142. *Organic Fluoro-compounds. Part IV. The Hoesch Reaction with Trifluoromethyl and Trichloromethyl Cyanides.*

By W. B. WHALLEY.

By the Hoesch reaction with trifluoromethyl cyanide, resorcinol, 2- and 4-ethylresorcinol, phloroglucinol mono- and tri-methyl ethers, 4-hydroxyveratrole, and 6-methoxy-3-methylcoumarone give the corresponding ω-trifluoromethyl ketones. These, although moderately stable to alkali, ultimately undergo the haloform reaction.

Trichloromethyl cyanide furnished the corresponding ω-trichloroacetophenones from a more restricted range of phenols, but the reaction proceeded readily with hydroxy- and methoxy-coumarones and phloroglucinol monomethyl ether. These derivatives are very easily hydrolysed to the corresponding acids, and in particular provide an alternative route to certain 2-carboxycoumarones and an approach to the hitherto inaccessible 2 : 4-dihydroxy-6-methoxybenzoic acid (XII; R = OH). Conditions are detailed for the direct conversion of the ω-trichloroacetophenones into the corresponding methyl esters and for the rapid reduction of the trichloroacetyl group to the ethyl group. A Gattermann aldehyde synthesis, using ω-trichloro-2 : 4-dihydroxy-6-methoxyacetophenone (VII; R = H), and subsequent hydrolysis of the 3-formyl derivative readily provides the difficultly accessible 2 : 6-dihydroxy-4-methoxybenzaldehyde.

THEORETICAL considerations appear to indicate that ω-trifluoroacetophenones should undergo the haloform reaction with the production of the corresponding acid and fluoroform, and indeed, one example (ω-trifluoroacetophenone) is quoted by Simons and Ramler (*J. Amer. Chem. Soc.*, 1943, **65**, 389). With the object of using the *C*-trifluoroacetyl group as a protecting group (easily removable by conversion into the acid and subsequent decarboxylation) for reactive positions in phenols and particularly in phloroglucinol, an investigation of the preparation of such ketones by the Hoesch synthesis was initiated. The literature (cf., *inter alia*, Houben, *Ber.*, 1926, **59**, 5880) appeared to indicate that ω-trichlorohydroxyacetophenones are not generally available, because trichloromethyl cyanide reacts with phenols with the preferential production of the corresponding phenyl trichloroacetimidate hydrochlorides rather than the ketones; and it seemed that trifluoromethyl cyanide, which has not been previously employed in the Hoesch ketone synthesis, might be more useful. However, the trifluoromethyl ketones were found to be more stable than had been expected and consequently the behaviour of trichloromethyl cyanide in the Hoesch condensation was re-examined.

The production of the corresponding ω-trifluoroacetophenones from a number of phenols and trifluoromethyl cyanide proceeded normally,* furnishing the ketones in high yield and necessitating only slight alterations in the usual experimental conditions occasioned by the low boiling point of the cyanide (see Experimental). Resorcinol gave ω-trifluoro-2 : 4-dihydroxyacetophenone (I), readily methylated with methyl iodide–potassium carbonate and then hydrolysed by alkali to 2 : 4-dimethoxybenzoic acid, thus establishing the orientation of (I). 2- and 4-Ethylresorcinol behaved similarly, giving 2-ethyl- (IV; R = Et, R′ = H) and 5-ethyl-ω-trifluoro-2 : 4-dihydroxyacetophenone (IV; R = H, R′ = Et) respectively. 4-Hydroxyveratrole and phloroglucinol monomethyl ether furnished ω-trifluoro-2-hydroxy-4 : 5-dimethoxy- (II; R = CF_3) and ω-trifluoro-2 : 4-dihydroxy-6-methoxyacetophenone (III; R = H) respectively. The rather vigorous conditions necessary to hydrolyse (III; R = H) caused simultaneous decarboxylation of the acid moiety and the orientation of the ketone is assumed by analogy with that of the corresponding ω-trichlorophloroacetophenone (VII; R = H) and the known behaviour of phloroglucinol monomethyl ether under the conditions of the Hoesch synthesis. Methylation of (III; R = H) gave ω-trifluoro-2 : 4 : 6-trimethoxyacetophenone (VI; R = CF_3) identical with a specimen prepared by the interaction of phloroglucinol trimethyl ether and trifluoromethyl cyanide. Phloroglucinol, orcinol, and pyrogallol all failed to react with trifluoromethyl cyanide.

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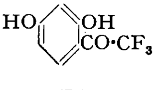
* Despite this normal behaviour in the Hoesch reaction attempts to prepare trifluoroacetaldehyde from trifluoromethyl cyanide by Stephen's reaction were unsuccessful. This is in agreement with Henne, Pelley, and Alm's findings (*J. Amer. Chem. Soc.*, 1950, **72**, 3370) which became available after the completion of this manuscript.

These ω-trifluoroacetophenones did not furnish 2 : 4-dinitrophenylhydrazones under the usual conditions and were rather surprisingly stable to the action of alkali, but under moderately vigorous conditions underwent fission to give a gas (presumably fluoroform) and the corresponding acid, usually in low yield because of partial decarboxylation. Methylation with methyl iodide–potassium carbonate proceeded normally and fully; attempted Clemmensen reduction caused rapid resinification, presumably owing to the action of the liberated hydrofluoric acid. The strong electron affinity of the trifluoroacetyl group is illustrated by the ease of dissolution of all these ω-trifluorohydroxyacetophenones in sodium hydrogen carbonate solution.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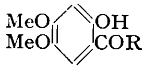
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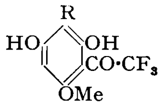
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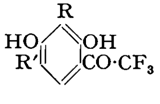
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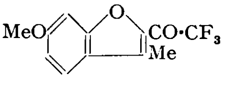
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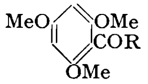
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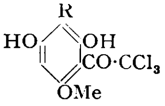
ω-Trifluoro-2 : 4-dihydroxy-6-methoxyacetophenone (III; R = H), readily underwent the Gattermann reaction to give ω-trifluoro-3-formyl-2 : 4-dihydroxy-6-methoxyacetophenone (III; R = CHO), the orientation of which is inferred by analogy with the corresponding trichloro-compound (VII; R = CHO).

The Hoesch synthesis with 6-methoxy-3-methylcoumarone and trifluoromethyl cyanide gave, with remarkable facility and in high yield the trifluoromethyl ketone (V) converted by alkaline hydrolysis into 6-methoxy-3-methylcoumarone-2-carboxylic acid (XI; R = Me; R′ = OH).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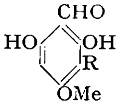
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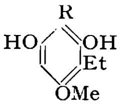
(IX.)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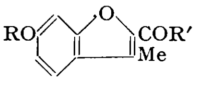
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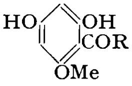
(XII.)

Turning then to trichloromethyl cyanide, we found the Hoesch synthesis to fail completely with phloroglucinol, resorcinol, orcinol, and pyrogallol, but to proceed readily with phloroglucinol monomethyl ether, giving (VII; R = H). By the Gattermann synthesis this yielded ω-trichloro-3-formyl-2 : 4-dihydroxy-6-methoxyacetophenone (VII; R = CHO) in good yield. The compounds (VII; R = H = CHO) readily dissolved in warm 2N-sodium hydrogen carbonate with the evolution of chloroform (cf. Houben and Fischer, *J. pr. Chem.*, 1929, [ii], **123**, 313) and the production of 2 : 4-dihydroxy-6-methoxybenzoic acid (XII; R = OH) and its 3-formyl derivative (VIII; R = CO_2H) respectively. Esterifying the former acid with diazomethane or warming (VII; R = H) with methyl alcohol containing a trace of potassium hydroxide readily gave methyl 2 : 4-dihydroxy-6-methoxybenzoate (XII; R = OMe). When an aqueous solution of (VIII; R = CO_2H) was gently refluxed for 5 minutes in an atmosphere of nitrogen, quantitative conversion into 2 : 6-dihydroxy-4-methoxybenzaldehyde (VIII; R = H) occurred, thus providing a much superior route to this difficultly accessible substance (Karrer and Bloch, *Helv. Chim. Acta*, 1927, **10**, 378; Karrer, Lichtenstein, and Helfenstein, *ibid.*, 1929, **12**, 991). The non-identity of the ester (XII; R = OMe) with methyl 2 : 6-dihydroxy-4-methoxybenzoate and the production of 2 : 6-dihydroxy-4-methoxybenzaldehyde (VIII; R = H) from (VII; R = CHO) clearly established the orientation of the acid (XII; R = OH), the parent ω-trichloroacetophenone (VII; R = H), and the aldehyde (VII; R = CHO). Methyl 2 : 4-dihydroxy-6-methoxybenzoate (XII; R = OMe) gave rise by the

Gattermann method to the aldehydo-ester (VIII; R = CO_2Me) which on hydrolysis furnished (VIII; R = H) in low yield, thus affording additional evidence for the orientation previously adduced for (XII; R = OH), (XII; R = OMe), and (VII; R = H).

Clemmensen reduction converted the ω-trichloroacetophenones (VII; R = H) and (VII; R = CHO) readily almost quantitatively into 1-ethyl-2 : 4-dihydroxy-6-methoxybenzene (X; R = H) and 3-ethyl-2 : 6-dihydroxy-4-methoxytoluene (X; R = Me). The Clemmensen reduction of α-halogeno-ketones appears to have been reported in only two instances (Johnson and Hodge, *J. Amer. Chem. Soc.*, 1913, **35**, 1014, and Funke and Ristic, *J. pr. Chem.*, 1936, **146**, 151) where the $-CO\cdot CH_2Cl$ group was reduced to an ethyl group.

In contrast to the behaviour of the corresponding ω-trifluoroacetophenones, attempted methylation of (VII; R = H) by methyl iodide–potassium carbonate removed the trichloromethyl residue with quantitative formation of methyl 2 : 4 : 6-trimethoxybenzoate (VI; R = OMe). ω-Trichloro-2 : 4 : 6-trimethoxyacetophenone (VI; R = CCl_3) was formed directly by the Hoesch condensation of trichloromethyl cyanide and phloroglucinol trimethyl ether, and on Clemmensen reduction readily furnished 1-ethyl-2 : 4 : 6-trimethoxybenzene.

Resorcinol monomethyl ether and trichloromethyl cyanide gave ω-trichloro-4-hydroxy-2-methoxyacetophenone (IX) in good yield, together with a very small amount of the isomeric 2-hydroxy-4-methoxy-compound; (IX) was hydrolysed by alkali to 4-hydroxy-2-methoxybenzoic acid. Similarly, 4-hydroxyveratrole and trichloromethyl cyanide readily gave ω-trichloro-2-hydroxy-4 : 5-dimethoxyacetophenone (II; R = CCl_3) which furnished 2-hydroxy-4 : 5-dimethoxybenzoic acid on gentle hydrolysis and was readily converted into methyl 2-hydroxy-4 : 5-dimethoxybenzoate by warm methanol containing a trace of potassium hydroxide.

6-Hydroxy- (Karrer and Widmer, *Helv. Chim. Acta*, 1919, **2**, 454) and 6-methoxy-3-methylcoumarone (Foster, Robertson, and Healey, *J.*, 1939, 1597) readily gave 6-hydroxy- and 6-methoxy-3-methyl-2-trichloroacetylcoumarone (XI; R = H, R′ = CCl_3; R = Me, R = CCl_3) respectively, the orientations being established by alkaline hydrolysis to the corresponding acids. The entry of the trifluoroacetyl and trichloroacetyl groups into the α-position of a hydroxy- or methoxy-3-methylbenzofuran nucleus is in accordance with recent work by Mackenzie and Robertson, (*J.*, 1949, 2057) and affords additional confirmation of the behaviour of this nucleus in the Hoesch condensation (contrast Karrer *et al.*, *Helv. Chim. Acta*, 1919, **2**, 454; 1921, **4**, 718).

Methylation by the methyl iodide–potassium carbonate method of (XI; R = H, R′ = CCl_3), as in the previously described instance of (VII; R = H), took place with the concomitant replacement of the trichloromethyl group by the methoxyl group and the production of methyl 6-methoxy-3-methylcoumarone-2-carboxylate (XI; R = Me, R′ = OMe). 2-Trichloroacetyl-6-methoxy-3-methylcoumarone (XI; R = Me, R′ = CCl_3) was readily converted, in high yield, into the methyl and the ethyl ester (XI; R = Me, R′ = OMe or OEt) respectively when warmed with the appropriate alcohol containing 1 drop of 60% potassium hydroxide solution. Conversion of the trichloroacetyl group into the carbomethoxy-residue under these conditions succeeded in all the cases examined, but attempts to produce the ethyl esters in a similar manner very frequently gave only the corresponding acid; the trifluoromethyl ketones always furnished quantitative yields of the corresponding acids with either alcohol and could not be converted directly into either ester (cf. Houben and Fischer, *Ber.*, 1931, **64**, 2636).

The rapid conversion of the trichloroacetyl group into the ethyl, carboxy-, and carbomethoxy-group provides a useful method, in the limited number of instances where the appropriate ω-trichloroacetophenones are available, for the preparation of *C*-ethyl-phenols, -acids, and -methyl esters.

EXPERIMENTAL.

All the trifluoromethyl ketones described below retained traces of water very tenaciously, and after purification by crystallisation specimens for analysis were sublimed in a high vacuum, whereafter satisfactory analytical results were obtained.

ω-Trifluororesacetophenone (I; R = H).—A solution of resorcinol (4 g.) in ether (125 ml.) containing powdered zinc chloride (3 g.) was saturated at about −5° with hydrogen chloride, and trifluoromethyl cyanide (12 g.) (prepared from trifluoroacetamide and phosphoric oxide) was then passed into the mixture. An almost colourless crystalline mass rapidly separated, and after 24 hours at 0° the complex was separated, washed with more ether, and dissolved in water (40 ml.) and the solution heated on the steam-bath for 15 minutes. The red oil which separated did not readily solidify and was taken up in ether, the extract dried and evaporated, and the residue repeatedly extracted with warm light petroleum, giving *ω-trifluororesacetophenone* (4·7 g.) in long, slender, colourless needles, m. p. 103° (Found: C, 46·2; H, 3·0; F, 27·6. $C_8H_5O_3F_3$ requires C, 46·6; H, 2·4; F, 27·7%). The ketone does not give a 2 : 4-dinitrophenylhydrazone under the usual conditions, and is readily soluble in ether, acetone, benzene, and alcohol, and moderately soluble in petroleum, and the alcoholic solution exhibits a strong red-brown ferric reaction. The compound is very sparingly soluble in hot water, but dissolves readily in cold 2N-sodium hydrogen carbonate and 2N-sodium hydroxide from which it is precipitated substantially unchanged by acids 8 hours later.

Methylation of this ketone (1 g.) in boiling acetone (75 ml.) containing potassium carbonate (4 g.) and methyl iodide (5 ml.) during 5 hours furnished the *dimethyl ether* (1 g.) in massive, colourless prisms, m. p. 52°, from light petroleum (Found: C, 50·6; H, 3·5; F, 23·4. $C_{10}H_9O_3F_3$ requires C, 51·3; H, 3·8; F, 24·4%). The substance is insoluble in cold 2N-sodium hydrogen carbonate and 2N-sodium hydroxide, but when heated for 15 minutes on the steam-bath with 15% potassium hydroxide solution dissolves rapidly to give an almost colourless solution, with the brisk evolution of fluoroform. Acidification of the solution gave 2 : 4-dimethoxybenzoic acid, identical with an authentic specimen. The dimethyl ether gives no ferric reaction in alcohol, does not furnish a 2 : 4-dinitrophenylhydrazone, and is very soluble in acetone, alcohol, benzene, and ether, and moderately soluble in light petroleum.

3-*Ethyl*-ω-*trifluoro*-2 : 4-*dihydroxyacetophenone* (IV; R = Et, R′ = H).—A solution of 2-ethylresorcinol (2 g.) in ether (100 ml.) containing zinc chloride (2 g.) was saturated at 0° with hydrogen chloride, and trifluoromethyl cyanide (7 g.) passed into the mixture, whereupon a crystalline, almost colourless ketimine salt rapidly separated. After 24 hours at 0° the solid was separated, washed with ether, and dissolved in water (40 ml.), and the solution heated on the steam-bath during 15 minutes, the ketone then separating. Crystallisation from light petroleum gave 3-*ethyl*-ω-*trifluoro*-2 : 4-*dihydroxyacetophenone* in shimmering colourless leaflets (2·5 g.), m. p. 139° (Found: C, 51·0; H, 3·5; F, 24·8. $C_{10}H_9O_3F_3$ requires C, 51·3; H, 3·8; F, 24·4%). The ketone is readily soluble in ether, acetone, alcohol, and benzene, slowly soluble in cold 2N-sodium hydrogen carbonate, gives no 2 : 4-dinitrophenylhydrazone under the usual conditions, exhibits a strong red-brown ferric reaction in alcohol, and is precipitated unchanged after 6 hours when dissolved in 2N-sodium hydroxide.

Methylation in boiling acetone, with potassium carbonate–methyl iodide, furnished 3-ethyl-ω-trifluoro-2 : 4-dimethoxyacetophenone as a colourless oil which on hydrolysis on the steam-bath during 15 minutes with 15% potassium hydroxide solution gave a quantitative yield of 3-ethyl-2 : 4-dimethoxybenzoic acid, m. p. 128°. Sprenger and Ruoff (*J. Org. Chem.*, 1946, **11**, 189) record m. p. 128—129°.

5-*Ethyl*-ω-*trifluoro*-2 : 4-*dihydroxyacetophenone* (IV; R = H; R′ = Et).—4-Ethylresorcinol (2 g.), treated as in the foregoing case, gave the *ketone* (2·4 g.) as long, slender needles, m. p. 99° (from light petroleum) (Found: C, 51·6; H, 4·0; F, 24·9%), having the same properties as its 3-ethyl isomer.

Methylation gave the *dimethyl ether*, which formed slender, glistening prisms (from aqueous methanol), m. p. 65° (Found: C, 54·3; H, 5·6; F, 21·3. $C_{12}H_{13}O_3F_3$ requires C, 55·0; H, 5·0; F, 21·7%). This ketone gave a negative ferric reaction in alcohol, and no 2 : 4-dinitrophenylhydrazone, was soluble in all the usual organic solvents, and was hydrolysed on the steam-bath during 15 minutes with 15% potassium hydroxide solution to 5-ethyl-2 : 4-dimethoxybenzoic acid, m. p. 130°. Desai and Hamid (*Proc. Indian Acad. Sci.*, 1937, **6a**, 287) record m. p. 126°.

ω-*Trifluoro*-2 : 4-*dihydroxy*-6-*methoxyacetophenone* (III; R = H).—Under the above conditions phloroglucinol monomethyl ether (4 g.) and trifluoromethyl cyanide (12 g.) yielded ω-*trifluoro*-2 : 4-*dihydroxy*-6-*methoxyacetophenone*, which separated from benzene in glistening pale yellow plates (2·2 g.), m. p. 154° (Found: C, 45·9; H, 2·7; F, 24·6. $C_9H_7O_4F_3$ requires C, 45·8; H, 3·0; F, 24·2%). This ketone does not furnish a 2 : 4-dinitrophenylhydrazone under the usual conditions, exhibits a strong red-brown ferric reaction in alcohol, is easily soluble in alcohol, acetone, ether, and ethyl acetate, moderately soluble in benzene, and less soluble in light petroleum, and dissolves readily in cold 2N-sodium hydrogen carbonate and 2N-sodium hydroxide, from which it is precipitated by acids, substantially unchanged, after 6 hours.

ω-*Trifluoro*-3-*formyl*-2 : 4-*dihydroxy*-6-*methoxyacetophenone* (III; R = CHO).—When a solution of ω-trifluoro-2 : 4-dihydroxy-6-methoxyacetophenone (III; R = H) (1 g.) in ether (75 ml.) containing zinc cyanide (0·5 g.) and hydrogen cyanide (4 ml.) was saturated at 0° with hydrogen chloride, the coloured crystalline aldimine salt rapidly separated. 24 Hours later the complex was dissolved in water (50 ml.) and heated on the steam-bath during 24 minutes. The *aldehyde* separated from the cooled hydrolysate in reddish-brown crystals, purified by crystallisation from aqueous methanol (charcoal) or by vacuum sublimation (140°/0·1 mm.), to give almost colourless prisms (0·3 g.), m. p. 129°, exhibiting a red-brown ferric reaction in alcohol and very soluble in alcohol (Found: C, 45·8; H, 3·0. $C_{10}H_7O_5F_3$ requires C, 45·5; H, 2·7%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in orange-yellow needles, m. p. 278° (decomp.) (Found: N, 12·8. $C_{16}H_{11}O_8N_4F_3$ requires N, 12·6%).

All attempts to remove the $-CF_3$ group by alkaline hydrolysis using a wide variety of conditions were unsuccessful, the rather vigorous conditions required causing resinification.

ω-*Trifluoro*-2 : 4 : 6-*trimethoxyacetophenone* (VI; R = CF_3).—(*a*) Methylation of ω-trifluoro-2 : 4-dihydroxy-6-methoxyacetophenone in boiling acetone by potassium carbonate–methyl sulphate during 6 hours gave a quantitative yield of ω-trifluoro-2 : 4 : 6-trimethoxyacetophenone in shimmering, colourless, slender plates (from aquous methanol), m. p. 60°, identical with a specimen prepared by method (*b*).

(*b*) When a solution of phloroglucinol trimethyl ether (1 g.) in ether (50 ml.) containing zinc chloride (1 g.) was saturated at 0° with hydrogen chloride, followed by trifluoromethyl cyanide (3·5 g.), the ketimine salt rapidly separated in yellow prisms. 24 Hours later the product was hydrolysed with water (50 ml.) during 15 minutes on the steam-bath. The oil which separated solidified on cooling and on crystallisation from aqueous alcohol or, more conveniently, distillation at 100°/0·1 mm., gave the *ketone* (1·7 g.) which had the usual properties of the class; it had m. p. and mixed m. p. 60°, with a specimen prepared by method (*a*), and mixed with methyl 2 : 4 : 6-trimethoxybenzoate had m. p. *ca.* 40° (Found : C, 50·0; H, 4·5; F, 21·3. $C_{11}H_{11}O_4F_3$ requires C, 50·0; H, 4·2; F, 21·6%).

ω-*Trifluoro*-2-*hydroxy*-4 : 5-*dimethoxyacetophenone* (II; R = CF_3).—4-Hydroxyveratrole (3 g.) in ether (100 ml.) similarly gave this *ketone* which separated from light petroleum in stout, pale yellow-green prisms (3 g.), m. p. 82° (Found : C, 47·5; H, 3·8; F, 23·3. $C_{10}H_9O_4F_3$ requires C, 48·0; H, 3·6; F, 22·8%), readily soluble in the usual organic solvents, slowly soluble in 2N-sodium hydrogen carbonate, giving an olive-green ferric reaction in alcohol and no 2 : 4-dinitrophenylhydrazone. Hydrolysis during 10 minutes on the steam-bath with 2N-sodium hydroxide furnished 2-hydroxy-4 : 5-dimethoxybenzoic acid, identical with an authentic specimen (Head and Robertson, *J.*, 1931, 2432).

2-*Trifluoroacetyl*-6-*methoxy*-3-*methylcoumarone* (V).—This *coumarone* was obtained from 6-methoxy-3-methylcoumarone (Kostanecki and Tambor, *Ber.*, 1909, **42**, 901) (2 g.) under our usual conditions and formed, from aqueous methanol, very pale yellow, stout, massive prisms (3 g.), m. p. 87°, unchanged by sublimation at 100°/0·1 mm. (Found : C, 56·0; H, 3·5; F, 22·2. $C_{12}H_9O_3F_3$ requires C, 55·8; H, 3·5; F, 22·1%). Its properties resembled those of its analogues and it was rapidly hydrolysed by 2N-sodium hydroxide to the 2-carboxylic acid (100%), m. p. and mixed m. p. 190° (decomp.), identical with an authentic specimen (Foster, Robertson, and Healey, *J.*, 1939, 1597).

ω-*Trichloro*-2 : 4-*dihydroxy*-6-*methoxyacetophenone* (VII; R = H).—A solution of phloroglucinol monomethyl ether (5 g.) in ether (70 ml.), containing powdered zinc chloride (4 g.) and trichloromethyl cyanide (10 g.), was saturated at 0° with hydrogen chloride. 24 Hours later the colourless crystalline precipitate was separated, washed with ether, and hydrolysed as above. The product separated as an oil which crystallised. ω-*Trichloro*-2 : 4-*dihydroxy*-6-*methoxyacetophenone* (4—5 g.) separated from benzene in almost colourless needles, or from aqueous methanol in glittering pale cream prisms, m. p. 152° (Found : C, 37·7; H, 2·6; Cl, 35·1. $C_9H_7O_4Cl_3$ requires C, 37·9; H, 2·5; Cl, 37·4%). It affords no 2 : 4-dinitrophenylhydrazone under the usual conditions, is readily soluble in acetone, ether, and alcohol, and the alcoholic solution gives a weak red-brown colour with ferric chloride.

1-*Ethyl*-2 : 4-*dihydroxy*-6-*methoxybenzene* (X; R = H).—(*a*) 2 : 4-Dihydroxy-6-methoxyacetophenone (1 g.) in methanol (20 ml.) was added to zinc amalgam (10 g.), concentrated hydrochloric acid (20 ml.), and water (10 ml.), and the mixture refluxed until a test portion exhibited a negative ferric reaction in alcohol (4 hours). The cooled mixture was diluted with water (100 ml.) and extracted with ether (3 × 75 ml.). Evaporation of the washed, dried extract and crystallisation of the residue from benzene–light petroleum gave 1-*ethyl*-2 : 4-*dihydroxy*-6-*methoxybenzene* (0·6 g.) as glistening, colourless plates, m. p. 109°, exhibiting a negative ferric reaction in alcohol (Found : C, 64·2; H, 7·2. $C_9H_{12}O_3$ requires C, 64·3; H, 7·2%). The *di*-p-*nitrobenzoate* separated from much alcohol or aqueous acetic acid in pale cream-coloured needles, m. p. 164° (Found : N, 6·3. $C_{23}H_{18}O_9N_2$ requires N, 6·0%).

(*b*) ω-Trichloro-2 : 4-dihydroxy-6-methoxyacetophenone (0·9 g.) was similarly reduced (5 minutes' refluxing) to the same substance (0·3 g.), colourless plates (from light petroleum), m. p. 109°, identical with an authentic specimen. The di-*p*-nitrobenzoate, m. p. 164°, was identical with the previous specimen.

Methyl 2 : 4-*Dihydroxy*-6-*methoxybenzoate* (XII; R = OMe).—(*a*) ω-Trichloro-2 : 4-dihydroxy-6-methoxyacetophenone (2 g.) was dissolved in 2N-sodium hydroxide (12 ml.) with cooling. An odour of chloroform became apparent immediately, and 30 minutes later the solution was acidified with 2N-hydrochloric acid and the precipitate collected and crystallised rapidly from aqueous methanol (charcoal), giving 2 : 4-*dihydroxy*-6-*methoxybenzoic acid* in almost colourless, squat prisms (1·1 g.), m. p. 200° (decomp.) (Found : C, 51·9; H, 4·4. $C_8H_8O_5$ requires C, 52·2; H, 4·3%). The acid is readily soluble in cold 2N-sodium hydrogen carbonate and gives a deep red-brown ferric reaction in alcohol. A suspension of the acid (1·7 g.) in chloroform (10 ml.), treated with ethereal diazomethane, rapidly clarified; the resultant solution was washed with 2N-sodium hydrogen carbonate (25 ml.), dried, and evaporated, giving an almost quantitative yield of *methyl* ester in colourless prisms (from aqueous methanol) or colourless clusters of feathery needles (from benzene), m. p. 194° (Found : C, 54·4; H, 5·0. $C_9H_{10}O_5$ requires C, 54·5; H, 5·1%). The ester gave a deep red-brown ferric reaction in alcohol and was sparingly soluble in ether and chloroform and easily soluble in methanol and ethanol.

(*b*) When ω-trichloro-2 : 4-dihydroxy-6-methoxyacetophenone (0·5 g.) in methanol (10 ml.) containing 60% potassium hydroxide (1 drop) was heated under reflux during 5 minutes, and the solution cooled, acidified with hydrochloric acid, diluted with water, and made alkaline with 2N-sodium hydrogen carbonate, the methyl ester (0·35 g.) was obtained, having m. p. and mixed m. p. 194° and identical with the specimen prepared by method (*a*). Attempts to prepare the ethyl ester in this manner were unsuccessful.

Methyl 3-*Formyl*-2 : 4-*dihydroxy*-6-*methoxybenzoate* (VIII; R = CO_2Me).—The foregoing ester (0·8 g.) in ether (150 ml.) containing zinc cyanide (0·5 g.) and hydrogen cyanide (5 ml.) was saturated at 5° with hydrogen chloride. 24 Hours later the colourless crystalline precipitate was separated, washed with ether, dissolved in water (75 ml.), and the solution rapidly heated to boiling. *Methyl* 3-*formyl*-2 : 4-*dihydroxy*-6-*methoxybenzoate* (0·7 g.) separated from the cooled hydrolysate and crystallised from much methanol in colourless slender prisms, m. p. 184° (Found : C, 53·2; H, 4·6. $C_{10}H_{10}O_6$ requires C, 53·1; H, 4·5%). The aldehyde gave a deep red-brown colour with alcoholic ferric chloride, and the 2 : 4-*dinitrophenylhydrazone* separated from much acetic acid in brick-red, slender prisms, m. p. 299° (decomp.) (Found : N, 13·6. $C_{16}H_{14}O_9N_4$ requires N, 13·8%).

2 : 6-*Dihydroxy*-4-*methoxybenzaldehyde* (VIII; R = H).—(*a*) When the preceding aldehydo-ester (0·5 g.) was refluxed in an atmosphere of nitrogen during 45 minutes with 2N-sodium hydroxide (5 ml.) the solution became deep red. After acidification and purification by vacuum-sublimation a small yield of 2 : 6-dihydroxy-4-methoxybenzaldehyde was obtained.

(*b*) A solution of ω-trichloro-2 : 4-dihydroxy-6-methoxyacetophenone (1·5 g.) in ether (100 ml.) containing zinc cyanide (1 g.) and hydrogen cyanide (5 ml.) was saturated with hydrogen chloride at 0° and 24 hours later the colourless crystalline precipitate was collected and hydrolysed. ω-*Trichloro*-3-*formyl*-2 : 4-*dihydroxy*-6-*methoxyacetophenone* crystallised from benzene in massive, almost colourless prisms (1·2 g.), m. p. 150° (Found : C, 38·3; H, 2·2; Cl, 34·0. $C_{10}H_7O_5Cl_3$ requires C, 38·3; H, 2·2; Cl, 34·0%). It exhibited a red-brown ferric reaction in alcohol and the 2 : 4-*dinitrophenylhydrazone* separated from aqueous alcohol in rosettes of bright crimson needles, m. p. 247° (decomp.) (Found : N, 12·0. $C_{16}H_{11}O_8N_4Cl_3$ requires N, 11·3%). This aldehydo-ketone (2 g.) was warmed gently with 2N-sodium hydrogen carbonate (20 ml.) until a clear solution was obtained (*ca.* 3 minutes). The cooled solution was acidified with 2N-hydrochloric acid, and the product crystallised from aqueous methanol, giving almost colourless needles of 2 : 4-*dihydroxy*-3-*formyl*-6-*methoxybenzoic acid* (*ca.* 100%), m. p. 185° (decomp.), exhibiting a deep red-brown ferric reaction in alcohol (Found : C, 50·8; H, 3·7. $C_9H_8O_6$ requires C, 50·9; H, 3·8%).

A mixture of the acid (0·9 g.) and water (15 ml.) containing a few drops of methanol was refluxed in an atmosphere of nitrogen during 15 minutes to give a clear solution. On cooling 2 : 6-dihydroxy-4-methoxybenzaldehyde (0·65 g.) separated in almost colourless needles, m. p. 141—142° (Found : C, 57·2; H, 4·8. Calc. for $C_8H_8O_4$: C, 57·1; H, 4·8%) (Karrer and Bloch, *loc. cit.*, record m. p. 139—140°).

3-*Ethyl*-2 : 6-*dihydroxy*-4-*methoxytoluene* (X; R = Me).—A solution of ω-trichloro-3-formyl-2 : 4-dihydroxy-6-methoxyacetophenone (0·5 g.) in methanol (10 ml.) was added in one portion to concentrated hydrochloric acid (10 ml.), water (5 ml.), and amalgamated zinc (5 g.), and the mixture refluxed until a portion gave no precipitate with aqueous 2 : 4-dinitrophenylhydrazine sulphate solution (10 minutes). The cooled mixture was extracted with ether (4 × 25 ml.), and the dried extracts were evaporated, giving 3-*ethyl*-2 : 6-*dihydroxy*-4-*methoxytoluene* (0·3 g.) which separated from benzene–light petroleum in clusters of colourless prisms, m. p. 112°, unchanged by sublimation (140°/0·1 mm.), and having no ferric reaction in alcohol (Found : C, 65·9; H, 7·8. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7%). The *di*-p-*nitrobenzoate* separated from methanol in very pale greenish-yellow needles, m. p. 178° (Found : N, 6·4. $C_{24}H_{20}O_9N_2$ requires N, 5·8%).

ω-*Trichloro*-2 : 4 : 6-*trimethoxyacetophenone* (VI; R = CCl_3).—A solution of phloroglucinol trimethyl ether (5 g.) in ether (100 ml.) containing zinc chloride (5 g.) and trichloromethyl cyanide (10 g.) was saturated at 0° with hydrogen chloride. The ketimine salt was hydrolysed in the usual way. The *product* (3·5 g.) crystallised from aqueous methanol in colourless, long, slender needles, or from benzene–light petroleum in stout, massive, colourless prisms, m. p. 116° (Found : C, 42·3; H, 3·5; Cl, 33·7. $C_{11}H_{11}O_4Cl_3$ requires C, 42·2; H, 3·5; Cl, 34·0%). It exhibits a negative ferric reaction in alcohol, does not give rise to a 2 : 4-dinitrophenylhydrazone under the usual conditions, and is stable to 2N-sodium hydroxide solution even on prolonged boiling.

Reduction of the ketone (1·5 g.) in methanol (10 ml.) during 15 minutes with concentrated hydrochloric acid (10 ml.), water (5 ml.) and zinc amalgam (5 g.) gave an almost quantitative yield of 1-ethyl-2 : 4 : 6-trimethoxybenzene, m. p. 28° (Dean and Nierenstein, *J. Amer. Chem. Soc.*, 1924, **46**, 2801, record m. p. 29—30°). When ω-trichloro-2 : 4-dihydroxy-6-methoxyacetophenone (0·5 g.) was treated during 6 hours in boiling acetone (50 ml.) with potassium carbonate (5 g.) and methyl sulphate (0·5 g.) the product was methyl 2 : 4 : 6-trimethoxybenzoate (0·3 g.), m. p. 70°, identical with an authentic specimen.

ω-*Trichloro*-4-*hydroxy*-2-*methoxyacetophenone* (IX).—A solution of resorcinol monomethyl ether (2 g.) and trichloromethyl cyanide (4 g.) gave this *ketone* (1·5 g.) in the usual way as rosettes of almost colourless prisms (from benzene), m. p. 144°, which exhibited a negative ferric reaction in alcohol and did not furnish a 2 : 4-dinitrophenylhydrazone under the usual conditions (Found : C, 40·0; H, 2·4; Cl, 39·7. $C_9H_7O_3Cl_3$ requires C, 40·2; H, 2·6; Cl, 39·5%). The mother-liquors from the crystallisation contained a small quantity of ω-trichloro-2-hydroxy-4-methoxyacetophenone, as indicated by the pale brown ferric reaction of the crude product, but the substance was present in quantity too small to be readily isolated.

The ketone readily dissolved in cold 2N-sodium hydrogen carbonate with immediate evolution of chloroform and quantitative production of 4-hydroxy-2-methoxybenzoic acid, m. p. 182° (decomp.). Bergmann and Dangschat (*Ber.*, 1919, **52**, 383) give m. p. 187—189° (decomp.).

ω-*Trichloro*-2-*hydroxy*-4 : 5-*dimethoxyacetophenone* (II; R = CCl_3).—When prepared similarly from 4-hydroxyveratrole (2 g.) and trichloromethyl cyanide (4 g.), this *compound* crystallised from aqueous methanol in shimmering, long, slender, yellow prisms (1 g.), m. p. 107°, easily soluble in alcohol, ether, and acetone, having a green-brown ferric reaction in alcohol, and furnishing no 2 : 4-dinitrophenylhydrazone under the usual conditions (Found : C, 40·2; H, 2·5. $C_{10}H_9O_4Cl_3$ requires C, 40·0; H, 3·0%). Its solution in cold 2N-sodium hydroxide immediately evolved chloroform, and on acidification furnished a quantitative yield of 2-hydroxy-4 : 5-dimethoxybenozic acid identical with an authentic specimen (Head and Robertson, *loc. cit.*).

When 1 drop of 50% potassium hydroxide was added to a suspension of the ketone (0·1 g.) in methanol (5 ml.) solution occurred immediately with the production of a quantitative yield of methyl 2-hydroxy-4 : 5-dimethoxybenzoate, m. p. 95—96°. Arnold and Bordwell (*J. Amer. Chem. Soc.*, 1942, **64**, 2983) record m. p. 95—96°.

2-*Trichloroacetyl*-6-*hydroxy*-3-*methylcoumarone* (XI; R = H, R′ = CCl_3).—6-Hydroxy-3-methylcoumarone (0·5 g.) and trichloromethyl cyanide (1 g.), etc., gave this *ketone* as pale greenish-yellow plates (0·3 g.) (from aqueous methanol), m. p. 180°, exhibiting a negative ferric reaction in alcohol and did not form a 2 : 4-dinitrophenylhydrazone under the usual conditions (Found : C, 45·2; H, 2·4; Cl, 35·4. $C_{11}H_7O_3Cl_3$ requires C, 45·1; H, 2·4; Cl, 36·3%). Treatment in boiling acetone with methyl iodide–potassium carbonate during 3 hours gave a quantitative yield of *methyl* 6-*methoxy*-3-*methylcoumarone*-2-*carboxylate* (XI; R = Me, R′ = OMe) which separated in colourless needles, m. p. 90°, from aqueous methanol (Found: C, 65·6; H, 5·6. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%).

2-*Trichloroacetyl*-6-*methoxy*-3-*methylcoumarone* (XI; R = Me, R′ = CCl_3).—6-Methoxy-3-methylcoumarone (2 g.) similarly gave 2-*trichloroacetyl*-6-*methoxy*-3-*methylcoumarone* in long, slender, glistening, pale yellow prisms, m. p. 154°, did not give a 2 : 4-dinitrophenylhydrazone under the usual conditions and had a negative ferric reaction in alcohol (Found: C, 46·8; H, 2·8; Cl, 35·1. $C_{12}H_9O_3Cl_3$ requires C, 46·9; H, 2·9; Cl, 34·7%). Heating this ketone (1 g.) in 2N-sodium hydroxide (25 ml.) and methanol (5 ml.) on the steam-bath for 10 minutes gave chloroform and the 2-carboxylic acid, m. p. 190°, identical with an authentic specimen (Foster, Robertson, and Healey, *loc. cit.*).

A solution of the ketone (0·5 g.) in methanol (15 ml.) containing 60% potassium hydroxide solution (1 drop) was refluxed during 5 minutes, cooled, and diluted with water; ethyl 6-methoxy-3-methylcoumarone-2-carboxylate (0·4 g.) separated, having m. p. 70°, identical with an authentic specimen (Kostanecki and Lampe, *Ber.*, 1908, **41**, 1330). The methyl ester was similarly prepared in quantitative yield and was identical with an authentic specimen.

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