NUCLEAR OXIDATION IN THE FLAVONE SERIES

Part XI. A New Synthesis of Nobiletin

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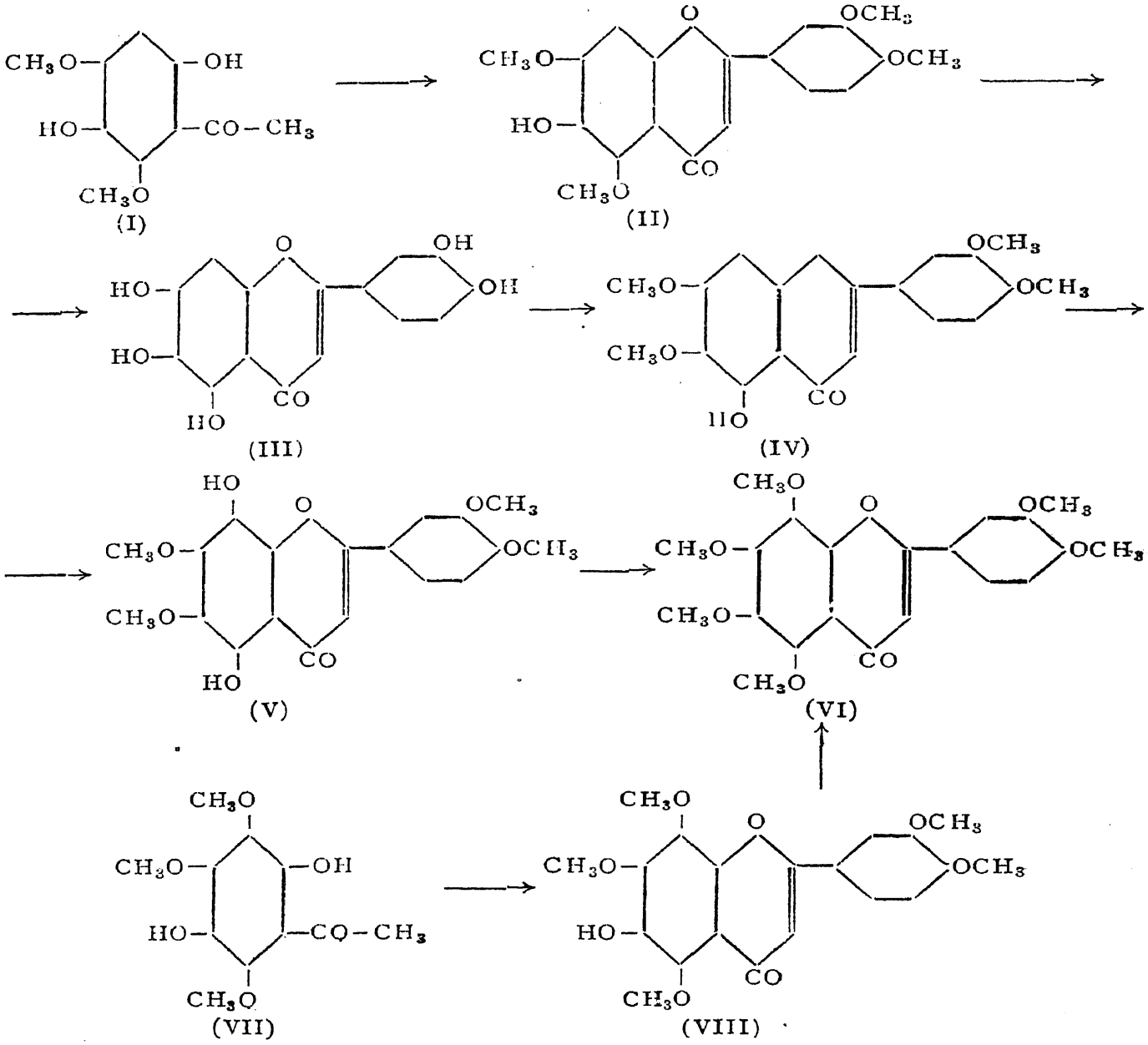
The experiments on nuclear oxidation in the flavone series published recently from this laboratory are important in three different respects. (1) They have effected considerable simplification in the synthesis of many of the flavones and flavonols; (2) the establishment of the constitution of flavone derivatives such as glycosides and methyl ethers has been rendered easier and more definite; (3) they serve as model experiments for schemes of biogenesis of the members of this group. In Part VII[1] the nuclear oxidation of baicalein and scutellarein leading to the preparation of 6:8-dihydroxy-chrysin and 6:8-dihydroxy-apigenin and their derivatives was described. But these compounds have not so far been found to occur in nature. The well-known representative of this group of flavones having hydroxyl groups in all the four positions 5:6:7:8, is nobiletin[2] which is the hexamethyl ether of 6:8-dihydroxyluteolin. It was first synthesised by Horii[3] starting from 2-hydroxy-3:4:5:6-tetramethoxy-acetophenone and adopting the Baker-Venkatraman method. The synthesis of nobiletin and nornobiletin using the method of nuclear oxidation is described in this paper.

For this synthesis 6-hydroxy-luteolin, a higher member of the baicalein series of flavones was required. It has not so far been described in the literature and has now been made by condensing 2:5-dihydroxy:4:6-dimethoxy acetophenone (I)[4] with the anhydride and sodium salt of veratric acid adopting the method of Allan and Robinson. This method which is so eminently successful in the synthesis of the flavonols offers some difficulties when applied to flavones and hence alternative methods like that of Baker and Venkatraman have been sought to be used. One of the main difficulties is acylation in the 3-position which is now realised to take place invariably in this condensation. But it is our experience that the 3-acyl group could be conveniently removed by boiling with aqueous sodium carbonate without complications from other decompositions. Using this extra step the method is capable of much wider use in the case of flavones also. In the particular example under consideration there was also partial demethylation in the 5-position leading to a mixture. Instead of attempting to

separate it, it was directly demethylated to yield 6-hydroxy-luteolin (III) which exhibits all the characteristic properties of the baicalein group of flavones.



As in other cases of nuclear oxidation, preliminary partial methylation of (III) was effected forming the 6 : 7 : 3′ : 4′-tetramethyl ether (IV) leaving the 5-hydroxyl free. Oxidation with alkaline persulphate proceeded smoothly and yielded the quinol (V). Subsequent methylation produced nobiletin (VI) and demethylation nor-nobiletin. These products had all the properties and reactions described in the literature.

As a check the synthesis of nobiletin starting from 2 : 5-dihydroxy-3 : 4 : 6-trimethoxyacetophenone (VII)[5] and condensing directly with sodium veratrate and veratric anhydride has also been carried out. Even here the

6-hydroxy-compound (VIII) could not be obtained pure due to partial demethylation in the course of the condensation. But fairly satisfactory yields of nobiletin could be obtained by methylating the mixture. This procedure appears to be more convenient than that adopted by Horii.[3]

Experimental

Condensation of 2 : 5-*Dihydroxy*-4 : 6-*dimethoxy-açetophenone* (I) *with veratric anhydride and sodium veratrate*

The ketone[4] (2 g.) was intimately mixed with veratric anhydride (10 g.) and sodium veratrate (3 g.) and heated in an oil-bath at 180° for 4 hours under vacuum. The hard mass was then broken up and refluxed with 10% alcoholic potash for half an hour. The alcohol was removed under reduced pressure, the residue dissolved in water and the reddish-brown solution saturated with carbon dioxide. The precipitated flavone was extracted with ether, the ether solution was dried over anhydrous sodium sulphate and the solvent distilled off. The bright yellow solid was boiled with 5% aqueous sodium carbonate for ½ hour to hydrolyse the 3-acyl group and then the clear solution acidified and the precipitate recrystallised from rectified spirit; yield, 0·7 g. It was found to have a melting point ranging from 190° to 206° and was therefore considered to be a mixture of the 6-hydroxy (II) and the 5 : 6-dihydroxy flavone derivatives; this was supported by its colour with ferric chloride. The mixture was used directly for demethylation. It dissolved in alkali to a bright yellow solution and gave a brown colour with ferric chloride in alcoholic solution.

5 : 6 : 7 : 3′ : 4′-*Pentahydroxy-flavone* (*III*)

The mixture of the 6-hydroxy and the 5 : 6-dihydroxy compounds obtained above (0·6 g.) was dissolved in acetic anhydride (15 c.c.) and to the solution was added hydriodic acid (d. 1·7; 15 c.c.) cautiously with cooling. The solution was refluxed gently for 1 hour and then diluted with aqueous sulphur dioxide solution. The precipitated hydroxy-flavone was filtered off and washed thoroughly with sulphur dioxide water and finally with water. It was dried and recrystallised from dry ethyl acetate when it was obtained as a bright yellow solid appearing as yellow rectangular plates under the microscope and melting at 315° with decomposition. Yield 0·4 g. (Found: C, 59·2; H, 3·6; $C_{15}H_{10}O_7$ requires C, 59·6 and H, 3·3%.)

The pentahydroxy flavone gave with ferric chloride a brown colour in alcoholic solution. With sodium bicarbonate solution the compound quickly dissolved giving a transient green colour to the solution which rapidly changed into brown. With aqueous sodium carbonate and sodium hydroxide, it

gave brown solutions. The compound responded to Bargellini's test; there was an immediate precipitation of green flocks on adding sodium amalgam to an alcoholic solution, the solution itself remaining yellowish-brown.

5-Hydroxy-6 : 7 : 3′ : 4′-tetramethoxy-flavone (IV)

The above pentahydroxy-flavone (0·6 g.) was dissolved in anhydrous acetone (50 c.c.) and to the solution were added redistilled dimethyl sulphate (1·2 c.c.) and freshly ignited potassium carbonate (6 g.). The mixture was refluxed on a water-bath for a period of 6 hours at the end of which the solution was filtered and evaporated. The 5-hydroxy compound was obtained as a yellow solid and was purified by recrystallisation from rectified spirit; yield 0·4 g. It appeared as yellow rectangular prisms and rods under the microscope and melted at 223–4°. (Found: C, 63·3; H, 5·2; $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·0%). The substance dissolves to a bright yellow solution in sodium hydroxide and gives a brown colour with ferric chloride in alcoholic solution.

5 : 6 : 7 : 3′ : 4′-Pentamethoxy-flavone

The mixture of the compounds obtained from the Allan-Robinson condensation (0·2 g.) was methylated with dimethyl sulphate (0·5 c.c.) and anhydrous potassium carbonate (2 g.) in anhydrous acetone medium by refluxing for 30 hours. The acetone solution was then filtered and evaporated and the colourless solid was purified by recrystallisation from rectified spirit when it appeared as colourless long rectangular plates and needles and melted at 142–3°. Yield 0·1 g. (Found: C, 63·1; H, 5·8; $C_{20}H_{20}O_7$, $\frac{1}{2}$ H_2O requires C, 63·0; H, 5·5%.)

It gave bright yellow solutions with concentrated hydrochloric and sulphuric acids and developed a red colour on reduction with magnesium powder and hydrochloric acid in an alcoholic solution.

5 : 8-Dihydroxy-6 : 7 : 3′ : 4′-tetramethoxy-flavone (V)

To a stirred solution of 5-hydroxy-6 : 7 : 3′ : 4′-tetramethoxy-flavone (IV) (0·5 g.) dissolved in a mixture of pyridine (10 c.c.) and aqueous sodium hydroxide (2 g. in 20 c.c. of water) was added a solution of potassium persulphate (2 g. in 50 c.c. of water) during a period of 2 hours. The mixture was stirred for another hour more and the deep red solution was allowed to stand for 24 hours. It was then just acidified with hydrochloric acid and the unreacted 5-hydroxy compound filtered and the last traces removed by extracting the filtrate with ether. 15 c.c. of strong hydrochloric acid was then added to the aqueous solution and heated in a boiling water-bath for $\frac{1}{2}$ hour. After cooling, the solution was extracted repeatedly with ether and the

ether solution dried over anhydrous sodium sulphate and the solvent distilled off. The orange yellow solid recrystallised from alcohol when it was obtained as golden yellow broad rectangular plates melting at 212–13°. Yield 0·2 g. (Found: C, 61·2; H, 5·1; $C_{19}H_{18}O_8$ requires C, 60·9 and H, 4·8%).

The compound dissolves to an orange red solution in sodium hydroxide; it gives a deep brown-red colour with ferric chloride in alcoholic solution and the colour becomes darker on adding excess of the reagent.

5:6:7:8:3′:4′-*Hexamethoxy-flavone* (*Nobiletin*) (*VI*)

The above 5:8-dihydroxy-compound (0·2 g.) was methylated with redistilled dimethyl sulphate (1·0 c.c.) and anhydrous potassium carbonate (2 g.) in dry acetone solution by refluxing for a period of 30 hours. The acetone solution was filtered off and the inorganic salts washed with a little acetone. On distilling off the solvent a pale yellow solid was obtained which was recrystallised from dry ethyl acetate. Nobiletin was obtained as pale yellow elongated rectangular prisms and needles melting sharp at 129–30°. (Found: C, 62·6; H, 5·4; $C_{21}H_{22}O_8$ requires C, 62·7 and H, 5·5%.)

The synthetic compound had all the properties of the natural specimen as described by Robinson and Tseng.[2] The mixed melting point with the compound obtained by the Allan-Robinson method (described later) was undepressed.

Nornobiletin

Nobiletin (0·2 g.) was dissolved in acetic anhydride (4 c.c.) and cautiously treated with hydriodic acid (4 c.c., d., 1·7) with cooling. The dark red solution was refluxed for 30 minutes at 145° (oil-bath) and then poured into ice-water. The liberated iodine was decomposed by means of sulphur dioxide and the precipitated hydroxy-flavone filtered and dried. It was recrystallised from a large excess of absolute alcohol when nornobiletin was obtained as deep yellow rectangular prisms, melting with decomposition at 310–12°. Yield 0·12 g. The compound was also soluble in boiling ethyl acetate and gave all the colour reactions recorded in the literature.[2]

Condensation of 2:5-*dihydroxy*-3:4:6-*trimethoxy acetophenone with veratric anhydride and sodium veratrate*

A mixture of the ketone[5] (2 g.), veratric anhydride (10 g.) and sodium veratrate (4 g.) was heated in an oil-bath at 180° for 4 hours under vacuum. At the end of this operation, the solid was suspended in alcohol (50 c.c.) and refluxed for 30 minutes after the addition of an alcoholic solution of potassium hydroxide (4 g. in 10 c.c.). The alcohol was removed under

reduced pressure, the residue dissolved in water and filtered. The filtrate was saturated with carbon dioxide and the precipitated flavone extracted with ether. After the removal of the ether, a yellow oil was obtained which did not solidify even after it was kept in the ice-box for 2 days. It was then boiled with 5% aqueous sodium carbonate for ½ hour. Even then the product did not turn into a solid. It gave a brownish-green colour with an alcoholic solution of ferric chloride and seemed to be a mixture containing some partially demethylated product (5: 6-dihydroxy-compound) also. It was therefore directly used for methylation.

5: 6: 7: 8: 3′: 4′-*Hexamethoxy-flavone* (*Nobiletin*) (*VI*)

A solution of the above product in dry acetone (30 c.c.) was treated with dimethyl sulphate (1 c.c.) and anhydrous potassium carbonate (5 g.). The mixture was refluxed on a water-bath for 20 hours and at the end of this period the acetone solution was filtered off and the residue washed with hot acetone. On removal of the solvent, a yellow oil was obtained which soon solidified to a pale yellow solid. Purification was effected by recrystallisation from ethyl acetate when nobiletin was obtained as pale yellow rectangular prisms melting sharp at 130–31°. It did not dissolve in alkali and gave no colour with alcoholic ferric chloride. The mixed melting point with the sample obtained by the method of nuclear oxidation was not depressed.

Summary

Nobiletin has been synthesised by adopting the method of nuclear oxidation of the flavone skeleton. For this purpose 6-hydroxyluteolin has been prepared for the first time and subjected to partial methylation, oxidation and final methylation successively whereby nobiletin is obtained. Demethylation of this yields nornobiletin having all the properties described in the literature. Nobiletin has also been prepared independently from 2: 5-dihydroxy-3: 4: 6-trimethoxy-acetophenone by condensation with sodium veratrate and veratric anhydride and subsequent methylation.

References

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