5:6:7:8-HYDROXYFLAVONOLS

Part III.A Simplified Synthesis

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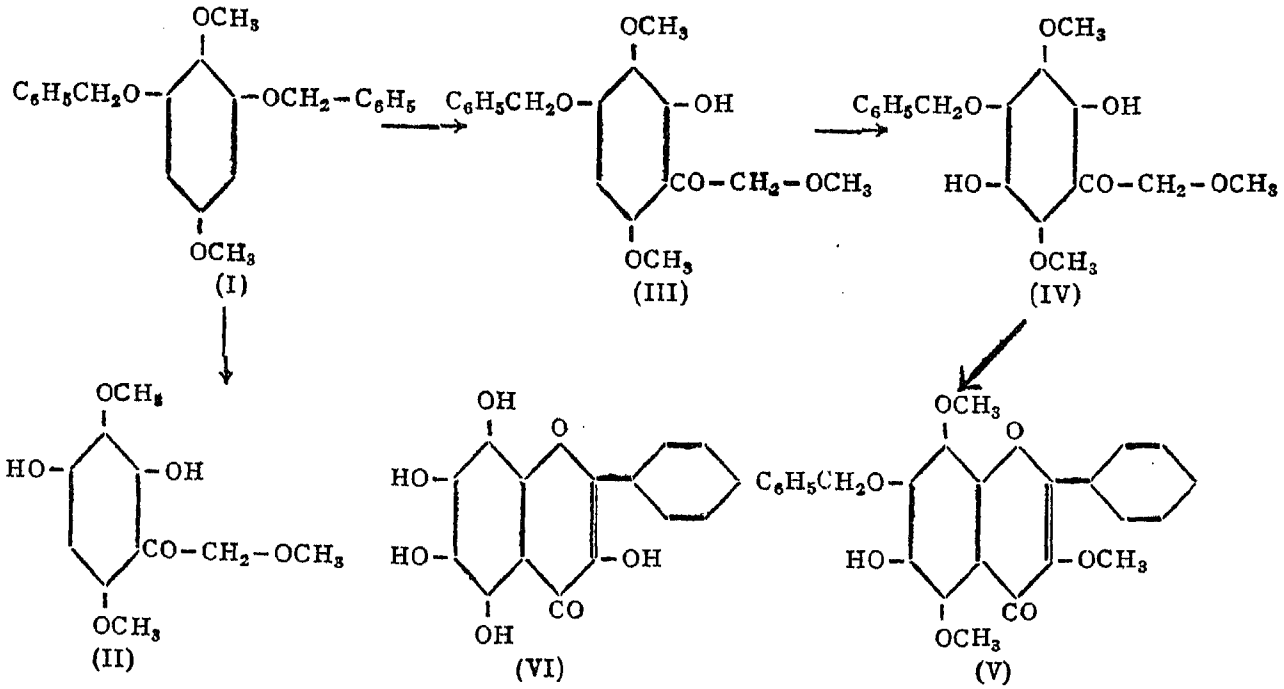
A method of total synthesis of these highly hydroxylated flavonols and their derivatives was described in Part II.[1] As an intermediate stage compounds with the 6-hydroxyl free and the others methylated could be obtained. By suitable choice of the acid component used for the Allan-Robinson condensation and by partial demethylation of the product it is possible to have further free hydroxyl groups in the 3 and 5 positions and also in the side phenyl nucleus. Since these flavonols occur mostly as partial methyl ethers, methods of preparing such ethers become important. A method of total synthesis which is simpler and which further offers possibilities of having the hydroxyl in the 7-position free has now been successfully investigated and the results are presented in this paper.

In the preparation of 2:4-dihydroxy-ω:3:6-trimethoxy-acetophenone (II), the Hoesch condensation with the dibenzyloxydimethoxybenzene (I) gave rise to a by-product[2] which varied in amount depending on the conditions employed. This substance is now shown to be 2-hydroxy-ω:3:6 trimethoxy-4-benzyloxyacetophenone (III). It is possible by a suitable adjustment of the experimental conditions (using excess of ether and a shorter period of condensation) to effect only the debenzylation of the benzyloxy group ortho to the carbonyl and obtain the derivative (III) as the major product of the reaction. Its constitution is definite, as it yields on further debenzylation in the usual manner the 2:4-dihydroxy-acetophenone (II) from which it differs in regard to its solubility in water and aqueous sodium carbonate. The use of this benzyl ether (III) obviates the necessity for partial methylation as in the case of the 2:4-dihydroxyacetophenone (II) and by oxidation with potassium persulphate in alkaline solution, the pentahydroxybenzene derivative 2:5-dihydroxy-ω:3:6-trimethoxy-4-benzyloxyacetophenone (IV) is obtained from it in moderately good yields. This constitution for the dihydroxyacetophenone is supported by analogy with compounds obtained in a similar manner. Further, there is only one available position for the new hydroxyl group to enter

and the persulphate oxidation of phenolic compounds is known to yield always the corresponding quinol derivatives provided the necessary para position is free.



When condensed with benzoic anhydride and sodium benzoate according to the method of Allan and Robinson the acetophenone (IV) yielded the corresponding 6-hydroxyflavonol derivative (V). This compound dissolved in aqueous alkali with an yellow colour and gave no characteristic ferric reaction; in these properties it closely resembled similar flavone derivatives having the 6-hydroxyl alone free.[1] On demethylation it yielded the pentahydroxyflavonol, 6 : 8-dihydroxy galangin (VI) whose identity was confirmed by comparison with a sample obtained by other methods[1, 3] and also by the preparation of the acetate.

The synthesis of the flavonols of this group can thus be effected in a fewer number of stages and in fairly good yields. Further by the debenzylation of the 6-hydroxyflavonol derivatives (V), it is possible to get the 6 : 7-dihydroxy compounds. Again by adopting known methods of methylation and partial demethylation several partial methyl ethers of this group of flavonols could be obtained.

Experimental

2-Hydroxy-ω : 3 : 6-trimethoxy-4-benzyloxyacetophenone (III).—

1 : 4-Dimethoxy-2 : 6-dibenzyloxybenzene (5 g.) was brought into complete solution in enough dry ether and methoxyacetonitrile (4 c.c.) and finely

powdered fused zinc chloride (1 g.) were added. A rapid stream of dry hydrogen chloride was passed through the solution which was cooled by means of ice-salt mixture. In about an hour, the ketimine hydrochloride separated as an orange-red crystalline crust and the hydrogen chloride gas was passed for further two hours. The container was then corked tight and left in the refrigerator for 24 hours. The supernatant ether solution was decanted off and the crystalline solid washed thrice with 20 c.c. portions of dry ether. Water (100 c.c.) was then added while cooling the flask under the tap and the hydrolysis effected by heating the mixture on the water-bath at 60–70° for half an hour with frequent stirring. The ketimine hydrochloride gradually went into solution with the simultaneous separation of a pale yellow crystalline solid. Unless the hydrolysis was carefully conducted the product was a deep-brown semi-solid which did not easily solidify. After cooling, the solid was filtered, washed and crystallised twice from dilute alcohol using a little animal charcoal. Yield, 1·5 g. After a third crystallisation from the same solvent, 2-hydroxy-ω: 3: 6-trimethoxy-4-benzyloxyacetophenone was obtained as narrow rectangular plates and prisms and it melted at 109–110°. It was very sparingly soluble in hot water and dissolved in 10% aqueous sodium hydroxide from which a sparingly soluble sodium salt separated. Its solution in alcohol developed a brown-pink colouration with ferric chloride. (Found: C, 65·2; H, 6·3. $C_{18}H_{20}O_6$ requires C, 65·1; H. 6·0%).

Debenzylation.—

The foregoing benzyl ether (0·5 g.) was dissolved in glacial acetic acid (4 c.c.) and after the addition of hydrochloric acid (d, 1·16; 2 c.c.) the solution was heated on the boiling water-bath for one hour. Water (50 c.c.) was then added and the solution extracted twice with ether. The ether solution was washed with water and the solid obtained after removal of the solvent was crystallised from hot water. It was obtained as long colourless needles and melted at 149–150°. The melting point was not depressed on admixture with an authentic sample of 2: 4-dihydroxy-ω: 3: 6-trimethoxyacetophenone.

2: 5-*Dihydroxy-ω*: 3: 6-*trimethoxy-4-benzyloxyacetophenone* (*IV*).—

To a constantly stirred solution of the above acetophenone (4 g.) in aqueous sodium hydroxide (75 c.c. containing 3 g. of sodium hydroxide) was added dropwise during the course of 3 hours, a solution of potassium persulphate (4 g.) in water (75 c.c.), the temperature being maintained at 15–20° throughout the addition. After allowing to stand over-night, the

mixture was rendered just acid to litmus by adding concentrated hydrochloric acid, while cooling the flask under the tap. The solution was filtered to remove the unchanged original ketone that was precipitated and extracted once with ether. To the clear deep-red aqueous solution was added concentrated hydrochloric acid (10 c.c.) along with benzene (25 c.c.) and the mixture heated on the water-bath at 45–50° for half an hour. After cooling, it was thoroughly shaken, the benzene layer separated and the aqueous solution extracted twice with benzene. The combined benzene extract was dried over sodium sulphate and distilled under diminished pressure. The 2 : 5-dihydroxy-compound was thus obtained as a deep yellow viscous oil which did not solidify on keeping in the refrigerator for 48 hours and did not crystallise even after repeated attempts using benzene-petroleum ether mixture. Yield, 0·4 g. It was easily soluble in the ordinary organic solvents. Its solution in alcohol gave a transient green colouration with a drop of ferric chloride and turned deep reddish-brown on the addition of a few more drops of the reagent; it deposited a brown precipitate after about an hour. The dihydroxy compound dissolved in aqueous sodium carbonate and hydroxide to give orange-red solutions which turned reddish-brown on keeping. No precipitate was obtained with lead acetate in alcoholic solution.

3 : 5 : 6 : 7 : 8-*Pentahydroxyflavone* (6 : 8-*Dihydroxy galangin, VI*): *Allan-Robinson Condensation.*—

To an intimate mixture of benzoic anhydride (2 g.) and sodium benzoate (0·5 g.) was added a solution of the above dihydroxy ketone (0·6 g.) in dry ether. The solvent was carefully distilled off and the mixture heated at 175–180° for 4 hours in an oil-bath under diminished pressure. After cooling, the pale brown cake was broken up, dissolved in alcohol (20 c.c.) and the mixture heated under reflux for 10 minutes. A solution of potassium hydroxide (3 g.) in water (8 c.c.) was then gradually added and the refluxing continued for a further period of 20 minutes. After distilling off the alcohol under reduced pressure, the brown residue was dissolved in water (50 c.c.), filtered to remove some insoluble matter, and saturated with carbon dioxide. The crude flavone was precipitated as a brown semi-solid and the mixture was therefore ether extracted and the ether solution dried over sodium sulphate. On distilling off the solvent, the substance was obtained again as a semi-solid and was directly used for demethylation. Yield, 0·4 g. It was readily soluble in alcohol, acetone and glacial acetic acid and dissolved in aqueous sodium hydroxide with an yellow colour. Its alcoholic solution gave no prominent characteristic colour with ferric chloride. Its solution

in concentrated sulphuric acid was yellow and exhibited no fluorescence. With magnesium and hydrochloric acid it gave an orange-yellow colour in alcoholic solution.

Demethylation.—

The above product (0·3 g.) was dissolved in acetic anhydride (5 c.c.) and cautiously treated with hydriodic acid (d, 1·7; 5 c.c.). The solution was then heated in an oil-bath at 135–140° for two hours, cooled, and diluted with water saturated with sulphur dioxide. The yellow solid that separated was collected, washed with water, dried and crystallised twice from ethyl acetate. Yield, 0·2 g. On recrystallisation from the same solvent, the tetrahydroxyflavonol was obtained as yellow narrow rectangular plates which slowly turned greenish-brown on exposure to air. It melted at 257–58°; it was identical in every respect with an authentic sample of 6:8-dihydroxy galangin obtained by other methods and the mixed melting point was undepressed. (Found in material dried *in vacuo* at 120–125° for two hours: C, 59·8; H, 3·6; $C_{15}H_{10}O_7$ requires C, 59·6; H. 3·3%).

3:5:6:7:8-*Pentaacetoxyflavone.*—

The tetrahydroxyflavonol (0·1 g.) was acetylated by boiling with acetic anhydride (2 c.c.) and a few drops of pyridine for 3 hours. The penta-acetate crystallised from ethyl acetate as colourless flat needles and narrow rectangular plates and melted at 207–208° with slight sintering at 204°. The melting point was undepressed on admixture with the penta-acetate of 6:8-dihydroxy galangin obtained by other methods. (Found: C, 58·7; H, 3·9; $C_{25}H_{20}O_{12}$ requires C, 58·6; H, 3·9%).

Summary

A satisfactory procedure for the preparation of 2-hydroxy-ω:3:6-trimethoxy-4-benzyloxy-acetophenone is described. Oxidation of this to the 2:5-dihydroxyketone (IV), its condensation with the anhydride and sodium salt of benzoic acid and subsequent demethylation yield 6:8-dihydroxy-galangin. This constitutes a simplified method for the synthesis of 5:6:7:8-hydroxyflavonols and their methyl ethers.

References

1. Murti, Row and Seshadri .. *Proc. Ind. Acad. Sci.*, A, 1946, **24**, 233.
2. Rao, Rao and Seshadri .. *Ibid.*, 1944, **19**, 88.
3. Seshadri and Venkateswarlu .. *Ibid.*, 1946, **23**, 192.