NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XXXIII. A New Synthesis of 5:6-Dihydroxy Flavone

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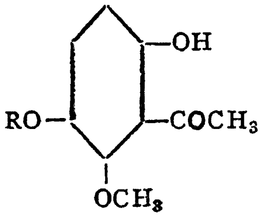
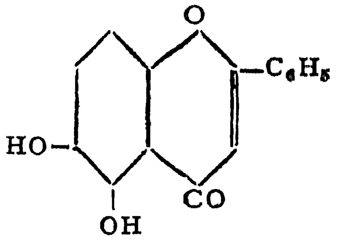
In Part XXVIII[1] in which the preparation of 6-hydroxy primetin was described, it was mentioned that the alternative method of synthesis involving 5:6-dihydroxy flavone (II) would be rather tedious. The really laborious part was the making of this dihydroxy flavone. Baker[2] first made it by employing 2:5-dihydroxy-6-methoxy acetophenone (I, R = H) and 2-hydroxy-5:6-dimethoxy acetophenone (I, R = CH$_3$) as intermediates for carrying out the flavone synthesis. Nakazawa[3] used for this purpose 2:5-dibenzoyloxy-6-methoxy acetophenone. Iyer and Venkataraman[4] later started with 6-hydroxy flavone (III) which is readily made from quinacetophenone. An amino group was introduced into the 5-position *via.*, an azo dye and converted into the hydroxyl by known methods. In this simplified synthesis the yields in the final stages did not appear to have been satisfactory and a better method seemed to be desirable.

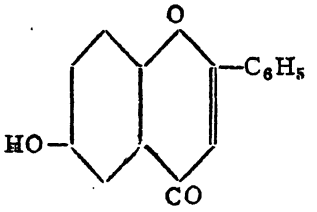


(I)

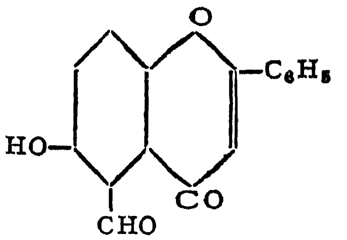
R=H or CH$_3$



(II)



(III)



(IV)

This has now been worked out using the two stage process of nuclear oxidation.[5] 6-Hydroxy flavone condenses fairly readily with hexamine to yield the 5-aldehyde (IV) which is then oxidised by means of alkaline hydrogen peroxide. The product and its derivatives agree with the requirements of 5:6-dihydroxy flavone and not the 6:7-dihydroxy compound.[4, 6] The yield is about 40% and thus is now available a satisfactory method for the synthesis of this compound.

Partial methylation of (II) to 5-hydroxy-6-methoxy flavone was carried out by Baker[2] with dilute alcoholic potash and excess of dimethyl sulphate. He obtained the same compound by the partial demethylation of 5:6-dimethoxy flavone also. The partial methylation has now been carried out more conveniently in dry acetone solution with dimethyl sulphate and anhydrous potassium carbonate.

EXPERIMENTAL

6-*Hydroxy-flavone-5-aldehyde* (*IV*)

The preparation of 6-hydroxy flavone was described by Chadha and Venkataraman.[6] For the preparation of quinacetophenone required for this purpose improved methods have been recently reported.[7]

6-Hydroxy flavone (1 g.) and hexamine (3 g.) were dissolved in glacial acetic acid (10 c.c.) and the solution heated (air condenser) in a boiling water-bath for 6 hours. Hydrochloric acid (1:1, 10 c.c.) was added and the solution again heated for 5 minutes in the water-bath. It was then diluted with an equal volume of water and left overnight. The solid that separated out was filtered and extracted with acetone or benzene. An insoluble by-product was left behind. The hydroxy aldehyde crystallised from the solution as colourless needles. After a further crystallisation from these solvents it melted at 220–22°. Yield 0·5 g. (Found: C, 71·9; H, 4·0; $C_{16}H_{10}O_4$ requires C, 72·2; H, 3·8%). It gave a blood red colour with alcoholic ferric chloride. In cold aqueous sodium hydroxide (10%) it was practically insoluble, but on warming formed a deep pink solution. With 2:4-dinitrophenyl hydrazine it formed a dark orange red derivative which when crystallised from alcohol-acetic acid mixture melted at 292–94°.

Oxidation to 5:6-*dihydroxy flavone* (*II*)

The above hydroxy flavone aldehyde (0·5 g.) was dissolved in pyridine (10 c.c.) and treated with N/2 sodium hydroxide (5 c.c.). On adding water (3 to 5 c.c.) a clear red solution was formed. It was cooled in ice-water to about 20° and 6% hydrogen peroxide (2·5 c.c.) added dropwise with shaking during the course of half an hour. The mixture was allowed to stand with occasional shaking for 2 hours, acidified with dilute hydrochloric acid (1:1) and the deep yellow precipitate filtered. When crystallised from ethyl acetate or absolute alcohol it separated as yellow prisms melting at 189–90°. Yield 0·4 g. Mixed melting point with a sample prepared by the method of Baker[2] was undepressed. It gave an intense olive green colour with alcoholic ferric chloride and formed a dark red insoluble sodium salt with aqueous sodium hydroxide. The diacetate and dimethyl ether melted at 164° and 196° respectively agreeing with the melting points given earlier by Baker.[2]

5-*Hydroxy*-6-*methoxy flavone*

5:6-Dihydroxy flavone (0·5 g.) in acetone (50 c.c.) was treated with anhydrous potassium carbonate (3·0 g.) and dimethyl sulphate (0·21 c.c.) and the contents refluxed for 6 hours. The solvent was distilled off and water added to the residue. The undissolved greenish yellow solid was filtered and washed with water. After crystallisation from alcohol, 5-hydroxy-6-methoxy flavone was obtained as long needles melting at 128–29°. Baker[2] gives the same melting point. It gave an intense bluish green colour with alcoholic ferric chloride and formed an insoluble orange sodium salt with aqueous sodium hydroxide. Yield 0·4 g.

SUMMARY

Using the two stage process of ortho oxidation, 5 : 6-dihydroxy flavone has been made from 6-hydroxy flavone.

REFERENCES

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