A NEW EFFECT OF HYDROGEN BOND FORMATION (CHELATION)

Part VII. Hydrogen Peroxide Oxidation of Some 2′-Substituted Chalkones and Flavanones

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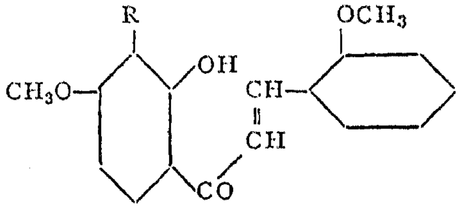
In our previous communications[1, 2] were reported the extraordinary properties of 2′-hydroxy and methoxy flavanones and 2′-methoxy chalkones. In view of these features and particularly because of the failure to convert the 2′-hydroxy and methoxy flavanones into flavones by iodine and sodium acetate[2] it was considered necessary to study the reaction of these compounds towards alkaline hydrogen peroxide. Further the conversion of chalkones to known derivatives of flavonols would add support to their constitutions. The results obtained in the course of this study are recorded in this paper.

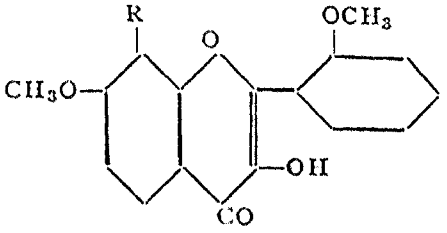
It has already been pointed out[3] that chalkones without a substituent in the 6-position yield flavonols on oxidation with hydrogen peroxide while a substituent in this position causes the formation of benzal-coumaranones. The behaviour of 2′-methoxy chalkones is in agreement with this generalisation. Thus 2-hydroxy-4 : 2′-dimethoxy chalkone (I *a*) and 2-hydroxy-3 : 4 : 2′-trimethoxy chalkone (I *b*) give rise to the expected 7 : 2′-dimethoxy (II *a*) and 7 : 8 : 2′-trimethoxy (II *b*) flavonols. The former (II *a*) on methylation yields the trimethyl ether recently reported by Jain *et al.*[4] The products in these cases are exclusively flavonols as shown by their complete solubility in aqueous sodium hydroxide and positive ferric reaction.

Similar oxidation of 2-hydroxy-6 : 2′-dimethoxy chalkone (III *a*), and 2-hydroxy-4 : 6 : 2′ : 4′-tetramethoxy chalkone (III *b*) yields the corresponding benzal-coumaranones (IV *a* and IV *b*). The products separate from the alkaline solution, give no colour with ferric chloride and develop a deep red colour with concentrated sulphuric acid.

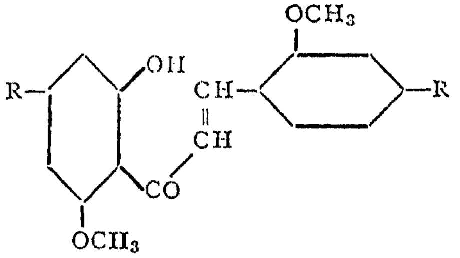
A very different result is obtained when the 2′-hydroxy flavanones are treated under the same conditions with alkaline hydrogen peroxide. 5-Methoxy-2′-hydroxy, 5 : 7-dimethoxy-2′-hydroxy and 5 : 7 : 4′-trimethoxy-2′-hydroxy flavanones remain unaffected and are recovered completely unchanged. Variations in the strength of alkali or quantities of hydrogen peroxide used have no effect. In this resistance to oxidation the influence of the 2′-hydroxyl in the flavanone seems to be similar to that of the 5-hydroxyl



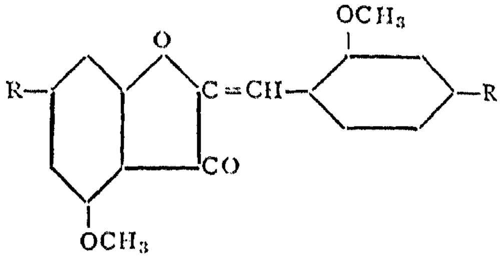
(I)



(II)



(III)



(IV)

a, R=H
b, R=OCH_3

group, for under the same conditions 5-hydroxy-2′-methoxy flavanone and naringenin-7 : 4′-dimethyl ether are also recovered unchanged after treatment with alkaline hydrogen peroxide.

A possible explanation for the absence of oxidation in the case of these 2′- and 5-hydroxy flavanones seems to be in their stability and their inability to change into the chalkone form. The work of Reichel and Steudel[5] definitely shows that ordinary flavanones are unaffected by alkaline hydrogen peroxide and it is only after conversion to the chalkones that the reagent is able to have any action. But the remarkable feature is that whereas these flavanones unsubstituted in the pyrone nucleus are unreactive and do not give even the flavones, the corresponding 3-hydroxy flavanones, which have been shown to be intermediates by Reichel and Steudel[5] in the formation of flavanols from chalkones, undergo dehydrogenation readily in the presence of the hydrogen peroxide or air. Obviously a hydroxyl substituent in the 3-position plays an important part in the mechanism of further oxidation. Similar observations have been made regarding 3-hydroxy flavanones occurring in nature. Pew[6] recorded that 3-hydroxy naringenin and 3-hydroxy eriodictyol underwent ready dehydrogenation even by air. Similar results have been obtained in our laboratories in the course of our work on this group of compounds.

EXPERIMENTAL

7 : 2′-*Dimethoxy-flavonol* (*II a*)

2-Hydroxy-4 : 2′-dimethoxy chalkone (I *a*) required for this reaction was made from equimolecular proportions of peonol and *o*-methoxy benzaldehyde using the sodium ethoxide method.[1] It was obtained in a semi-solid form and could not be crystallised and was used as such for the oxidation. An ice-cooled solution of the chalkone (1 g.) in aqueous hydroxide (20 c.c.; 2N) was treated with hydrogen peroxide (5 c.c.; 15%) during the course of 5 minutes and the solution left in the ice-bath for 2 hours. The dark coloured solution was then acidified with hydrochloric acid (ice-cold 1 : 1) and directly extracted with ether. The ether solution was dried over sodium sulphate, the ether distilled off and the residue dissolved in a mixture of hot ethyl acetate and petrol. A pale yellow solid gradually separated on cooling the solution. It crystallised from alcohol as pale yellow aggregates of thin rectangular plates melting at 158–60°. It gave a brown colour with ferric chloride in alcoholic solution and was easily soluble in aqueous sodium hydroxide (Found: C, 66·7; H, 5·3; $C_{17}H_{14}O_5$, $\frac{1}{2}$ H_2O requires C, 66·5; H, 4·9%).

3 : 7 : 2′-*Trimethoxy flavone* (*resodatiscetin trimethyl ether*)

The above flavonol (0·2 g.) was methylated with excess of dimethyl sulphate (0·2 c.c.) and anhydrous potassium carbonate (1 g.) in acetone solution. The methyl ether crystallised from alcohol as colourless prisms melting at 135–6°, was identical with an authentic sample of 3 : 7 : 2′-trimethoxy flavone[4] and a mixed melting point with that sample was undepressed.

7 : 8 : 2′-*Trimethoxy flavonol* (*II b*)

2-Hydroxy-3 : 4 : 2′-trimethoxy chalkone (I *b*)[1] (0·5 g.) was oxidised with hydrogen peroxide (3 c.c.; 15%) in sodium hydroxide solution (15 c.c.; 2N) and alcohol (10 c.c.) under conditions described in an earlier experiment. After leaving overnight the alkaline solution was acidified and the yellow solid that separated was filtered, washed with water and crystallised from alcohol. It separated in the form of yellow stout rectangular prisms melting at 107–8°. It gave a brown colour with ferric chloride, yellow colour with concentrated sulphuric acid and was soluble in aqueous sodium hydroxide (Found: C, 66·2; H, 5·3; $C_{18}H_{16}O_6$ requires C, 65·8; H, 4·9%).

4 : 2′-*Dimethoxy benzalcoumaranone* (*IV a*)

2-Hydroxy-6 : 2′-dimethoxy chalkone (III *a*)[1] (1·0 g.) was dissolved in alcohol (10 c.c.) and sodium hydroxide (15 c.c.; 2N) and the cooled solution treated with hydrogen peroxide (5 c.c.; 15%). A bright yellow solid began to separate out after 2 hours. The mixture was left in the refrigerator overnight and the solid that separated was filtered and washed with water. Dilution of the filtrate gave more of the solid. On crystallising from alcohol the product separated as bright yellow elongated rectangular rods and prisms melting at 203–4°. Yield 0·6 g. It gave no colour with ferric chloride and with concentrated sulphuric acid developed a bright red colour thus agreeing with the requirements of the benzalcoumaranone structure. Acidification of the alkaline filtrate gave no solid product (Found: C, 72·1; H, 5·1; $C_{17}H_{14}O_4$ requires C, 72·4; H, 5·0%).

4: 6: 2′: 4′-*Tetramethoxy benzalcoumaranone* (*IV b*)

2-Hydroxy-4: 6: 2′: 4′-tetramethoxy chalkone (III *b*)[1] (1·0 g.) was oxidised under the same conditions using the same quantities of reagents as in the previous experiment and the product worked up. It crystallised from alcohol as yellow rectangular prisms melting at 172–4°. It gave no colour with ferric chloride but with concentrated sulphuric acid gave a deep red colour (Found: C, 66·2; H, 5·7; $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3%).

Action of alkaline hydrogen peroxide on 2′-hydroxy and 5-hydroxy flavanones

The following flavanones were used for the reaction under the various experimental conditions: (i) 5-methoxy-2′-hydroxy flavanone,[1] (ii) 5: 7-dimethoxy-2′-hydroxy flavanone,[1] (iii) 5: 7: 4′-trimethoxy-2′-hydroxy flavanone,[1] (iv) 5-hydroxy-2′-methoxy flavanone,[2] and (v) 5-hydroxy-7: 4′-dimethoxy flavanone.[7] The experimental conditions are given below:

(*a*) The flavanone (0·5 g.) was dissolved in alcohol (10 c.c.) and aqueous sodium hydroxide (15 c.c.; 10%) and the solution cooled in ice-water. It was then treated with aqueous hydrogen peroxide (5 c.c.; 15%) and left overnight in the refrigerator. Acidification of the solution deposited a colourless solid which was filtered, washed with water and crystallised from alcohol.

(*b*) The quantities of both sodium hydroxide and hydrogen peroxide were doubled and the reaction mixture was left overnight at room temperature.

(*c*) The flavanone (0·5 g.) was dissolved in alcohol (10 c.c.) and aqueous sodium hydroxide (15 c.c.; 10%) and the solution was treated with a much stronger hydrogen peroxide (5·0 c.c.; 30%) at 0°. After standing in the refrigerator for 24 hours it was worked up as in experiment (*a*).

(*d*) This was carried out only with naringenin dimethyl ether.[7] It (0·5 g.) was dissolved in sodium hydroxide (10 c.c.; 10%) and a minimum amount of pyridine to give a clear solution and the mixture treated with hydrogen peroxide (5 c.c.; 30%) at 0°.

In all the cases it was found that the compounds were recovered unchanged from the reaction. They were identified by their colour reactions, crystal structures, melting points and mixed melting points with authentic samples of the original compounds. There was hardly any appreciable loss of the flavanones during the treatment with hydrogen peroxide.

SUMMARY

In their behaviour towards alkaline hydrogen peroxide 2′-methoxy chalkones behave normally and yield flavonols if the 6-position is free and benzalcoumaranones if this position has a methoxyl group. On the other hand 2′-hydroxy flavanones and 5-hydroxy flavanones remain unaffected. This result is explicable on the basis that these hydroxy flavanone structures are stable and do not undergo change into the corresponding chalkone structures which alone suffer oxidation.

REFERENCES

1. Narasimhachari, Rajagopalan and Seshadri *Proc. Ind. Acad. Sci.*, 1952, 36A, 231.
2. ——— .. *Ibid.*, 1953, 37A, 620.
3. Geissman and Fukushima .. *J.A.C.S.*, 1948, **70**, 1686.
Balakrishna *et al.* .. *Proc. Ind. Acad. Sci.*, 1949, **30A**, 120.
Narasimhachari and Seshadri .. *Ibid.*, 1949, **30A**, 216.
4. Jain *et al.* .. *Ibid.*, 1952, **36A**, 217.
5. Reichel aad Steudel .. *Ann.*, 1942, **553**, 83.
6. Pew .. *J.A.C.S.*, 1948, **70**, 3031.
7. Narasimhachari and Seshadri .. *Proc. Ind. Acad. Sci.*, 1948, **28A**, 223.