# NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

## Part XX. Oxidation of Gossypetin to 6 : 8-Dihydroxy Quercetin

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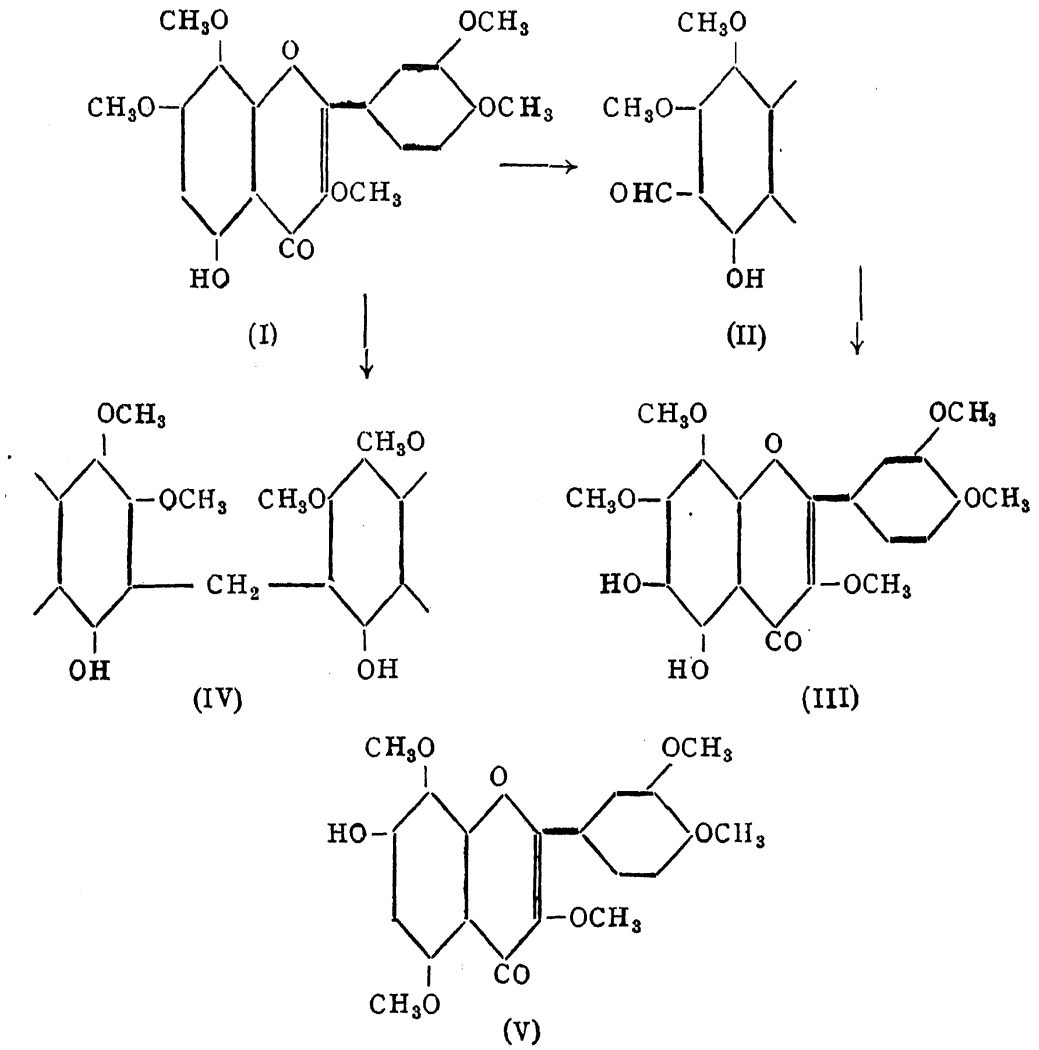
It was reported[1] earlier that the oxidation of gossypetin pentamethyl ether (I) with a free hydroxyl group in the 5-position could not be carried out by means of alkaline persulphate. Ortho-oxidation in the 6-position did not take place with this reagent (single stage process). Since the two-stage ortho-oxidation was subsequently found to proceed quite satisfactorily in the 8 and 5′ positions[2] of flavone derivatives, attempt has now been made to utilize this method for the oxidation of the above mentioned gossypetin derivative in the 6- position. This experiment was particularly needed for the planning of other work in progress in this laboratory and the choice of gossypetin was made because of its fairly easy accessibility. Further the oxidation product, 6: 8-dihydroxy quercetin (III) was required in connection with the study of the physiological properties of hydroxy flavones and an investigation of alternative methods for its preparation would be useful in order to get it in the best yield. Other methods of preparation were described earlier.[3, 1]

Gossypetin pentamethyl ether (I) could be readily made by the partial methylation of gossypetin. On condensation with hexamine in acetic acid solution, it was found to give a mixture of two products in almost equal proportions. One of these was the 6-aldehyde (II) capable of forming readily a dinitrophenyl hydrazone and undergoing oxidation with alkaline hydrogen peroxide to the 5: 6-dihydroxy compound (III) which represents a new type of partial methyl ether. It undergoes further methylation to yield the known heptamethyl ether of 6: 8-dihydroxy quercetin. The method is general and is capable of application to the whole series. The second product of hexamine condensation exhibits no aldehydic properties and agrees with the requirements of the diflavonyl methane formula (IV).

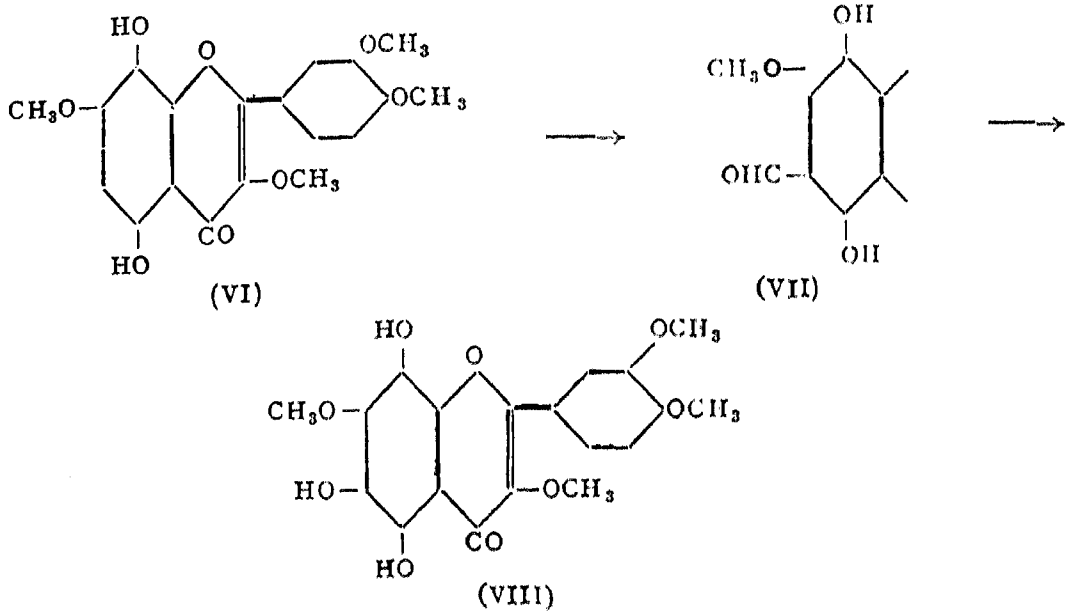
The behaviour of the isomeric pentamethyl ether of gossypetin with a free 7-hydroxy group (V) was next examined. This substance is readily obtained by the hydrolysis of gossypitrin pentamethyl ether and can also




be synthesised by the method adopted by Baker, Nodzu amd Robinson[4] with the simplification suggested by Rao, Rao and Seshadri.[5] But it did not undergo condensation with hexamine and was recovered unchanged. This marked difference in the behaviour of the two isomeric partial methyl ethers of gossypetin may be explained on the basis of a possible fixation of aromatic double bonds, the bond between the 5 and 6 positions exhibiting marked double bond character and the one between 6 and 7 positions lacking it.[6]

A marked improvement in the synthetic work could be effected if the above mentioned ortho-oxidation can be carried out with the tetramethyl ether of gossypetin having free hydroxyl groups in the 5 and 8 positions (VI). This quinol can be easily made starting from quercetin, preparing quercetin-tetramethyl ether and oxidising it with alkaline persulphate.[7] Actually the new procedure is not only feasible but is further advantageous because the quinol condenses with hexamine readily and yields only one product, the aldehyde (VII) which can subsequently be oxidised with hydrogen peroxide to the hydroxy-quinol derivative in good yield. The final compound again represents a new type of partial methyl ethers, having the three hydroxyl

groups in the 5, 6 and 8 positions free (VIII). On methylation it yields the same heptamethyl-ether of dihydroxy quercetin as mentioned above. These experiments have also considerable synthetic value in allied fields and they are being investigated.




## EXPERIMENTAL

### 3:7:8:3′:4′-*O*-pentamethyl-gossypetin-6-aldehyde (*II*)

Pentamethyl gossypetin (2 g.) was dissolved in glacial acetic acid (25 c.c.), hexamine (10 g.) added and the mixture gently refluxed on a wire-gauze for 6 hours. The solution which was bright yellow in the beginning turned dark red; at the end of the period a mixture of fuming hydrochloric acid (d. 1·19) and water (1 : 1; 20 c.c.) was added and the refluxing continued for another 15 minutes. The solution was cooled, diluted with a large volume of water, saturated with sodium chloride and allowed to stand overnight. A bright yellow solid separated which was filtered, washed with water and crystallised from alcohol-acetic acid mixture. The aldehyde separated out crystalline and pure. After a second crystallisation from the same solvent it was obtained as small yellow prisms melting at 181–2°. Yield, 0·6 g. It was sparingly soluble in alcohol and ether but dissolved readily in acetone and acetic acid. It gave an yellow solution in concentrated sulphuric acid and a brown colour with ferric chloride in alcoholic solution (Found: C, 60·8; H, 5·1; $C_{21}H_{20}O_9$ requires C, 60·6 and H, 4·8%).

The dinitrophenyl hydrazone was prepared by boiling the compound with dinitrophenyl hydrazine in alcoholic solution for 10 minutes. On

recrystallisation from alcohol it melted at 264–5° with decomposition and appeared as orange yellow plates under the microscope (Found: C, 54·2; H, 3·9; $C_{27}H_{24}N_4O_{12}$ requires C, 54·4 and H, 4·0%).

On diluting with water the mother-liquor from the crystallisation of the aldehyde a yellow compound was precipitated which was purified by recrystallisation from alcohol. It appeared as slender yellow needles under the microscope and melted at 95–6°. It dissolved in alkalies to a yellow solution and gave a pale brown colour with ferric chloride in alcoholic solution (Found: C, 62·0; H, 5·4; $C_{41}H_{40}O_{16}$ requires C, 62·4 and H, 5·1%).

The compound did not give a dinitro phenyl hydrazone. It was unaffected on oxidation with hydrogen peroxide in alkaline solution for half an hour, but on keeping longer veratric acid could be isolated from the reaction mixture.

5: 6-*Dihydroxy*-3: 7: 8: 3′: 4′-*pentamethoxy flavone* (*III*)

The above aldehyde (1 g.) was suspended in 5 c.c. of 2N sodium hydroxide and enough pyridine added to dissolve it. The yellow solution was cooled in ice-water and 6% hydrogen peroxide (6 c.c.) was added in small quantities during 15 minutes with thorough mixing. The mixture assumed a deep reddish-brown colour. It was left in the ice-bath for another fifteen minutes with occasional shaking. The solution was then acidified with dilute hydrochloric acid, the yellow turbid solution saturated with common salt and extracted with ether. The ether extract was dried over anhydrous sodium sulphate and the solvent removed. The yellow solid residue was crystallised from alcohol when it was obtained as yellow plates and prisms melting at 230–31°. Yield 0·4 g. It gave yellow solutions with concentrated sulphuric acid and aqueous sodium hydroxide; with ferric chloride in alcoholic solution it gave a greenish brown colour turning deep brown-red with excess (Found: C, 59·5; H, 5·2; $C_{20}H_{20}O_9$ requires C, 59·4 and H, 4·9%).

The dihydroxy compound was completely methylated in acetone solution by means of dimethyl sulphate and anhydrous potassium carbonate. The heptamethyl ether melted at 130–1° and did not depress the melting point of an authentic sample of heptamethyl-6: 8-dihydroxy-quercetin.[3, 1] On demethylating the dihydroxy compound with hydriodic acid in the usual manner 6: 8-dihydroxy quercetin was obtained which was identical in all respects with an authentic specimen.

5: 8-*Dihydroxy*-3: 7: 3′: 4′-*tetramethoxy flavone*-6-*aldehyde* (*VII*)

5: 8-Dihydroxy-3: 7: 3′: 4′-tetramethoxy flavone (3 g.) and hexamine (12 g.) were condensed in glacial acetic acid solution (30 c.c.) and the product worked up according to the procedure already described. The crude yellow solid that was first obtained crystallised from alcohol as clusters of yellow long slender rods turning brown at 220° and melting at 270–2° with decomposition. The substance gave a deep brown-red colour with ferric chloride in alcoholic solution and a deep yellow solution in concentrated sulphuric acid. Yield, 1·0 g. (Found: C, 60·1; H, 4·6; $C_{20}H_{18}O_9$ requires C, 59·7 and H, 4·5%).

The compound gave a dinitrophenyl hydrazone readily which when crystallised from alcohol melted at 241–2° with decomposition and appeared as dark red prisms under the microscope (Found: C, 53·2; H, 3·6; $C_{26}H_{22}N_4O_{12}$ requires C, 53·6 and H, 3·8%).

5: 6: 8-*Trihydroxy*-3: 7: 3′: 4′-*tetramethoxy flavone* (*VIII*)

The above aldehyde (1 g.) was suspended in 6 c.c. of 2N sodium hydroxide and pyridine (10 c.c.) was added to bring it into solution. The oxidation was carried out with 6% hydrogen peroxide (6 c.c.) cooling in ice-water and the product worked up as already described. An yellow oil was first obtained which quickly solidified on rubbing with a glass rod. It was recrystallised from alcohol when it came out as glistening rectangular prisms melting at 272–3°. Yield 0·3 g. It was sparingly soluble in alcohol and gave a dark red colour with ferric chloride in alcohol solution (Found: C, 58·6; H, 4·7; $C_{19}H_{18}O_9$ requires C, 58·5 and H, 4·6%). On complete methylation and demethylation it yielded the heptamethoxy and hepta-hydroxy flavones respectively which were identical in all respects with the samples already described.

## Summary

The two stage process of ortho-oxidation is applied to partial methyl ethers of gossypetin in order to introduce a new hydroxyl in the 6 position. The pentamethyl ether with a free hydroxyl in the 7- position does not react with hexamine. On the other hand, its isomer with a free 5-hydroxyl yields a mixture of products, one of which is the 6-aldehyde which could be oxidised by means of hydrogen peroxide. A more satisfactory procedure is to use the tetramethyl ether having the 5 and 8 hydroxyls free. It yields only the 6-aldehyde and subsequent oxidation with hydrogen peroxide leads to the formation of 5: 6: 8-trihydroxy compound. The products are useful partial methyl ethers and yield 6: 8-dihydroxy-quercetin on demethylation and its heptamethyl ether on methylation.

## References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7. Rao and Seshadri .. *Ibid.*, 1947, **25**, 417.