*Synthetical Experiments in the Benzopyrone Series. A Synthesis of 6-Methyl*iso*flavones.*

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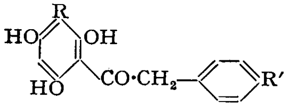
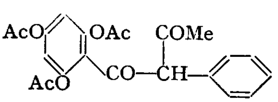
By use of acetyl chloride and pyridine at 0°, 5 : 7-dihydroxy-2 : 6-dimethyl*iso*flavone and its 4′-methoxy-derivative have been synthesised. Their 7-methyl ethers are identical with the nuclear methylation products of 5 : 7-dihydroxy-2-methyl*iso*flavone and its 4′-methoxy-derivative. By means of ethoxalyl chloride 6-methylgenistein 7 : 4′-dimethyl ether has been prepared; it is identical with the product of nuclear methylation of genistein.

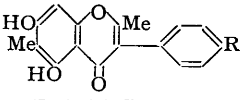
Ienger, Mehta, Seshadri, and Varadarajan [*J. Sci. Ind. Res.* (*India*), 1954, **13**, *B*, 166] reported that attempts to synthesise 5 : 7-dihydroxy-2 : 6-dimethyl*iso*flavone failed, because heating benzyl 2 : 4 : 6-trihydroxy-3-methylphenyl ketone (I*b*) with sodium acetate and acetic anhydride gave the isomeric 2 : 8-dimethyl*iso*flavone, the 2-hydroxyl group of the ketone being unexpectedly more reactive. A similar result has now been obtained with the 4-methoxybenzyl ketone (I*c*). The object has, however, been achieved by employing milder conditions, namely, acetyl chloride and pyridine at 0°. In exploratory experiments, benzyl 2 : 4 : 6-trihydroxyphenyl ketone (I*a*) was employed. The immediate product was the triacetoxy-diketone (II). When it was refluxed with aqueous sodium carbonate, deacetylation and ring closure took place simultaneously, giving 5 : 7-dihydroxy-2-methyl*iso*flavone. Similarly, from benzyl 2 : 4 : 6-trihydroxy-3-methylphenyl ketone (I*b*) and its 4-methoxybenzyl analogue (I*c*), 5 : 7-dihydroxy-2 : 6-dimethyl*iso*flavone (III*a*) and its 4'-methoxy-derivative (III*b*) were prepared. Their partial methyl ethers (7-OMe) proved to be identical with the nuclear methylation products of 5 : 7-dihydroxy-2-methyl*iso*flavone and 2-methylgenistein 4'-methyl ether (Ienger *et al.*, *loc. cit.*). By use of ethoxalyl chloride (Baker, Chadderton, Harborne, and Ollis, *J.*, 1953, 1852) with the ketone (I*c*), 6-methylgenistein 4'-methyl ether (IV) has been obtained through the intermediate ester (VI). Its 7-methyl ether (V) is identical with the nuclear methylation product of genistein prepared according to Baker and Robinson (*J.*, 1926, 2713).



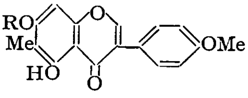
(I) (*a*) R = R' = H
(*b*) R = Me, R' = H
(*c*) R = Me, R' = OMe



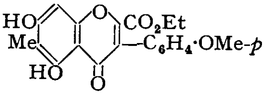
(II)



(III) (*a*) R = H
(*b*) R = OMe



(IV) R = H
(V) R = Me



(VI)

EXPERIMENTAL

α-*Acetylbenzyl* 2 : 4 : 6-*Triacetoxyphenyl Ketone* (II).—To benzyl 2 : 4 : 6-trihydroxyphenyl ketone (I*a*) (5 g.) (Chapman and Stephen, *J.*, 1923, 404) in dry pyridine (60 c.c.) at 0° was added acetyl chloride (6·3 c.c.) with stirring. After 24 hr. at 0°, ice-water was added and the solution was extracted with ether. The extract was washed with ice-cold dilute hydrochloric acid, then with water, and dried ($MgSO_4$). Ether was distilled off and the orange-red semi-solid residue mixed with alcohol (25 c.c.) and left for 6 hr. in the refrigerator, where it became crystalline. The *diketone* crystallised from alcohol (charcoal) as colourless plates, m. p. 118—120° (3 g.). It did not give any colour with alcoholic ferric chloride and was insoluble in aqueous sodium hydroxide in the cold (Found : C, 63·8; H, 5·1. $C_{22}H_{20}O_8$ requires C, 64·1; H, 4·9%).

5 : 7-*Dihydroxy*-2-*methyl*iso*flavone*.—The diketone (2 g.) was refluxed with 10% aqueous sodium carbonate (80 c.c.) for 2 hr., then cooled and acidified. The precipitated *iso*flavone crystallised from alcohol (charcoal) as pale yellowish-brown prisms (1 g.), m. p. and mixed m. p. 228° (Baker and Robinson, *J.*, 1925, 1984).

α-*Acetylbenzyl* 2 : 4 : 6-*Triacetoxy*-3-*methylphenyl Ketone*.—The ketone (I*b*) (3 g.) (Ienger *et al.*, *loc. cit.*), pyridine (50 c.c.), and acetyl chloride (4 c.c.) were used and the product worked up as in the previous case. The *diketone* crystallised from alcohol (charcoal) as colourless rhombohedral plates, m. p. 110—112° (1·9 g.), giving no ferric reaction and insoluble in cold aqueous sodium hydroxide (Found : C, 65·1; H, 5·3. $C_{23}H_{22}O_8$ requires C, 64·8; H, 5·2%).

5 : 7-*Dihydroxy*-2 : 6-*dimethyl*iso*flavone* (III*a*).—The foregoing diketone (1 g.) was hydrolysed with 10% aqueous sodium carbonate (40 c.c.). The iso*flavone* crystallised from dilute alcohol (charcoal) as colourless rectangular plates and needles, m. p. 249—251° (0·6 g.), giving with alcoholic ferric chloride an initial violet colour which changed to deep green with excess of the reagent (Found : C, 72·1; H, 4·9. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0%). Its 7-methyl ether was prepared by use of 1 mol. of methyl sulphate and potassium carbonate in acetone, and crystallised from alcohol as colourless needles, m. p. 188—190° alone or mixed with the nuclear methylation product of 5 : 7-dihydroxy-2-methyl*iso*flavone (Ienger *et al.*, *loc. cit.*).

5 : 7 : 4'-*Trimethoxy*-2 : 8-*dimethyl*iso*flavone*.—Benzyl 2-hydroxy-4 : 6 : 4'-trimethoxy-3-methylphenyl ketone (1 g.) (Seshadri and Varadarajan, *Proc. Indian Acad. Sci.*, 1953, **37**, *A*, 145), acetic anhydride (20 c.c.), and sodium acetate (3 g.) were refluxed at 180—185° for 12 hr. and while still hot poured over crushed ice. After 6 hr. the solid was filtered off and washed with water. The iso*flavone* crystallised from dilute alcohol as stout rectangular prisms, m. p. 182—183° (0·4 g.) (Found : C, 70·1; H, 6·1. $C_{20}H_{20}O_5$ requires C, 70·6; H, 5·9%).

5 : 7-*Dihydroxy*-4'-*methoxy*-2 : 8-*dimethyl*iso*flavone*.—Benzyl 2 : 4 : 6-trihydroxy-4'-methoxy-3-methylphenyl ketone (I*c*) (2 g.) (*idem, loc. cit.*), acetic anhydride (30 c.c.), and fused sodium acetate (5 g.) were refluxed at 180—185° for 12 hr. 5 : 7-*Diacetoxy*-4'-*methoxy*-2 : 8-*dimethyl*iso-

flavone crystallised from alcohol as colourless needles, m. p. 192—194° (1·1 g.) (Found : C, 67·0; H, 5·0. $C_{22}H_{20}O_7$ requires C, 66·7; H, 5·0%), giving no ferric reaction.

The diacetoxy*iso*flavone (1 g.) was hydrolysed by boiling 10% aqueous sodium carbonate (60 c.c.) for 2 hr. The *dihydroxy*iso*flavone* crystallised from alcohol (charcoal) as colourless needles, m. p. 239—241° (0·6 g.), which with alcoholic ferric chloride gave an initial violet colour which changed to deep green with excess of the reagent (Found : C, 69·3; H, 5·6. $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·1%).

5-*Hydroxy*-7 : 4′-*dimethoxy*-2 : 8-*dimethyl*iso*flavone*.—(a) *By partial demethylation.* 5 : 7 : 4′-Trimethoxy-2 : 8-dimethyl*iso*flavone (0·2 g.) in dry ether at 0° was treated with a similar solution of anhydrous aluminium trichloride (0·25 g.) with constant shaking in 20 min. After occasional shaking for 2 hr., it was set aside for 24 hr. at room temperature. Ether was then distilled off and ice and hydrochloric acid were added. The mixture was heated on a boiling-water bath for 15 min. and cooled. The yellow solid was filtered and washed with water. The iso*flavone* crystalised from alcohol (charcoal) as colourless prismatic needles, m. p. 178—179° (0·13 g.), giving with alcoholic ferric chloride an initial violet colour which changed to deep green with excess of reagent (Found : C, 70·4; H, 5·8. $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·5%).

(b) *By partial methylation.* 5 : 7-Dihydroxy-4′-methoxy-2 : 8-dimethyl*iso*flavone (0·4 g.) was refluxed with methyl sulphate (0·11 c.c., 1 mol.) and potassium carbonate (1·6 g.) in acetone for 3 hr. The product crystallised from alcohol (charcoal) as needles, m. p. and mixed m. p. 178—179° (0·35 g.).

5 : 7-*Dihydroxy*-4′-*methoxy*-2 : 6-*dimethyl*iso*flavone* (III*b*).—The trihydroxy-4′-methoxy-3-methyl ketone (I*c*) (3·7 g.), dry pyridine (40 c.c.), and acetyl chloride (4·6 c.c.) were used for the condensation. The intermediate diketone did not crystallise and was deacetylated with aqueous sodium carbonate. The solid product obtained on acidifying the carbonate solution crystallised from alcohol (charcoal) as colourless lance-shaped crystals, m. p. 242—244° (mixed with the isomeric 2 : 8-dimethyl derivative described above, 216°) (1·5 g.), giving with alcoholic ferric chloride an initial violet colour which changed to deep green with excess of the reagent (Found : C, 69·2; H, 5·0%). The *diacetate* (acetic anhydride and pyridine) crystallised from alcohol (charcoal) as hexahedral plates and tablets, m. p. 230—232° (Found : C, 67·1; H, 4·7. $C_{22}H_{20}O_7$ requires C, 66·7; H, 5·0%).

5-*Hydroxy*-7 : 4′-*dimethoxy*-2 : 6-*dimethyl*iso*flavone*.—The dihydroxy*iso*flavone (III*b*) (0·2 g.), dry acetone (70 c.c.), methyl sulphate (0·06 c.c., 1 mol.), and potassium carbonate (0·6 g.) were refluxed for 4 hr. The product crystallised from alcohol (charcoal) as colourless flat needles and rectangular plates, m. p. 198—200° alone or mixed m. p. with the nuclear methylation product of 2-methylgenistein 4′-methyl ether (Ienger *et al.*, *loc. cit.*) (0·15 g.), giving with ferric chloride a deep pink colour which changed to deep green with excess of the reagent.

Ethyl 5 : 7-*Dihydroxy*-4′-*methoxy*-6-*methyl*iso*flavone*-2-*carboxylate* (VI).—The ketone (I*c*) (5 g.), pyridine (70 c.c.), and ethoxalyl chloride (9 c.c.) (Southwick and Seivard, *J. Amer. Chem. Soc.*, 1949, **71**, 2535) were used for the condensation. The *ester* crystallised from benzene (charcoal) as pale yellow needles, m. p. 176—178° (4 g.) (ferric chloride reaction deep violet, changing to deep green with excess of the reagent) (Found : C, 64·5; H, 5·0. $C_{20}H_{18}O_7$ requires C, 64·9; H, 4·9%).

5 : 7-*Dihydroxy*-4′-*methoxy*-6-*methyl*iso*flavone* (IV).—The above ester (0·5 g.) was refluxed with 5% aqueous sodium carbonate (60 c.c.) for 2 hr. and the solution acidified. The solid product was filtered off, washed with water, and dried. It dissolved in aqueous sodium hydrogen carbonate with effervescence. The acid (0·27 g.) was heated for 5 min. at 275°. The dark red mass was ground with aqueous sodium hydrogen carbonate, filtered, washed with water, and dried. The iso*flavone* crystallised from benzene (charcoal) as colourless rectangular prisms, m. p. 210—212° (0·21 g.) (ferric chloride reaction deep pink, changing to deep green with excess of the reagent) (Found : C, 68·1; H, 4·8. $C_{17}H_{14}O_5$ requires C, 68·4; H, 4·7%).

5-*Hydroxy*-7 : 4′-*dimethoxy*-6-*methyl*iso*flavone* (V).—The above dihydroxy*iso*flavone (0·2 g.) was methylated with exactly one mol. of methyl sulphate and potassium carbonate in acetone. The dimethoxy-compound crystallised from alcohol as colourless rectangular plates, m. p. 200—201° undepressed on admixture with the nuclear methylation product of genistein (Baker *et al.*, *J.*, 1926, 2713).

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