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THE EXTRACTIVES OF *PISCIDIA ERYTHRINA* L.—II

SYNTHETICAL EVIDENCE CONCERNING THE STRUCTURE OF ICHTHYNONE

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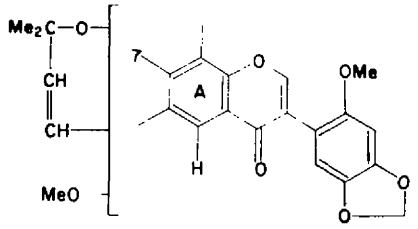
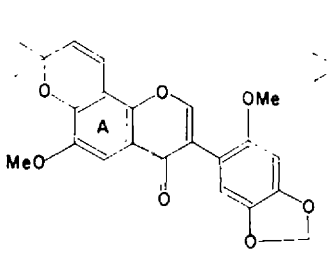
Abstract—Partial synthesis has shown that a degradation product of ichthynone is the salicylic acid (Vc): this establishes the constitution (II) for ichthynone.

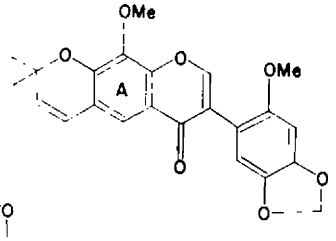
THE preceding paper[1] describes the evidence leading to the derivation of the partial formula (I) for ichthynone and since all the known[2] isoflavones and related isoflavonoids are oxygenated in position 7, structures II or III were strongly preferred for ichthynone on biogenetic grounds. However, further evidence was required to distinguish between these structural possibilities.



I



II



III

Of the two biogenetically acceptable structures II and III considered for ichthynone, the structure II was favoured on two grounds.[1] The dimethoxychroman, $C_{11}H_{12}O(OMe)_{12}$, obtained by the degradation of ichthynone, was not identical with

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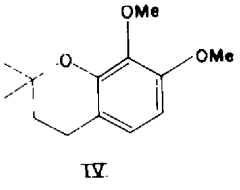
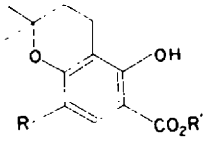
[1] J. S. Paul Schwarz, Allen I. Cohen, W. D. Ollis, E. A. Kaczka and L. M. Jackman, *Tetrahedron* **20**, 1317 (1964).
[2a] W. K. Warburton, *Quart. Revs.* **8**, 67 (1954).
[2b] K. Venkataraman, *Fortsch. Chem. org. Nat.* **17**, 1 (1959).
[2c] W. D. Ollis, *The Chemistry of Flavonoid Compounds* (Edited by T.A. Geissman), p. 353. Pergamon, Oxford (1961).

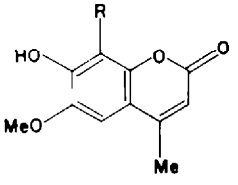
7,8-dimethoxy-2,2-dimethylchromanIV. This clearly excluded structure III, whereas the observation that the UV spectrum of the dimethoxychroman, $C_{11}H_{12}O(OMe)_2$ corresponded to a 1,2,4-trioxygenated benzene chromophore indicated that ichthynone probably had the structure II. If this structural assignment were correct, then it followed that the salicylic acid, $C_{12}H_{13}O_4(OMe)$, obtained[1] from dihydroichthynone (cf. II), would have the structure Vc. This acid was characterized as its methyl ester and this methyl ester (Vd) has now been unambiguously synthesized and shown to be identical with the degradation product of dihydro-ichthynone. This establishes the constitution of ichthynone as the isoflavone (II).



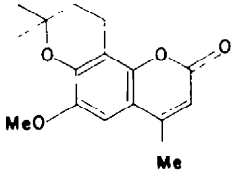
IV



Va R=R'=H
Vb R=OH; R'=H
Vc R=OMe; R'=H
Vd R=OMe; R'=Me



VIa R=H
VIb R=$Me_2C=CH-CH_2$



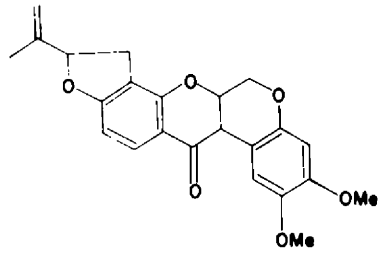
VII

Our initial approaches to the salicylic acid (Vc) involved the synthesis of the coumarin (VII). Reaction[3] of 6-methoxy-7-hydroxy-4-methylcoumarin[4] (VIa) with $\gamma\gamma$-dimethylallyl bromide[5] gave the 8-$\gamma\gamma$-dimethylallyl derivative (VIb) which, by an acid-catalysed cyclization, gave the required coumarin (VII). A number of attempts was made to hydrolyse this coumarin (VII) with alkali, but even under conditions which were successful[6] with closely related compounds, the coumarin (VII) was recovered unchanged. Its stability to alkali recalls similar observations[7] which have been made with other 7-alkoxylated coumarins; it is probably associated with the easy cyclization of the corresponding *o*-hydroxycinnamic acids. In order to try to circumvent this difficulty, various attempts were made to oxidize the coumarin (VII)

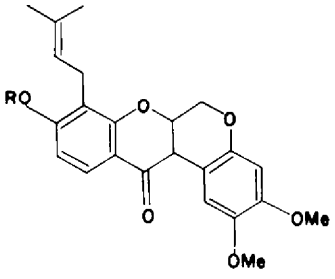
[3] F. A. L. Anet, G. K. Hughes and E. Ritchie, *Austral. J. Sci. Res.* **2**, 608 (1949).
[4] L. Velluz and G. Amiard, *Bull. Soc. Chim.*, Fr. **15**, 1109 (1948).
[5] H. Staudinger, W. Kreis and W. Schilt, *Helv. Chim. Acta* **5**, 750 (1962).
[6] *Organic Syntheses* Coll. Vol. III; p. 281. Wiley, New York, (1955).
[7] S. Wawzonek, *Heterocyclic Compounds* (Edited by R. C. Eldderfield), Vol 2; p. 210. Wiley, New York, (1951); D. B. Limaye and K. M. Kulkarni, *Rasayanam* **1**, 208 (1941); *Chem. Abstr.* **36**, 1033 (1942).

directly to the salicylic acid (Vc) with alkaline hydrogen peroxide, but these were unsuccessful.

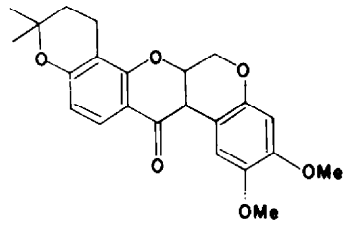
An alternative approach was then considered involving nuclear *p*-hydroxylation of *β*-dihydrotubaic acid (Va) by the Elbs alkaline persulphate method.[8] *β*-Dihydrotubaic acid (Va) has been prepared[9] by the following route. Catalytic hydrogenation of rotenone (VIII) yields rotenonic acid[10] (IXa) which, by acid catalysed cyclization, gives *β*-dihydrorotenone[9] (X). Alkaline cleavage of *β*-dihydrorotenone (X) gives *β*-dihydrotubaic acid (Va).



VIII



IXa R=H
IXb R=Me



X

Elbs persulphate oxidation[11] of *β*-dihydrotubaic acid (Va) gave the acid (Vb) which was partially methylated with dimethyl sulphate and potassium carbonate in refluxing benzene to give the methyl ester (Vd). This substance (Vd) was identical with the methyl ester of the salicylic acid, $C_{12}H_{13}O_4(OMe)$, obtained[1] from ichthynone, thus establishing the structure of ichthynone as II.

Certain other aspects of this work may now be considered. The formation of rotenonic acid* (IXa) from rotenone (VIII) involves the hydrogenolysis of an allylic ether and it has been assumed[10] that this is associated with migration of the olefinic

* This name is generally used for this compound although its acidity is due to the *p*-hydroxycarbonyl grouping.[12]

[8] T. R. Seshadri, *The Chemistry of Flavonoid Compounds* (Edited by T. A. Geissman) p. 175. Pergamon, Oxford (1961).

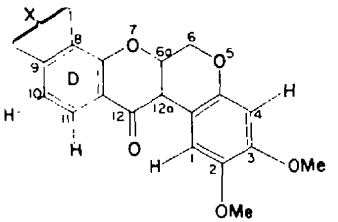
[9] H. L. Haller, *J. Amer. Chem. Soc.* **53**, 733 (1931).

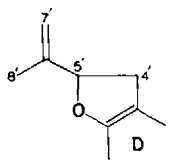
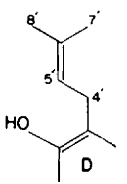
[10] F. B. LaForge and L. E. Smith, *J. Amer. Chem. Soc.* **51**, 2574 (1929).

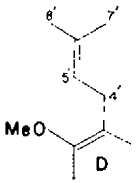
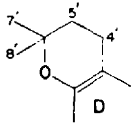
[11] S. Rajagopalan, T. R. Seshadri and S. Varadarajan, *Proc. Ind. Acad. Sci.* **30**, 265 (1949).

[12] F. B. LaForge, H. L. Haller and L. E. Smith, *Chem. Revs.* **12**, 191 (1933).

CHEMICAL SHIFTS (τ) FOR THE INDICATED PROTONS IN ROTENOIDS



	1-H	4-H	2-OMe and 3-OMe	10-H	11-H	X	Protons in X-residue
Rotenone (VIII)	3·20	3·57	6·23 6·18	3·50 (d, J = 9)	2·13 (d, J = 9)		4′-H, ~6·7 and 7·0, AB of ABX system 5′-H, 4·73 (t, J = 8·5) 7′-H, 4·92 and 5·10, broadened singlets 8′-Me, 8·23
Rotenonic acid (IXa)	3·20	3·53	6·25 6·20	3·47 (d, J = 9)	2·25 (d, J = 9)		4′-H, 6·62 (d, J = 8) 5′-H, ~4·8 (t, J ~ 8) 7′-Me, 8·30 8′-Me, 8·22 OH, 3·53

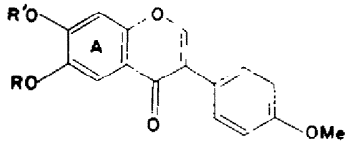
Rotenonic acid methyl ether (IXb)	3·18	3·53	6·23 6·18	3·40 (d, J = 9)	2·13 (d, J = 9)		4'-H, 6·68 (d, J ~ 8) 5'-H, broad ~4·8 7'-Me, 8·35 8'-Me, 8·22 OMe, 6·13
β-Dihydrorotenone (X)	3·15	3·53	6·22 6·18	3·53 (d, J = 9)	2·25 (d, J = 9)		4'-H, 7·32 (t, J = 6·5) 5'-H, 8·25 (t, J = 6·5) 7'-Me and 8'-Me, 8·65 and 8·70

For abbreviations see Table 1 in preceding paper. The numbering of protons in the X residue is arbitrary and does not conform to nomenclature rules.

bond. Related cleavages *with* rearrangement are known.[13] As the most direct proof of a rearrangement of this type is provided by the NMR spectral characteristics[14] of the $\gamma\gamma$-dimethylallyl group when it is bonded to an aromatic ring, the NMR spectra of rotenonic acid (IXa) and its methyl ether were determined. Some features of the NMR spectra of rotenone and rotenonic acid have been reported previously[15] and are included in the Table as models.

The NMR spectra recorded in the Table are in full accord with their indicated structures. These spectra also show a common complex pattern (τ 5·1–6·5), not indicated in the Table, due to the four protons in positions 6, 6_a, and 12_a, which constitute an ABCD system.[15] The spectra of rotenonic acid and its methyl ether indicate unequivocally the presence of a $\gamma\gamma$-dimethylallyl group[14] and show that the catalytic hydrogenolysis of the allylic ether grouping in rotenone is accompanied by bond migration.[13]

During the early stages of the investigation of the structure of ichthynone, its UV spectrum was misleading, and in this connection 6,7-dihydroxy-4′-methoxyisoflavone (XIa) was synthesized as a model. This isoflavone is not known as a natural product,[2] although its 6-methyl ether, afromosin (XIb), occurs naturally.[16,17] The UV spectra of several related isoflavones are summarized below.



XIa R=R′=H
XIb R=Me, R′=H
XIc R=R′=Me

UV ABSORPTION SPECTRA OF ISOFLAVONES λ_{max} mμ(ϵ_{max}) in ethanol

6,7-Dihydroxy-4′-methoxyisoflavone (XIa)	231	(24, 550)	258	(33, 110)	326	(13, 490)
Afromosin (XIb)[16]			258	(23, 440)	320	(10, 000)
6,7,4′-Trimethoxyisoflavone (XIc)[16]			261	(50, 120)	320	(19,950)
Ichthynone (II)[1]	232	(33, 600)	262	(24, 300)	309	(14, 100)
					331	(11, 000)
					345	(9, 400)
Dihydroichthynone (cf. II)[1]	233 sh	(24, 400)	256 sh	(15, 700)	312	(18, 700)
Jamaicin (cf. II; 6-OMe = 6-H)[18]	232	(30, 500)	263	(34, 700)	306	(14, 500)

It may be noted that the isoflavones (XIa, XIb, XIc) and ichthynone (II) all exhibit high intensity absorption in the 320–340 mμ region which is not usually regarded as

[13] W. G. Dauben and P. D. Hance, *J. Amer. Chem. Soc.* **77**, 2451 (1955); W. G. Dauben, J. S. Paul Schwarz, W. K. Hayes and P. D. Hance, *Ibid.* **82**, 2239 (1960).
[14] B. F. Burrows, W. D. Ollis and L. M. Jackman, *Proc. Chem. Soc.* 177 (1960).
[15] L. Crombie and J. W. Lown, *J. Chem. Soc.* 755 (1962).
[16] T. B. H. McMurry and C. Y. Theng, *J. Chem. Soc.* 1491 (1960).
[17] J. B. Harborne, O. R. Gottlieb and M. T. Magalhães, *J. Org. Chem.* **28**, 881 (1963).
[18] J. A. Moore and S. Eng. *J. Amer. Chem. Soc.* **78**, 395 (1956); A. L. Kapoor, A. Aebi and J. Büchi, *Helv. Chim. Acta* **40**, 1574 (1957); O. A. Stamm, H. Schmid and J. Büchi, *Ibid.* **1**, 2006 (1958).

being typical of compounds of the isoflavone type.[2,19] The unusual chromophoric characteristics of some of these compounds has been attributed[17] to their 2,4,5-oxygenation pattern of ring A and a similar comment has been made[17] concerning the atypical UV spectrum of 6,7,3',4'-tetrahydroxyflavanone.[20] The UV spectrum of ichthynone in the 300-350 mμ region is certainly unusual for an isoflavone, but it is doubtful if this should be associated solely with the 2,4,5-oxygenation of its ring A. The isoflavones osajin and pomiferin have a different ring A oxygenation pattern from that of ichthynone, yet they still show long wavelength absorption.[21] In this connection it is probably relevant that ichthynone, osajin and pomiferin all have a chromene system conjugated with ring A. When the chromene double bond is reduced as in dihydroichthynone, then its UV spectrum is more like that of the model isoflavones (XIa, XIb, and XIc). However, it should be noted that the differences between the UV spectra of ichthynone and dihydroichthynone are much greater than the differences between jamaicin and dihydrojamaicin. It is clear that conjugation involving chromene double bonds may be associated with unexpectedly large bathochromic shifts and that comparison of the corresponding chromans with models may be more directly informative in such cases.

EXPERIMENTAL

M.ps are uncorrected.

8-(γγ-Dimethylallyl)-7-hydroxy-6-methoxy-4-methylcoumarin (VIb). A solution of NaOH (300 mg) in water (2 ml) was added at 0° to a vigorously stirred solution of 7-hydroxy-6-methoxy-4-methylcoumarin[4] (1 g) in acetone (25 ml). After 20 min the yellow precipitate was collected, dried over phosphoric anhydride (24 hr), then suspended in anhydrous benzene (25 ml), and heated under reflux with γγ-dimethylallyl bromide (3 ml). The benzene was removed under diminished press. and the residue was treated with dil. acid and extracted with chloroform. This extract after washing with 2N NaOH yielded *8-(γγ-dimethylallyl)-7-hydroxy-6-methoxy-4-methylcoumarin* (620 mg, 47%) as colourless needles, m.p. 179–180° from ethanol, ν_{max} (nujol) 3320, 1718, and 1618 cm^{-1}, λ_{max} (ethanol) 216 mμ (ε 15,970), 232 mμ (ε 15,320), 300 mμ sh (ε 4,610), 344 mμ (ε 12,460). (Found: C, 70·27; H, 6·86. $C_{16}H_{18}O_4$ requires: C, 70·05; H, 6·61%).

7,8-(2',2'-Dimethylchromano)-6-methoxy-4-methylcoumarin (VII). A solution of 8-(γγ-dimethylallyl)-7-hydroxy-6-methoxy-4-methylcoumarin (100 mg) in glacial acetic acid (5 ml) and conc. HCl (0·25 ml) was heated under reflux for 3 hr and the residue obtained by evaporation under diminished press. crystallized from aqueous ethanol giving *7,8-(2',2'-dimethylchromano)-6-methoxy-4-methylcoumarin* (82 mg; 82%) as pale yellow prisms, m.p. 201–202°, ν_{max} (nujol) 1710 and 1610 cm^{-1}, λ_{max} (ethanol) 212 mμ (ε 29,450), 231 mμ (ε 16,970), 310 mμ sh (ε 3,770), 347 mμ (ε 10,960). (Found: C, 70·24; H, 6·64. $C_{16}H_{16}O_4$ requires: C, 70·05; H, 6·61%).

Rotenonic acid methyl ether (IXb). Dimethyl sulphate (4 ml) was added during 1 hr to a vigorously stirred mixture of rotenonic acid (IXa; 14 g), anhydrous potassium carbonate (40 g), and acetone (100 ml) which was heated under reflux. After a further 2 hr, the mixture was cooled, water (500 ml) was added, and chloroform extraction yielded a product (13·46 g) which was chromatographed on silica using benzene as solvent. This yielded rotenonic acid methyl ether (7 g) as colourless prisms, m.p. 142°, from methanol. (Found: C, 70·6; H, 6·6; OMe, 21·5. $C_{21}H_{17}O_5(OMe)_3$ requires: C, 70.2; H, 6·3; OMe, 22·7%).

5,8-Dihydroxy-2,2-dimethylchroman-6-carboxylic acid (Vb). β-Dihydrotubaic acid, m.p. 175–176°, ν_{max} (nujol) 3195, 1665, 1629 cm^{-1}, λ_{max} (ethanol) 263 mμ (ε 14,650), 297 m (μ 5,180) was prepared from β-dihydrorotenone (X) *via* rotenonic acid (IXa) as described by Haller.[9]

A solution of potassium persulphate (950 mg) in water (15 ml) was added during 4 hr at 10° to a stirred solution of β-dihydrotubaic acid (Va; 800 mg) in 8% NaOH aq. (10 ml). After a further

[19] L. Jurd, *The Chemistry of Flavonoid Compounds*, (Edited by T. A. Geissman) p. 107. Pergamon, Oxford (1961).

[20] J. B. Harborne and T. A. Geissman, *J. Amer. Chem. Soc.* **78**, 829 (1956).

[21] Ref. 2c, p. 367.

24 hr at room temp, the mixture was neutralized with dil. HCl and extracted with ether. Conc. HCl (6 ml) and Na_2SO_3 (1 g) were added to the aqueous phase and after heating (100°) for 30 min, cooling and ether extraction yielded a crystalline product (240 mg). Recrystallization from aqueous ethanol gave 5,8-*dihydroxy*-2,2-*dimethylchroman*-6-*carboxylic acid* (160 mg; 19%) as colourless needles, m.p. 179°; it gave a green-brown coloration with ethanolic ferric chloride, ν_{max} (nujol) 3535, 3498, ~3210, 1668, and 1628 cm^{-1}, λ_{max} (ethanol) 213 mμ(ε 18,900), 225 mμ sh (ε 12,160), 267 mμ (ε 9,095), 323 mμ (ε 5,380). (Found: C, 60·32; H, 6·14. $C_{12}H_{14}O_5$ requires: C, 60·50; H, 5·92%).

6-*Carbomethoxy*-5-*hydroxy*-8-*methoxy*-2,2-*dimethylchroman* (Vd). A mixture of 5,8-dihydroxy-2,2-dimethylchroman-6-carboxylic acid (130 mg), anhydrous potassium carbonate (500 mg), dimethyl sulphate (0·11 ml), and anhydrous benzene (5 ml) was heated under reflux for 4 hr, cooled, ether added, and the solid removed. The filtrate yielded a solid which was recrystallized from light petroleum (b.p. 40–60°) giving 6-*carbomethoxy*-5-*hydroxy*-8-*methoxy*-2,2-*dimethylchroman* (42 mg; 28%) as colourless prisms, m.p. 111°; it gave intense blue-green coloration with ethanolic ferric chloride, ν_{max} (chloroform) ~3200, 1665, 1628 cm^{-1}, λ_{max} (ethanol) 213 mμ (ε 21,580), 230 mμ sh (ε 14,520), 270 mμ (ε 13,430), 320 mμ (ε 6,950). (Found: C, 63·33; H, 6·87; OMe, 22·62. Calc. for $C_{12}H_{11}O_3(OMe)_2$: C, 63·14; H, 6·81; OMe, 23·31%).

This ester was identical (mixed m.p., IR and NMR spectra) with one of the degradation products of dihydroichthynone (see preceding paper).

4-*Methoxybenzenyl*-2,4,5-*trihydroxyphenyl ketone*. 1, 2, 4-Trihydroxybenzene (13·0 g), *p*-methoxybenzyl cyanide (15·2 g), and powdered zinc chloride (15·0 g) were suspended in anhydrous ether and saturated with hydrogen chloride at 0° for 5 hr. The mixture was stored at 0° for 1 week, and then the supernatant liquid was decanted from the heavy red oil which had separated. This oil was washed with dry ether (2 × 250 ml), then water (450 ml) and conc. HCl (10 ml) were added and the mixture heated (2 hr) on a steam bath under a N_2 atmosphere. After cooling, the crystalline product was collected and recrystallized from aqueous ethanol giving 4-*methoxybenzyl*-2,4,5-*trihydroxyphenyl ketone* (10·3 g; 36%) as straw-coloured needles, m.p. 181·5–182·5°, ν_{max} (nujol) ~3300 and 1650 cm^{-1}, λ_{max} (ethanol) 219 μ (ε 20,420), 244 mμ (ε 12,020), 283 mμ (ε 12,300), 354 mμ (ε 7,940). (Found: C, 65·52; H, 5·24; OMe, 11·25. $C_{14}H_{11}O_5(OMe)$ requires: C, 65·75; H, 5·43; OMe, 11·30%).

Methylation of this ketone using dimethyl sulphate and potassium carbonate in acetone gave the known 4-methobenzyl-2,4,5-trimethoxyphenyl ketone, m.p. 87°[16] (Found: C, 68·01; H, 6·39; OMe, 38·4. Calc. for $C_{14}H_8O(OMe)_4$: C, 68·30; H, 6·40; OMe, 39·2%).

2-*Carbethoxy*-6,7-*dihydroxy*-4′-*methoxyisoflavone*. Ethoxalyl chloride (16·0 g) was added dropwise at 0° during 1 hr to a stirred solution of 4-methoxybenzyl-2,4,5,trihydroxyphenyl ketone (7·65 g) in anhydrous pyridine (60 ml). The mixture was stored at 0° for 60 hr, poured into water, and extracted with chloroform. This extract, after shaking with 2N HCl, yielded 2-carbethoxy-6,7-dihydroxy-4′-methoxyisoflavone (9·48 g; 90%) as pale yellow prisms, m.p. 237–238°, from aqueous methanol, λ_{max} (ethanol) 215 mμ (ε 12,590), 240 mμ (ε 9,120), 341 mμ (ε 38,000). (Found: C, 63·82; H, 4·63. $C_{19}H_{16}O_7$ requires: C, 64·0; H, 4·50%).

6,7-*Dihydroxy*-4′-*methoxyisoflavone* (XIa). The preceding ester (7·79 g) was dissolved in acetone (100 ml), water (1500 ml), and 2N NaOH (75 ml), and after standing at room temp under a N_2 atmosphere for 12 hr, 2N H_2SO_4 was added and the precipitated acid (6·31 g; 88%) collected.

This acid (2·0 g) was decarboxylated in portions (25 mg) by heating it in small ignition tubes in a Wood's metal bath (280–285°) for 2·5 min. The tubes were then extracted with hot ethanol and concentration followed by recrystallization from ethanol gave 6,7-*dihydroxy*-4′-*methoxyisoflavone* (1·30 g; 78%) as pale brown prisms, m.p. 291·5–192·5° (dec), ν_{max} (nujol) 3505, 3150, and 1632 cm^{-1} λ_{max} (ethanol) 231 mμ (ε 24,550), 258 mμ (ε 33,110), 326 mμ (ε 13,490). (Found: C, 67·47; H, 4·23; OMe, 10·94. $C_{15}H_9O_4(OMe)$ requires: C, 67·75; H, 4·39; OMe, 10·91%).

Methylation of this isoflavone gave the known 6,7,4′-trimethoxy-isoflavone, m.p. 174–175°.[16]