NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XVII. A Synthesis of Oroxylin-A

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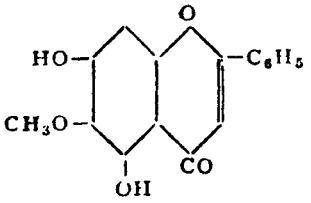
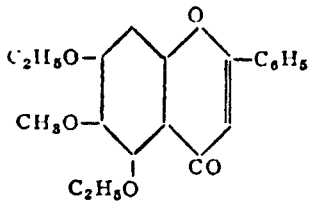
The isolation of Oroxylin-A in a pure condition was recently reported.[1] In the same communication its constitution (I) was established by preparing its diethyl ether and showing that it is identical with a synthetic sample of 5:7-diethoxy-6-methoxy flavone (II). Oroxylin-A itself has now been synthesised and the experiments carried out in this connection are described in this paper.

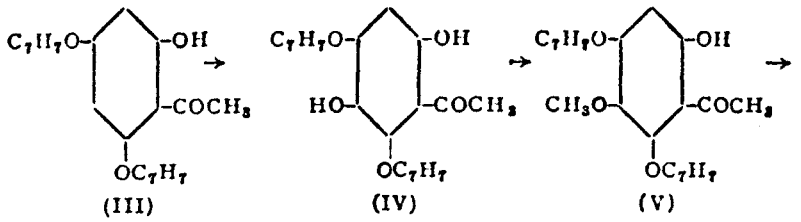


(I)

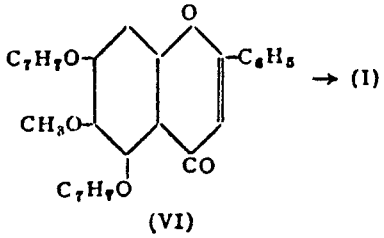


(II)

The general method adopted is that of baicalein and scutellarein synthesis of Sastri and Seshadri[2] in which the nuclear oxidation of a phloroacetophenone derivative is an essential stage. A simple scheme explored first was as follows:—



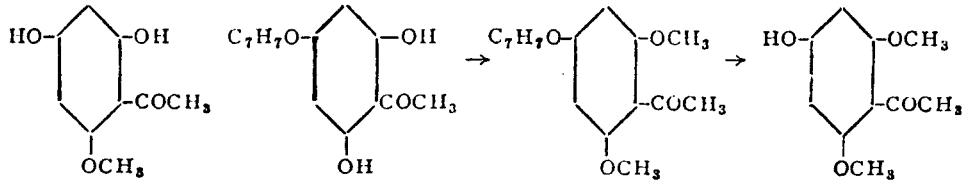
(III) (IV) (V)



(VI)

The benzylation of phloroacetophenone was earlier reported[3] to yield a nuclear benzylated product. By employing suitable conditions it has now been possible to make the dibenzyl ether (III). Its constitution has been established by methylation with excess of dimethyl sulphate and subsequent debenzylation whereby 2:4-dihydroxy-6-methoxy acetophenone (VII)[4] is obtained. But so far experiments to oxidise this dibenzyl ether have not been successful.

In the search for a better starting material mono-benzylation of phloroacetophenone has next been attempted. Employing a little over one mole of benzylchloride a mono-benzyl ether could be obtained fairly readily. It is a pure individual with a sharp melting point and on examination has proved to be the 4-benzyl ether (VIII). Its constitution has been established by carrying out complete methylation (IX) followed by debenzylation whereby 2:6-dimethoxy-4-hydroxy-acetophenone (X)[5] is obtained.

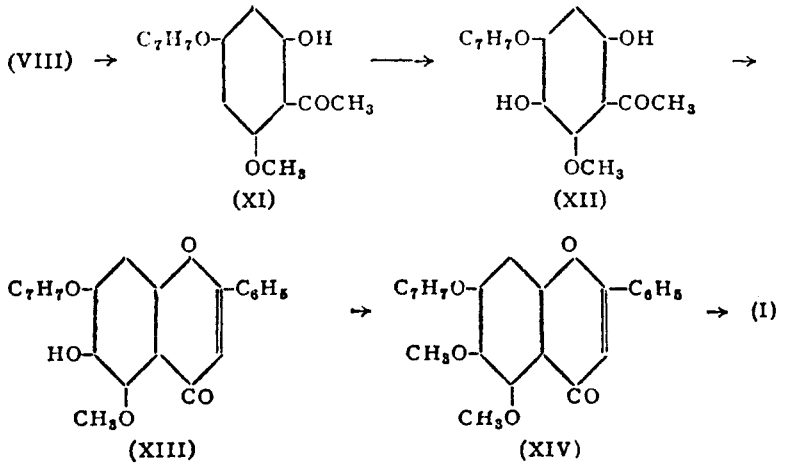


(VII) (VIII) (IX) (X)

The course of the mono-benzylation of phloroacetophenone follows that of partial benzoylation and methylation so far recorded. By the benzoylation of phloroacetophenone and phloropropiophenone Canter, Curd and Robertson[5] obtained mainly the *p*-monobenzoates and only in small amounts the isomeric orthobenzoates. Earlier Karrer[6] employed phlorobutyrophenone and phlorobenzophenone and obtained only the corresponding para benzoates. More recently Kuhn, *et al.*,[7] methylated ω-methoxy-phloroacetophenone using restricted quantities of diazomethane and obtained only the *p*-methyl ether in a poor yield. As Robertson, *et al.*, have remarked it is quite possible that in all these cases traces of the isomeric ortho-compounds are produced but have escaped detection.

Partial methylation with dimethyl sulphate of the mono-benzyl ether (VIII) has yielded 4–O-benzyl-6-O-methyl-phloroacetophenone (XI). This can be debenzylated to the monomethyl-phloroacetophenone (VII). The reverse of this process, that is the benzylation of 2-methyl-phloroacetophenone has been reported by Gulati and Venkataraman.[4] The product obtained by their method is identical with the one made from (VIII). Oxidation of (XI) proceeds satisfactorily forming the quinol ketone (XII). During the subsequent Allan-Robinson condensation using this quinol

ketone (XII) and benzoic anhydride and sodium benzoate partial demethylation in the 5-position of the flavone seems to take place, because the product gives a prominent ferric reaction. Hence the stage (XIII) has not been definitely characterised. On methylation, however, the dimethyl-monobenzyl ether of baicalein (XIV) can be obtained pure. By the action of hydrobromic acid in acetic acid on this substance debenzylation and partial demethylation in the 5-position take place yielding oroxylin-A (6-O-methyl baicalein) (I). The suitability of this reagent for the removal of the 5-methoxyl has been shown by the earlier work of Shah, Virkar and Venkataraman and Seshadri and Venkateswarlu using calycopterin methyl ethers.[8] In the present case oroxylin-A is obtained pure and the synthetic sample agrees in every respect with the natural sample described recently.[1] For confirming the identity the diacetate and diethyl ether have also been prepared and compared with the natural samples.



Experimental

4-*O*-*Benzyl-phloracetophenone* (*VIII*)

Dry phloracetophenone (2 g.) was dissolved in anhydrous acetone (25 c.c.) and to the solution were added redistilled benzyl chloride (1·0 c.c.) and freshly ignited potassium carbonate (10 g.). The mixture was refluxed on a water-bath for 3 hours with occasional shaking. The red solution was filtered, the solvent distilled off and the benzyl chloride removed by passing steam. The red oily product solidified on cooling and was purified by recrystallisation from a large quantity of alcohol. The monobenzyl ether was thus obtained as cream-coloured prisms melting with decomposition at 188–9°. Yield, 0·4 g.

The compound was sparingly soluble in alcohol but dissolved readily in acetone. It dissolved in aqueous sodium hydroxide to give a pale yellow solution and was reprecipitated by the addition of acid. In alcoholic solution, it gave a brown colour with ferric chloride. Unlike the dimethyl and the dibenzyl ethers of phloracetophenone, the monobenzyl ether did not give any colour with concentrated nitric acid. (Found: C, 69·5; H, 5·7; $C_{15}H_{14}O_4$ requires C, 69·8 and H, 5·4%).

The above mono-benzyl ether (0·5 g.) was methylated using excess of dimethyl sulphate (0·5 c.c.) and anhydrous potassium carbonate (5 g.) in dry acetone medium (20 c.c.) by boiling for 20 hours. The product did not solidify even on keeping in the refrigerator for several days. So it was debenzylated by heating with concentrated hydrochloric acid (5 c.c.) in glacial acetic acid solution (10 c.c.). The mixture was diluted with water and extracted with ether. On evaporating the ether and then removing the benzyl chloride in steam, 2:6-dimethyl phloracetophenone (X) separated out. It crystallised from dilute alcohol as colourless rectangular rods and melted at 183–4°.

4-O-Benzyl-6-O-methyl-phloracetophenone (XI)

To a solution of the mono-benzyl ether (1·3 g.) in dry acetone (50 c.c.) were added freshly distilled dimethyl sulphate (0·5 c.c.) and ignited potassium carbonate (5 g.) and the mixture was gently refluxed on a water-bath for 6 hours. The inorganic salts were then filtered and washed with warm acetone; the filtrate was concentrated and the residue treated with water when the benzyl-methyl ether separated as an oil which completely solidified on keeping in the refrigerator. It was crystallised once from alcohol and then from acetone-petroleum ether mixture when it was obtained as colourless flat needles melting at 73–4°. Yield 1·0 g. The compound was soluble with difficulty in sodium hydroxide solution, sparingly soluble in alcohol and easily in acetone. It gave a pinkish brown colour with ferric chloride in alcohilic solution and turned blue with concentrated nitric acid. (Found: C, 70·2; H, 6·2; $C_{16}H_{16}O_4$ requires C, 70·6 and H, 5·9%).

On debenzylation with concentrated hydrochloric acid in glacial acetic solution, 2-methyl phloracetophenone was obtained, mp. 203–4°, which did not depress the melting of an authentic specimen. Further the benzyl-methyl ether was identical with the sample obtained by the benzylation of 2-O-methyl-phloracetophenone according to the procedure of Gulati and Venkataraman.[4]

2: 5-*Dihydroxy-4-benzyloxy-6-methoxy-acetophenone (XII)*

2-Hydroxy-4-benzyloxy-6-methoxy acetophenone (XI; 13·0 g.) was dissolved in pyridine (15 c.c.) and aqueous sodium hydroxide (20 g. in 150 c.c. of water) added. To the continuously stirred mixture was let in a solution of potassium persulphate (15 g. in 350 c.c. of water) dropwise during the course of 4 hours, the flask being kept at a temperature of 15–20°. The stirring was continued for a further period of 2 hours and the deep red solution allowed to stand for 24 hours. The reaction mixture was then rendered acid to congo-red by addition of hydrochloric acid, the precipitated unchanged ketone (6·0 g.) filtered off, and the aqueous filtrate was extracted once with ether to remove the last traces. It was then treated with sodium sulphite (5 g.), concentrated hydrochloric acid (50 c.c.) and benzene (100 c.c.) and the mixture heated in a boiling water-bath for half-an-hour. The reaction mixture was cooled, the benzene layer separated and the aqueous solution repeatedly extracted with ether. The total benzene and ether extracts were dried over anhydrous sodium sulphate and the solvents distilled off, the last 100 c.c. being removed under reduced pressure. The dihydroxy compound was obtained as a yellow oil which solidified on cooling and scratching with a glass-rod. It was crystallised from dilute alcohol when it was obtained as stout yellow prisms melting at 161–2°. Yield, 1·7 g. The yield and purity of the compound were found to suffer considerably on longer heating for hydrolysis or evaporating the extracts with exposure to air.

The compound was moderately soluble in hot water, readily in alcohol and acetone, but sparingly in light petroleum. Its solution in aqueous sodium hydroxide was yellow in the beginning and turned reddish brown on standing. In alcoholic solution it gave a transient green colouration with ferric chloride which rapidly turned brown. (Found: C, 67·1; H, 5·8; $C_{16}H_{16}O_5$ requires C, 66·8 and H, 5·6%).

Allan-Robinson condensation

The dihydroxy ketone obtained above (2·9 g.) was intimately mixed with benzoic anhydride (13·6 g.) and sodium benzoate (5·7 g.) and the mixture was heated *in vacuo* for 4 hours. The cake was broken up, suspended in alcohol and refluxed for half-an-hour on a water-bath after the addition of aqueous sodium hydroxide (5 g. in 10 c.c. of water). The alcohol was removed under reduced pressure, the residue dissolved in water, the dark-brown solution filtered and saturated with carbon dioxide. It was extracted with ether, the ether extract dried over anhydrous sodium sulphate

and the solvent removed. An yellow oil was obtained which turned into a solid on rubbing with a glass rod. To hydrolyse any 3-benzoyl compound that might have been formed, the solid was refluxed with 5% aqueous sodium carbonate (20 c.c.) for one hour. The yellow solution was filtered and acidified when the product was precipitated as a yellowish-brown solid. It could be crystallised from rectified spirit. But it gave a deep greenish-brown colour with ferric chloride in alcoholic solution and did not have a sharp melting point. It, therefore, appeared to be a mixture of the 6-hydroxy and 5:6-dihydroxy (partially demethylated) compounds and hence was directly used for methylation after thorough drying.

5:6-*Dimethoxy-7-benzyloxy-flavone* (*XIV*)

The above mixture (0·5 g.) was refluxed in dry acetone (25 c.c.) solution with ignited potassium carbonate (5 g.) and freshly distilled dimethyl sulphate (0·5 c.c.) for a period of 30 hours. The acetone solution was filtered and the potassium salts washed with a small quantity of hot acetone. On distilling off the solvent from the filtrate, a pale yellow, viscous oil was obtained which solidified on leaving in the ice-chest for a few days. The product crystallised from absolute alcohol as colourless plates melting at 168–9°. It did not dissolve in aqueous sodium hydroxide and did not give colour with ferric chloride. (Found: C, 73·9; H, 4·9; $C_{24}H_{20}O_5$ requires C, 74·2 and H, 5·2%).

5:7-*Dihydroxy-6-methoxy-flavone*: *Oroxylin-A* (*I*)

5:6-Dimethoxy-7-benzyloxy flavone XIV (0·5 g.) was dissolved in glacial acetic acid (10 c.c.), hydrobromic acid in glacial acetic acid solution (10 c.c.) added and the mixture heated at 60° for one hour. The solution was cooled, diluted with water and extracted with ether and the solvent removed from the extract. After distilling off the benzyl bromide in steam, an yellow oil was left behind. It solidified on leaving in the ice-chest overnight and rubbing with a glass rod. The compound crystallised from alcohol as pale yellow plates and prisms melting at 219–20°; the mixed melting point with a pure natural sample of Oroxylin-A was undepressed. It was identical in all its properties and colour reactions with the natural sample. (Found: OMe, 10·7%; $C_{16}H_{12}O_5$ requires OCH_3, 10·9%).

For further confirmation, the acetate and the ethyl ethers were also prepared using the synthetic specimen. They were identical with the natural samples and the mixed melting points were undepressed,

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2-Hydroxy-4: 6-dibenzyloxy-acetophenone (III)

Phloracetophenone (2·5 g.) which had been previously dried in an air oven at 120° for two hours, was dissolved in dry acetone (80 c.c.) and freshly ignited potassium carbonate (8 g.) and benzyl chloride (4·2 c.c.) were added and the mixture refluxed for 20 hours on a water-bath with occasional shaking. At the end of this period, acetone was distilled off and water added to dissolve the inorganic salts. The solution was steam-distilled to remove traces of benzyl chloride. The remaining oil was extracted with ether, washed with very dilute aqueous sodium hydroxide and then with water. The solid obtained by evaporating the ether solution was crystallised from methyl alcohol when 2-hydroxy-4: 6-dibenzyloxy-acetophenone separated out as colourless rectangular rods melting at 98–100°. Yield, 1·5 g.

It was soluble in acetone, alcohol and petroleum ether. Like the corresponding dimethyl ether of phloracetophenone, it was sparingly soluble in aqueous alkali. It gave an intense reddish-brown colour with alcoholic ferric chloride and a deep blue colour with conc. nitric acid. (Found: C, 75·7; H, 5·4; $C_{22}H_{20}O_4$ requires C, 75·9 and H, 5·7%.)

The above dibenzyl ether (1 g.) was methylated using acetone (50 c.c.), dimethyl sulphate (0·8 c.c.) and anhydrous potassium carbonate (5 g.) and boiling for 15 hours. The inorganic salts were filtered off and washed with warm acetone. The acetone filtrate was evaporated and the residue taken up in ether and washed with aqueous sodium hydroxide and water. On evaporating the ether solution a reddish brown oil was obtained which was directly subjected to debenzylation using glacial acetic acid (10 c.c.) and concentrated hydrochloric acid (4 c.c.) and heating on a boiling water-bath for one hour. Excess of water was added and the oily product ether-extracted. The ether solution was shaken with aqueous bicarbonate to remove the acetic acid and subsequently with 1% aqueous sodium hydroxide. On acidifying the alkaline solution, a semi-solid product was obtained. It crystallised from benzene as cream-coloured prisms melting at 203–4° alone or in admixture with an authentic sample of 2-methyl phloracetophenone.

SUMMARY

Phloroacetophenone-2: 4-dibenzyl ether is prepared; it does not undergo persulphate oxidation satisfactorily. Monobenzylation of phloroacetophenone yields the 4-benzyl ether readily; it is partially methylated to the 2-methyl-4-benzyl ether. Starting with this compound, persulphate oxidation, Allan-Robinson condensation using benzoic anhydride and sodium

benzoate and methylation produce 5:6-dimethoxy-7-benzyloxyflavone. Hydrobromic acid causes besides debenzylation, demethylation in the 5-position. The final product is the 6-methyl ether of baicalein which is identical with oroxylin-A isolated from the root and stem barks of *Oroxylum indicum*.

References

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