

NUCLEAR OXIDATION IN THE FLAVONE SERIES

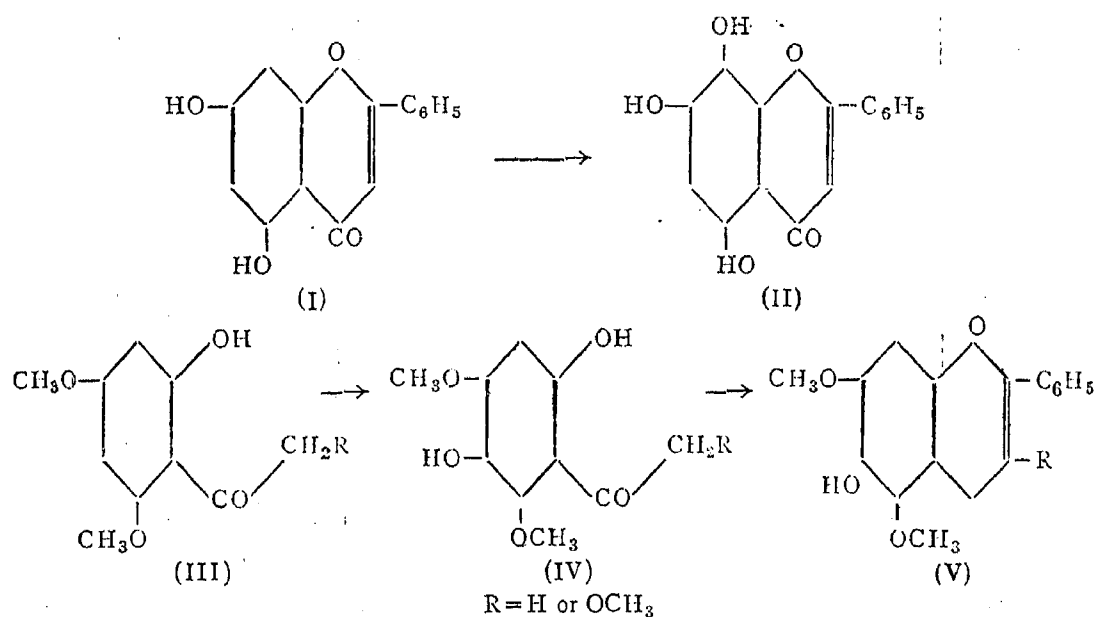
Part IX. Oxidation of Related Chalkones

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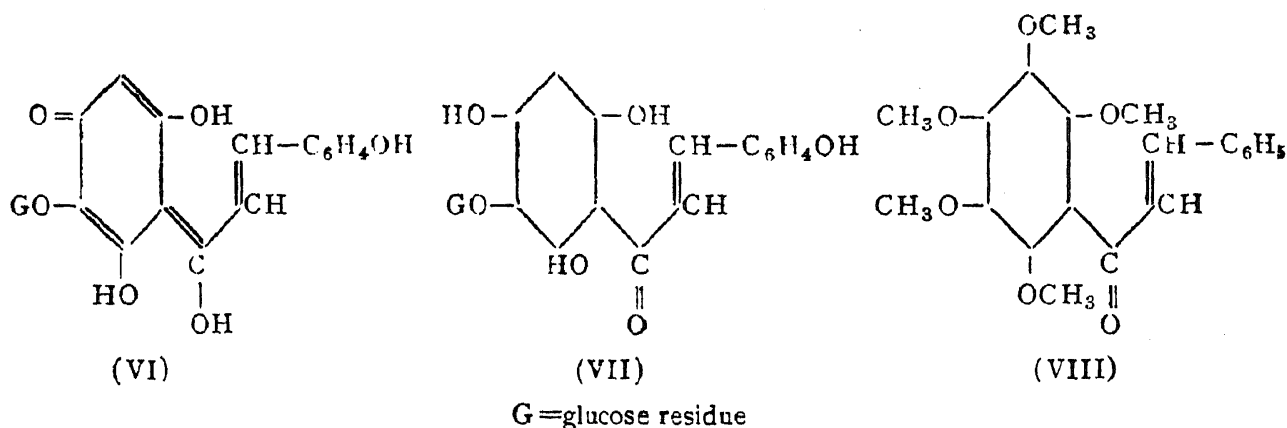
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FROM the results recorded in the earlier papers of this series it is clear that the introduction of a hydroxyl group in the 8-position (II) of naturally occurring flavones by nuclear oxidation is quite facile and that this process is most possibly adopted in phytochemical synthesis. On the other hand the 6-position of the flavone structure does not appear to be available for oxidation and hence in the formation of flavones with a hydroxyl in the 6-position (baicalin and quercetagenin series) a precursor with the pyrone ring not yet closed would appear to be involved in the oxidation. As appropriate model experiments the oxidation of phloroacetophenone dimethyl ether and of its ω -methoxy derivative (III) could be mentioned.^{1, 7} It was, however, considered desirable to study the behaviour in this oxidation of compounds like chalkones and dibenzoylmethanes which are closely related to the flavones and which can be eventually converted into flavones. The results of exploratory experiments using chalkones are described in this paper.

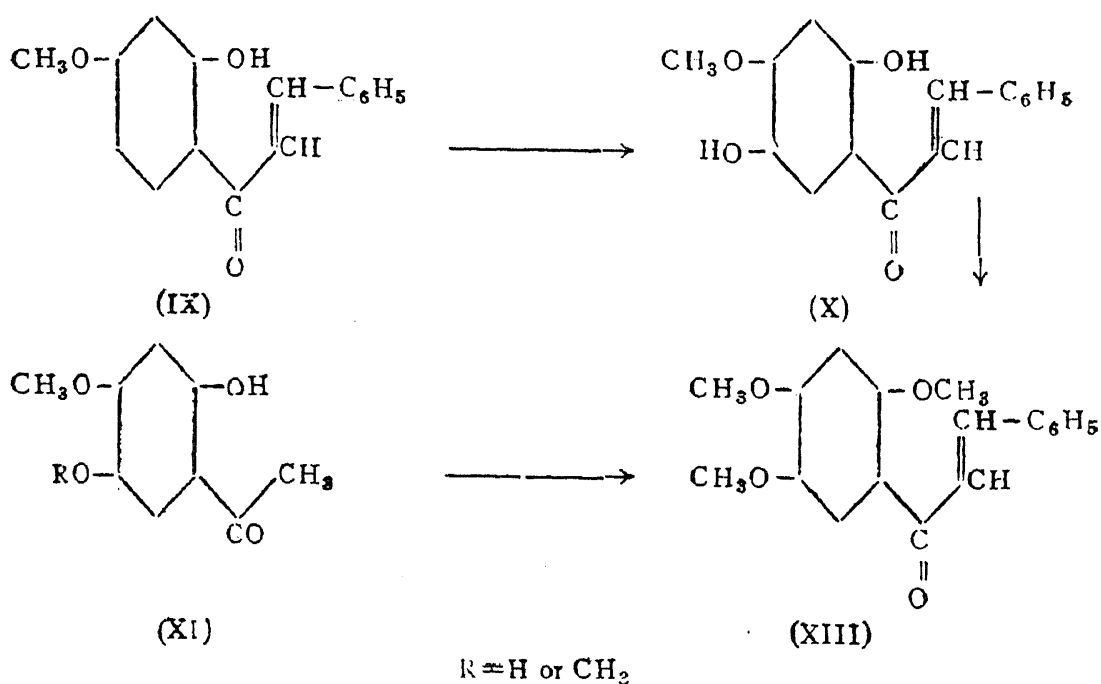


Besides their relationship to flavones, members of the chalkone group are otherwise also important because they occur in nature. Examples of:

chalkones having additional hydroxyl groups in the phloroglucinol nucleus are found in carthamin (VI) and isocarthamin² (VII) which are glucosides and pedicellin (VIII)³, pedicin and their allies which are fully or partly methylated compounds.

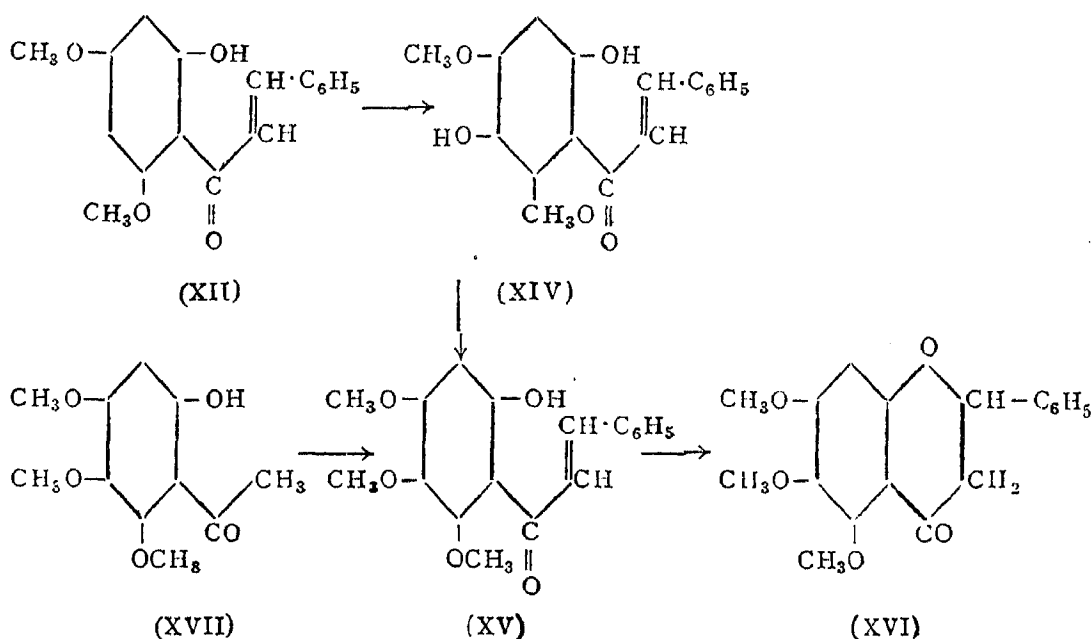


Experiments on the nuclear oxidation of chalkones are not only of interest in regard of biogenesis, but they could also be expected to be useful for the preparation of certain types of compounds which cannot be easily obtained from the appropriate ketone and aldehyde components by condensation. For example chalkone (X) is the direct result of the nuclear oxidation of chalkone (IX) whereas it cannot be conveniently made by the condensation of ketone (XI, R = H) with benzaldehyde. The presence of free hydroxyl groups and particularly *p*-dihydroxyl groups in the reacting components lead to complications and to failure in the condensation.



2-Hydroxy-4-methoxy-chalkone (IX) and 2-hydroxy-4:6-dimethoxy-chalkone (XII) have now been subjected to nuclear oxidation using alkaline persulphate. In order to get good yields of the products it is necessary to

use lower temperatures for the oxidation and gentler conditions for hydrolysing the sulphate formed as the intermediate stage. For confirming the constitution of the product (X) obtained in the first case, it has been fully methylated. The trimethyl ether is found to be identical with 2:4:5-trimethoxy chalkone (XIII) prepared from 2-hydroxy-4:5-dimethoxy-acetophenone (XI, R = CH₃) by condensation with benzaldehyde and subsequent methylation (*cf.* Bargellini *et al.*⁴). In the second case the dihydroxy-chalkone (XIV) has been partially methylated (XV) and then converted into the trimethoxy-flavanone which is found to be identical with 5:6:7-trimethoxy-flavanone (XVI) obtained independently from 2-hydroxy-4:5:6-trimethoxy-acetophenone (XVII) as indicated below:—



EXPERIMENTAL

2-Hydroxy-4-methoxy-chalkone (IX)

This compound was prepared earlier by Bargellini and Monti.⁵ The following conditions employing excess of the aldehyde and ordinary room temperature give rise to good yields.

A solution of 2-hydroxy-4-methoxy-acetophenone (3.0 g.) and benzaldehyde (6 c.c.) in alcohol (20 c.c.) was cooled to 0° and potassium hydroxide (30.0 g. in 24 c.c. of water) was added in small quantities at a time with shaking. The flask was stoppered tight and kept for two days at the laboratory temperature. The contents were then diluted with water, extracted with ether to remove the unreacted aldehyde and then acidified. The chalkone which separated as a yellow solid was freed from benzoic acid by treatment

with ice-cold sodium bicarbonate solution. On recrystallisation from alcohol it was obtained as stout elongated hexagonal crystals melting at 105–6°, the m.p. recorded by Bargellini and Monti being 106–8°. Yield 3.0 g.

2:5-Dihydroxy-4-methoxy-chalkone (X)

To a stirred solution of 2-hydroxy-4-methoxy-chalkone (IX) (1.0 g.) in a mixture of pyridine (10 c.c.) and aqueous sodium hydroxide (0.6 g. in 20 c.c.) were added dropwise potassium persulphate solution (1.5 g. in 50 c.c.) and aqueous sodium hydroxide (0.6 g. in 20 c.c.) during the course of 2 hours. After allowing the solution to stand for 24 hours, it was neutralised (congo-red) with dilute hydrochloric acid and extracted twice with ether. The clear brown aqueous solution was treated with sodium sulphite (2.0 g.) and concentrated hydrochloric acid (20 c.c.). On heating the solution at 100° for 15 minutes an orange-yellow solid separated out which was filtered and washed. When recrystallised from alcohol it separated as long stout rectangular plates melting at 168–70°. With alcoholic ferric chloride it gave a brown colour. Yield, 0.25 g. (Found: C, 71.6; H, 4.9; $C_{16}H_{14}O_4$ requires C, 71.1, H, 5.2%.)

2:4:5-Trimethoxy-chalkone (XIII)

A solution of the above 2:5-dihydroxy-4-methoxy-chalkone (X) (0.2 g.) in dry acetone (20 c.c.) was treated with dimethyl sulphate (1 c.c.) and anhydrous potassium carbonate (5.0 g.). After refluxing for ten hours the potassium salts were filtered off and washed with warm acetone. On removing the solvent from the acetone solution the trimethoxy-chalkone was obtained as a bright yellow solid. It crystallised from alcohol as fine needles melting at 115–16°. Yield 0.15 g. Its solution in concentrated sulphuric acid was orange-red. A mixed melting point with the sample of 2:4:5-trimethoxy-chalkone obtained from 2-hydroxy-4:5-dimethoxy-acetophenone (XI, R = CH₃) was undepressed. The condensation of this ketone (1.0 g.) with benzaldehyde (2 c.c.) was effected under conditions already described. 2-Hydroxy-4:5-dimethoxy-chalkone (yield, 1.0 g.) crystallised from absolute alcohol as bright-yellow needles. Methylation with dimethyl sulphate and potassium carbonate yielded the trimethoxy chalkone melting at 115–16°.

2-Hydroxy-4:6-dimethoxy-chalkone (XII)

This chalkone was prepared earlier by Kostanecki and Tambor.⁶ By employing excess of aldehyde and following the procedure already mentioned in this paper better yields could be obtained. 2-Hydroxy-4:6-dimethoxy-acetophenone (3.0 g.) when condensed with benzaldehyde (6 c.c.) yielded

the above chalcone (2.0 g.) as an orange coloured solid. It crystallised from alcohol as fine needles melting at 91–92°.

2:5-Dihydroxy-4:6-dimethoxy-chalcone (XIV)

To a stirred solution of 2-hydroxy-4:6-dimethoxy-chalcone (XII) (1.0 g.) in a mixture of pyridine (10 c.c.) and aqueous sodium hydroxide (1.0 g. in 30 c.c.) was added dropwise potassium persulphate solution (1.5 g. in 40 c.c. of water) during the course of two hours. Further steps were as already described for a similar case. The crude dihydroxy compound was extracted with ether and recrystallised from aqueous alcohol when it was obtained as fine needles, melting at 156–58°. With alcoholic ferric chloride it gave a deep brown colour. Yield 0.2 g. (Found: C, 67.9; H, 5.5; $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%.)

5:6:7-Trimethoxy-flavanone (XVI)

(i) A solution of the above 2:5-dihydroxy-4:6-dimethoxy-chalcone (1.0 g.) in dry acetone (20 c.c.) and dry benzene (40 c.c.) was treated with dimethyl sulphate (0.5 c.c.) and anhydrous potassium carbonate (5.0 g.). After refluxing for six hours the potassium salts were filtered and washed with warm benzene. The benzene filtrate was extracted with 5% aqueous sodium hydroxide four times. The combined alkaline extracts were run into ice-cold dilute hydrochloric acid, extracted with ether and the ether solution washed with 4% aqueous sodium carbonate. On distilling off the solvent 2-hydroxy-4:5:6-trimethoxy-chalcone (XV) was obtained as a bright yellow oil and could not be crystallised. With alcoholic ferric chloride it gave a reddish-brown colour. Yield 0.7 g. It was directly used for conversion into the flavanone. A solution of the chalcone (0.6 g.) in 50% aqueous alcohol (50 c.c.) was treated with concentrated sulphuric acid (1.5 c.c.) and the resulting solution boiled under reflux for 24 hours. On concentrating the solution the trimethoxy-flavanone separated out as a colourless crystalline solid. It was filtered and washed first with a weak solution of sodium hydroxide and then with water. On crystallisation from alcohol it was obtained as colourless needles melting at 154–55°. It gave no colour with alcoholic ferric chloride but a pink solution with magnesium and hydrochloric acid. Mixed melting point with the sample obtained by the method given below indicated no depression. (Found: C, 68.3; H, 5.7; $C_{18}H_{18}O_5$ requires C, 68.8; H, 5.7%.)

(ii) 2-Hydroxy-4:5:6-trimethoxy-acetophenone (XVII) was obtained by the method of Sastri and Seshadri.⁷ It (1.0 g.) was condensed with benzaldehyde (3 c.c.) under the conditions employed in previous cases. The

product (XV) (0.6 g.) was again a bright yellow liquid and could not be crystallised. When converted into the flavanone it yielded 5:6:7-trimethoxyflavanone (XVI) melting at 154–55° and identical with the sample described above in every respect.

SUMMARY

It is shown that the nuclear oxidation of hydroxy-chalkones can be successfully effected thereby introducing a fresh hydroxyl in the 5-position which corresponds to the 6-position in flavanones and flavones. 2-Hydroxy-4-methoxy-chalkone and 2-hydroxy-4:6-dimethoxy-chalkone have thus been oxidised to the 2:5-dihydroxy compounds. In the first case the product is shown to be 2:5-dihydroxy-4-methoxy-chalkone by complete methylation and identification of the derivative as 2:4:5-trimethoxy-chalkone. In the second case it is proved to be 2:5-dihydroxy-4:6-dimethoxy-chalkone by partial methylation and conversion into 5:6:7-trimethoxyflavanone.

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