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THE SYNTHESIS OF PENDULETIN

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Abstract—A total synthesis of penduletin was achieved, conclusively proving the proposed structure for this substance.

In a recent paper[1], the structure of penduletin, a natural product isolated as its glucoside Pendulin from *Brickelia pendula* (Schrad) A. Gray, was reported to be the 4′,5-dihydroxy-3,6,7-trimethoxyflavone. There was enough evidence in favor of this formula, but it was felt necessary to carry out a total synthesis to prove it conclusively.

It was possible to synthesize penduletin (scheme 1), by following, in essence, the steps described by Goldsworthy and Robinson[2] in their first effort to synthesize tangeretin. As described under "Experimental", the end product (XIII) proved to be identical with penduletin, by the mixed melting point and the infrared absorption curves, as well as by the comparison of the 5-hydroxy-3,6,7-trimethoxy-4′-benzyloxyflavone (XII) with the compound obtained by benzylation of penduletin. Both compounds had identical infrared spectra, the melting points were the same and the admixture did not depress it.

EXPERIMENTAL†

The sequence in the synthesis as shown in Scheme 1 was carried out, from (I) to (V), following the method of Goldsworthy and Robinson,[2] with the exception of (II) (4-nitroveratrole), which was obtained as described by Clark.[3]

4,6-*Diaminoveratrole* (VI). 4,6-Dinitroveratrole (V) (20 g) was dissolved in ethanol (600 ml) and was hydrogenated with 1 g of 5% palladium in charcoal as catalyst. There was an absorption of 16·8 l. of hydrogen at 585 mm and 20°. After removal of the catalyst by filtration, the solution was concentrated in an atmosphere of carbon dioxide under vacuum. The white crystalline residue (12 g) showed m.p. 106–107° and gave positive tests for the *m*-diamino grouping, with nitrous acid (dark red) and with ferric chloride (purple).

4,5-*Dimethoxyresorcinol* (VII). A mixture of 10 g of 4,6-diaminoveratrole (VI), 1·8 g of crystalline stannous chloride and 500 ml of water was heated in portions in sealed tubes at 120° during 48 hr. Hydrogen sulphide was bubbled through the confined reaction products to eliminate the metallic ions as sulphides, which were filtered. The filtrate was concentrated to 75 ml (under vacuum and carbon dioxide atmosphere) and extracted with chloroform. The organic extracts were evaporated

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† All melting points were determined with a Kofler block. The infrared spectra were determined, in Nujol, in a Perkin-Elmer model 21 double-beam spectrophotometer.

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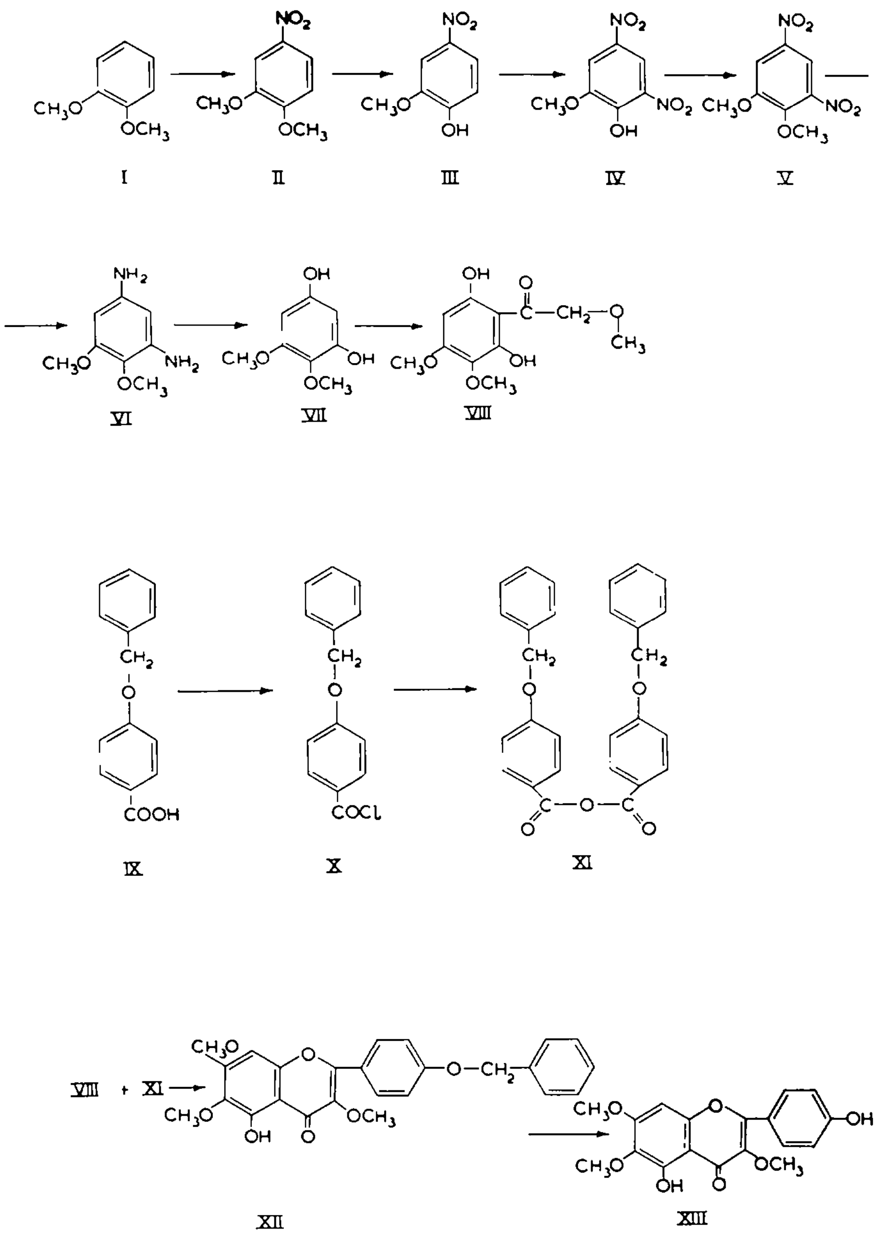
[1] S. E. Flores and J. Herrán, *Tetrahedron* 2, 308 (1958).

[2] L. J. Goldsworthy and R. Robinson, *J. Chem. Soc.* 46 (1937).

[3] E. P. Clark, *J. Amer. Chem. Soc.* 53, 3431 (1931).



Scheme I

to dryness and the residue was crystallized from a very small amount of water, affording 1 g of product with m.p. 76°. The melting point, after drying under vacuum, was raised to 115–116°.

By treating the aqueous phase with more stannous chloride and repeating the hydrolysis as described, it is possible to obtain more (VII).

2,6-Dihydroxy-ω-3,4-trimethoxyacetophenone (VIII). This compound was obtained as described by Goldsworthy and Robinson[2] from (VII), and its physical constants were as described by these authors.

p-*Benzyloxybenzoic anhydride* (XI). From *p*-hydroxybenzoic acid, the benzyl ether (IX) was prepared[4] and then the corresponding acid chloride[5] (X). The anhydride XI, which was prepared by the same method,[5] showed m.p. 118–119°.

5-*Hydroxy*-3,6,7-*trimethoxy*-4'-*benzyloxyflavone* (XII). The condensation of (VIII) with (XI) was carried out as described by Goldsworthy and Robinson,[2] but the product was purified by chromatography on Magnesol as described by Ice and Wender.[6] The product (XII) showed m.p. 132–134°. By benzylation of penduletin,[1] the same compound was obtained, and a mixture of them did not show a depression of the m.p. and the infrared spectra were identical.

4',5-*Dihydroxy*-3,6,7-*trimethoxyflavone* (*penduletin*) (XIII). The cleavage of the benzyl ether in order to obtain the desired end product was done as described by Heap and Robinson,[7] but the product was purified by chromatography on Magnesol. The product was proved to be identical with the natural penduletin[1] by the infrared spectrum and the melting point of the mixture.

[4] J. B. Cohen and H. W. Dudley, *J. Chem. Soc.* **97**, 1732 (1910).

[5] E. C. Horning, *Organic Syntheses* Coll. Vol. 3, p. 28. Wiley, New York (1955).

[6] C. H. Ice and S. H. Wender, *Analyt. Chem.* **24**, 1616 (1952).

[7] T. Heap and R. Robinson, *J. Chem. Soc.* 67 (1929).