

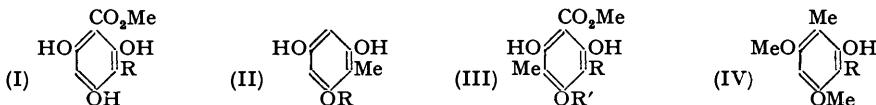
740. A New Synthesis of *C*-Methylphloroglucinol.

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Syntheses of *C*-methylphloroglucinol and some of its derivatives from *s*-trihydroxybenzoates (type I; R = H), by way of the *C*-formyl- (type I; R = CHO) and *C*-methyl-esters (type I; R = Me), are described.

For the preparation of *C*-methylphloroglucinol and its derivatives a variety of methods has been described, *viz.* (a) the stepwise or simultaneous substitution of hydroxyl groups for amino-groups in trinitrotoluene (*e.g.* Weidel and Wenzel, *Monatsh.*, 1898, **19**, 223) or aminonitrotoluenes (Curd and Robertson, *J.*, 1933, 437), (b) the decarboxylation of suitable *C*-alkylated *s*-trihydroxybenzoic acids obtained by the *C*-alkylation of *s*-trihydroxybenzoic acid (Herzig *et al.*, *Monatsh.*, 1888, **9**, 217, 882; 1889, **10**, 735; 1893, **14**, 376; 1900, **21**, 852, 866; 1901, **22**, 215; 1902, **23**, 81; Margulies, *ibid.*, 1888, **9**, 1045; 1889, **10**, 459; Pollak, *ibid.*, 1897, **18**, 745; Will, *Ber.*, 1884, **17**, 2107; Curd and Robertson, *loc. cit.*), (c) the direct synthesis from the requisite aliphatic components (*cf.* Curd and Robertson, *loc. cit.*), and (d) the simultaneous catalytic reduction and debenzoylation of suitable benzylated phloroglucinaldehydes (*e.g.* Birch, Flynn, and Robertson, *J.*, 1936, 1834) with a palladium-charcoal catalyst or the reduction of phloroglucinaldehyde and its *O*-monomethyl ether with a Raney nickel catalyst (McGookin, Robertson, and Simpson, *J.*, 1951, 2021). With the possible exception of the last method these procedures are more or less unsatisfactory for the preparation of this phenol and its derivatives in quantity. The present investigation was therefore initiated with the objective of providing a new route to *C*-methylphloroglucinol and its derivatives, required for several synthetical investigations in progress in these laboratories.

The method now described utilises the easy reduction of the appropriate formyltrihydroxybenzoate by the Clemmensen method, followed by the hydrolytic elimination of the carbomethoxy-residue, giving high yields of the requisite phenols.



Thus, *e.g.*, the reduction of methyl 3-formyl-2 : 4 : 6-trihydroxybenzoate (I; R = CHO) readily gives methyl 2 : 4 : 6-trihydroxy-3-methylbenzoate (I; R = Me) which on hydrolytic decomposition with aqueous alkali furnishes *C*-methylphloroglucinol (II; R = H). Similarly, methyl 2 : 4 : 6-trihydroxy-3-methylbenzoate (I; R = Me) furnishes 2 : 4 : 6-trihydroxy-*m*-xylene by way of the intermediates (III; R = CHO, R' = H) and (III; R = Me, R' = H), respectively, and methyl 3-formyl-2 : 6-dihydroxy-4-methoxy-5-methylbenzoate (III; R = CHO, R' = Me) (Robertson and Whalley, *J.*, 1950, 1882) yields 4 : 6-dihydroxy-2-methoxy-*m*-xylene by way of (III; R = R' = Me).

A new route to 2-hydroxy-4 : 6-dimethoxytoluene (IV; R = H) is described; the reduction of *C*-formylphloroacetophenone provides a convenient route to *C*-methylphloroacetophenone (*cf.* Robertson, Whalley, and Yates, *J.*, 1950, 3117).

EXPERIMENTAL.

Methyl 3-Formyl-2 : 4 : 6-trihydroxybenzoate.—A solution of methyl 2 : 4 : 6-trihydroxybenzoate (Herzig, Wenzel, and Graetz, *Monatsh.*, 1902, **23**, 86) (5 g.) and hydrogen cyanide (10 ml.) in ether (200 ml.) was saturated with hydrogen chloride at 0°, and 24 hours later the crystalline aldimine salt was collected, washed with ether, and rapidly heated with water (300 ml.) to 100°. *Methyl 3-formyl-2 : 4 : 6-trihydroxybenzoate* separated from the cooled hydrolysate, and on crystallisation from methanol formed needles (5 g.), m. p. 169°, which were sparingly soluble in alcohol, almost insoluble in benzene or light petroleum, and having a red-brown ferric reaction in alcohol (Found : C, 51.1; H, 3.9. $C_9H_8O_6$ requires C, 50.9; H, 3.7%). The *oxime* formed needles, m. p. 201° (decomp.), from dilute methanol (Found : N, 6.2. $C_9H_8O_6N$ requires N, 6.2%).

C-Methylphloroglucinol.—A solution of the foregoing formyl-ester (10 g.) in warm methanol (250 ml.) was added dropwise during 20 minutes to warm concentrated hydrochloric acid (125 ml.), containing water (35 ml.) and amalgamated zinc dust (100 g.), and the mixture then heated under reflux for 15 minutes, cooled, and extracted with ether, giving methyl 2 : 4 : 6-trihydroxy-3-methylbenzoate which

separated from benzene-light petroleum (b. p. 60—80°) in rosettes of prisms (8.7 g.), m. p. 146° (cf. Herzig, Wenzel, and Graetz, *Monatsh.*, 1902, **23**, 105). On being boiled with 10% aqueous potassium hydroxide (100 ml.) in nitrogen for 3 hours this ester gave C-methylphloroglucinol (6.6 g.), m. p. 214°, which was isolated with ether.

Similarly, the hydrolytic decomposition of methyl 2:6-dihydroxy-4-methoxy-3-methylbenzoate (Robertson and Whalley, *loc. cit.*) gave an almost quantitative yield of hydrated C-methylphloroglucinol β -monomethyl ether, m. p. 88—89°, which on sublimation at 140°/0.1 mm. gave the anhydrous phenol, m. p. 119° (Found: C, 62.5; H, 6.7. Calc. for $C_8H_{10}O_3$: C, 62.3; H, 6.5%) (cf. Boehm, *Annalen*, 1898, **302**, 187, who gives m. p. 117—118°).

2-Hydroxy-4:6-dimethoxytoluene (IV; R = H).—Methyl sulphate (8 g.) was added gradually during 3 hours to a boiling solution of methyl 2:4:6-trihydroxy-3-methylbenzoate (7 g.) in acetone (100 ml.) containing potassium carbonate (10 g.), and the mixture then heated for 1 hour. On isolation methyl 2-hydroxy-4:6-dimethoxy-3-methylbenzoate (IV; R = CO_2Me) (6 g.) separated from methanol in prisms, m. p. 146° (Robertson and Curd, *loc. cit.*, give m. p. 144—145°). Hydrolysis of this ester (3 g.) with boiling 20% potassium hydroxide solution (20 ml.) during 2 hours gave 2-hydroxy-4:6-dimethoxytoluene (2.2 g.), m. p. 66° (Robertson and Curd, *loc. cit.*, record m. p. 67—68°).

Methyl 3-Formyl-2:4:6-trihydroxy-5-methylbenzoate.—The interaction of methyl 2:4:6-trihydroxy-3-methylbenzoate (4 g.) and hydrogen cyanide (9 ml.) in ether (200 ml.), saturated at 0° with hydrogen chloride, followed by hydrolysis of the aldimine salt with water at 100° furnished *methyl 3-formyl-2:4:6-trihydroxy-5-methylbenzoate* which separated from methanol in slender prisms (4.3 g.), m. p. 168°, having a plum-coloured ferric reaction in alcohol (Found: C, 52.9; H, 4.4. $C_{10}H_{10}O_6$ requires C, 53.1; H, 4.4%). The *oxime* formed small needles, m. p. 195°, from dilute methanol (Found: N, 6.2. $C_{10}H_{11}O_6N$ requires N, 5.8%).

CC-Dimethylphloroglucinol.—Reduction of methyl 3-formyl-2:4:6-trihydroxy-5-methylbenzoate (3 g.) by the method employed for methyl 3-formyl-2:4:6-trihydroxybenzoate gave methyl 2:4:6-trihydroxy-3:5-dimethylbenzoate which crystallised from dilute methanol in long prisms (2.7 g.), m. p. 139° (Found: C, 56.5; H, 5.4. Calc. for $C_{10}H_{12}O_5$: C, 56.6; H, 5.7%) (cf. Herzig, Wenzel, and Altmann, *Monatsh.*, 1901, **22**, 219), and which, with boiling 10% aqueous potassium hydroxide, gave an almost quantitative yield of *CC-dimethylphloroglucinol*, m. p. 162° after purification from benzene-ethyl acetate (Weidel and Wenzel, *Monatsh.*, 1898, **19**, 237, record m. p. 161°).

4:6-Dihydroxy-2-methoxy-m-xylene.—Reduction of methyl 3-formyl-2:6-dihydroxy-4-methoxy-5-methylbenzoate (Robertson and Whalley, *loc. cit.*) (0.5 g.), dissolved in methanol (15 ml.), with amalgamated zinc (5 g.) and a boiling mixture of concentrated hydrochloric acid (15 ml.) and water (5 ml.) for 15 minutes gave methyl 2:6-dihydroxy-4-methoxy-3:5-dimethylbenzoate which formed prisms (0.4 g.), m. p. 99°, from dilute methanol, and had a green ferric reaction (Found: C, 58.0; H, 6.1. Calc. for $C_{11}H_{14}O_5$: C, 58.4; H, 6.2%) (cf. Herzig *et al.*, *Monatsh.*, 1902, **23**, 102, who give m. p. 96—98°). On elimination of the carbomethoxy-group, this ester (0.3 g.) gave 4:6-dihydroxy-2-methoxy-*m*-xylene (0.2 g.), m. p. 145° (Found: C, 64.0; H, 7.0. Calc. for $C_9H_{12}O_3$: C, 64.3; H, 7.1%) (cf. Boehm, *Annalen*, 1903, **329**, 294, who gives m. p. 147—148°).

3-Formyl-2:4:6-trihydroxy-5-methylacetophenone.—This compound was prepared by the interaction of C-methylphloroacetophenone (2 g.), zinc cyanide (2 g.), and hydrogen cyanide (5 ml.) in ether, saturated at 0°, for 24 hours followed by rapid heating to boiling of the aldimine salt with water (150 ml.). The *formyl-ketone* separated from dilute methanol in rosettes of almost colourless needles (2 g.), m. p. 134°, having a red-brown ferric reaction in alcohol (Found: C, 57.4; H, 5.1. $C_{10}H_{10}O_5$ requires C, 57.1; H, 4.8%). The 2:4-dinitrophenylhydrazone formed orange needles, m. p. 294—295° (decomp.), from much acetic acid (Found: N, 14.1. $C_{18}H_{14}O_8N_4$ requires N, 14.4%).

C-Formylphloroacetophenone, m. p. 182—183°, was prepared in excellent yield by the same method, without the aid of aluminium chloride as described by Shah and Shah (*J.*, 1939, 949), who give m. p. 180—182°. On being gently heated with a mixture of methanol (40 ml.), hydrochloric acid (25 ml.), water (15 ml.), and amalgamated zinc (20 g.) until a test portion gave a negative reaction with 2:4-dinitrophenylhydrazine sulphate solution (3—4 minutes), this formyl-ketone (4.5 g.) gave C-methylphloroacetophenone (2.2 g.) in almost colourless needles, m. p. 210—211°, identical with an authentic specimen (Curd and Robertson, *loc. cit.*).