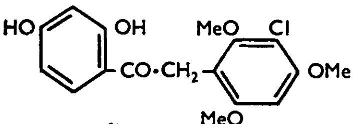
615. *Some Chlorinated Derivatives of Phloroglucinol.*

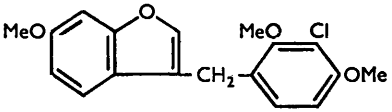
By G. Lloyd and W. B. Whalley.

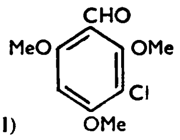
Phosphorus pentachloride converts 2 : 4 : 6-trimethoxyphenylacetic acid into 3-chloro-2 : 4 : 6-trimethoxyphenylacetyl chloride, but decarboxylates 2 : 4 : 6-trimethoxybenzoic acid. 2 : 4 : 6-Trimethoxyphenylglyoxylic acid and thionyl chloride give 2 : 4 : 6-trimethoxybenzoyl chloride.

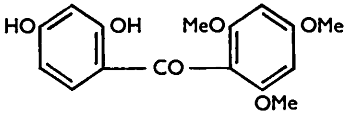
We have found [1] that, contrary to Freudenberg and Harder's statement,[2] attempts to prepare 2 : 4 : 6-trimethoxyphenylacetyl chloride from phosphorus pentachloride and the appropriate acid gave an anomalous acid chloride. Friedel–Crafts condensation of this acid chloride with resorcinol gave a compound now shown to be 3′-chloro-2 : 4-dihydroxy-2′ : 4′ : 6′-trimethoxydeoxybenzoin (I). It was readily converted into 3-(3-chloro-2 : 4 : 6-trimethoxybenzyl)-6-methoxycoumarone (II) and several derivatives thereof.

The structure of these compounds follows from hydrolysis of the acid chloride to 3-chloro-2 : 4 : 6-trimethoxyphenylacetic acid, which was oxidised to 3-chloro-2 : 4 : 6-trimethoxybenzaldehyde (III), and synthesised from this aldehyde by standard methods. Since 2 : 4 : 6-trimethoxybenzoyl chloride is not described in the literature we tried to prepare it from the acid by phosphorus pentachloride, but decarboxylation occurred under a wide variety of conditions to produce phloroglucinol trimethyl ether (cf. Holmes, White,


(I)


(II)


(III)


(IV)

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[1] Whalley and Lloyd, following paper.

[2] Freudenberg and Harder, *Annalen*, 1926, **451**, 213.

and Wilson[3]). Thionyl chloride and 2 : 4 : 6-trimethoxyphenylglyoxylic acid, however, give the requisite 2 : 4 : 6-trimethoxybenzoyl chloride (cf. Acree[4]) since interaction with resorcinol furnished 2 : 4-dihydroxyphenyl 2 : 4 : 6-trimethoxyphenyl ketone (IV), the structure of which was proved by an alternative synthesis. In our hands treatment of 2 : 4 : 6-trimethoxybenzoic and of 2 : 4 : 6-trimethoxyphenylacetic acid with thionyl chloride furnished intractable products.

The preparation of some chlorinated derivatives of phloroglucinol is also described.

EXPERIMENTAL

(With R. B. TRAVERS.) 3-(3-*Chloro*-2 : 4 : 6-*trimethoxybenzyl*)-6-*methoxycoumarone* (II).—The product obtained from 2 : 4 : 6-trimethoxyphenylacetic acid (12·5 g.) and phosphorus pentachloride (17 g.) was slowly added in nitrobenzene (50 ml.) at 10° to resorcinol (10 g.) in nitrobenzene (50 ml.) containing aluminium chloride (20 g.). Next day the product was isolated in the usual manner and the dark semicrystalline mass (20 g.) remaining after removal of the nitrobenzene in steam was purified from aqueous methanol, to furnish 3′-*chloro*-2 : 4-*dihydroxy*-2′ : 4′ : 6′-*trimethoxydeoxybenzoin* (12 g.), needles, m. p. 175°, having an intense red-brown ferric reaction in alcohol [Found : C, 58·0; H, 5·0; Cl, 10·4; OMe, 26·1. $C_{14}H_8O_3Cl(OMe)_3$ requires C, 58·0; H, 4·8; Cl, 10·0; OMe, 26·4%].

Heating this ketone (10 g.) with excess of methyl iodide and potassium carbonate (10 g.) in acetone (100 ml.) for 1 hr. furnished 3′-*chloro*-2-*hydroxy*-4 : 2′ : 4′ : 6′-*tetramethoxydeoxybenzoin* (8 g.) which separated from acetone in prisms, m. p. 169°, giving an intense red-brown ferric reaction in alcohol [Found : C, 59·1; H, 5·4; Cl, 9·6; OMe, 34·2. $C_{14}H_7ClO_2(OMe)_4$ requires C, 58·9; H, 5·2; Cl, 9·7; OMe, 33·9%].

The latter ketone (5 g.) with ethyl bromoacetate (2·5 g., 1·05 mol.) containing potassium carbonate (10 g.) in boiling acetone (100 ml.) yielded in 8 hr. 3′-*chloro*-2-*ethoxycarbonylmethoxy*-4 : 2′ : 4′ : 6′-*tetramethoxydeoxybenzoin* (4·5 g.), prisms, m. p. 120° (from ethanol), having a negative ferric reaction in ethanol (Found : C, 58·7; H, 5·5; Cl, 7·7. $C_{22}H_{23}O_8Cl$ requires C, 58·7; H, 5·1; Cl, 7·9%). This (5 g.) was quantitatively hydrolysed by aqueous-alcoholic 2N-sodium hydroxide (100 ml.) in 30 min. to 2-*carboxymethoxy*-3′-*chloro*-4 : 2′ : 4′ : 6′-*tetramethoxydeoxybenzoin*, which separated from benzene or from acetone in prisms, m. p. 207° [Found : C, 56·8; H 5·1; Cl, 8·0; OMe, 29·4. $C_{16}H_9ClO_4(OMe)_4$ requires C, 56·5; H, 5·0; Cl, 8·4; OMe, 29·2%].

Cyclisation of this acid (2 g.) in boiling acetic anhydride (20 ml.) containing sodium acetate (5 g.), during 1½ hr., furnished 3-(3-*chloro*-2 : 4 : 6-*trimethoxybenzyl*)-6-*methoxycoumarone* (1·5 g.) which separated from methanol in prisms, m. p. 131° [Found : C, 62·7; H, 5·3; Cl, 8·9; OMe, 33·6. $C_{15}H_7ClO(OMe)_4$ requires C, 63·0; H, 5·2; Cl, 9·7; OMe, 34·2%]. The yellow solution of this coumarone in concentrated sulphuric acid became blue when warmed.

Oxidation of this coumarone (0·5 g.) in acetic acid (20 ml.) with chromium trioxide (0·3 g.) on the steam-bath during 10 min. followed by dilution with water (50 ml.) furnished a semicrystalline solid, which was purified from methanol to furnish 3′-chloro-2-hydroxy-4 : 2′ : 4′ : 6′-tetramethoxydeoxybenzoin (0·1 g.) (cf. Schönberg, Badran, and Starkowsky[5]).

3-(3-*Chloro*-2 : 4 : 6-*trimethoxybenzyl*)-2 : 3-*dihydro*-6-*methoxycoumarone*.—(*a*) A solution of the previous coumarone (1 g.) in acetic acid (75 ml.) containing a catalyst prepared from charcoal (0·5 g.) and palladium chloride (0·25 g.) was shaken in hydrogen; absorption (50 ml., 0·6 mol.) ceased after 2 hr. Crystallisation of the product from methanol gave unchanged coumarone (0·2 g.) and then 3-(3-*chloro*-2 : 4 : 6-*trimethoxybenzyl*)-2 : 3-*dihydro*-6-*methoxycoumarone* (0·2 g.), needles, m. p. 92° (Found : C, 62·8; H, 6·2; Cl, 10·0. $C_{19}H_{21}O_5Cl$ requires C, 62·6; H, 6·1; Cl, 9·7%).

(*b*) 3-(3-Chloro-2 : 4 : 6-trimethoxybenzyl)-6-methoxycoumarone (2 g.) in alcohol (100 ml.) containing Raney nickel (10 g.) was heated under reflux for 20 hr. The concentrated filtrate deposited unchanged starting material (1·2 g.) and then 3-(3-chloro-2 : 4 : 6-trimethoxybenzyl)-2 : 3-dihydro-6-methoxycoumarone (0·5 g.) identical with the product from method (*a*).

3-*Chloro*-2 : 4 : 6-*trimethoxyphenylacetic Acid*.—(*a*) 2 : 4 : 6-Trimethoxyphenylacetic acid (5 g.) was warmed with phosphorus pentachloride (7 g.) to 30° and after the initial reaction had

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[3] Holmes, White, and Wilson, *J.*, 1950, 2810.

[4] Acree, *J. Amer. Chem.*, 1913, **50**, 389.

[5] Schönberg, Badran, and Starkowsky, *ibid.*, 1955, **77**, 1019.

subsided the mixture was heated on the steam-bath during 5 min. After removal of the phosphorus oxychloride in a vacuum the residual brown solid was warmed on the steam-bath during 1 hr. with 2N-sodium hydroxide (100 ml.). Acidification then precipitated 3-*chloro*-2 : 4 : 6-*trimethoxyphenylacetic acid* which separated from aqueous methanol in needles (4·8 g.), m. p. 168° (Found: C, 51·3; H, 5·3; Cl, 14·0. $C_{11}H_{13}O_5Cl$ requires C, 50·8; H, 5·0; Cl, 13·7%). When 2 : 4 : 6-trimethoxyphenylacetic acid was treated as described by Freudenberg and Harder[3] for the preparation of the acid chloride, hydrolysis of the product furnished only 3-chloro-2 : 4 : 6-trimethoxyphenylacetic acid.

(*b*) A solution of phloroglucinol trimethyl ether (1 g.) in chloroform (50 ml.) containing phosphorus pentachloride (4 g.) was kept at 20° during 3 hr. and then evaporated on the steam-bath. The colourless solid obtained by the addition of water to the residue was purified from aqueous methanol and then from light petroleum (b. p. 60—80°), to furnish 2-*chloro*-1 : 3 : 5-*trimethoxybenzene* (1·1 g.) in plates, m. p. 93° [Found: C, 53·2; H, 5·6; Cl, 17·5; OMe, 45·2. $C_6H_2Cl(OMe)_3$ requires C, 53·3; H, 5·4; Cl, 17·5; OMe, 45·9%].

A solution of this compound (1 g.) in ether (25 ml.) containing zinc chloride (1 g.) and hydrogen cyanide (2 ml.) was saturated at 0° with hydrogen chloride. 24 Hr. later the semicrystalline precipitate was collected and added to water (100 ml.) containing 2N-sodium hydroxide (20 ml.), and the mixture heated to the b. p. during 15 min.; the aldimine complex dissolved to form a clear solution. On cooling, 3-*chloro*-2 : 4 : 6-*trimethoxybenzaldehyde* separated and crystallised from light petroleum (b. p. 60—80°) in needles (0·5 g.), m. p. 122° [Found: C, 52·1; H, 5·0; Cl, 15·2; OMe, 40·5. $C_7H_2OCl(OMe)_3$ requires C, 52·0; H, 4·8; Cl, 15·4; OMe, 40·3%]. The *oxime* separated from aqueous alcohol in prisms, m. p. 192° (Found: C, 48·7; H, 5·0; N, 5·7. $C_{10}H_{12}O_4NCl$ requires C, 49·0; H, 4·9; N, 5·7%).

Reduction of this aldehyde (1·2 g.) during 4 hr. by the Clemmensen method furnished 3-*chloro*-2 : 4 : 6-*trimethoxytoluene* which separated from aqueous alcohol in needles (0·6 g.), m. p. 95° [Found: C, 55·5; H, 6·3; OMe, 42·9; Cl, 16·3. $C_7H_4Cl(OMe)_3$ requires C, 55·3; H, 6·0; OMe, 42·9; Cl, 16·4%]. This compound did not furnish an aldehyde by the Gattermann method.

The aldehyde (0·7 g.), sodium acetate (0·5 g.), hippuric acid (1 g.), and acetic anhydride (2 ml.) were heated on the steam-bath for 1 hr., then diluted with 50% aqueous ethanol (100 ml.), and the product was collected 4 hr. later. Purification from aqueous ethanol furnished the *azlactone* (0·8 g.) in yellow needles, m. p. 161° (Found: C, 61·4; H, 4·4; N, 3·7. $C_{19}H_{16}O_5NCl$ requires C, 61·0; H, 4·3; N, 3·7%).

This azlactone (0·7 g.) in 10% aqueous sodium hydroxide (100 ml.) was refluxed for 6 hr. After separation of the benzoic acid by the use of sulphur dioxide 3-*chloro*-2 : 4 : 6-*trimethoxyphenylpyruvic acid* was obtained in plates, m. p. 115° (0·35 g.), from hot water (Found: C, 46·9; H, 5·0. $C_{12}H_{13}O_6Cl,H_2O$ requires C, 47·1; H, 4·9%).

A stirred solution of this acid (0·25 g.) in 3% aqueous sodium hydroxide (30 ml.) was treated at 0° with 50-vol. hydrogen peroxide (4 ml.) during 15 min. 48 Hours later the solution was acidified and the precipitate purified from aqueous methanol to furnish 3-chloro-2 : 4 : 6-trimethoxyphenylacetic acid (0·2 g.) in needles, m. p. 169°, identical with the specimen prepared by method (*a*) (Found: C, 50·3; H, 5·1%).

2 : 4-*Dichloro*-1 : 3 : 5-*trimethoxybenzene*.—(*a*) A solution of 1 : 3 : 5-trimethoxybenzene (1 g.) in ether (50 ml.) was treated at 0° with sulphuryl chloride (1·5 ml.) in three portions during 30 min. 2 Hr. later the ether was evaporated. The residual 2 : 4-*dichloro*-1 : 3 : 5-*trimethoxybenzene* (1·5 g.) crystallised from methanol in needles, m. p. 129° [Found: C, 45·5; H, 4·4; Cl, 29·7; OMe, 39·1. $C_6HCl_2(OMe)_3$ requires C, 45·6; H, 4·3; Cl, 29·9; OMe, 39·2%].

(*b*) A solution of 1 : 3 : 5-trimethoxybenzene (3 g.) in chloroform (25 ml.) containing phosphorus pentachloride (10 g.) was kept at room temperature until the chloride had dissolved. The solvent was then evaporated, water added, and the crystalline residue purified from light petroleum (b. p. 60—80°) to give 2 : 4-dichloro-1 : 3 : 5-trimethoxybenzene (4·2 g.) in needles, m. p. 129°, identical with the specimen prepared by method (*a*).

Oxidation of 3-*Chloro*-2 : 4 : 6-*trimethoxyphenylacetic Acid*.—A solution of this acid (1 g.) in acetic acid (50 ml.) containing chromium trioxide (1·5 g.) was refluxed during 1 hr.; then the solvent was removed. Separation of the residue into neutral and acidic fractions furnished a neutral substance which was purified from light petroleum (b. p. 60—80°) to yield 3-chloro-2 : 4 : 6-trimethoxybenzaldehyde (0·2 g.), m. p. and mixed m. p. 120°.

3-*Chloro*-2 : 4 : 6-*trimethoxybenzoic Acid*.—A suspension of 3-chloro-2 : 4 : 6-trimethoxybenzaldehyde (0·5 g.) in boiling 10% sodium hydroxide solution (50 ml.) was oxidised by addition during ½ hour of potassium permanganate (0·3 g.) in water (20 ml.). The acidic product, crystallised from water, furnished 3-*chloro*-2 : 4 : 6-*trimethoxybenzoic acid* (0·3 g.) in needles, m. p. 185—186° (decomp.) [Found : C, 48·8; H, 4·8; Cl, 14·7; OMe, 37·2. $C_7H_2O_2Cl(OMe)_3$ requires C, 48·8; H, 4·5; Cl, 14·4; OMe, 37·7%].

3 : 5-*Dichloro*-2 : 4 : 6-*trimethoxytoluene*.—Prepared by the addition during 1 hr. of sulphuryl chloride (3 ml.) to a solution of phloroglucinaldehyde (2 g.) in ether (50 ml.) at 0°, followed by removal of solvent at room temperature 24 hr. later, 3 : 5-*dichloro*-2 : 4 : 6-*trihydroxybenzaldehyde* (3 g.) separated from ethyl acetate–light petroleum (b. p. 60—80°) in plates, m. p. 142° (Found : C, 38·0; H, 2·0; Cl, 32·5. $C_7H_4O_4Cl_2$ requires C, 37·7; H, 1·8; Cl, 31·8%). The *oxime* formed pale yellow prisms, m. p. 178° (decomp.), from aqueous ethanol (Found : C, 5·9. $C_7H_5O_4Cl_2N$ requires N, 5·9%).

Methylation of this aldehyde (1 g.) by methyl sulphate–acetone–potassium carbonate (4 hr.) gave 3 : 5-*dichloro*-2 : 4 : 6-*trimethoxybenzaldehyde* (100%) which from light petroleum (b. p. 60—80°) formed pale yellow needles, m. p. 115°, not giving a ferric reaction in alcohol [Found : C, 45·7; H, 3·9; Cl, 25·7; OMe, 35·1. $C_7HOCl_2(OMe)_3$ requires C, 45·3; H, 3·8; Cl, 26·8; OMe, 35·1%]. The *oxime* separated from aqueous alcohol in pale yellow needles, m. p. 202° [Found : C, 43·1; H, 4·0; N, 5·3. $C_7H_2ONCl_2(OMe)_3$ requires C, 42·9; H, 3·9; N, 5·0%].

Clemmensen reduction of this aldehyde (1 g.) furnished 3 : 5-*dichloro*-2 : 4 : 6-*trimethoxytoluene* (0·8 g.) in needles, m. p. 98°, from aqueous methanol [Found : C, 47·9; H, 5·1; OMe, 37·2; Cl, 28·2. $C_7H_3Cl_2(OMe)_3$ requires C, 47·8; H, 4·8; OMe, 37·1; Cl, 28·3%].

2 : 4 : 6-*Trimethoxy*-3-*methylbenzaldehyde*.—2 : 4 : 6-Trihydroxy-3-methylbenzaldehyde (10 g.) with methyl sulphate–potassium carbonate–acetone (50 hr.) furnished 2 : 4 : 6-*trimethoxy*-3-*methylbenzaldehyde*, plates [from light petroleum (b. p. 60—80°)], m. p. 84°, very soluble in the usual organic solvents and giving no ferric reaction in alcohol [Found : C, 63·3; H, 6·9; OMe, 44·1. $C_8H_5O(OMe)_3$ requires C, 62·9; H, 6·7; OMe, 44·3%]. The *oxime* separated from methanol in prisms, m. p. 160° (Found : N, 6·4. $C_{11}H_{15}O_5N$ requires N, 5·8%).

2 : 4-*Dimethoxyphenyl* 2 : 4 : 6-*Trimethoxyphenyl Ketone*.—(*a*) Thionyl chloride (2·0 g., 1 mol.) was added gradually during 1 hr. to a suspension of 2 : 4 : 6-trimethoxyphenylglyoxylic acid [6] (5 g.) in chloroform (25 ml.) at 0°. Next day the chloroform was removed at 20° from the clear reaction mixture, and a solution of the residual pale red syrup in nitrobenzene (15 ml.) was added to a solution of resorcinol (10 g.) in nitrobenzene (25 ml.) containing aluminium chloride (5 g.) at 0°. After 48 hr. the product was isolated in the usual manner and purified from aqueous methanol, to furnish 2 : 4-*dihydroxyphenyl* 2 : 4 : 6-*trimethoxyphenyl ketone* (7 g.) in needles, m. p. 160°, giving an intense red-brown ferric reaction in alcohol (Found : C, 63·0; H, 5·3. $C_{16}H_{16}O_6$ requires C, 63·2; H, 5·3%).

Methylation as above (3 hr.) gave 2 : 4-*dimethoxyphenyl* 2 : 4 : 6-*trimethoxyphenyl ketone* in prisms, m. p. 142°, from methanol [Found : C, 64·8; H, 6·6; OMe, 46·7. $C_{13}H_5O(OMe)_5$ requires C, 65·1; H, 6·0; OMe, 48·4%].

(*b*) Prepared by the interaction of 2 : 4-dimethoxybenzoyl chloride and phloroglucinol in nitrobenzene in the usual manner during 24 hr. 2 : 4-*dimethoxyphenyl* 2 : 4 : 6-*trihydroxyphenyl ketone* separated from aqueous methanol in yellow needles, m. p. 176°, giving an intense red-brown ferric reaction in alcohol [Found : C, 62·0; H, 5·2; OMe, 21·7. $C_{13}H_8O_4(OMe)_2$ requires C, 62·4; H, 4·8; OMe, 21·4%]. Methylation furnished the pentamethoxy-ketone identical with the product from method (*a*).

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[6] Hargreaves, McGookin, and Robertson, unpublished work.