NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XXVIII. Synthesis of 6-Hydroxy Primetin

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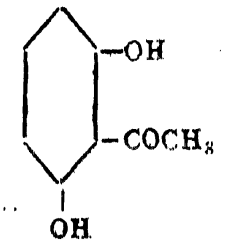
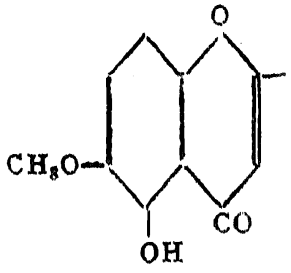
SINCE it has now been definitely established that gardenin is a flavonol having the rare 5:6:8- arrangement of hydroxyls in the condensed benzene ring,[1] analogous flavones could also be expected to be discovered in nature. For their synthesis, a procedure similar to the one adopted for the total synthesis of 5:6:8-trihydroxy flavonol[1] (6-hydroxy galangin) could be followed. This would start from γ-resacetophenone (I) and pass through the 6-methoxy-5-hydroxy compounds (II),[2] but as it involves a large number of steps, it may be considered to be tedious and inconvenient.

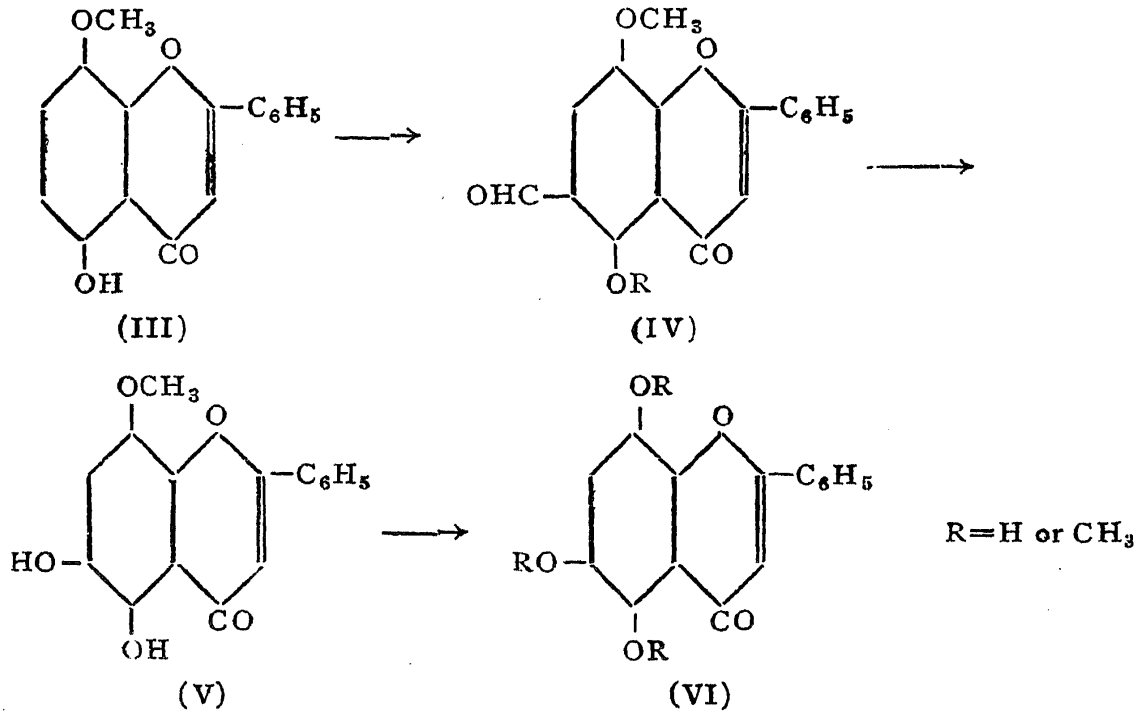


(I)

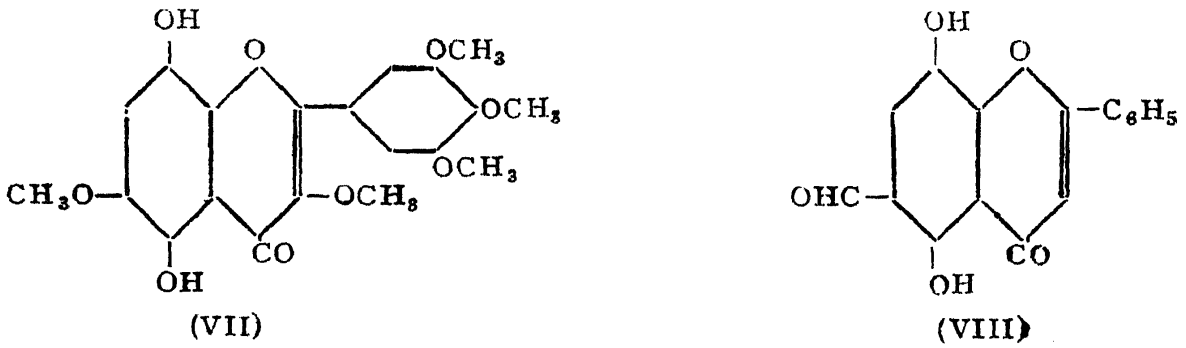


(II)

A new and more direct route involving the two stage process of nuclear oxidation[3] has now been explored and successfully worked out. It has been rendered possible by the simplified synthesis of primetin, described by Rajagopalan, Rao and Seshadri.[4] In this, primetin is partially methylated to 5-hydroxy-8-methoxy flavone (III). On being condensed with hexamine in glacial acetic acid solution, it yields the 6-aldehyde (IV) in 80% yield. That the 6-position is activated by the 5-hydroxyl in this reaction has been shown in a closely related case by Murti and Seshadri.[5] The above aldehyde (IV) is easily oxidised to 5:6-dihydroxy-8-methoxy flavone (V) by means of alkaline hydrogen peroxide. The colour reactions of this product are in agreement with the given structure. It is demethylated with hydriodic acid to 6-hydroxy primetin (VI, R = H) and also methylated to yield 5:6:8-trimethoxy flavone (VI, R = CH_3).



A shorter route for the synthesis of 6-hydroxy primetin seemed to be possible. In a test experiment, it was noticed that gardenin quinol (VII)[1] did not yield any product on treatment with hexamine. Hence it appeared that the 8-hydroxyl group does not activate the 7-position adequately. On the other hand, it had been established that the 6-position is activated by the 5-hydroxyl group quite satisfactorily. Therefore, if primetin itself could be condensed with hexamine, it would yield the 6-aldehyde (VIII), which could be directly oxidised to 6-hydroxy primetin. However, the reaction was not found to proceed well and the aldehyde was obtained in an impure condition and in a poor yield and hence the scheme had to be abandoned.



Experimental

5-Hydroxy-8-methoxy flavone (III).—This was first prepared by Nagai and Hattori[6] by methylation of primetin with diazomethane. Baker[7] obtained it by the partial demethylation of 5:8-dimethoxy flavone. The partial methylation of primetin has now been carried out very satisfactorily using dimethyl sulphate in dry acetone medium.

Primetin (1·0 g.) dissolved in acetone (100 c.c.) was treated with freshly distilled dimethyl sulphate (0·45 c.c.) and potassium carbonate (5·0 g.) and refluxed for 6 hours. The potassium salts were filtered off and washed with warm acetone. The solvent was distilled off and the residue treated with a small quantity of alcohol and filtered. The solid thus obtained when crystallised from alcohol, yielded 5-hydroxy-8-methoxy flavone as thin yellow needles melting at 210°. It gave an intense bluish green colour with alcoholic ferric chloride. Yield 0·7 g.

5-*Hydroxy*-8-*methoxyflavone*-6-*aldehyde* (*IV*).—The above compound (0·6 g.) in glacial acetic acid (20 c.c.) was heated with hexamine (2·0 g.) for 6 hours in a boiling water-bath. The hot solution was treated with hot hydrochloric acid (1 : 1, 20 c.c.), cooled and diluted with water. The yellow solid that separated was filtered and washed with water. Crystallisation from alcohol-acetic acid mixture yielded the aldehyde as very fine yellow needles melting at 246–47°. It gave a bluish green colour with alcoholic ferric chloride. It was sparingly soluble in ethyl acetate, alcohol, benzene and acetone. Yield 0·5 g. (Found: C, 68·7, H, 4·3; $C_{17}H_{12}O_5$ requires C, 68·9; H, 4·1%).

The 2 : 4-dinitrophenyl hydrazone, prepared by refluxing an alcoholic solution of the aldehyde with dinitro-phenylhydrazine melted at 320° (decomp.).

5 : 6-*Dihydroxy*-8-*methoxy flavone* (*V*).—The above aldehyde (0·5 g.) was dissolved in pyridine (20 c.c.) and sodium hydroxide (2·1 c.c. of 1 N; 1·2 mole) was added. The solution was cooled in ice and treated with 6% hydrogen peroxide (3 c.c.), added drop by drop, with shaking. The flask was corked and left at room temperature for 2 hours. The solution was neutralised with ice-cold dilute hydrochloric acid. The solid obtained was filtered and crystallised from alcohol. 5 : 6-Dihydroxy-8-methoxy flavone separated as orange-yellow fine needles melting at 184–85°. With alcoholic ferric chloride, it gave a green colour which slowly changed to brown. It dissolved in aqueous sodium hydroxide to give a pale yellow solution. (Found: C, 67·4; H, 4·2; $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·2%).

5 : 6 : 8-*Trihydroxy flavone* (6-*Hydroxy primetin*) (*VI*, $R = H$).—5 : 6-Dihydroxy-8-methoxy flavone (0·3 g.) was dissolved in acetic anhydride (5 c.c.) and treated with hydriodic acid (10 c.c., d. 1·7) with cooling. The solution was heated in an oil-bath at 140° for one hour. The resulting product was diluted with water saturated with sulphur dioxide, when a yellow solid separated out. This was filtered and crystallised from dilute alcohol, when it separated as pale yellow short needles melting at 236–37°.

With alcoholic ferric chloride, it gave a brown colour. The colour deepened considerably with further addition of the reagent. In aqueous sodium hydroxide it formed a deep red solution, rapidly changing to brown pink, which slowly faded to brownish yellow and finally yellow. It dissolved in aqueous sodium carbonate to give a deep violet-brown solution fading slowly to yellow. It was partially soluble in aqueous sodium bicarbonate to give a pale brown colour. (Found: C, 66·9; H, 4·0; $C_{15}H_{10}O_5$ requires C, 66·7; H, 3·7%).

5:6:8-*Triacetoxy flavone*.—The trihydroxy flavone (0·1 g.) was dissolved in acetic anhydride (8 c.c.) and treated with a few drops of dry pyridine and refluxed for 2 hours in an oil-bath. The reaction product was poured into water containing pieces of ice. The colourless solid was filtered and crystallised from ethyl acetate. The triacetoxy flavone came out as thin rectangular plates melting at 214°. (Found: C, 63·7; H, 4·3; $C_{21}H_{16}O_8$ requires C, 63·6; H, 4·0%).

5:6:8-*Trimethoxy flavone* (*VI*, $R = CH_3$).—5:6-Dihydroxy-8-methoxy flavone (V) (0·2 g) in acetone (50 c.c.) was refluxed with dimethyl sulphate (0·3 c.c.) and anhydrous potassium carbonate (2·0 g.) for 20 hours. The potassium salts were filtered off and washed with warm acetone. On distilling off the solvent from the filtrate and adding water, a crystalline solid separated out. When crystallised from very dilute alcohol, the trimethoxy flavone separated as thin colourless plates melting at 158–59°. (Found: C, 69·0; H, 5·4; $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·1%).

Summary

For the synthesis of 5:6:8-trihydroxy flavone (6-hydroxy primetin), the two stage ortho-oxidation process is applied to primetin monomethyl ether. A good yield of the 6-aldehyde is obtained, which undergoes oxidation to 5:6-dihydroxy-8-methoxy flavone. Subsequent demethylation yields 6-hydroxy primetin. Its properties and reactions and derivatives are described.

References

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6. Nagai and Hattori .. *Acta Phytochim.*, 1930, **5**, 1.
7. Baker .. *J. C. S.*, 1939, 1922.