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## **191.** *Nobiletin. Part II.*

By ROBERT ROBINSON and KWONG-FONG TSENG.

Nobiletin, a hexamethoxyflavone occurring in the peel of the fruits of *Citrus nobilis*, Lour, is probably 5 : 6 : 7 : 8 : 3′ : 4′-*hexamethoxyflavone*.

NOBILETIN (previous paper) has been demethylated to a *hexahydroxyflavone*, which is converted into a *hydroxypentamethoxyflavone* by the action of diazomethane. Further methylation with regeneration of nobiletin could be effected by the method of Baker and Robinson (J., 1928, 3115).

The resistant hydroxyl is assumed from analogy to be that situated in position 5, ortho to the carbonyl of the flavone nucleus. This result excluded formula (III) of those figured in the foregoing paper. It was then found that acetoveratrone is one of the products of the hydrolysis of nobiletin by alcoholic potassium hydroxide. Therefore nobiletin is probably 5 : 6 : 7 : 8 : 3′ : 4′-*hexamethoxyflavone* (I of the foregoing paper). The synthesis of nobiletin is projected.

## EXPERIMENTAL.

*Hydrolysis of Nobiletin with Formation of Acetoveratrone.*—Nobiletin (3·2 g.) was hydrolysed by means of alcohol (100 c.c.) and aqueous potassium hydroxide (100 c.c. of 20%) at the b. p. for 4 hours. The ethereal solution (*A*; preceding paper) was evaporated, leaving an oil (1 g.) which could not be crystallised. It contained a phenolic substance (deep olive-green ferric reaction in alcoholic solution) and an attempt to prepare the oxime of this was made by Lapworth and Steele's method (J., 1911, **99**, 1884). The colourless crystalline oxime was recrystallised from water; m. p. 140°, alone or mixed with the oxime of acetoveratrone (Pictet and Gams, *Ber.*, 1909, **42**, 2947) (Found: C, 61·2; H, 6·6; N, 7·2. Calc. for $C_{10}H_{13}O_3N$: C, 61·4; H, 6·6; N, 7·2%).

5 : 6 : 7 : 8 : 3′ : 4′-*Hexahydroxyflavone.*—A mixture of nobiletin (0·2 g.), hydriodic acid (5 c.c., *d* 1·8), and phenol (3 g.) was heated (bath at 145°) for 3 hours in a current of carbon dioxide; a test then showed that methyl iodide was no longer being produced. On cooling, the heptahydroxyflavylium iodide separated in slender, yellow needles, which were collected on an alundum plate and washed with sulphurous acid and then with water. The free *hexahydroxyflavone* was crystallised from acetic acid containing a little alcohol by concentration of the solution on the steam-bath. The deep yellow needles had m. p. 310—314° (decomp.) after blackening at 290° (Found: C, 56·5; H, 3·5. $C_{15}H_{10}O_8$ requires C, 56·6; H, 3·2%). The substance is readily soluble in methyl alcohol, ethyl alcohol, ethyl acetate, and acetone, moderately readily soluble in ether, and sparingly soluble in cold acetic acid, water or light petroleum. Its solution in sulphuric acid is orange in colour, those in concentrated hydrochloric acid and in nitric acid are yellow. It is very sparingly soluble in cold aqueous sodium bicarbonate, but dissolves on heating to a yellow solution. In aqueous sodium carbonate, it dissolves in the cold to a brown solution; this turns reddish-brown in 15 minutes. In aqueous potassium hydroxide a red solution is first obtained and this becomes brownish-yellow on keeping.

Oxidation occurs readily in dilute solution; even a boiling suspension in water gradually acquires a blue colour. The behaviour with solutions prepared from the B.D.H. universal buffer was as follows: Suspended in a solution of $p_H$ 8·1, a light yellow solution was at once obtained; this became greenish-yellow after 5 minutes, yellowish-green after 10 minutes, green after 15 minutes, and deep green after 20 minutes. At $p_H$ 9·0 the colours at corresponding times were: yellow, greenish-yellow, yellowish-green, light green, light green. At $p_H$ 10·4 they were: bright yellow, greenish-yellow, greenish-yellow, brown, brown. At $p_H$ 11·0 they were: orange-yellow, orange-red, brownish-red, brownish-red, brownish-red. After 12 hours most of the colour disappeared in all cases.

The ferric reaction of the new hexahydroxyflavone in alcoholic solution is an olive-green coloration. Lead acetate gives a brown precipitate in alcoholic solution. The potassium salt deposited from a solution in alcoholic potassium hydroxide consists of yellow prisms; potassium acetate in alcoholic solution gives a brownish-red precipitate.

The substance is a good adjective dye; on mordanted cotton the following colours were observed: weak aluminium, dull brownish-yellow; strong aluminium, deep brownish-yellow; aluminium and iron, brownish-olive; strong iron, black; weak iron, olive-grey. The dyeings show a resemblance to those given by quercetagetin (Baker, Nodzu, and Robinson, J., 1929, 76).

The hexahydroxyflavone reduces silver nitrate in aqueous solution, giving a black precipitate and occasionally a pink coloration of the solution.

The *hexa-acetate*, prepared by the action of acetic anhydride and pyridine (bath at 145°) during 2 hours, crystallised from alcohol in silky needles, m. p. 226—228° (Found: C, 56·6; H, 3·9. $C_{27}H_{22}O_{14}$ requires C, 56·9; H, 3·8%). The *hexa-benzoate*, prepared by the pyridine–benzoyl chloride method, at first in the cold and later by gentle heating on the steam-bath, crystallised from alcohol in white needles, m. p. 235—236° (Found : C, 72·2; H, 3·7. $C_{57}H_{34}O_{14}$ requires C, 72·6; H, 3·6%).

5-*Hydroxy*-6 : 7 : 8 : 3′ : 4′-*pentamethoxyflavone*.—Owing to the ease with which the hexahydroxyflavone is oxidised in alkaline solution, methylation was carried out by the use of diazomethane. The gas (from 10 c.c. of nitrosomethylurethane) was introduced into a solution of the above hexahydroxyflavone (0·1 g.) in acetone (30 c.c.). The liquid assumed an orange and then a yellow colour and nitrogen was evolved. Next day the solution was concentrated by distillation and, on cooling, yellow needles, m. p. 138°, separated. The *substance* was recrystallised from methyl alcohol and the m. p. raised to 145° (Found : C, 61·7; H, 5·2. $C_{20}H_{20}O_8$ requires C, 61·8; H, 5·2%). The substance depressed the m. p. of nobiletin and an alcoholic solution developed an olive-green coloration on the addition of ferric chloride.

On treatment with methyl sulphate and 20% aqueous sodium hydroxide in the presence of acetone (Baker and Robinson, *loc. cit.*), nobiletin was produced, m. p. 132° alone or mixed with the natural product (Found : C, 62·4; H, 5·6%).

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY.

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