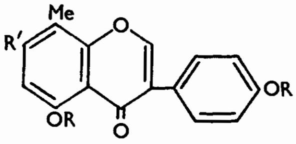
345. 5 : 4′-*Dihydroxy-8-methyl*iso*flavone, and a Note on Lotoflavin.*

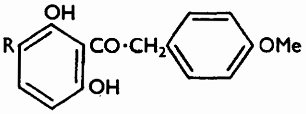
By W. B. Whalley.

The *iso*flavone named in the title has been synthesised and is not identical with " tatoin " from soya-beans.

The isolation from soya-beans of three substances which were formulated as 5 : 7 : 4′-trihydroxy-8-methyl-, 5 : 7 : 2′-trihydroxy-8-methyl-, and 5 : 7 : 2′-trihydroxy-*iso*flavone, has been reported by Okano and Beppu.[1] The synthesis of the two *C*-methyl*iso*flavones[2] and of 5 : 7 : 2′-trihydroxy*iso*flavone[2,3,4] has conclusively demonstrated the inaccuracy of this claim whilst doubt has been expressed[3] about the identity of a fourth substance, " tatoin," isolated from the same source by Okano and Beppu[1] and by Bhandari, Bose, and Siddiqui,[5] and formulated as 5 : 4′-dihydroxy-8-methyl*iso*flavone (I; R = R′ = H). The synthesis of this *iso*flavone is now described.



(I)



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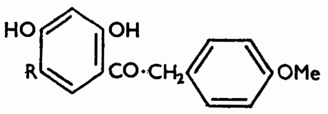

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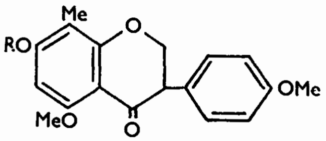

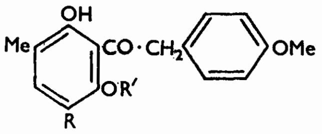

(V)

Condensation of *p*-methoxyphenylacetyl chloride with methyl 2 : 4-dihydroxy-5-methylbenzoate furnished the requisite 2 : 6-dihydroxy-4′-methoxy-5-methoxycarbonyl-3-methyldeoxybenzoin (V; R = CO_2Me, R′ = H), which was simultaneously hydrolysed

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[1] Okano and Beppu, *J. Agric. Chem. Soc. Japan*, 1939, **15**, 645; *Chem. Abs.*, 1940, **34**, 429.

[2] Whalley, *J. Amer. Chem. Soc.*, 1953, **75**, 1059.

[3] Baker, Harborne, and Ollis, *J.*, 1953, 1860.

[4] Karmarkar, Shah, and Venkataraman, *Proc. Indian Acad. Sci.*, 1952, **36**, *A*, 552.

[5] Bhandari, Bose, and Siddiqui, *J. Sci. Ind. Res. India*, 1949, **8**, *B*, 217; *Chem. Abs.*, 1950, **44**, 3987.

and decarboxylated to yield 2 : 6-dihydroxy-4′-methoxy-3-methyldeoxybenzoin (V; R = R′ = H), the orientation of which follows from the method of preparation, the characteristic green ferric reaction, and the non-identity with the isomeric 2 : 4-dihydroxy-4′-methoxy-5-methyldeoxybenzoin (III; R = Me). Monomethylation of the deoxybenzoin (V; R = R′ = H) furnished the expected monohydric phenol (V; R = H, R′ = Me) which was converted by standard methods into 5 : 4′-dihydroxy-8-methyl-*iso*flavone (I; R = R′ = H) the orientation of which, and hence of the cognate derivatives, was unequivocally established by the isolation of 2-hydroxy-4-methoxytoluene from fusion of the dimethyl ether (I; R′ = H, R = Me) with potassium hydroxide.

The properties of 5 : 4′-dihydroxy-8-methyl*iso*flavone and of the derivatives clearly establish its non-identity with Okano and Beppu's [1] "tatoin" and we are inclined to the view of Baker *et al.*[3], that "tatoin" is most likely identical with daidzein. Melting points of derivatives are as follows:

		Diacetate	Dimethyl ether
"Tatoin" (Okano and Beppu [1])	318°	185°	165°
,, (Bhandari *et al.*[5])	316—317	185	—
5 : 4′-Dihydroxy-8-methyl*iso*flavone	180	174	137

Many abortive routes were explored. 2 : 6-Dihydroxy-4′-methoxydeoxybenzoin (II; R = H) (an obvious key intermediate) could not be prepared from 2 : 6-dimethoxybenzonitrile and *p*-methoxybenzylmagnesium bromide since, as expected, 1 : 2-di-(*p*-methoxyphenyl)ethane was the only product, whilst *p*-methoxyphenylacetyl chloride and methyl 4 : 6-dihydroxy*iso*phthalate failed to react (cf. the successful use [4] of phenylacetyl chloride in this reaction). The condensation, under Friedel–Crafts conditions, of *p*-methoxyphenylacetyl chloride and methyl 2 : 4-dihydroxybenzoate furnished no detectable quantity of the ester (II; R = CO$_2$Me) (cf. *inter al.*, Naik, Thakor, and Shah [6]), but gave the isomeric 2 : 4-dihydroxy-4′-methoxy-5-methoxycarbonyldeoxybenzoin (III; R = CO$_2$Me), the orientation of which was established by decarboxylation to 2 : 4-dihydroxy-4′-methoxydeoxybenzoin (III; R = H). Furthermore, the hydrogenolysis of the toluene-*p*-sulphonates of phenols with Raney nickel which has been exploited in the flavone series (cf. *inter al.*, Akluwalia, Mukerjee, and Seshadri [7]) for the elimination of the 7-hydroxyl group failed, despite repeated attempts, to replace the toluene-*p*-sulphonyloxy-residue in 5 : 4′-dimethoxy-8-methyl-7-toluene-*p*-sulphonyloxy*iso*flavone (I; R′ = toluene-*p*-sulphonyloxy, R = Me) and gave two substances which from their general properties, analyses, and infrared spectra are formulated as 7-hydroxy-5 : 4′-dimethoxy-*iso*flavanone (IV; R = H) and the corresponding toluene-*p*-sulphonate (IV; R = toluene-*p*-sulphonyl).

Lotoflavin.—Before the nature of the pigment, lotoflavin, from *Lotus arabicus* had been elucidated by Wheeler *et al.*,[8] we had considered the possibility that it was the unknown 5 : 7 : 2′ : 4′-tetrahydroxy*iso*flavone. Although this hypothesis was compatible with the available data (for a comprehensive summary see Wheeler *et al.*[8]), the synthesis of this *iso*flavone and several derivatives clearly showed this suggestion to be untenable.

EXPERIMENTAL

Methyl 2 : 4-Dihydroxy-5-methylbenzoate.—(*a*) Prepared in 90% yield by the methylation of 2 : 4-dihydroxy-5-methylbenzoic acid with diazomethane, the *ester* separated from aqueous methanol in stout prisms, m. p. 108° (Found: C, 58·7; H, 5·3; OMe, 17·0. C$_8$H$_7$O$_3$·OMe requires C, 59·3; H, 5·5; OMe, 17·0%). (*b*) A solution of 2 : 4-dihydroxy-5-methylbenzoic acid (25 g.) in methanol (150 ml.) containing sulphuric acid (15 ml.) was refluxed for 60 hr., after which most of the methanol was evaporated under reduced pressure and the residue diluted with water (100 ml.). Purification of the crystalline precipitate from aqueous methanol gave the ester (15 g.), identical with that prepared by method (*a*).

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[6] Naik, Thakor, and Shah, *Proc. Indian Acad. Sci.*, 1953, **37**, *A*, 765.

[7] Akluwalia, Mukerjee, and Seshadri, *J.*, 1954, 3988.

[8] Doporto, Gallagher, Gowan, Hughes, Philbin, Swain, and Wheeler, *J.*, 1955, 4249.

5 : 4′-*Dihydroxy*-8-*methyl*iso*flavone* (I; R = R′ = H).—Powdered aluminium chloride (10 g.) was added to a solution of methyl 2 : 4-dihydroxy-5-methylbenzoate (4·5 g.) in nitrobenzene (40 ml.) at 5°, followed by a solution of *p*-methoxyphenylacetyl chloride (from 5 g. of acid) in nitrobenzene (25 ml.). The mixture was kept at 30° during 12 days, and after isolation in the usual manner the solid product was repeatedly extracted with methanol and the extracts were concentrated to furnish 2 : 6-*dihydroxy*-4′-*methoxy*-5-*methoxycarbonyl*-3-*methyldeoxybenzoin* in needles (2·1 g.), m. p. 116°, having an intense red-brown ferric reaction in alcohol [Found : C, 65·0; H, 5·8; OMe, 18·5. $C_{16}H_{12}O_4(OMe)_2$ requires C, 65·4; H, 5·5; OMe, 18·8%].

A solution of this deoxybenzoin (6·5 g.) in alcohol (50 ml.) and water (50 ml.) containing potassium hydroxide (7 g.) was refluxed for 1½ hr. 2 : 6-*Dihydroxy*-4′-*methoxy*-3-*methyldeoxybenzoin* was obtained which crystallised from methanol in pale yellow prisms (4·5 g.), m. p. 164°, having an intense green ferric reaction in alcohol and insoluble in 2N-sodium hydrogen carbonate, but readily soluble in 2N-sodium hydroxide (Found : C, 70·2; H, 5·9; OMe, 11·4. $C_{15}H_{13}O_3{\cdot}OMe$ requires C, 70·6; H, 5·9; OMe, 11·4%). The mixed m. p. of this ketone with an authentic specimen of 2 : 4-dihydroxy-5-methyl-4′-methoxydeoxybenzoin, m. p. 155°, was about 120°.

Methylation of this ketone (2·8 g.) with dimethyl sulphate (1·5 g., 1·05 ml.) and potassium carbonate in boiling acetone occurred during 1 hr.; a solution of the product in ether was washed with N-sodium hydroxide to remove a trace of alkali-soluble material. Evaporation of the solvent gave 2-hydroxy-6 : 4′-dimethoxy-3-methyldeoxybenzoin as an oil (2·1 g.) having an intense green ferric reaction in alcohol. Cyclisation of this methyl ether (2·1 g.) with ethyl formate (25 ml.) and sodium dust (2 g.) during 24 hr. at 0° furnished an oil which was refluxed in acetic acid (15 ml.) for 5 min. The product, in benzene, was chromatographed on alumina to give 5 : 4′-*dimethoxy*-8-*methyl*iso*flavone* which separated from aqueous methanol or benzene–light petroleum (b. p. 60—80°) in needles (1·1 g.), m. p. 137°, devoid of a ferric reaction [Found : C, 72·5; H, 5·4; OMe, 20·1. $C_{16}H_{10}O_2(OMe)_2$ requires C, 73·0; H, 5·4; OMe, 20·9%]. Demethylation of this *iso*flavone (0·4 g.) in boiling hydriodic acid (5 ml., *d* 1·7) and acetic acid (from 2 ml. of anhydride) during 20 min. gave 5 : 4′-*dihydroxy*-8-*methyl*iso*flavone*, straw-coloured needles (0·3 g), m. p. 180°, from aqueous acetic acid (Found: C, 71·3; H, 4·4. $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%). This *iso*flavone, which has an intense green ferric reaction in alcohol, furnished 5 : 4′-dimethoxy-8-methyl*iso*flavone upon remethylation and gave a *diacetate*, prisms, m. p. 175° (from methanol) (Found: C, 67·8; H, 4·5. $C_{20}H_{16}O_6$ requires C, 68·2; H, 4·6%).

Alkali Degradation of 5 : 4′-*Dimethoxy*-8-*methyl*iso*flavone*.—A mixture of 5 : 4′-dimethoxy-8-methyl*iso*flavone (0·4 g.), potassium hydroxide (2 g.), water (2 ml.), and methanol (3 ml.) was heated to 240° and kept thereat for 40 min. The phenolic fraction was isolated in the usual manner from an acidified solution of the cooled reaction mixture in water (25 ml.) and distilled at 160°/0·5 mm., to give 2-hydroxy-4-methoxytoluene (50 mg.), identical with an authentic specimen.

1 : 2-*Di*-(p-*methoxyphenyl*)*ethane*.—The interaction of the Grignard reagent from *p*-methoxybenzyl bromide with 2 : 6-dimethoxybenzonitrile (Robertson[9]) furnished only unchanged nitrile together with the ethane which separated in plates, m. p. 128°, from methanol, identical with an authentic specimen [Found : C, 79·0; H, 7·3; OMe, 25·5. Calc. for $C_{14}H_{12}(OMe)_2$: C, 79·3; H, 7·5; OMe, 25·6%]. Späth[10] records m. p. 126—127°. Demethylation furnished 1 : 2-*di*-(p-*hydroxyphenyl*)*ethane* in needles, m. p. 198°, from aqueous methanol (Found : C, 77·8; H, 6·5. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·6%).

Methyl 4 : 6-*Dihydroxy*iso*phthalate*.—4 : 6-Dihydro*iso*phthalic acid (20 g.) was refluxed in methanol (300 ml.) containing sulphuric acid (25 ml.) for 100 hr. The product which separated on cooling was purified from methanol in prisms (17 g.), m. p. 146°. Jois, Manjunath, and Siddappa[11] record m. p. 147° for material prepared by another method.

2 : 4-*Dihydroxy*-4′-*methoxy*-5-*methyldeoxybenzoin* (III; R = Me).—Prepared by the Hoesch condensation of 4-methylresorcinol (5 g.) and 4-methoxybenzyl cyanide (7 g.) in ether (125 ml.) containing zinc chloride (4 g.) during 3 days, 2 : 4-dihydroxy-4′-methoxy-5-methyldeoxybenzoin (4 g.) separated from light petroleum (b. p. 60—80°) in prisms, m. p. 154°, having an

[9] Robertson, *J.*, 1933, 1163.

[10] Späth, *Monatsh.*, 1913, **34**, 1999.

[11] Jois, Manjunath, and Siddappa, *Half-yearly J., Mysore Univ.*, 1932, **6**, 96; *Chem. Abs.*, 1933, **27**, 5069.

intense red-brown ferric reaction in alcohol (Found: C, 70·4; H, 5·9. Calc. for $C_{16}H_{16}O_4$: C, 70·6; H, 5·9%). Bhandari, Bose, and Siddiqui [5] record m. p. 139—140°.

5-*Carboxy*-2 : 4-*dihydroxy*-4′-*methoxydeoxybenzoin* (III; R = CO_2H).—A solution of *p*-methoxyphenylacetyl chloride (10 g.) in nitrobenzene (25 ml.) was added at 0° to nitrobenzene (80 ml.) containing aluminium chloride (20 g.) and methyl 2 : 4-dihydroxybenzoate (12 g.). After 48 hr. the product was isolated and the nitrobenzene recovered by steam-distillation. A solution of the semicrystalline residue in 4N-potassium hydroxide (400 ml.) was refluxed for ½ hr., to give 5-*carboxy*-2 : 4-*dihydroxy*-4′-*methoxydeoxybenzoin* (8·5 g.) which separated from aqueous methanol in prisms, m. p. 200°, having an intense blood-red ferric reaction in alcohol (Found: C, 63·5; H, 5·1; OMe, 9·5. $C_{15}H_{11}O_5$·OMe requires C, 63·6; H, 4·7; OMe, 10·2%). This ketone was soluble in 2N-sodium hydrogen carbonate and was unaffected by boiling 20% (w/v) aqueous potassium hydroxide solution during 1½ hr.

Methylation by the dimethyl sulphate–potassium carbonate method in boiling acetone during 4 hr. gave, quantitatively, 2 : 4 : 4′-*trimethoxy*-5-*methoxycarbonyldeoxybenzoin* which formed plates, m. p. 157°, from methanol and had no ferric reaction in alcohol [Found: C, 65·7; H, 5·8; OMe, 36·0. $C_{15}H_8O_2(OMe)_4$ requires C, 66·3; H, 5·8; OMe, 36·0%].

Decarboxylation of 5-carboxy-2 : 4-dihydroxy-4′-methoxydeoxybenzoin (2 g.) in boiling quinoline (15 ml.) containing copper bronze (0·5 g.) was effected during 5 min. (longer reaction caused extensive decomposition). The product crystallised from benzene and then from aqueous methanol in needles (0·45 g.), m. p. 158°, identical with an authentic specimen of 2 : 4-dihydroxy-4′-methoxydeoxybenzoin.

5 : 4′-*Dimethoxy*-8-*methyl*-7-*toluene*-p-*sulphonyloxy*iso*flavone* (I; R′ = toluene-*p*-sulphonyloxy, R = Me).—Interaction of 2 : 4-dihydroxy-6 : 4′-dimethoxy-3-methyldeoxybenzoin [3] (8 g.), benzyl bromide (5·0 g., 1·1 mol.), and potassium carbonate (20 g.) in boiling acetone (250 ml.) during 3 hr., gave 4-*benzyloxy*-2-*hydroxy*-6 : 4′-*dimethoxy*-3-*methyldeoxybenzoin* (8 g.) which separated from methanol in needles, m. p. 118°, with an intense violet ferric reaction in alcohol (Found: C, 73·2; H, 6·5. $C_{24}H_{24}O_5$ requires C, 73·5; H, 6·2%).

Cyclisation of this ketone (7·5 g.) with sodium dust (3 g.) and ethyl formate (50 ml.) furnished 7-*benzyloxy*-2-*hydroxy*-5 : 4′-*dimethoxy*-8-*methyl*iso*flavanone* (6·5 g.), prisms, m. p. 127° (decomp.), from methanol, devoid of a ferric reaction (Found: C, 68·7; H, 5·9. $C_{25}H_{24}O_6,H_2O$ requires C, 68·5; H, 6·0%). When boiled for 5 min. in acetic acid it was converted quantitatively into 7-*benzyloxy*-5 : 4′-*dimethoxy*-8-*methyl*iso*flavone* which formed needles, m. p. 168°, from methanol (Found: C, 74·1; H, 5·2. $C_{25}H_{22}O_5$ requires C, 74·6; H, 5·5%). Catalytic debenzylation of this *iso*flavone (3 g.) in acetic acid (100 ml.) with a catalyst prepared from charcoal (1 g.), palladium chloride (0·4 g.), and hydrochloric acid (5 ml.) for 1 hr. gave quantitatively 7-hydroxy-5 : 4′-dimethoxy-8-methyl*iso*flavone identical with that prepared by another method.[2] The *toluene*-p-*sulphonate*, prepared quantitatively in pyridine at room temperature during 48 hr., separated from acetone in prisms, m. p. 212° [Found: C, 64·8; H, 5·4; OMe, 13·7. $C_{25}H_{22}O_7S(OMe)_2$ requires C, 64·4; H, 4·7; OMe, 13·3%].

Of numerous attempts to remove the toluene-*p*-sulphonyl group by reduction from this *iso*flavone, the following experiment is typical. A rapid stream of hydrogen was passed through a solution of the toluene-*p*-sulphonate (1 g.) in methanol (2 l.) containing Raney nickel (5 g.) for 1 hr. and the concentrated solution was then fractionally crystallised to yield: (*a*) unchanged material (0·1—0·2 g.); (*b*) 7-*hydroxy*-5 : 4′-*dimethoxy*-8-*methyl*iso*flavanone* (0·1 g.), needles, m. p. 260°, from ethanol, devoid of a ferric reaction and readily soluble in cold 2N-sodium hydroxide [Found: C, 68·0; H, 5·8; OMe, 20·2. $C_{16}H_{12}O_3(OMe)_2$ requires C, 68·7; H, 5·7; OMe, 19·7%] (the mixed m. p. with the corresponding *iso*flavone was *ca.* 245°); and (*c*) 5 : 4′-*dimethoxy*-8-*methyl*-7-*toluene*-p-*sulphonyloxy*iso*flavanone* (0·1 g.), needles, m. p. 149°, from ethanol devoid of a ferric reaction and insoluble in 2N-sodium hydroxide [Found: C, 63·8; 64·1; H, 5·1, 5·0; OMe, 13·3. $C_{23}H_{20}O_5S(OMe)_2$ requires C, 64·4; H, 4·7; OMe, 13·3%].

4-*Methylresorcinol* (With J. STAUNTON).—The following process is a substantial improvement upon those previously described. A solution of 2 : 4-dihydroxybenzaldehyde (40 g.) in water (200 ml.) and concentrated hydrochloric acid (200 ml.) containing zinc amalgam (200 g.) was stirred vigorously for 2 hr., with the addition of further hydrochloric acid (50 ml.) after 1 hr. Next day the decanted solution was saturated with ammonium sulphate and exhaustively extracted with ether, and the extract distilled to give 4-methylresorcinol (19—20 g.), m. p. 99—100°.

5 : 7 : 2′ : 4′-*Tetrahydroxy*iso*flavone*.—A solution of 5 : 7 : 2′ : 4′-tetramethoxy*iso*flavone [12] (3·7 g.) in benzene (100 ml.) containing aluminium chloride (10 g.) was heated on the steam-bath for 4 hr. The product was purified from aqueous methanol or aqueous acetic acid, to furnish 5 : 7 : 2′ : 4′-*tetrahydroxy*iso*flavone* (2·5 g.) in pale yellow needles, m. p. 272°, having an intense red violet-brown ferric reaction in alcohol (Found : C, 62·7; H, 3·8. $C_{15}H_{10}O_6$ requires C, 62·9; H, 3·5%).

Methylation with dimethyl sulphate–potassium carbonate in boiling acetone for ½ hr. furnished an almost quantitative yield of 5-*hydroxy*-7 : 2′ : 4′-*trimethoxy*iso*flavone* which separated from methanol in needles, m. p. 154°, with an intense red-brown ferric reaction [Found : C, 65·1; H, 5·2; OMe, 27·7. $C_{15}H_7O_3(OMe)_3$ requires C, 65·8; H, 4·9; OMe, 28·4%]. 5-*Acetoxy*-7 : 2′ : 4′-*trimethoxy*iso*flavone* separated from methanol in plates, m. p. 204°, devoid of a ferric reaction (Found : C, 64·6; H, 5·3. $C_{20}H_{18}O_7$ requires C, 64·9; H, 4·9%).

The 4-methylresorcinol was prepared by Mr. K. Turner, B.Sc., and the analyses were performed by Mr. A. S. Inglis, M.Sc., and his associates of this Department.

UNIVERSITY OF LIVERPOOL. [*Received, November 15th*, 1956.]

[12] Whalley, *J.*, 1953, 3366; King and Neil, *J.*, 1952, 4752.