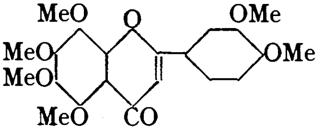
190. *Nobiletin. Part I.*

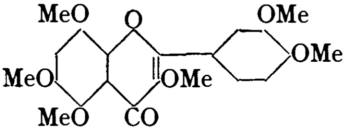
By Kwong-Fong Tseng.

An oil extracted by cold methyl alcohol from *Citrus nobilis*, Lour, affords nobiletin, a hexamethoxyflavone containing a veratryl nucleus.

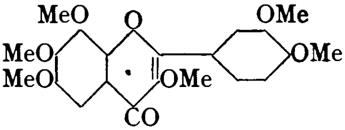
The author has already shown (Tseng and Yu, *J. Chinese Pharm. Assoc.*, 1936, **1**, 1) that the Chinese drug chen-pi (*Citrus nobilis*, Lour) from the province of Szechuen contains hesperidin, which was isolated in a crystalline condition by extraction of the drug with hot methyl alcohol (*cf.* Tiemann and Will, *Ber.*, 1881, **14**, 948, whose method has been improved). Much oily matter is recovered by a prior extraction with cold methyl alcohol and from this a new crystalline substance, $C_{21}H_{22}O_8$, has now been isolated. The reactions of this substance, which may be termed *nobiletin*, and the fact that its molecule contains six methoxyl groups characterise it as a hexamethoxyflavone, $C_{15}H_4O_2(OMe)_6$. It is similar in properties to, but not identical with, the known isomerides, namely, myricetin, gossypetin and quercetagetin hexamethyl ethers and thapsin dimethyl ether. Hydrolysis of nobiletin with alcoholic potassium hydroxide affords veratric acid, so the substance must correspond to one of the formulæ (I), (II), and (III).



(I.)



(II.)



(III.)

Tangeritin is a pentamethoxyflavone isolated by Nelson (*J. Amer. Chem. Soc.*, 1934, **56**, 1392) from *Citrus nobilis deliciosa*; it was shown by synthesis to be 3 : 5 : 6 : 7 : 4′-pentamethoxyflavone (Goldsworthy and Robinson, J., 1937, 46). The occurrence of different polymethoxyflavones in *Citrus* species is of interest, as it indicates the possession by the plant of a remarkably potent methylation mechanism.

EXPERIMENTAL.

Isolation and Properties of Nobiletin.—The dried peel (12 kg.) of the fruit obtained from Chunking in Western China was powdered and extracted in a percolator with about three times its weight of methyl alcohol, the process occupying about a week. The extraction was twice repeated and the combined extracts were concentrated to half-volume and treated with methanolic lead acetate. The precipitate contained chiefly derivatives of tannins and chlorophyll and the filtrate from it was de-leaded by means of hydrogen sulphide, filtered, and concentrated. The residue (*ca.* 5 kg.) was a red oil. This material (1 kg.) was triturated with ether, which extracted a yellowish-brown oil, and the less soluble residue was treated with methyl alcohol. It dissolved for the most part, but a colourless waxy solid remained and this was collected.

The methanolic solution was again treated with lead acetate exactly as before and the filtrate from lead sulphide was concentrated to a small bulk. On keeping in the ice-chest, an amorphous waxy solid separated. This was collected, and the filtrate concentrated further and chilled. Light yellow crystals (*ca.* 30 g.), m. p. 129—130°, separated and on recrystallisation from methyl alcohol the m. p. was raised to 134° (12 g.) [Found: C, 62·6; H, 5·5; MeO, 46·7, 46·0; *M* (Rast in camphor), 391. $C_{21}H_{22}O_8$ requires C, 62·7; H, 5·5; 6MeO, 46·3%; *M*, 402].

Nobiletin is readily soluble in ethyl acetate, chloroform, benzene, nitrobenzene and pyridine, moderately readily soluble in the simple alcohols, and very sparingly soluble in cold ether and water. It is insoluble in aqueous alkalis and gives no ferric reaction. It dissolves in concentrated mineral acids to intensely yellow solutions and the solution in sulphuric acid exhibits a weak green fluorescence. Addition of magnesium to its alcoholic hydrochloric acid solution causes the development of a red colour, obviously due to the formation of a flavylium salt. The substance is optically inactive and it does not reduce Fehling's solution.

Hydrolysis with Alcoholic Potash.—The method of Nelson (*loc. cit.*) was followed. A mixture of nobiletin (1 g.), alcohol (50 c.c.), and aqueous potassium hydroxide (50 c.c. of 20%) was refluxed for 6 hours and then concentrated to half its volume. After dilution with water (50 c.c.) the solution was saturated with carbon dioxide and extracted with ether (*A*; see following paper); the separated aqueous layer was acidified and extracted with ether. The residue from the solvent crystallised (m. p. 175°) and after recrystallisation from water the colourless needles had m. p. 179·5° and were identified as veratric acid (Found: C, 59·6; H, 5·5; MeO, 33·6. Calc. for $C_9H_{10}O_4$: C, 59·3; H, 5·5; 2MeO, 34·1%).

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