NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XLIII. The Preparation and *p*-Oxidation of Flavones Analogous to Datiscetin and Morin

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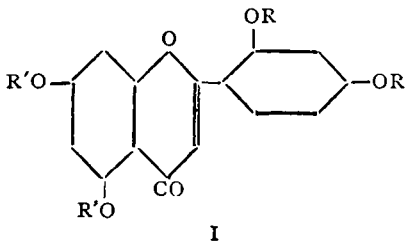
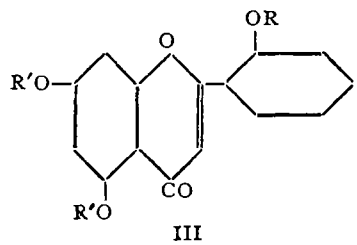
HYDROXY or methoxy flavones with a hydroxyl or methoxyl group in the 2′-position are of rare occurrence. The two definitely known examples belonging to the flavonol series are (i) datiscetin (2′: 3: 5: 7-tetrahydroxy flavone) and (ii) morin (2′: 4′: 3: 5: 7-pentahydroxy flavone). Lotoflavin[1] was considered to be a member of this type belonging to the flavone series (5: 7: 2′: 4′-tetrahydroxy flavone) (I *a*). Synthesis of a substance of this constitution was made by Robinson and Venkataraman[2] using the general procedure of Allan and Robinson; it involved a stage of demethylation with hydriodic acid. The properties of the product were different from those of lotoflavin whose constitution has therefore remained unsettled. At about the same time Algar, Cullinane and Ryan[3] condensed phloracetophenone dimethyl ether with the ester of dimethyl-β-resorcylic acid and subjected the diketone thus obtained to treatment with hydriodic acid. They considered this product to be 5: 7: 2′: 4′-tetrahydroxy flavone (I *a*) and reported that it resembled lotoflavin in its properties. However when phloracetophenone trimethyl ether was employed in this synthesis the isomeric 7: 2′: 4′: 6′-tetrahydroxy flavone (II) was reported to have been obtained. More recently Philbin and Wheeler[4] have in a preliminary note recorded that this type of isomerisation takes place in the presence of hydriodic acid under pressure at elevated temperatures. In order to throw more light on this problem the synthesis of 5: 7: 2′-trihydroxy (III *a*) and 5: 7: 2′: 4′-tetrahydroxy (I *a*) flavones has now been repeated using as demethylating agent, anhydrous aluminium chloride which is known to produce no isomeric change and also hydriodic acid. The products obtained by the two methods are found to be identical showing thereby that under the ordinary conditions of demethylation with hydriodic acid, isomeric change involving 2′-hydroxy group does not occur. This has also been confirmed by remethylating the hydroxy flavone in one case as mentioned below.

The preparation of 5: 7: 2′-trihydroxy flavone (III *a*) was made earlier by Kostanecki and Webel[5] by the condensation of phloracetophenone trimethyl



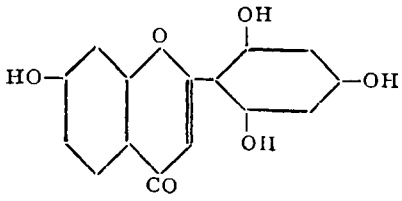
I

a, R = R' = H
b, R = CH_3, R' = H
c, R = R' = CH_3

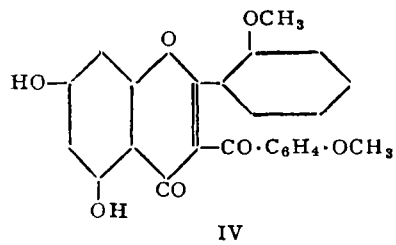


III

a, = R = R' = H
b, = R = CH_3, R' = H
c, = R = R' = CH_3



II



IV

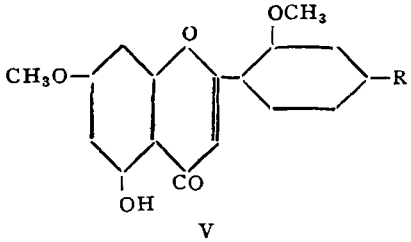
ether with *o*-methoxy benzoic ester and subsequent ring closure and demethylation of the resulting diketone with hydriodic acid. For our present work phloracetophenone has been condensed with the anhydride and sodium salt of O-methyl salicylic acid. The 3-acyl derivative (IV) is obtained as an intermediate stage and is deacylated by boiling with sodium carbonate solution. The resulting 2'-methoxy-5: 7-dihydroxy flavone (III *b*) is demethylated by boiling with hydriodic acid for 3 hours. The demethylation of this substance could not be effected using anhydrous aluminium chloride because of its sparing solubility in benzene. This difficulty is overcome by fully methylating it to 5: 7: 2'-trimethoxy flavone (III *c*) which is soluble in benzene and undergoes demethylation smoothly. The samples of trihydroxy flavone obtained by both the methods are found to be identical and hence it could be concluded that there is no isomeric change during demethylation by boiling with hydriodic acid.

5: 7-Dihydroxy-2': 4'-dimethoxy flavone (I *b*) has been prepared according to the method of Robinson and Venkataraman (*loc. cit.*) using phloracetophenone and the anhydride and sodium salt of 2: 4-dimethoxy benzoic acid. Better yield of the pure product is obtained by introducing a stage of boiling with sodium carbonate in order to hydrolyse any 3-acyl group. This dimethyl ether is directly demethylated with hydriodic acid and also the tetramethyl ether (I *c*) prepared from it is subjected to demethylation with anhydrous aluminium chloride. Products from the two methods are again found to be identical. It may be concluded that in these cases the pyrone

ring does not undergo opening under the conditions adopted and hence no rearrangement is brought about. That there is no isomeric change during the demethylation with hydriodic acid has been further confirmed by re-methylating the product whereby the original tetramethyl ether (I *c*) is obtained.

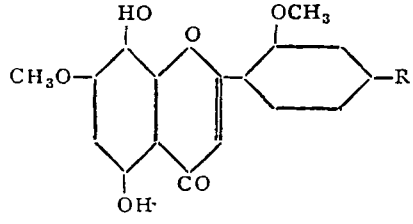
The experiments of Algar, Cullinane and Ryan[3] have now been repeated. From the results reported in the experimental part of this paper, it is clear that the tetrahydroxy flavone sample obtained by them was impure. Purification has now been effected by conversion into the acetate and the subsequent deacetylation. The purified product agrees in every respect with the sample obtained by Robinson and Venkataraman and differs markedly from lotoflavin. Thus all doubts regarding the nature of tetrahydroxy flavone (I *a*) obtained by different methods are cleared up.

In earlier parts of this series a number of typical examples of *p*-nuclear oxidation of flavones have been described. Particular mention may be made of Parts II[6] and XVIII[7] in which nuclear oxidations of chrysin, tectochrysin, acacetin and higher members were reported. The products were the derivatives of 5: 7: 8-hydroxy flavones. Members of this flavone series are not so common, wogonin being the only naturally occurring member. Nobiletin may also be said to belong to this series, but it also contains further a substituent in the 6-position. In earlier work[7] another interesting point was brought out. The 5: 7: 8-hydroxy or methoxy compounds which are easily prepared synthetically undergo isomeric change during demethylation with hydriodic acid to yield members of the 5: 6: 7-hydroxy series which are more commonly occurring. This provides in fact a more handy method of synthesising these compounds. The nuclear oxidation of 5: 7-dihydroxy-2′: 4′-dimethoxy flavone (I *b*) with alkaline persulphate does not proceed satisfactorily. On the other hand, the trimethyl ether (V *a*) with only the 5-hydroxyl free undergoes this oxidation fairly well. The resulting quinol (VI *a*) on methylation yields 5: 7: 8: 2′: 4′-pentamethoxy flavone. Similarly 5-hydroxy-7: 2′-dimethoxy flavone (V *b*) has been obtained by the partial



V

a, R = OCH_3
b, R = H



XI

a, R = OCH_3
b, R = H

methylation of the 2′-methyl ether (III *b*) and this is oxidised with alkaline persulphate. Final methylation of this quinol (VI *b*) gives 5 : 7 : 8 : 2′-tetramethoxy flavone.

EXPERIMENTAL

5 : 7-*Dihydroxy-2′-methoxy flavone* (*III b*)

An intimate mixture of phloracetophenone (5 g.), *o*-methoxy benzoic anhydride (35 g.) and sodium *o*-methoxy benzoate (12 g.) was heated under reduced pressure at 180–85° for a period of 5 hours. The semi-solid mass so obtained was suspended in alcohol (150 c.c.) and refluxed with alkali (10 g. potassium hydroxide in 10 c.c. water) for 10 minutes. The alcohol was removed under reduced pressure and the residue dissolved in water (500 c.c.). The solution was filtered and extracted once with ether. It was then saturated with carbon dioxide for 3 hours when the crude 3-acyl derivative (IV) separated out. It was filtered and washed with water. It crystallised from alcohol in the form of almost colourless long thick prisms melting at 244–45° (Found: C, 68·9; H, 4·9; $C_{24}H_{18}O_7$ requires C, 69·0; H, 4·3%). It was hydrolysed by refluxing with aqueous sodium carbonate (5%; 300 c.c.) for 4 hours. The carbonate solution was cooled and acidified with hydrochloric acid. The solid that separated out was filtered and washed with sodium bicarbonate solution to remove the *o*-methoxy benzoic acid formed. The remaining flavone crystallised from alcohol as clusters of small prisms melting at 273–75°. Yield 2·5 g. It dissolved to a yellow solution in sulphuric acid giving pale blue fluorescence. With alcoholic ferric chloride, it gave a reddish brown colour and it dissolved in aqueous sodium hydroxide to give a pale-yellow solution (Found: C, 67·4; H, 4·3; $C_{16}H_{12}O_5$ requires C, 67·4; H, 4·6%).

5-*Hydroxy*-7 : 2′-*dimethoxy flavone* (*V b*)

This compound had earlier been made by Kostanecki and Webel[5] by the action of methyl iodide and potassium hydroxide on an alcoholic solution of 5 : 7 : 2′-trihydroxy flavone (III *a*). For the present work it was prepared by refluxing 5 : 7-dihydroxy-2′-methoxy flavone (III *b*) (1·0 g.) in dry acetone solution (100 c.c.) with redistilled dimethyl sulphate (0·35 c.c., I mole) and ignited potassium carbonate (5 g.) for 8 hours. The acetone solution was filtered and the potassium salts (A) washed with hot acetone. On removal of the solvent from the filtrate, the 5-hydroxy compound admixed with a small quantity of the fully methylated flavone was obtained. The mixture was treated with dilute alkali and the trimethyl ether removed by extraction with ether. The alkaline solution was acidified and the 5-hydroxy compound filtered and washed with water. The residual potassium salts (A) were

stirred up with water and acidified giving a little more of the 5-hydroxy compound. On recrystallisation from alcohol, the dimethyl ether came out as clusters of pale yellow needles and rods melting at 155–56°; yield (0·8 g.). It gave a brown red colour with ferric chloride in alcoholic solution (Found: C, 68·4; H, 4·7; $C_{17}H_{14}O_5$ requires C, 68·5; H, 4·7%).

5:7:2′-*Trimethoxy flavone* (*III c*)

5:7-Dihydroxy-2′-methoxy flavone (0·8 g.) in dry acetone was treated with excess of dimethyl sulphate and anhydrous potassium carbonate and the mixture was refluxed on a water-bath for 30 hours. The acetone solution was filtered and the potassium salts were washed with hot acetone. After distilling off the solvent, ice-water was added and the mixture allowed to stand in the refrigerator overnight. The pale yellow product that separated out was filtered and washed with water. It crystallised from alcohol as colourless needles melting at 176–77°. Yield, 0·6 g. It did not dissolve in sodium hydroxide solution and gave no colour with ferric chloride in alcoholic solution (Found: C, 69·2; H, 5·5; $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·1%).

Demethylation with hydriodic acid: 5:7:2′-*trihydroxy flavone* (*III a*)

5:7-Dihydroxy-2′-methoxy flavone (1·0 g.) was dissolved in acetic anhydride (15 c.c.) and to the solution hydriodic acid (10 c.c.) was added cautiously with cooling in ice water. The mixture was refluxed for 3 hours at 140° on an oil-bath and then diluted with a strong aqueous sodium sulphite solution. The reddish brown powder that had separated in about an hour was filtered, washed with water and dried. It crystallised from alcohol as pale yellow prisms melting at 283–85°. The melting point reported by Kostanecki and Webel was 281°. Yield, 0·3 g.

Demethylation with aluminium chloride: 5:7:2′-*trihydroxy flavone* (*III a*)

A solution of 5:7:2′-trimethoxy flavone (0·47 g.) in dry benzene (40 c.c.) was treated with powdered aluminium chloride (2 g.) and the mixture heated under reflux for 2 hours. The solvent was then distilled off completely and the residual aluminium chloride complex decomposed by cautiously adding pieces of ice and hydrochloric acid (4 c.c.). The resulting yellow powder was filtered and washed with water. It was purified by dissolving in 10% cold sodium carbonate solution (40 c.c.), filtering the solution and acidifying the filtrate with cold dilute hydrochloric acid. The trihydroxy flavone was obtained in an almost pure condition. It crystallised from alcohol as pale yellow prisms melting at 283–85°. Yield, 0·3 g. The compound developed a red colour with ferric chloride in alcoholic solution and dissolved in

dilute sodium hydroxide giving a yellow solution. In sulphuric acid solution it exhibited green fluorescence. The mixed melting point with the hydriodic acid demethylation product was undepressed.

5: 8-*Dihydroxy*-7: 2′-*dimethoxy flavone* (*VI b*)

To a mechanically stirred solution of 5-hydroxy-7: 2′-dimethoxy flavone (1·3 g.) in a mixture of pyridine (20 c.c.) and alkali (3·0 g. sodium hydroxide in 100 c.c. water) was added dropwise a solution of potassium persulphate (3 g.) during a period of 2 hours, the flask being cooled in a bath of cold water. The stirring was continued for 6 hours more and the solution left for 24 hours. It was then acidified to congo-red, the precipitate of the unchanged compound was filtered and the filtrate was extracted with ether. The solution was then made strongly acidic by the addition of concentrated hydrochloric acid and then heated on a boiling water-bath for 20 minutes. After cooling it was repeatedly extracted with ether, the ether solution distilled to remove the solvent and the quinol crystallised from benzene. The 5: 8-dihydroxy compound was obtained as golden yellow broad thin rectangular plates melting at 193–94°. Yield, 0·35 g. With ferric chloride in alcoholic solution, it gave a greenish brown colour which turned brown red with excess of the reagent. The compound gave a brown red solution in aqueous sodium hydroxide which slowly became colourless (Found: C, 64·9; H, 4·4; $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5%).

5: 7: 8: 2′-*Tetramethoxy flavone*

The above quinol (0·3 g.) was refluxed in dry acetone solution (20 c.c.) after the addition of dimethyl sulphate (0·3 c.c.) and ignited potassium carbonate (3 g.) for 30 hours. The tetramethyl ether crystallised from dilute alcohol in the form of colourless long thick prisms melting at 107–8°. Yield 0·15 g. It dissolved to a golden yellow solution in concentrated sulphuric acid with no fluorescence (Found: C, 66·7; H, 5·3; $C_{19}H_{18}O_6$ requires C, 66·6; H, 5·3%).

5-*Hydroxy*-7: 2′: 4′-*trimethoxy flavone* (*V a*)

The 5: 7-dihydroxy-2′: 4′-dimethoxy flavone (I *b*) was prepared by a modification of the method of Robinson and Venkataraman.[2] The crude product which usually contained some 3-acyl derivative was boiled for 3 hours with 5% aqueous sodium carbonate. The solution was acidified, the precipitated solid filtered and washed with aqueous sodium bicarbonate and finally with water. It crystallised from alcohol in the form of yellow needles melting at 269–70°.

The dihydroxy flavone (1·0 g.) was partially methylated by refluxing in dry acetone solution (50 c.c.) with dimethyl sulphate (0·3 c.c.; 1 mole) in

the presence of anhydrous potassium carbonate (2 g.) for 10 hours. The product on purification and crystallisation from acetone alcohol mixture was obtained as pale-yellow long thick rods melting at 163–4°. Yield, 0·8 g. It gave a brown-red colour with ferric chloride in alcoholic solution; it did not dissolve in 5% sodium hydroxide solution even on boiling, but only turned yellow due to the formation of a sparingly soluble sodium salt. (Found: C, 65·9; H, 5·6; $C_{18}H_{16}O_6$ requires C, 65·9; H, 6·0%).

5: 7: 2′: 4′-*Tetramethoxy flavone* (*I c*).

It was prepared as usual by the complete methylation of 5: 7-dihydroxy-2′: 4′-dimethoxy flavone (I *b*) in dry acetone solution. On crystallisation from alcohol, the tetra methyl ether came out as colourless prisms melting at 184–86°. Its alcoholic solution gave no colour with ferric chloride.

5: 7: 2′: 4′-*Tetrahydroxy flavone* (*I a*)

Method I.—The tetramethoxy flavone (I *c*) (0·3 g.) was demethylated using dry benzene (30 c.c.) and anhydrous aluminium chloride (2·0 g.) and the product was worked up exactly as in the similar case described earlier. The tetrahydroxy flavone crystallised from alcohol in the form of woolly needles. On heating in a capillary tube it darkened progressively from 290° onwards and melted down at 332–35°. It was further purified by conversion into the tetra acetate using acetic anhydride and pyridine. The acetate crystallised from benzene as colourless stout prisms melting at 158–59° (Robinson and Venkataraman gave the same melting point). It was deacetylated by boiling with alcoholic hydrochloric acid for half an hour. The product now melted definitely between 332–35° without any previous change.

Method II.—5: 7-Dihydroxy-2′: 4′-dimethoxy flavone (I *b*) was demethylated by boiling with hydriodic acid for two hours and the product worked up in the usual way. After one crystallisation from alcohol, this also darkened progressively from 290° onwards and melted down at 332–35°. Its purity could also be improved by the acetate method. The final sample agreed with the one obtained by method I and the mixed melting point was undepressed. This sample of tetrahydroxy flavone (0·1 g.) was remethylated in anhydrous acetone solution by boiling with excess of dimethyl sulphate and potassium carbonate for 30 hours. The fully methylated product crystallised from dilute alcohol melting at 184–86°. Yield, 70 mg. The mixed melting point with the sample of tetramethoxy flavone (I *c*) described earlier was undepressed.

Method III.—2-Hydroxy-4: 6: 2′: 4′-tetramethoxy benzoylacetophenone was prepared according to the method of Algar, Cullinane and Ryan.[3] It melted at 151°. The diketone (1 g.) was refluxed with acetic anhydride (10 c.c.) and hydriodic acid (10 c.c., d. 1·7) for two hours and the product worked up as in other demethylations. It crystallised from alcohol melting indefinitely between 280–300°. The m.p. did not improve appreciably on repeated crystallisations. It was therefore acetylated using acetic anhydride and pyridine. The acetate crystallised from alcohol melting at 158–59°. The mixed melting point of this acetate with a sample of 5: 7: 2′: 4′-tetraacetoxy flavone obtained by method I was undepressed. The acetate was deacetylated by boiling with alcohol hydrochloric acid mixture (1: 1) and the resulting tetrahydroxy flavone crystallised from alcohol. The purified sample then melted at 332–35°. The mixed melting point with 5: 7: 2′: 4′-tetrahydroxy flavone was undepressed. It dissolved to a pale yellow solution in concentrated sulphuric acid and gave a violet-blue fluorescence.

5: 8-*Dihydroxy*-7: 2′: 4′-*trimethoxy flavone* (*VI a*)

The 5-hydroxy-7: 2′: 4′-trimethoxy flavone (1·3 g.) was dissolved in a mixture of pyridine (20 c.c.) and alkali (3·5 g. sodium hydroxide in 100 c.c. of water) and was subjected to oxidation with potassium persulphate (3·1 g. in 100 c.c.), the flask being cooled in a bath of cold water. The product was worked up as described in the previous case. The recovered original compound amounted to 0·7 g. The oxidation product crystallised from benzene as bright yellow rectangular plates melting at 203–4°. With ferric chloride in alcoholic solution, it gave a greenish brown colour changing to deep brown red with excess. In aqueous sodium hydroxide an orange-red solution was obtained and the colour faded off slowly (Found: C, 62·6; H, 4·6; $C_{18}H_{16}O_7$ requires C, 62·9; H, 5·0%).

5: 7: 8: 2′: 4′-*Penta-methoxy flavone*

The above quinol (0·15 g.) was refluxed for 30 hours in dry acetone solution (20 c.c.) with dimethyl sulphate (0·2 c.c.) and anhydrous potassium carbonate (3 g.). The product crystallised from dilute alcohol as colourless long thin needles, melting at 152–53°. Yield, 0·1 g. (Found: C, 64·5; H, 5·8; $C_{20}H_{20}O_7$ requires C, 64·5; H, 5·3%).

SUMMARY

The synthesis of 5: 7: 2′-trihydroxy and 5: 7: 2′: 4′-tetrahydroxy flavones has been repeated using Allan-Robinson condensation and both hydriodic acid and anhydrous aluminium chloride as demethylating agents. With these

reagents and under ordinary conditions isomeric change involving the 2'-hydroxyl group does not occur. The tetrahydroxy flavone has also now been prepared by the procedure of Algar *et al.* The sample is found to be identical with the one obtained by the method of Robinson and Venkataraman and is different from lotoflavin. The nuclear oxidation of the partial methyl ethers of the two flavones has been carried out using alkaline persulphate.

References

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