NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XV. Further Synthesis of 7 : 8-Hydroxy-Flavonols Application of Dakins Reaction for Ortho-Oxidation

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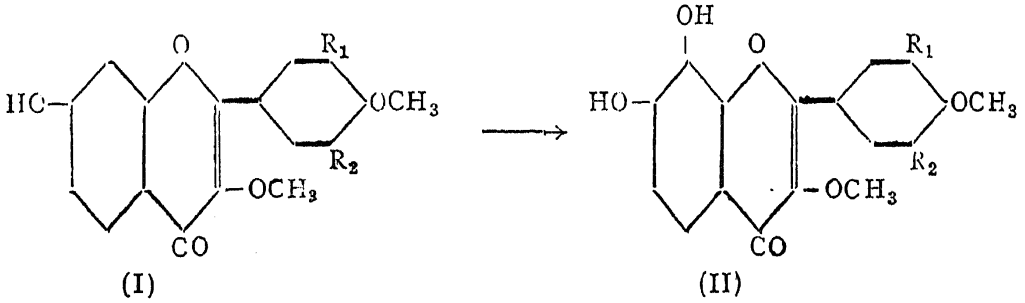
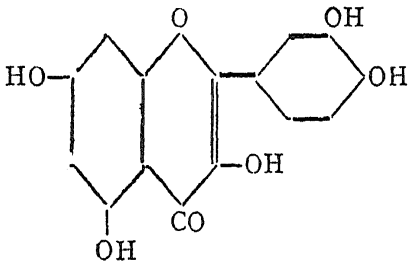
NUCLEAR oxidation by means of alkaline persulphate takes place readily in a position para to the activating hydroxyl group. On the other hand, ortho-oxidation of para-substituted phenols gives catechol derivatives in very poor yields or not at all. In an earlier publication[1] two favourable cases of ortho-oxidation in the flavone series were reported. 7-Hydroxy flavone and 3-methoxy-7-hydroxy flavone were employed for oxidation, the yields of the products being about 10 and 20% respectively. That they were 7 : 8-dihydroxy flavone derivatives was definitely established. In continuation of this work higher members of the 7-hydroxy-flavonol series with one, two and three methoxyl groups in the side phenyl nucleus (I *a*, *b* and *c*) have now been oxidised with persulphate, the resulting products being considered by analogy to be members of the 7 : 8-hydroxy-flavonol group (II*a*, *b* and *c*). The yields vary from 10 to 15%. Though these flavonols have not been so far discovered in nature, their occurrence seems to be quite possible and the present synthesis will render their future discovery easier. It should be remembered in this connection that anthoxanthins are far more varied in structure than the anthocyanins and several new types have been recently discovered.



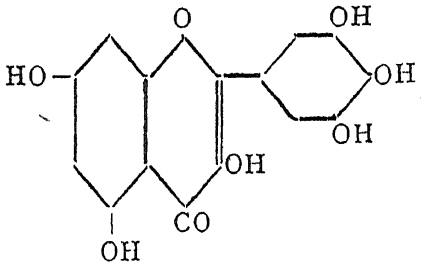
(*a*) $R_1 = R_2 = H$
(*b*) $R_1 = OCH_3, R_2 = H$
(*c*) $R_1 = R_2 = OCH_3$

In the experiments on nuclear oxidation in the flavone series described so far, the problem of the condensed benzene nucleus has been carefully investigated. As far as the side phenyl nucleus is concerned the most important oxidation that could be expected from the theory of biogenesis[2] is

represented by the conversion of quercetin (III) into myricetin (IV) in which a catechol unit undergoes change into a pyrogallol unit.

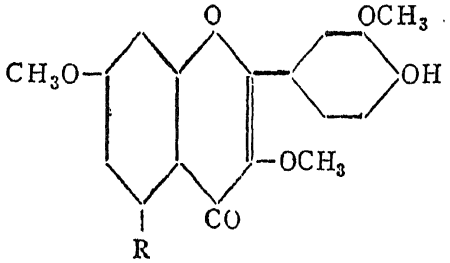


(III)

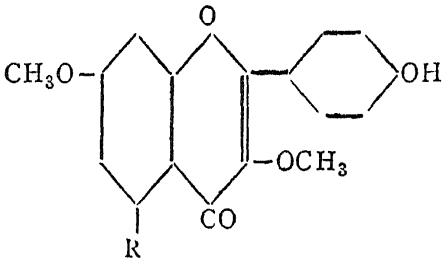


(IV)

Experiments have now therefore been carried out with alkaline persulphate to oxidise quercetin-tetramethyl-ether (V) and fisetin trimethyl ether (VI), but they are unsuccessful. Only minute quantities of impure products could be obtained which give brownish green ferric chloride colour. As simpler examples, kæmpferol trimethyl ether (VII) and 3:7-dimethoxy-4′-hydroxy flavone (VIII) have also been employed with no better results.



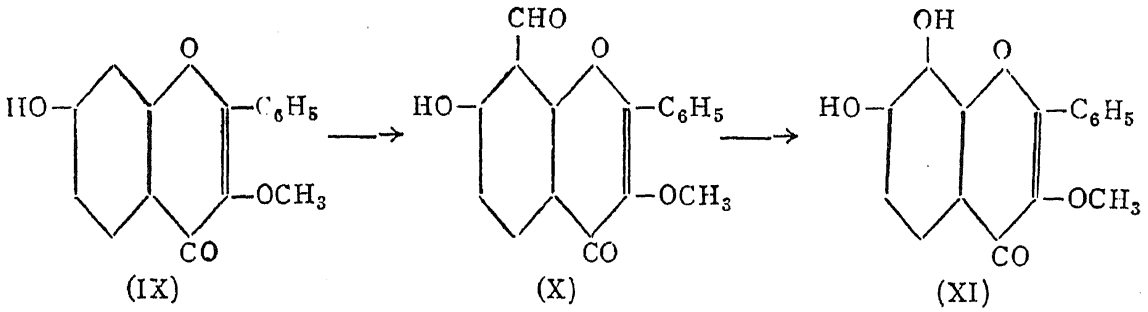
(V) R=OCH_3
(VI) R=H



(VII) R=OCH_3
(VIII) R=H

It has therefore to be concluded that this persulphate method is not suitable for ortho-oxidation in the side phenyl nucleus just as in many other cases also of benzenoid compounds in general. The more facile ortho-oxidation in the 8-position with this reagent seems to be in the nature of an exception depending upon the high reactivity of that position. There is no doubt, however, that ortho-oxidation does take place in the plant kingdom and particularly in the side phenyl nucleus of flavones. Only the laboratory analogy of nature's process does not seem to be the persulphate method in which a hydroxyl substitutes a nuclear hydrogen atom in a single stage. Some other process may be involved. It would appear that a multi-stage process as given below offers a better analogy: (1) converting the phenolic compound into an orthohydroxy aldehyde or ketone and (2) subjecting the aldehyde or ketone to oxidation with hydrogen peroxide (Dakin's reaction).[3] An ortho-dihydroxy compound results. Though Dakin's reaction has been successfully employed with simpler benzene derivatives particularly by Baker[4] in recent years, the only example[5] attempted in the flavone series (5-hydroxy-6-acetyl flavone) was reported unsuccessful. Consequently to begin with, it was considered necessary to test this reaction in the most

favourable case among the flavones, 3-methoxy-7-hydroxyflavone. An aldehyde was preferred to a ketone as more likely to be produced in nature and the hexamine method of aldehyde preparation was chosen as more approximate to the biogenetic process. 3-Methoxy-7-hydroxy-flavone-8-aldehyde (X) has been prepared and described by Rangaswami and Seshadri[6] in the course of their synthetic work on flavonofurans. This compound is easily made in good yields by the action of hexamine on 3-methoxy-7-hydroxy flavone (IX). The chief difficulty in its oxidation with hydrogen peroxide is its low solubility in alkali. A sparingly soluble sodium salt is produced if the concentration of the alkali is even moderately high. But by suitably adjusting its strength and by adding pyridine a clear solution could be obtained and from this by the action of hydrogen peroxide almost quantitative yields of 3-methoxy-7:8-dihydroxy flavone (XI) could be secured. Thus the two stage process produces about 60% yield of the ortho-dihydroxy flavone as against the yield of 20% by the persulphate method. These highly successful exploratory experiments on ortho-oxidation offer promise of extension for the synthesis and for the study of the biogenesis of anthoxanthins and related compounds.



(IX) (X) (XI)

Experimental

7:8-Dihydroxy-3:4'-dimethoxy-flavone (II a)

To a stirred solution of 7-hydroxy-3:4'-dimethoxy-flavone[7] (I *a*) (2 g.) in aqueous sodium hydroxide (2 g. in 30 c.c.), potassium persulphate (4 g. in 60 c.c. of water) was added dropwise during the course of three hours. The solution was kept between 15° and 20° throughout the addition. After 24 hours, it was neutralised with hydrochloric acid, when the unchanged flavone separated out. It was filtered and the filtrate extracted twice with ether to remove the last traces of it. Concentrated hydrochloric acid (30 c.c.) was then added and the solution heated on the water-bath for half an hour. It became bright orange-red and a brown solid gradually separated. After cooling the solution, the solid was filtered and crystallised from alcohol when it was obtained in the form of straw coloured elongated rectangular prisms melting at 269–70°. Yield, 0·2 g. It gave a green colour with ferric chloride in alcoholic solution. (Found: C, 64·6; H, 4·3; $C_{17}H_{14}O_6$.

requires C, 65·0; H, 4·5%.) Ether extraction of the filtered solution gave only a resinous product which could not be crystallised.

3 : 7 : 8 : 4′-*Tetramethoxy-flavone*

The above dihydroxy compound (0·2 g.) was refluxed in anhydrous acetone solution (30 c.c.) with dimethyl sulphate (0·3 c.c.) and anhydrous potassium carbonate (1 g.) for six hours. The solvent was then distilled off and water added to the residue. The colourless solid product was filtered and crystallised from alcohol. It was obtained in the form of colourless soft needles melting at 143–4°. It gave no colour with alcoholic ferric chloride and was not soluble in aqueous alkali. Yield, 0·2 g. (Found: C, 62·9; H, 6·0; loss on drying 4·7; $C_{19}H_{18}O_6$, H_2O requires C, 63·3; H, 5·6; H_2O loss, 5·0%).

7 : 8-*Dihydroxy*-3 : 3′ : 4′-*trimethoxy-flavone* (*II b*)

7-Hydroxy-3 : 3′ : 4′-trimethoxy-flavone (I *b*)[8] (2 g.) was hydroxylated by means of potassium persulphate following the procedure already described. The dihydroxy flavone separated from the aqueous solution as a brown solid. On crystallisation from alcohol, it was obtained in the form of very pale yellow rectangular plates and needles melting at 236°. Yield, 0·2 g. It gave a deep green colour with alcoholic ferric chloride. (Found: C, 62·5; H, 4·6; $C_{18}H_{16}O_7$ requires C, 62·8 and H, 4·7%.)

3 : 7 : 8 : 3′ : 4′-*Pentamethoxy flavone*

The above compound (0·2 g.) was methylated with dimethyl sulphate (0·3 c.c.) and anhydrous potassium carbonate (1 g.) in acetone solution (30 c.c.). It crystallised from alcohol in the form of colourless fibrous needles melting at 153–4°. Yield, 0·1 g. It gave no colour with alcoholic ferric chloride and was not soluble in aqueous alkali. (Found: C, 64·5; H, 5·4; $C_{20}H_{20}O_7$ requires C, 64·5 and H, 5·4%.)

7 : 8-*Dihydroxy*-3 : 3′ : 4′ : 5′-*tetramethoxy flavone* (*II c*)

Hydroxylation of 7-hydroxy-3 : 3′ : 4′ : 5′-tetramethoxy flavone[9] (I *c*) (2 g.) was effected with persulphate as in the other cases. The crude brown product was crystallised twice from alcohol when it was obtained in the form of aggregates of yellow rectangular plates melting at 229–30°. Yield, 0·3 g. It gave a grass green colour with alcoholic ferric chloride· (Found: C, 58·4; H, 4·8; $C_{19}H_{18}O_8$, H_2O requires C, 58·2 and H, 5·1%.)

3 : 7 : 8 : 3′ : 4′ : 5′-*Hexamethoxy flavone*

The dihydroxy flavone (II *c*) (0·2 g.) was methylated using dimethyl sulphate (0·3 c.c.) and anhydrous potassium carbonate (1 g.). The hexamethoxy flavone crystallised from alcohol in the form of colourless fibrous needles melting at 167°. Yield, 0·2 g. It gave no colour with ferric chloride

and was not soluble in aqueous alkali. (Found: C, 62·7; H, 5·5; $C_{21}H_{22}O_8$ requires C, 62·7 and H, 5·5%.)

Oxidation of 3-methoxy-7-hydroxy-flavone-8-aldehyde (X)

The flavone aldehyde[6] (X) (0·4 g.) was treated with N/2 sodium hydroxide (4 c.c.), pyridine (5 c.c.) and water (1 c.c.). The clear solution was kept vigorously shaken and 6% hydrogen peroxide (2 c.c.) slowly run in the course of ten minutes. The yellow solution gradually turned reddish brown. It was allowed to stand for three hours with occasional shaking. By this time the colour of the solution had appreciably deepened. It was then acidified with concentrated hydrochloric acid whereby a yellow solid was precipitated. It was filtered, washed and dried. The crude product weighed 0·4 g. When extracted with cold alcohol in which the original aldehyde was sparingly soluble, it dissolved completely. On adding water little by little till turbidity developed and allowing to stand, pale yellow rectangular plates separated out melting at 221°. It agreed in all its properties with an authentic sample of 3-methoxy-7: 8-dihydroxy-flavone and the mixed melting point was undepressed.

Summary

In continuation of Part VIII, members of the 3-methoxy-7-hydroxy-flavone series with one, two and three methoxyl groups in the side phenyl nucleus are subjected to ortho-oxidation with alkaline persulphate; the yield of the corresponding 7: 8-hydroxy compounds is 10 to 15%. On the other hand, attempts at ortho-oxidation by this method in the side phenyl nucleus have failed just as in several cases of simpler benzene derivatives. It is suggested that ortho-oxidation in nature should be considered to take place in multiple stages and this has been verified using a convenient example in the flavone series. 3-Methoxy-7-hydroxy-flavone undergoes change into the corresponding 8-aldehyde by the action of hexamine and this is converted into 3-methoxy-7: 8-dihydroxy flavone by means of alkaline hydrogen peroxide, the yields being very good.

References

1. Narasimhachari, Row and Seshadri .. *Proc. Ind. Acad. Sci.*, A, 1948, **27**, 37.
2. Robinson .. *Nature*, 1936, **137**, 172.
   Robinson, *et al.* .. *Phil. Trans. Roy. Soc.*, 1939, **230 B**, 149.
   Rao and Seshadri .. *Proc. Ind. Acad. Sci.*, A, 1943, **18**, 222.
3. Dakin .. *Am. Chem. J.*, 1909, **42**, 477.
4. Baker .. *J. C. S.*, 1932, 1282; 1934, 1681; 1941, 664.
5. ———— .. *Ibid.*, 1934, 1953.
6. Rangaswami and Seshadri .. *Proc. Ind. Acad. Sci.*, A, 1939, **9**, 7.
7. Rao and Seshadri .. *Ibid.*, 1948, **28**, 96.
8. Allan and Robinson .. *J. C. S.*, 1926, 2334.
9. Charlesworth and Robinson .. *Ibid.*, 1933, 268.