The Benzoylation and Benzylation of C-*Methylphloracetophenones.*

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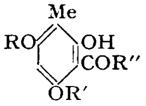
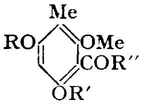
Benzoylation and benzylation studies of *C*-methylphloracetophenones have furnished routes to several new derivatives of *C*-methylphloracetophenone and to novel syntheses of 5 : 7 : 4′- and 5 : 7 : 2′-trimethoxy-6-methyl*iso*flavone.

WHILST the benzoylation of phloracetophenone gives exclusively 4-benzoyloxy-2 : 6-dihydroxyacetophenone (Canter, Curd, and Robertson, *J.*, 1933, 1245), *C*-methylphloracetophenone always gives a mixture of 4 : 6-dibenzoyloxy-2-hydroxy-3-methylacetophenone (I; R = R′ = Ph·CO, R″ = Me) and 6-benzoyloxy-2 : 4-dihydroxy-3-methylacetophenone (I; R′ = Ph·CO, R = H, R″ = Me) together with small amounts of unchanged *C*-methylphloracetophenone. The orientation of the monobenzoyl compound was readily established by methylation to 6-benzoyloxy-2 : 4-dimethoxy-3-methylacetophenone (II; R = R″ = Me, R′ = Ph·CO) followed by debenzoylation to the well-authenticated 6-hydroxy-2 : 4-dimethoxy-3-methylacetophenone (II; R′ = H, R = R″ = Me). Methylation of the dibenzoyl compound gave the ether (II; R = R′ = Ph·CO, R″ = Me) which was de-esterified to yield the hitherto unknown 4 : 6-dihydroxy-2-methoxy-3-methylacetophenone (II; R = R′ = H, R″ = Me), albeit in rather low overall yield.

(I)





(II)

The orientation of the phenol (II; R = R′ = H, R″ = Me) and hence of the cognate derivatives was established by the non-identity of the ketone with the remaining two isomeric *O*-monomethyl-*C*-methylphloracetophenones and by ethylation to 4 : 6-diethoxy-2-methoxy-3-methylacetophenone (II; R = R′ = Et, R″ = Me) which was also obtained by the methylation of 4 : 6-diethoxy-2-hydroxy-3-methylacetophenone.

Methylation of 4 : 6-dimethoxy-2-hydroxy-3-methylacetophenone (I; R = R′ = R″ = Me) which cannot be accomplished by the use of methyl iodide in acetone containing potassium carbonate (cf. Curd and Robertson, *J.*, 1933, 437) proceeds smoothly with methyl sulphate.

Benzylation of *C*-methylphloracetophenone (I; R = R′ = H, R″ = Me) furnished the 4 : 6-dibenzyl ether (I; R = R′ = Ph·CH$_2$, R″ = Me) which was converted into the methyl ether (II; R = R′ = Ph·CH$_2$, R″ = Me) and thence by catalytic debenzylation successively into (II; R = Ph·CH$_2$, R′ = H, R″ = Me) and (II; R = R′ = H, R″ = Me). Similarly 2 : 4 : 6-trihydroxy-4′-methoxy-3-methyldeoxybenzoin (I; R = R′ = H, R″ = p-MeO·C$_6$H$_4$·CH$_2$) (Whalley, *J. Amer. Chem. Soc.*, 1953, **75**, 1059) gave the 4 : 6-dibenzyl ether and thence the 4 : 6-dibenzyl 2 : 4′-dimethyl ether (II; R = R′ = Ph·CH$_2$, R″ = p-MeO·C$_6$H$_4$·CH$_2$), 6-hydroxy-2 : 4 : 4′-trimethoxy-3-methyldeoxybenzoin (II; R = Me, R′ = H, R″ = p-MeO·C$_6$H$_4$·CH$_2$), and 5 : 7 : 4′-trimethoxy-6-methyl*iso*flavone (Whalley, *loc. cit.*), thereby providing further evidence for the structure of this compound. Similarly, 5 : 7 : 2′-trimethoxy-6-methyl*iso*flavone (Whalley, *J.*, 1953, 3366) was synthesised from 2 : 4 : 6-trihydroxy-2′-methoxy-3-methyldeoxybenzoin.

EXPERIMENTAL

Benzoates of C-*Methylphloroglucinol.*—Benzoyl chloride (4·5 g.) was added with stirring in six portions during 10 min. to *C*-methylphloroglucinol (5 g.) in 2% sodium hydroxide solution (100 ml.) at 0°. The mixture was acidified to Congo-red and the sticky precipitate purified from methanol to give 4 : 6-*dibenzoyloxy*-2-*hydroxy*-3-*methylacetophenone* in prisms (1—1·3 g.), m. p. 149°, having an intense red-brown ferric reaction in alcohol (Found : C, 70·5; H, 4·8. C$_{23}$H$_{18}$O$_6$

requires C, 70·8; H, 4·7%). Concentration of the methanolic mother-liquors furnished 6-*benzoyloxy*-2 : 4-*dihydroxy*-3-*methylacetophenone* in colourless prisms (1 g.), m. p. 189° (from methanol), having an intense red-brown ferric reaction in alcohol (Found: C, 67·3; H, 4·7. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%). Methylation of this ketone (2 g.) by methyl sulphate–acetone–potassium carbonate gave 6-*benzoyloxy*-2 : 4-*dimethoxy*-3-*methylacetophenone*, which separated from aqueous methanol in tablets (2 g.), m. p. 89°, having a negative ferric reaction in alcohol [Found: C, 68·3; H, 5·6; OMe, 19·6. $C_{16}H_{12}O_3(OMe)_2$ requires C, 68·8; H, 5·8; OMe, 19·7%].

Hydrolysis of this ester (1 g.) with aqueous-methanolic 3N-potassium hydroxide (15 ml.) during 2 hr. at room temperature followed by isolation with ether furnished 6-hydroxy-2 : 4-dimethoxy-3-methylacetophenone (0·5 g.), m. p. 35°, having an intense violet ferric reaction in alcohol. Lindstedt and Misiorny (*Acta Chim. Scand.*, 1952, **6**, 1212) record m. p. 38—39°.

4 : 6-*Dihydroxy*-2-*methoxy*-3-*methylacetophenone* (II; R = R′ = H, R″ = Me).—(*a*) Methylation of 4 : 6-dibenzoyloxy-2-hydroxy-3-methylacetophenone (3 g.) during 24 hr., in boiling acetone containing potassium carbonate and methyl sulphate, furnished 4 : 6-dibenzoyloxy-2-methoxy-3-methylacetophenone as a colourless oil (3 g.), devoid of a ferric reaction and hydrolysed during 2 hr. at room temperature by aqueous-methanolic 3N-potassium hydroxide (30 ml.). 4 : 6-*Dihydroxy*-2-*methoxy*-3-*methylacetophenone* (0·7 g.), isolated by ether, was purified from benzene in very pale yellow plates, m. p. 142°, unchanged by sublimation at 180°/0·01 mm. and having an intense red-brown ferric reaction in alcohol (Found: C, 62·0; H, 6·4; OMe, 15·5. $C_9H_9O_3{\cdot}OMe$ requires C, 61·3; H, 6·2; OMe, 15·8%). (*b*) Benzylation of *C*-methylphloracetophenone (4 g.) with benzyl bromide (7·6 g., 2 mols.) in boiling acetone (75 ml.) containing potassium carbonate (15 g.) during 8 hr. gave 4 : 6-*dibenzyloxy*-2-*hydroxy*-3-*methylacetophenone*, prisms (from methanol) (2·5 g.), m. p. 145°, having an intense red-brown ferric reaction in alcohol (Found: C, 75·7; H, 5·8. $C_{23}H_{22}O_4$ requires C, 76·2; H, 6·1%). The yield could not be increased by variation in the conditions.

Methylation of this benzyl ether (3 g.) by methyl sulphate–acetone–potassium carbonate during 24 hr. furnished 4 : 6-*dibenzyloxy*-2-*methoxy*-3-*methylacetophenone* which separated from methanol in prisms (3 g.), m. p. 79°, having a negative ferric reaction in alcohol (Found: C, 76·1; H, 6·0. $C_{24}H_{24}O_4$ requires C, 76·6; H, 6·4%). Debenzylation of this ether (2 g.) in acetic acid (50 ml.) with palladium–charcoal occurred during 10 min. to furnish 4 : 6-dihydroxy-2-methoxy-3-methylacetophenone (1·1 g.) identical with the product prepared by method (*a*).

This ketone in boiling acetone containing methyl sulphate and potassium carbonate yielded quantitatively in 2 hr. 2 : 4 : 6-*trimethoxy*-3-*methylacetophenone* which was most readily purified by distillation to yield a colourless oil which rapidly solidified in plates, m. p. 44°, insoluble in 2N-sodium hydroxide, devoid of a ferric reaction in alcohol, very soluble in all the usual organic solvents, and identical with a specimen prepared in 90% yield by the methylation of 2-hydroxy-4 : 6-dimethoxy-3-methylacetophenone by methyl sulphate–potassium carbonate–acetone (48 hr.) [Found: C, 64·7; H, 7·4; OMe, 40·6. $C_9H_7O(OMe)_3$ requires C, 64·3; H, 7·2; OMe, 41·5%].

4 : 6-*Diethoxy*-2-*methoxy*-3-*methylacetophenone* (II; R = R′ = Et, R″ = Me).—*C*-Methylphloracetophenone (4 g.) with ethyl iodide or ethyl sulphate in boiling acetone containing potassium carbonate furnished 4 : 6-*diethoxy*-2-*hydroxy*-3-*methylacetophenone* (I; R = R′ = Et, R″ = Me) in pale yellow needles (4 g.), m. p. 147°, from alcohol [Found: C, 65·2; H, 7·7; OEt, 37·7. $C_9H_8O_2(OEt)_2$ requires C, 65·5; H, 7·6; OEt, 37·8%], with an intense red-brown ferric reaction in alcohol and sparingly soluble in this solvent. Methylation of this ketone proceeded quantitatively during 50 hr. on use of methyl sulphate and potassium carbonate in boiling acetone, to yield 4 : 6-*diethoxy*-2-*methoxy*-3-*methylacetophenone* in prisms, m. p. 51°, from aqueous methanol (Found: C, 66·3; H, 8·0. $C_{14}H_{20}O_4$ requires C, 66·6; H, 8·0%), identical with the ethylation product of 4 : 6-dihydroxy-2-methoxy-3-methylacetophenone.

4-*Hydroxy*-2 : 6-*dimethoxy*-3-*methylacetophenone* (II; R = H, R′ = R″ = Me).—(*a*) 4 : 6-Dihydroxy-2-methoxy-3-methylacetophenone (1 g.) with benzyl bromide (1 g.) in boiling acetone (25 ml.) containing potassium carbonate (4 g.) during 3½ hr. gave 4-*benzyloxy*-6-*hydroxy*-2-*methoxy*-3-*methylacetophenone*, needles (from methanol) (0·7 g.), m. p. 105°, having an intense green-brown ferric reaction in alcohol (Found: C, 71·2; H, 6·6; OMe, 11·1. $C_{16}H_{15}O_3{\cdot}OMe$ requires C, 71·3; H, 6·3; OMe, 10·8%). Methyl sulphate–acetone–potassium carbonate converted it quantitatively into 4-benzyloxy-2 : 6-dimethoxy-3-methylacetophenone, an oil, which on hydrogenolysis in acetic acid with palladium–charcoal gave quantitatively 4-*hydroxy*-2 : 6-*dimethoxy*-3-*methylacetophenone*, needles (from methanol), m. p. 121°, devoid of a ferric reaction in alcohol and oxidised readily in solution [Found: C, 62·6; H, 6·8; OMe, 28·3.

$C_9H_8O_2(OMe)_2$ requires C, 62·8; H, 6·7; OMe, 29·5%]. (*b*) 4 : 6-Dibenzyloxy-2-methoxy-3-methylacetophenone (2 g.) in methanol (30 ml.) containing a catalyst [prepared from charcoal (0·5 g.) and palladium chloride (30 ml. of 1% solution)] rapidly (5 min.) absorbed hydrogen (126 ml., 1 mol.). Isolation of the product at this stage furnished 4-benzyloxy-6-hydroxy-2-methoxy-3-methylacetophenone (1·3 g.), identical with that prepared by method (*a*).

5 : 7 : *4'-Trimethoxy-6-methyl*iso*flavone.*—Prepared by the addition during 3 hr. of benzyl bromide (6 g., 2 mols.) to 2 : 4 : 6-trihydroxy-4'-methoxy-3-methyldeoxybenzoin (Whalley, *J. Amer. Chem. Soc.*, 1953, **75**, 1059) (5 g.) in boiling acetone (100 ml.) containing potassium carbonate (20 g.) and isolated in the usual manner after a further 3 hr., 4 : 6-*dibenzoyloxy*-2-*hydroxy*-4'-*methoxy*-3-*methyldeoxybenzoin* separated from methanol (sparingly soluble) in prisms (3 g.), m. p. 129°, exhibiting an intense red-brown ferric reaction in alcohol (Found: C, 76·9; H, 6·4; OMe, 7·0. $C_{29}H_{25}O_4{\cdot}OMe$ requires C, 76·9; H, 6·0; OMe, 6·6%). This ketone (5 g.) with methyl sulphate–acetone–potassium carbonate furnished during 40 hr. 4 : 6-*dibenzyloxy*-2 : 4'-*dimethoxy*-3-*methyldeoxybenzoin* in prisms (5 g.) (from methanol), m. p. 106°, having a negative ferric reaction in alcohol [Found: C, 76·8; H, 6·8; OMe, 13·2. $C_{29}H_{24}O_3(OMe)_2$ requires C, 77·2; H, 6·3; OMe, 12·9%].

The ketone (3·6 g.) in acetic acid (150 ml.) containing a catalyst prepared from charcoal (1 g.) and palladium chloride (30 ml.; 1% solution) absorbed hydrogen (375 ml., 2 mols.) during 10 min. After removal of the solvent under reduced pressure 4 : 6-*dihydroxy*-2 : 4'-*dimethoxy*-3-*methyldeoxybenzoin* separated from methanol in needles (2·7 g.), m. p. 176°, having an intense olive-green ferric reaction in alcohol [Found: C, 67·4; H, 6·0; OMe, 20·5. $C_{15}H_{12}O_3(OMe)_2$ requires C, 67·5; H, 6·0; OMe, 20·5%]. Methylation of the ketone (1 g.) during 1½ hr. in boiling acetone (50 ml.) containing potassium carbonate (3 g.) and excess of methyl iodide gave 6-*hydroxy*-2 : 4 : 4'-*trimethoxy*-3-*methyldeoxybenzoin* in needles (1 g.), m. p. 88°, from aqueous methanol [Found: C, 68·4; H, 6·3; OMe, 29·5. $C_{15}H_{11}O_2(OMe)_3$ requires C, 68·3; H, 6·4; OMe, 29·4%]. The compound has an intense green ferric reaction in alcohol. Cyclisation of this ketone (1·5 g.) by sodium–ethyl formate gave 5 : 7 : 4'-trimethoxy-6-methyl*iso*flavone (0·8 g.), identical with the product prepared by the *C*-methylation of genistein (Whalley, *loc. cit.*).

5 : 7 : *2'-Trimethoxy-6-methyl*iso*flavone.*—Prepared as described previously, from 2 : 4 : 6-trihydroxy-2'-methoxy-3-methyldeoxybenzoin (Whalley, *loc. cit.*) (4 g.), 4 : 6-*dibenzyloxy*-2-*hydroxy*-2'-*methoxy*-3-*methyldeoxybenzoin* separated from methanol (sparingly soluble) in needles (2 g.), m. p. 146°, having an intense violet-red ferric reaction in alcohol (Found: C, 76·9; H, 6·0; OMe, 7·2. $C_{29}H_{25}O_4{\cdot}OMe$ requires C, 76·9; H, 6·0; OMe, 6·6%). This ketone (5 g.) furnished 4 : 6-*dibenzyloxy*-2 : 2'-*dimethoxy*-3-*methyldeoxybenzoin* which separated from methanol in prisms (5 g.), m. p. 107°, devoid of a ferric reaction in alcohol [Found: C, 76·8; H, 6·7; OMe, 13·5. $C_{29}H_{24}O_3(OMe)_2$ requires C, 77·2; H, 6·3; OMe, 12·9%].

Catalytic debenzylation in acetic acid, quantitative in 20 min., gave 4 : 6-*dihydroxy*-2 : 2'-*dimethoxy*-3-*methyldeoxybenzoin* which separated from light petroleum (b. p. 60—80°) in plates, m. p. 118°, exhibiting an intense green ferric reaction in alcohol [Found: C, 67·6; H, 6·0; OMe, 20·7. $C_{15}H_{12}O_3(OMe)_2$ requires C, 67·5; H, 6·0; OMe, 20·5%]. Methylation of this deoxybenzoin (0·8 g.) by methyl iodide–acetone–potassium carbonate during 30 min. gave 6-hydroxy-2 : 4 : 2'-trimethoxy-3-methyldeoxybenzoin (0·8 g.) identical with the previous specimen (Whalley, *loc. cit.*) and converted by sodium–ethyl formate into 2-*hydroxy*-5 : 7 : 2'-*trimethoxy*-6-*methyl*iso*flavanone* which separated from methanol in tablets (0·5 g.), m. p. 196—197° (decomp.), devoid of a ferric reaction in alcohol (Found: C, 65·8; H, 5·7. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·9%). This *iso*flavanone was converted quantitatively in boiling acetic acid (10 min.) into 5 : 7 : 2'-trimethoxy-6-methyl*iso*flavone (Whalley, *loc. cit.*).

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