

SYNTHESIS OF IRIGENIN AND OF TECTORIGENIN, DERIVATIVES
OF 5,7-DIHYDROXY-6-METHOXYISOFLAVONE

W. Baker, D. F. Downing, A. J. Floyd, B. Gilbert,
W. D. Ollis and R. C. Russell

University of Bristol

(Received 2 February 1960)

OF the twenty-one known natural isoflavones,¹ three, tectorigenin, irigenin, and caviunin, are derivatives of 5,7-dihydroxy-6-methoxyisoflavone. This particular orientation of substituents makes a direct synthesis difficult, but a method, which we believe to be general, for the synthesis of such isoflavones is now described in the cases of tectorigenin and irigenin. Tectorigenin has previously been synthesised,² but it is of interest to note that irigenin, although it

¹ W. K. Warburton, Quart. Rev. 8, 67 (1954).
K. Venkataraman, Fortschritte der Chem. Org. Nat. 17, 1 (1959).

² S. A. Kagal, S. S. Karmarkar and K. Venkataraman, Proc. Ind. Acad. Sci. 44A, 36 (1956).
L. Farkas, Private communication. Chem. Ber. forthcoming publication.

was the first natural isoflavone to be isolated (in 1893)³ and its structure was established in 1928,⁴ has not hitherto been synthesised.

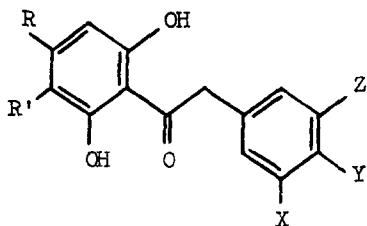
The main problem in the synthesis of 5,7-dihydroxy-6-methoxyisoflavones (II; R = OH, R' = OMe) from the appropriate deoxybenzoin (I; R = OH, R' = OMe) is that reactions leading to the formation of the heterocyclic ring could give either 5,7-dihydroxy-6-methoxyisoflavones (II; R = OH, R' = OMe) or 5,7-dihydroxy-8-methoxyisoflavones (III; R = OH, R' = OMe). In fact in our first attempt⁵ to synthesise tectorigenin (II; R = Y = OH, R' = OMe, X = Z = H), we believed that it had failed because the reaction of the deoxybenzoin (I; R = Y = OH, R' = OMe, X = Z = H) with ethoxalyl chloride had apparently yielded only one product which on hydrolysis and decarboxylation gave an isomer of tectorigenin, Ψ -tectorigenin (III; R = Y = OH, R' = OMe, X = Z = H). However, when the deoxybenzoin (I; R = X = OH, R' = Y = Z = OMe) was treated with ethoxalyl chloride, two isomeric products were formed.⁶ This observation led to the following synthesis of irigenin.

³ G. de Laire and F. Tiemann, Ber. 26, 2010 (1893).

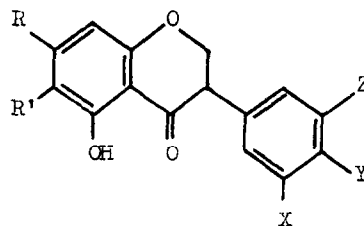
⁴ W. Baker, J. Chem. Soc. 1022 (1928). S

⁵ W. Baker, I. Dunstan, J. B. Harborne, W. D. Ollis and R. Winter, Chem. and Ind. 277 (1953).

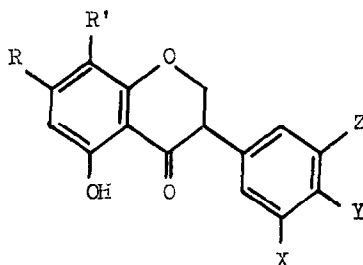
⁶ W. Baker and W. D. Ollis, Sci. Proc. Roy. Dublin Soc. 27, No. 6 119 (1956).



(I)



(II)



(III)

Iridonitrile* and iretol (Hoesch reaction) yielded the deoxybenzoin (I; $R = X = \text{OH}$, $R' = Y = Z = \text{OMe}$), m.p. $190-191^\circ$, which was identical with the deoxybenzoin obtained from monobenzylirigenin in the following manner. Monobenzylirigenin (II; $R = \text{Ph}\cdot\text{CH}_2\text{O}$, $R' = X = Y = \text{OMe}$, $Z = \text{OH}$, m.p. $174-175^\circ$, diacetate, m.p. 182°) was hydrolysed to the monobenzyl-deoxybenzoin (I; $R = \text{Ph}\cdot\text{CH}_2\text{O}$, $R' = X = Y = \text{OMe}$, $Z = \text{OH}$, m.p. $133-134^\circ$) then debenzylated (Pd-H_2 -ethanol). This deoxybenzoin

(I; R = X = OH, R' = Y = Z = OMe) and ethoxalyl chloride-pyridine⁷ yielded a mixture of the two possible 2-carbethoxyisoflavones (cf. II and III), since mild alkaline hydrolysis of the product and decarboxylation gave a mixture of irigenin (II; R = X = OH, R' = Y = Z = OMe) and ψ -irigenin (III; R = X = OH, R' = Y = Z = OMe). These were separated by chromatography on thick paper (Whatman No. 1 paper; solvent: benzene, acetic acid, formic acid, water - 8, 2, 1, 1 by volume). The synthetic irigenin, m.p. 190.5-191.5° (from chloroform), m.p. 185-186° (from aqueous ethanol), was identical with the natural product; the isomeric ψ -irigenin m.p. 158.5-159.5°, was characterised as its triacetate, m.p. 146.5-147°.

This successful synthesis of irigenin caused us to re-investigate the reaction carried out earlier⁵ which was designed to yield tectorigenin. By analogous methods it was shown that the deoxybenzoin (I; R = Y = OH, R' = OMe, X = Z = H) and ethoxalyl chloride do in fact give two products which have yielded tectorigenin (II; R = Y = OH, R' = OMe, X = Z = H), m.p. 228-230° and ψ -tectorigenin (III; R = Y = OH, R' = OMe, X = Z = H), m.p. 244-246°. This constitutes a new synthesis of natural tectorigenin.

These results disprove our earlier generalisation⁵ that ethoxalylolation of deoxybenzoin of the type (I) yield 2-carbethoxyisoflavones (cf. III) with a 5,7,8-orientation of substituents. This reaction in fact leads to a mixture of products (cf. II and III) whose composition is certainly

⁷ W. Baker and W. D. Ollis, Nature 169, 706 (1952).

W. Baker, J. Chadderton, J. B. Harborne and W. D. Ollis, J. Chem. Soc. 1852 (1953).

kinetically controlled. In some other ethoxalylations which we have carried out⁸ [e.g. reaction of (I; R = R' = OMe, X = Y = Z = H) or (I; R = R' = Y = OMe, X = Z = H) with ethoxalyl chloride], the products isolated had the 5,6,7-orientation (cf. II), but the yields were lower than is usual in this reaction.

A new isoflavone, caviunin, was recently isolated by Drs. O. R. Gottlieb and M. T. Magalhaes from Dalbergia nigra.⁹ It was shown to be 5,7-dihydroxy-6,2',4',5'-tetramethoxyisoflavone and its synthesis by the ethoxalylations method is being studied.

⁸ I. Dunstan, Dissertation, Bristol (1954).
C. J. Brown, Dissertation, Bristol (1954).

⁹ Private communication. We thank Dr. Gottlieb and Dr. Magalhaes for this information.

* Iridonitrile (3-hydroxy-4,5-dimethoxybenzyl cyanide) was synthesised by the following method (B. Gilbert, Dissertation, Bristol 1954). Methyl 3-hydroxy-4,5-dimethoxybenzoate was successively benzylated, reduced (LiAlH₄), and treated with thionyl chloride to give 3-benzyloxy-4,5-dimethoxybenzyl chloride; reaction with potassium cyanide and final debenylation (Pd - H₂ - EtOH) gave iridonitrile (an oil giving a benzoate, m.p. 103°).