The Synthesis of 4′, 5, 7-Trihydroxy-8-methoxyisoflavone

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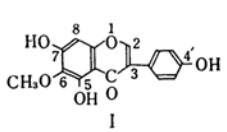
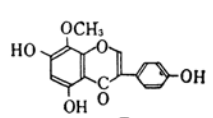
Tectorigenin[1] was isolated from *Iris tectorum Maxim* and the structure[2] of 4′, 5, 7-trihydroxy-6-methoxyisoflavone (I) was assigned to it, but it is not yet synthesized. We have been attempting the syntheses of this isoflavone and related compounds. The present paper describes the synthesis of 4′, 5, 7-trihydroxy-8-methoxyisoflavone (II), an isomer of tectorigenin. Although it was shown by W. Baker et al.[3] that 4′, 5, 7-trihydroxy-8-methoxyisoflavone (II) was obtained from 2, 4, 6-trihydroxy-3-methoxyphenyl 4-hydroxybenzyl ketone (IV) with the ethoxalylation process[4], their communication did not give any detailed description of the procedure or of the melting points of the compounds. It appeared of interest to investigate further W. Baker et al's method in detail for the following reason. If the direction of ring closure of the ketone (IV) was opposite to that observed by them, the possibility of the synthesis of tectorigenin might occur. So it seemed desirable to prepare 4′, 5, 7-trihydroxy-8-methoxy-isoflavone (II) by an unambiguous synthetic method for comparison with the isoflavone prepared with the ethoxalylation process. Specimens of the isoflavone prepared by two alternative methods (see Experimental) proved to be the same compound (II). The experiments described here established, therefore, the fact that 4′, 5, 7-trihydroxy-8-methoxyisoflavone (II) was obtained with the methoxalylation and the ethoxalylation process, the direction of ring closure being the same as that observed by W. Baker et al.[3].



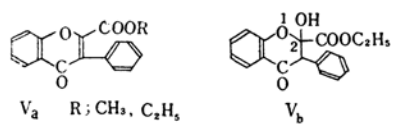
I



II

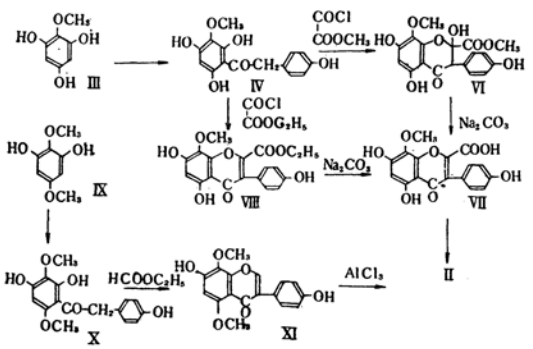
1) B. Shibata, *J. Pharm, Soc. Japan.* **47**, 380 (1927).
2) Y. Asahina, B. Shibata and Z. Ogawa, ibid., **48**, 1087 (1928).
3) W. Baker I. Dunstan, J. B. Harborne, W. D. Ollis and R. Winter, *Chem. and Ind.*, **1953**, 277.
4) W. Baker, J. Chadderton, J. B. Harborne and W. D. Ollis, *J. Chem. Soc.*, **1953**, 1852.

Iretol (III) when condensed with *p*-hydroxyphenylacetonitrile, gave 2, 4, 6-trihydroxy-3-methoxyphenyl 4-hydroxybenzyl ketone (IV), m. p. 220—1.5°. The ketone (IV) was treated at 0° with methoxalyl chloride in pyridine to give yellow crystals, m. p. 215—6.5°, which contained one molecule of water in excess of that required by the corresponding methyl isoflavone-2-carboxylate derivative (Va; R=CH_3). The cyclization of *o*-hydroxyphenyl benzyl ketones to isoflavone-2-carboxylic esters (Va; R=C_2H_5) with the ethoxalylation process was postulated as proceeding through the intermediates of type (Vb) which were isolated in some cases[4]. On the basis of this fact, it seemed reasonable to assume the structure of the yellow crystals to be methyl 2-hydroxyisoflavanone-2-carboxylate derivative (VI). This intermediate was converted into the corresponding isoflavone-2-carboxylic acid, m. p. 288—9° (VII) by mild alkaline hydrolysis and thence the acid was decarboxylated with copper powder in boiling quinoline to the isoflavone (II), m. p. 241—2°, in colorless needles, (its acetate, m. p. 167°). When the cyclization reaction was carried out with ethoxalyl chloride instead of methoxalyl chloride, the usual isoflavone-2-carboxylic ester, m. p. 219—20° (VIII), was obtained and it was converted into the acid (VII) by mild alkaline hydrolysis.



V_a R; CH_3, C_2H_5 V_b

2, 5-Dimethoxyresorcinol (IX) was condensed with *p*-hydroxyphenylacetonitrile by Hoesch reaction to give 2, 4-dihydroxy-3, 6-dimethoxyphenyl 4-hydroxybenzyl ketone (X), m. p. 98—9.5°. This ketone (X) was converted into 4', 7-dihydroxy-5, 8-dimethoxyisoflavone (XI) with ethyl formate in the presence of sodium. The action of aluminium chloride on XI in nitrobenzene caused partial demethylation (in the 5-position) without affecting the other methoxy group, and the demethylated product isolated was 4', 5, 7-trihydroxy-8-methoxyisoflavone, m. p. 238—9° (II). When this was mixed with the isoflavone which had been prepared with the methoxalylation and the ethoxalylation process, no melting point depression occured.



Experimental*

2, 4, 6-Trihydroxy-3-methoxyphenyl 4-hydroxybenzyl ketone (IV).—A solution of iretol (4.1 g.)[5] and *p*-hydroxyphenylacetonitrile (4.5 g.) in absolute ether (100 ml.) containing anhydrous zinc chloride (2 g.) was saturated at 0° with dry hydrogen chloride. After being kept over-night, the viscous oily layer was separated, washed twice with ether and hydrolyzed with water (150 ml.) on a steam-bath for an hour. The solid which was separated on cooling was purified from aqueous methanol to form the ketone (4.8 g.) in colorless needles. m. p. 220—1.5°, having a violet ferric reaction in alcohol.

Anal. Found: C, 62.43; H, 4.99. Calcd. for $C_{15}H_{14}O_6$: C, 62.07; H, 4.83%.

Methyl 2, 4', 5, 7-tetrahydroxy-8-methoxyisoflavanone-2-carboxylate (VI).—To a solution of 2, 4, 6-trihydroxy-3-methoxyphenyl 4-hydroxybenzyl ketone (2.4 g.) in pyridine (25 ml.), methoxalyl chloride (5.5 g.) was added drop by drop with stirring at 0°. After standing overnight, the mixture was poured into ice-water and extracted with chloroform. The chloroform solution was washed with dilute hydrochloric acid, dried over anhydrous sodium sulfate and evaporated. A part (0.3 g.) of the residue thus obtained was recrystallized from methanol. Yellow microcrystals, m. p. 215.5-6.5° were obtained.

Anal. Found: C, 57.49; H, 4.55. Calcd. for $C_{18}H_{16}O_9$: C, 57.45; H, 4.26%.

Alcoholic ferric chloride showed green color.

4', 5, 7-Trihydroxy-8-methoxyisoflavone-2-carboxylic acid (VII).—To a solution of the remaining crude ester (VI) in acetone (30 ml.), 3% aqueous sodium carbonate solution (30 ml.) was added, and the mixture was refluxed for four hours. Acetone being evaporated on a steam-bath, the solution was cooled by ice-water and filtered. The product was isolated by acidification of the filtrate with dilute hydrochloric acid. Upon purification from aqueous methanol it gave rise to 4', 5, 7-trihydroxy-8-methoxyisoflavone-2-carboxylic acid (1.1 g.) in orange yellow microcrystals, m. p. 288—9° (dec.), having a green ferric reaction in alcohol.

Anal. Found: C, 58.72; H, 3.82. Calcd. for $C_{17}H_{12}O_8$: C, 59.31; H, 3.51%.

* The melting points were uncorrected.

5) This was prepared from trinitroanisole by the analogous method to that used in the preparation of phloroglucinol. (H. T. Clarke and W. W. Hartman, *Organic Syntheses*, John Wiley and Sons, Inc., New York, 1932, Coll. Vol. I, p. 496).

Ethyl 4',5,7-trihydroxy-8-methoxyisoflavone-2-carboxylate (VIII) and the acid (VII)—Cyclization of 2,4,6-trihydroxy-3-methoxyphenyl 4-hydroxybenzyl ketone (1.7 g.) with ethoxalyl chloride (4.5 g.) in pyridine (25 ml.) in a similar way to that described before, followed by extraction with chloroform, gave rise to microcrystals of ethyl 4',5,7-trihydroxy-8-methoxyisoflavone-2-carboxylate, m. p. 219—20°.

Anal. Found: C, 61.22; H, 4.49. Calcd. for $C_{19}H_{16}O_8$: C, 61.29; H, 4.33%.

Hydrolysis of this ester in boiling acetone containing aqueous sodium carbonate solution gave rise to the free acid (0.8 g.) identical with the above sample.

2,4-Dihydroxy-3,6-dimethoxyphenyl 4-hydroxybenzyl ketone (X).—A solution of 2,5-dimethoxyresorcinol[6] (1.5 g.) and *p*-hydroxyphenylacetonitrile (1.2 g.) in absolute ether (50 ml.) containing anhydrous zinc chloride (0.5 g.) was saturated with hydrogen chloride at 0°. Isolation of the product in the usual way gave rise to the ketone (1.3 g.) which was purified from aqueous methanol in colorless needles, m.p. 98—9.5°, having a violet ferric reaction in alcohol.

Anal. Found: C, 62.70; H, 5.43. Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30%.

4',7-Dihydroxy-5,8-dimethoxyisoflavone (XI).—A solution of 2,4-dihydroxy-3,6-dimethoxyphenyl 4-hydroxybenzyl ketone (1 g.) in ethyl formate (20 ml.) was added drop by drop with stirring to a suspension of powdered sodium (1 g.) in ethyl formate (10 ml.) at −4° under nitrogen. The reaction mixture was allowed to stand overnight at 10°, and was decomposed by the addition of ice-water. Ethyl formate being removed in vacuo, the residual aqueous solution was acidified and warmed on a steam-bath. The precipitate was collected and recrystallized from methanol to 4',7-dihydroxy-5,8-dimethoxyisoflavone (0.2 g.) in colorless needles, m. p. 274—5°, having a negative ferric reaction in alcohol.

Anal. Found: C, 64.90; H, 4.65. Calcd. for $C_{17}H_{14}O_6$: C, 64.96; H, 4.49%.

4',5,7-Trihydroxy-8-methoxyisoflavone (II). Method (a).—A mixture of 4',5,7-trihydroxy-8-methoxyisoflavone-2-carboxylic acid (0.6 g.) and copper powder (0.6 g.) in quinoline (30 ml.) was heated with stirring under nitrogen for ten minutes at 230—40° (bath temperature). After cooling, the mixture was acidified with dilute hydrochloric acid and filtered. The filtrate was extracted with ether and the precipitate was also washed with ether. The combined ether solution was washed with dilute hydrochloric acid, with aqueous sodium carbonate solution, and finally with water. The ether solution being dried over sodium sulfate and evaporated, the residual product was purified from aqueous methanol and then ethyl acetate to 4',5,7-trihydroxy-8-methoxyisoflavone (0.1 g.) in colorles needles, m. p. 241—2°, having a green ferric reaction in alcohol.

Anal. Found: C, 63.97; H, 4.11. Calcd. for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03%.

Acetylation of this isoflavone by the acetic anhydride-pyridine method gave rise to its acetate which was purified from aqueous methanol in colorless needles, m. p. 167°, having a negative ferric reaction in alcohol.

Anal. Found: C, 62.36; H, 4.29. Calcd. for $C_{22}H_{18}O_9$: C, 61.97; H, 4.26%.

Method (b).—A mixture of 4',7-dihydroxy-5,8-dimethoxyisoflavone (0.1 g.) and aluminium chloride (0.2 g.) in nitrobenzene (10 ml.) was heated on a steam-bath for an hour. After cooling, ice-water was added and the nitrobenzene was removed by the steam distillation. The precipitate was filtered, and the unchanged substance (50 mg.) was recovered. By acidification of the filtrate with dilute hydrochloric acid, a crystalline precipitate, was separated. Purification from aqueous methanol gave 4',5,7-trihydroxy-8-methoxyisoflavone (30 mg.), colorless needles m. p. 238—9°. The mixed melting point with the product prepared by method (a) showed no depression.

Anal. Found: C, 63.56; H, 4.54. Calcd. for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03%.

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6) T. A. Geissman and T. G. Halsall, *J. Am. Chem. Soc.*, **73**, 1280 (1951).