NUCLEAR OXIDATION IN THE FLAVONE SERIES

Part VIII. 7: 8-Dihydroxy-Flavone and -Flavonol

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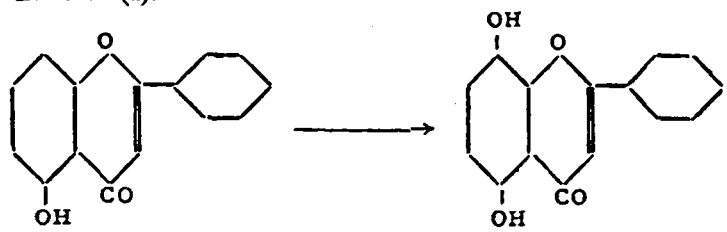
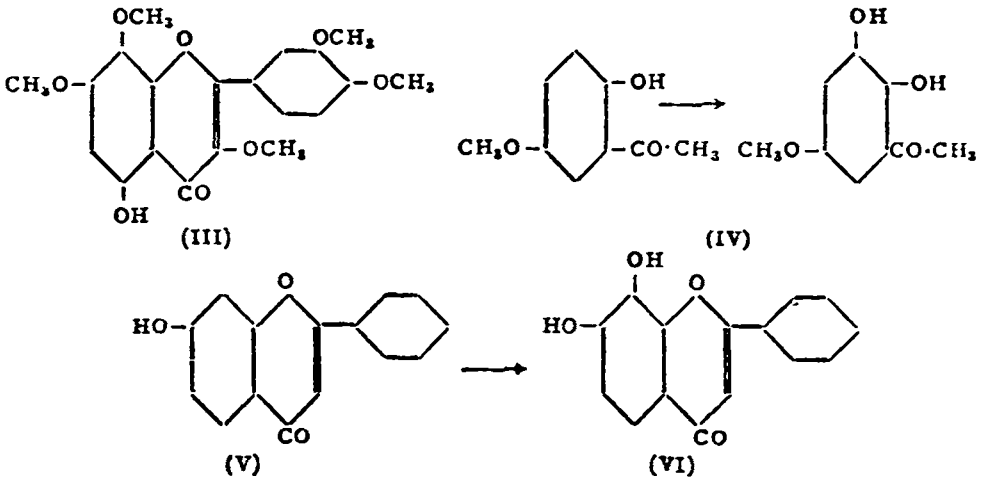
IN the large number of nuclear oxidations with alkaline persulphate published earlier in this series of papers[1] the new hydroxyl group entered the 8-position which is para to the already existing and activating hydroxyl group in the 5-position. The simplest example is the preparation of primetin (II) from 5-hydroxy-flavone (I).



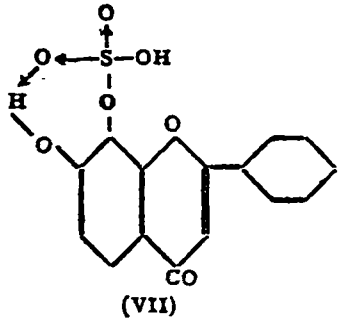
(I) (II)

Ortho oxidation was attempted with gossypetin-pentamethyl-ether (III); but it was not successful. The ortho position 6 was not appreciably affected. But Baker *et al.*[2] have reported that in a simpler case of a phenolic ketone (IV) oxidation in the ortho-position does occur, though the yield is extremely small (1%). With the idea of testing the feasibility of ortho-oxidation in the flavone series in the most favourable case the oxidation of 7-hydroxy-flavone has now been examined. In 7-hydroxy-chromones, flavones and coumarins the 8-position is fairly readily reactive as regards nitration, bromination, Claisen and Fries migrations. Hence this 8-position could be expected to undergo oxidation fairly easily. Further the simplicity of the compound is an advantage for the purpose of the test. Actually it is found that the oxidation of 7-hydroxy-flavone does take place though the yield (10%) is poor as compared with the para oxidations. The product has been identified as 7: 8-dihydroxy-flavone (VI) by comparison with an authentic sample, prepared from gallacetophenone.[3] The acetates and methyl ethers are also found to be identical.

In carrying out the above oxidation several times an observation has been made which is of some significance. After completing the oxidation



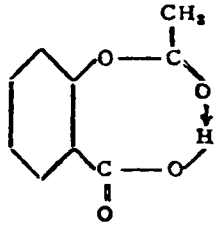
and removing the unchanged substance, the solution is strongly acidified with cooling and allowed to stand for a few minutes when a crystalline precipitate separates out. It is fairly readily soluble in water and alcohol and insoluble in ether and contains sulphur. It gives a brownish pink colour with alcoholic ferric chloride whereas 7-hydroxy-flavone gives no colour and 7: 8-dihydroxy-flavone a deep green colour characteristic of the catechol structure. Further the precipitate when hydrolysed with hydrochloric acid gives the test for sulphate and yields 7: 8-dihydroxy-flavone. It has the composition corresponding to the monosulphate of 7: 8-dihydroxy-flavone. It thus proves to be the intermediate stage in the persulphate oxidation mentioned in the first paper of this series[1] and not so far isolated in other cases. Its successful isolation in this particular oxidation should be attributed to its sparing solubility. This property and its colour reaction with ferric chloride suggest similarity with ortho hydroxy carbonyl compounds which are known to be chelated. The structure of the sulphate could therefore be represented as in (VII).



(VII)

This would involve a chelate ring of 7 atoms. Though chelate rings with 6 atoms may be more common, larger rings do not appear to be ruled out.

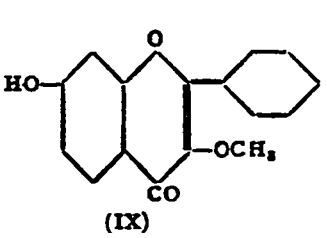
For example, the experiments on the Raman effect of aspirin[4] seem to suggest the existence of chelation involving a ring of 8-atoms as shown below (VIII).



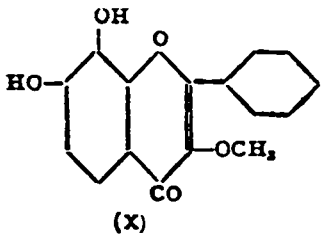
(VIII)

Another point that could be mentioned in connection with the easy isolation of the sulphate described above is the simplicity of the compound and the absence of other solubilising groups. In the case of the 3-methoxy analogue discussed below the sulphate could not be isolated pure though there was evidence of its separation in a small quantity in a colloidal condition.

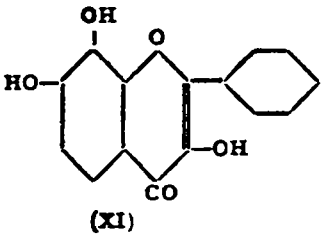
The application of this oxidation to the corresponding flavonols will be useful since it will make the 7 : 8-hydroxy-flavonols more easily available. Otherwise they have to be made by the roundabout method of Kostanecki since ω-methoxy-gallacetophenone has not yet been prepared. 3-Methoxy-7-hydroxy-flavone (IX) which is actually more easy to prepare and which is generally found to be far more reactive in the 8-position than the simpler 7-hydroxy flavone (V) has been subjected to oxidation with persulphate. The yield of the oxidation product is much better (20%) though it is still poor as compared with para oxidations in general. The product (X) has the characteristic properties of a 7 : 8-dihydroxy-compound. On methylation



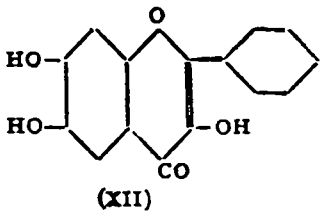
(IX)



(X)



(XI)



(XII)

it gives 3:7:8-trimethoxy-flavone and on demethylation 3:7:8-trihydroxy-flavone (XI). These agree with the description of Dobrzynski and Kostanecki[5] and are different in their properties from isomeric 3:6:7-trimethoxy- and trihydroxy-compounds[6] (XII). Particular mention must be made of lower melting point of 7:8-dihydroxy-flavonol, its deep red colour with alkali and lack of fluorescence in sulphuric acid solution. The 6:7-dihydroxy-flavonol gives only a pale yellow colour with alkali and its solutions have fluorescence. These points are brought out in the following table.

TABLE

	6 : 7-*Dihydroxy-flavonol*	7 : 8-*Dihydroxy-flavonol*
M.P. of Dihydroxy-flavonol ..	318°	249°
,, Triacetyl-derivative ..	191–2°	210–2°
,, Trimethyl-ether ..	175–6°	149–150°
,, 3-Mono-methyl-ether ..	242–4°	220–1°
Colour reactions of the hydroxy-flavonol		
With ferric chloride ..	Dark-greenish brown	Olive brown
,, sodium hydroxide ..	Yellow solution	Red solution
,, concentrated sulphuric acid..	Pale yellow solution with pale blue fluorescence	Yellow solution; no fluorescence
,, sodium carbonate ..	Pale yellow solution	Orange yellow solution
,, alcohol ..	Pale yellow solution; blue fluorescence	Bright yellow solution; no fluorescence

The above experiments show that though oxidation with persulphate does not proceed satisfactorily in the position ortho to an existing phenolic hydroxyl group, it takes place better when the 8-position of flavones is involved. This partly explains why the oxidation of flavones like chrysin with both the hydroxyl groups in the 5- and 7-positions free, takes place more easily than that of the 5-hydroxy compounds. In the former both the para and ortho activating effects exert.

EXPERIMENTAL

7-Hydroxy-flavone required for the oxidations was prepared from resacetophenone benzoate by the method of Baker.[3]

Nuclear Oxidation of 7-hydroxyflavone : preparation of 7:8-Dihydroxy-flavone (VI)

A solution of 7-hydroxy-flavone (2·4 g.) in aqueous alkali (2 g. in 30 c.c. of water) was treated with potassium persulphate solution (4 g. in 60 c.c. of water) during the course of three hours with continuous mechanical stirring, the temperature being kept between 15–20°. The liquid was deep orange red at the end of the addition. It was left overnight, then neutralised

with concentrated hydrochloric acid and the unchanged 7-hydroxy-flavone (1·0 g.) recovered by filtration. The filtrate was extracted twice with ether to remove the last traces of this flavone. Concentrated hydrochloric acid (30 c.c.) was added to the liquid and the mixture heated in the water-bath for 30 minutes. During the course of the hydrolysis, some brownish yellow product separated out. More of it settled down on cooling the mixture to the laboratory temperature. It was filtered, washed with water and crystallised twice from aqueous alcohol when it was obtained as pale yellow stout rhombic prisms melting at 240–42.° Yield 0·3 g. A mixed melting point determination with 7: 8-dihydroxy-flavone prepared from gallacetophenone benzoate[3] showed no depression. It gave a grass green colour with alcoholic ferric chloride and developed no fluorescence when dissolved in concentrated sulphuric acid or aqueous sodium hydroxide.

The diacetyl derivative was obtained by acetylating the above dihydroxy flavone with acetic anhydride and sodium acetate. It crystallised from aqueous alcohol in the form of colourless needles melting at 198–99°.

7: 8-Dihydroxy-flavone from the above experiments (0·2 g.) was methylated by refluxing in acetone solution with dimethyl sulphate (0·5 c.c.) and anhydrous potassium carbonate (1 g.) for 12 hours. The acetone solution was filtered and the potassium salts washed with hot acetone. The filtrate on evaporation deposited colourless crystals which were recrystallised twice from alcohol. The 7: 8-dimethoxy-flavone was obtained in the form of thin rectangular rods melting at 151–2°. Its melting point was not depressed when admixed with an authentic sample of 7: 8-dimethoxy-flavone (Found: C, 71·9; H, 5·3; $C_{17}H_{14}O_4$ requires C, 72·4 and H, 5·0%).

In a repetition of the above experiment after the removal of the unchanged flavone, the neutral reddish brown liquid was treated while cooling under the tap with concentrated hydrochloric acid (30 c.c.). On stirring with a glass-rod, bright shining yellow crystals of the sulphate (VII) separated out in the course of a few minutes. They were collected and thoroughly washed with ether. Yield: 0·3 g. They melted at 225–7° with slight sintering at 220° and appeared as elongated rectangular prisms under the microscope.

To estimate the sulphate in the compound, it was hydrolysed by heating with 1 : 1-hydrochloric acid for 15 minutes in a water-bath and the precipitated flavone filtered off. The sulphate was then precipitated with barium chloride and estimated gravimetrically (Found: SO_4, 28·8; $C_{15}H_{10}O_7S$ requires SO_4, 28·8%).

Nuclear Oxidation of 7-hydroxy-3-methoxyflavone: Preparation of 7:8-dihydroxy-3-methoxyflavone (X)

To a mechanically stirred solution of 7-hydroxy-3-methoxy-flavone (2·4 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 at 15–20° throughout the addition. After 24 hours, the solution was neutralised with hydrochloric acid when the unchanged flavone separated out. It was recovered by filtration. The filtrate was extracted twice with ether to remove the last traces. The solution was then rendered strongly acidic by adding concentrated hydrochloric acid (30 c.c.). The liquid which became bright orange-red by this time was heated on the water-bath for about half an hour. There was a gradual separation of a brown solid. On cooling more and more separated out in the form of brown coloured needles. It was filtered, washed with water, and crystallised twice from alcohol when it was obtained as pale yellow rectangular plates melting at 220–21°. Yield, 0·5 g. It gave grass-green colour with ferric chloride in alcoholic solution. There was no fluorescence in concentrated sulphuric acid solution. When its alcoholic solution was treated with magnesium and concentrated hydrochloric acid a bright orange-red colour was developed (Found: C, 59·6; H, 5·1; $C_{16}H_{12}O_5$, $2H_2O$ requires C, 60·0 and H, 5·0%).

The diacetyl-derivative was obtained by refluxing the above flavone with acetic anhydride and dry pyridine for 15 minutes and pouring it into water. It crystallised from ethyl acetate-petroleum ether mixture in the form of micaceous rectangular plates melting at 127–8° (Found: C, 65·5; H, 4·4; $C_{20}H_{16}O_7$ requires C, 65·2 and H, 4·3%).

Methylation of the oxidation product: Preparation of 3:7:8-trimethoxy-flavone

7:8-Dihydroxy-3-methoxy-flavone (0·2 g.) was refluxed in acetone solution with dimethyl sulphate (0·5 c.c.) and anhydrous potassium carbonate (2 g.). After 12 hours, the acetone was evaporated and water added to the residue. The methyl ether separated out as a pale yellow solid. It was crystallised from alcohol using a pinch of animal-charcoal. 3:7:8-trimethoxy flavone was obtained in the form of fibrous needles when the crystallisation was rapid. When slowly crystallised aggregates of colourless rectangular prisms were obtained melting at 149–50°. Yield, 0·15 g. (Found: C, 69·3; H, 5·3; $C_{18}H_{16}O_5$ requires C, 69·2; and H, 5·1%).

Demethylation of 7 : 8-*dihydroxy*-3-*methoxy-flavone*: *Preparation of* 3 : 7 : 8-*trihydroxy flavone* (*XI*)

Freshly distilled hydriodic acid (d. 1·7; 17·5 c.c.) was slowly added to the solution of 7 : 8-dihydroxy-3-methoxy-flavone (0·75 g.) in acetic anhydride (10 c.c.) and the solution was refluxed for 1½ hours. It was cooled and water added when a pale yellow precipitate separated out along with some free iodine. Sulphur dioxide was now passed through the mixture till the iodine was completely removed. It was then extracted with ether three times. All the solid went into the ether layer which was finally washed twice with sulphur dioxide water. On removing the ether from the extract by evaporation, a bright yellow crystalline solid was deposited. The compound was crystallised twice from ethyl acetate when the trihydroxy-flavone was obtained as aggregates of rectangular rods melting at 248–9°. Yield, 0·5 g.

It gave a stable red solution in aqueous alkali and an olive brown colour with alcoholic ferric chloride. Its solution in concentrated sulphuric acid was yellow without any fluorescence. It agreed with 7 : 8-dihydroxy-flavonol in all properties as described by Dobrzynski and Kostanecki[5] (Found: C, 66·8; H, 3·6; $C_{15}H_{10}O_5$ requires C, 66·7 and H, 3·7%).

The trihydroxy-flavone was acetylated by refluxing for 20 minutes with acetic anhydride and dry pyridine. The product, obtained on dilution with water, crystallised from alcohol in the form of white needles melting at 210–12°. Dobrzynski and Kostanecki gave the melting point as 210°.

Summary

The possibility of ortho nuclear oxidation in the flavone series has been tested using 7-hydroxy-flavone and 3-methoxy-7-hydroxy-flavone. By means of alkaline persulphate 7 : 8-dihydroxy-flavone (10% yield) and 3-methoxy-7 : 8-dihydroxy-flavone (20% yield) could be obtained. This seems to offer an easier method of preparing the flavonol, 3 : 7 : 8-trihydroxy flavone. The intermediate stage of the sulphate could be isolated pure from 7-hydroxy-flavone.

References

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2. Baker, Brown and Scott .. *J. C. S.*, 1939, 1926.
3. Baker .. *Ibid.*, 1933, 1387.
4. Murty and Seshadri .. *Proc. Ind. Acad. Sci.*, A, 1944, **19**, 17.
5. Dobrzynski and Kostanecki *Ber.*, 1904, **37**, 2806.
6. Rao, Row and Seshadri .. *Proc. Ind. Acad. Sci.*, A, 1945, **22**, 297.