to the decanted reaction liquor gave rise to a quantitative yield of *1-ethylphloroglucinol 1 : 3-dimethyl ether*, which separated from aqueous methanol in glistening plates, m. p. 153° (Found: C, 65·9; H, 8·3. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7%).

The same ethyl compound was produced when a mixture of the foregoing ω-trichloroacetophenone (0·6 g.), zinc dust (2 g.), and acetic acid (5 ml.) was heated under reflux for 30 minutes and the product isolated in the usual manner.

When zinc dust (2 g.) was added in small portions during 3 minutes to a solution of the previous ω-trichloroacetophenone (0·6 g.) in acetic acid (5 ml.) a violent reaction occurred. After being heated on the steam-bath for 2 minutes the product was isolated in the usual manner; purification from aqueous methanol gave a quantitative yield of 4-hydroxy-2 : 6-dimethoxyacetophenone, m. p. 185° (Canter, Curd, and Robertson, *loc. cit.*, record m. p. 185°).

ω-Trifluoro-4-hydroxy-2 : 6-dimethoxyacetophenone (VIII; R = CO·CF_3).—A solution of phloroglucinol dimethyl ether (2·5 g.) in ether (50 ml.) containing zinc chloride (2 g.) was saturated at room temperature with hydrogen chloride, and trifluoromethyl cyanide (6 g.) was then introduced. 4 Hours later the yellow crystalline precipitate was collected and heated on the steam-bath during 15 minutes with water (50 ml.). The crystalline solid (1·5 g.) which separated from the cooled hydrolysate was steam-distilled; *ω-trifluoro-2-hydroxy-4 : 6-dimethoxyacetophenone* (0·2 g.) was collected and crystallised from aqueous methanol, forming bright yellow prisms, m. p. 87°, having an intense red-brown ferric reaction in alcohol (Found: C, 48·2; H, 4·2; F, 23·8. $C_{10}H_9O_4F_3$ requires C, 48·0; H, 3·6; F, 22·8%).

The non-volatile *ω-trifluoro-4-hydroxy-2 : 6-dimethoxyacetophenone* (1·0 g.) separated from aqueous methanol in almost colourless, long, slender needles, m. p. 155°, having a negative ferric reaction in alcohol (Found: C, 48·2; H, 4·1%).

ω-Trifluoro-2 : 6-dihydroxy-4-methoxy-3-methylacetophenone.—Prepared from a solution of 2-methylphloroglucinol 1-methyl ether (1·4 g.) in the usual manner, the *ketone* (0·5 g.) separated from benzene in bright yellow, massive prisms, m. p. 145°, unchanged by sublimation and having an intense violet-brown ferric reaction in alcohol (Found: C, 48·2; H, 4·0; F, 24·3. $C_{10}H_9O_4F_3$ requires C, 48·0; H, 3·6; F, 22·8%).

ω-Trifluoro-2-hydroxy-4 : 6-dimethoxy-3-methylacetophenone.—Prepared from α-methylphloroglucinol 1 : 5-dimethyl ether (1·1 g.) and trifluoromethyl cyanide in the usual way, *ω-trifluoro-2-hydroxy-4 : 6-dimethoxy-3-methylacetophenone* (0·75 g.) separated from methanol in long, massive, rectangular, bright yellow prisms, m. p. 100°, having an intense green-brown ferric reaction in alcohol (Found: C, 49·9; H, 4·3. $C_{11}H_{11}O_4F_3$ requires C, 50·0; H, 4·2%). Sublimation at 100°/0·01 mm. gave the ketone in small squat intensely yellow prisms. Hydrolysis of this ketone with 4N-sodium hydroxide on the steam-bath during 10 minutes gave a quantitative yield of 2-hydroxy-4 : 6-dimethoxy-3-methylbenzoic acid, m. p. 182° (Curd and Robertson, *loc. cit.*, record m. p. 182°).

Methyl 2-Methylindole-3-carboxylate (XV; R = CO_2Me).—When a solution of 2-methyl-3-trichloroacetylindole (Fischer, *Ber.*, 1931, **64**, 2645) (0·5 g.) in methanol (17 ml.) containing aqueous 60% potassium hydroxide (1 drop) was refluxed for 5 minutes, and the solution cooled and diluted with water *methyl 2-methylindole-3-carboxylate* separated in quantitative yield, and was recrystallised from aqueous methanol in plate-like aggregates of needles, m. p. 165°, identical with the product obtained by the methylation of 2-methylindole-3-carboxylic acid with diazomethane (Found: N, 7·4. $C_{11}H_{11}O_2N$ requires N, 7·0%).

(With G. B. Sankey.) *2-Carbethoxy-4-hydroxy-3-methylcoumarone* (XIII; R = CO_2Et).—(*a*) The condensation of 2-acetylresorcinol (2·5 g.) and ethyl bromoacetate (2·0 g.) in boiling acetone (100 ml.) containing potassium carbonate (20 g.) was effected during 3 hours. Purification of the product from aqueous ethanol gave *ethyl (2-acetyl-3-hydroxyphenoxy)acetate* (2·9 g.) in almost colourless prisms, m. p. 74—75°, exhibiting a deep crimson ferric reaction in alcohol (Found: C, 60·9; H, 6·1. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%). Hydrolysis of this ester (1·0 g.) with 2N-sodium hydroxide (10 ml.) on the steam-bath during 30 minutes furnished (2-acetyl-3-hydroxyphenoxy)acetic acid which was not purified but cyclised directly by refluxing it during 80 minutes with sodium acetate (2·5 g.) and acetic anhydride (8 g.). The resultant solution was poured on ice (50 g.), and the oily coumarone acetate isolated with ether and hydrolysed on the steam-bath (1 hour) with 2N-sodium hydroxide. Acidification of the clear solution gave a brown granular solid which was purified from hot water, giving *4-hydroxy-3-methylcoumarone* (0·4 g.) in long, slender needles, m. p. 111°, having no ferric reaction in alcohol and dissolving in cold concentrated sulphuric acid to a red solution which became deep violet when warmed (Found: C, 72·5; H, 5·4. $C_9H_8O_2$ requires C, 73·0; H, 5·4%).

A solution of this coumarone (2·1 g.) in ether (100 ml.) containing zinc chloride (4·0 g.) and trichloromethyl cyanide (4 g.) was saturated with hydrogen chloride at 5°. 48 Hours later the semicrystalline ketimine complex was separated, dissolved in water (100 ml.), and hydrolysed on the steam-bath during 15 minutes, whereupon a pale green crystalline solid separated. Purification from light petroleum–

benzene gave *4-hydroxy-3-methyl-2-trichloroacetylcoumarone* (1·7 g.) in rosettes of bright green prisms, m. p. 159°, giving no ferric reaction in alcohol (Found: C, 45·6; H, 2·5. $C_{11}H_7O_3Cl_3$ requires C, 45·1; H, 2·4%).

When a solution of the ketone (1·2 g.) in ethanol (15 ml.) containing 2 drops of 60% potassium hydroxide was refluxed for 5 minutes and the product isolated in the normal way, *2-carbethoxy-4-hydroxy-3-methylcoumarone* separated from aqueous ethanol in slender prisms, m. p. 155°, identical with the product obtained by method (*b*) (Found: C, 66·0; H, 5·9. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%). This compound gives no ferric reaction in alcohol and dissolves in cold concentrated sulphuric acid to a pale yellow solution which becomes deep violet on being warmed.

(*b*) A solution of ethyl (2-acetyl-3-hydroxyphenoxy)acetate (2 g.) in ethanol (15 ml.) containing sodium ethoxide (from 0·2 g. of sodium) was refluxed for 1 hour. After dilution with water (100 ml.) and acidification with hydrochloric acid, the buff precipitate was extracted with 2N-sodium hydrogen carbonate and purified from light petroleum–benzene giving 2-carbethoxy-4-hydroxy-3-methylcoumarone (0·2 g.), m. p. 155°, identical in every way with the product from method (*a*).

The 2 : 4-*dinitrophenylhydrazone* of ω-trifluoro-2 : 4-dimethoxyacetophenone separated during 1 week at room temperature and crystallised from alcohol in rosettes of orange needles, m. p. 195° (Found: N, 13·3. $C_{16}H_{13}O_6N_4F_3$ requires N, 13·5%).

Prepared similarly the 2 : 4-*dinitrophenylhydrazone* of 6-methoxy-2-trifluoroacetylcoumarone formed blood-red prisms, m. p. 190—191° (decomp.), from alcohol (Found: N, 12·5. $C_{18}H_{13}O_6N_4F_3$ requires N, 12·8%).

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