NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XXXVII. Isomerisation of 2:3-dimethyl-5:7:8-trihydroxy chromone

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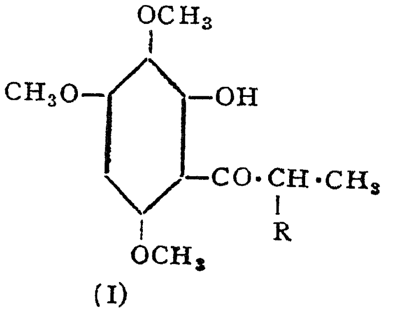
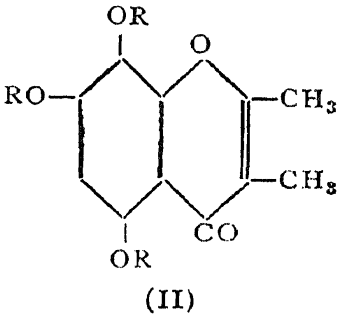
In earlier publications[1–4] dealing with the members of the flavone, chromone and isoflavone series, it has been established that when the 3-position is unsubstituted, isomeric change from the 5:7:8-trihydroxy type into the 5:6:7-trihydroxy type takes place on boiling with hydriodic acid. But if a methoxyl (hydroxyl) or a phenyl group should be present in this position, the isomeric change is prevented.[3–5] Substitution in the 2-position does not seem to have any effect. In order to get information as to whether a free hydrogen in the 3-position is essential in this isomeric change and any kind of substitution will prevent it, experiments have now been carried out with chromones having a methyl group in this position. The simplest example will be 2:3-dimethyl-5:7:8-trimethoxy chromone (II *b*). This has now been prepared from 2-hydroxy-3:4:6-trimethoxy propiophenone (I *a*)[6] by conversion into its α-acetyl derivative (I *b*) and subsequent chromone ring closure. Demethylation of this substance (II *b*) with aluminium chloride in benzene solution yields a trihydroxy compound having all the properties expected for the 5:7:8-trihydroxy arrangement (II *a*). This reagent is known not to produce any rearrangement (see for example wogonin dimethyl ether[1].)



(I)

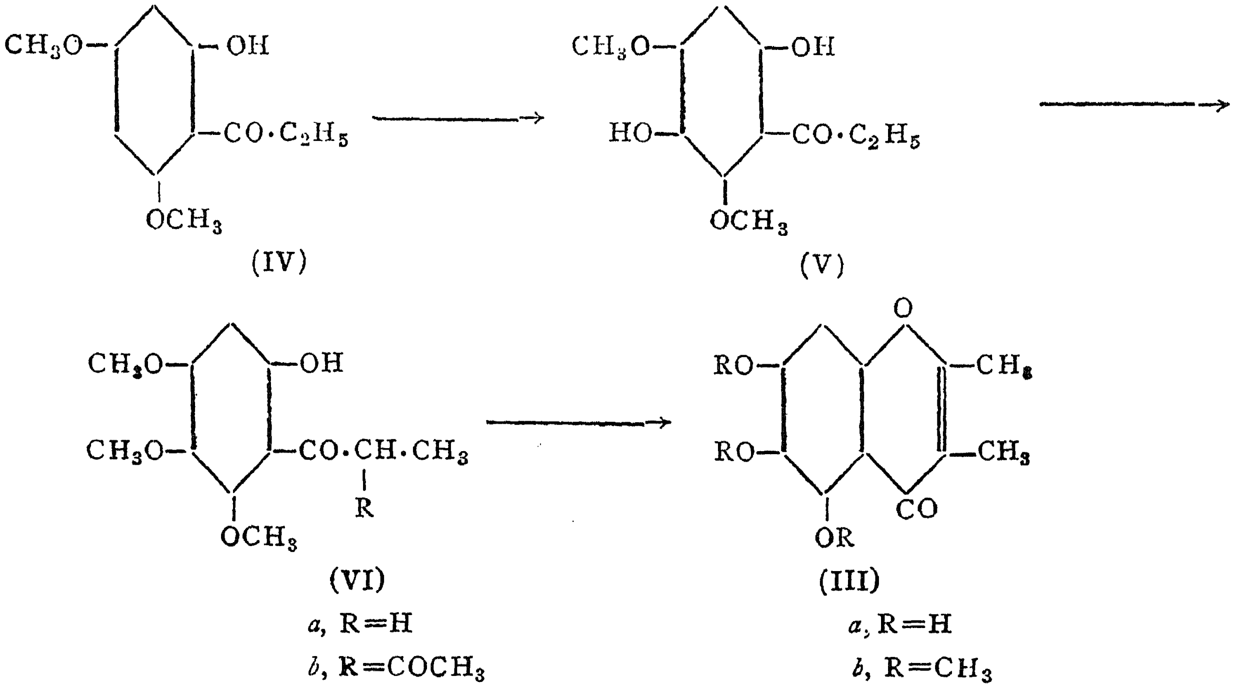
a, R=H
b, R=COCH$_3$



(II)

a, R=H
b, R=CH$_3$

On the other hand, hydriodic acid yields a different product giving different reactions. It should therefore be 2:3-dimethyl-5:6:7-trihydroxy chromone (III *a*). On methylation, it gives rise to a trimethyl ether (III *b*) different from the original 2 : 3-dimethyl-5 : 7 : 8-trimethoxy chromone (II *b*). Thus, even though the 3-position is substituted by a methyl group, the isomeric change has occurred and hence it could be concluded that the presence of a hydrogen atom in this position is not essential for this purpose and that the nature of the substituent is also important.



For purposes of comparison, an authentic sample of 2 : 3-dimethyl-5 : 6 : 7-trimethoxy chromone (III *b*) has now been prepared starting from 2-hydroxy-4 : 6-dimethoxy propiophenone (IV). It is first subjected to nuclear oxidation by alkaline persulphate to yield 2 : 5-dihydroxy-4 : 6-dimethoxy propiophenone (V), which is partially methylated to (VI *a*) and employed for chromone ring closure through the diketone (VI *b*) as intermediate according to the procedure described above for the synthesis of the isomeric trimethoxy chromone (II *b*).

EXPERIMENTAL

2-*Hydroxy*-3 : 4 : 6-*trimethoxy propiophenone* (I *a*)

This was prepared earlier by Bargellini[6] by the interaction of 1 : 2 : 3 : 5-tetramethoxy benzene and propionyl chloride in presence of aluminium chloride in carbon disulphide solution. The reaction has now been more conveniently carried out in ether solution.

Tetramethoxy benzene (11 g.) was added to a solution of anhydrous aluminium chloride (11 g.) in dry ether (100 c.c.) cooled to 0°. Propionyl chloride (6·5 c.c.) was then added to the cooled mixture with vigorous stirring during the course of one hour and the mixture was set aside for 24 hours. The yellow aluminium chloride complex that had separated was decomposed by the cautious addition of concentrated hydrochloric acid (15 c.c.) and pieces of ice. The mixture was then heated on a water-bath for half an hour, the ether being allowed to distil away. The hot mixture was extracted with benzene (150 c.c.) and the benzene extract washed twice with dilute hydrochloric acid and then once with water. It was then extracted exhaustively with aqueous sodium hydroxide (10%). On acidification of the combined alkaline extract, 2-hydroxy-3 : 4 : 6-trimethoxy acetophenone separated as a light yellow powder. It was filtered, washed with water and crystallised from alcohol, when it came out as long thick fawn coloured rectangular prisms melting at 129–30°. Yield 7·5 g. Bargellini[6] reported the m.p. as 124–26°.

2-*Hydroxy*-3 : 4 : 6-*trimethoxy-α-acetyl propiophenone* (*I b*)

A solution of 2-hydroxy-3 : 4 : 6-trimethoxy propiophenone (2 g.) in dry ethyl acetate (20 c.c.) was added to powdered sodium (2 g.) just covered with a layer of dry ether. When the initial reaction was over, the mixture was heated under reflux on a water-bath. The yellow sodium salt of the diketone began to separate after about twenty minutes. After one hour, more ethyl acetate (10 c.c.) was added and the refluxing continued for 4 hours. The yellow sodium salts were dissolved in ice cold water; the aqueous solution was separated from unreacted ethyl acetate and acidified with glacial acetic acid. The diketone separated as pale yellow crystals on leaving overnight in the refrigerator. These were collected and washed with a small quantity of ether. It crystallised from a mixture of chloroform and petroleum ether as colourless rectangular prisms with tapering edges and melted at 133–34°. Yield 1·45 g. With ferric chloride in alcoholic solution, it gave a pale greenish brown colour (Found: C, 59·9; H, 6·2; $C_{14}H_{18}O_6$ requires C, 59·6; H, 6·4%).

2 : 3-*Dimethyl*-5 : 7 : 8-*trimethoxy chromone* (*II b*)

The above diketone (1·3 g.) was dissolved in rectified spirits (15 c.c.), concentrated sulphuric acid (4 drops) added and the solution refluxed on a water-bath for 15 minutes. It was then cooled and diluted with water and the precipitated crystalline mass was recrystallised from dilute alcohol. 2 : 3-Dimethyl-5 : 7 : 8-trimethoxy chromone came out as colourless silky needles melting at 160–61°. Yield 1 g. It did not give any colour with ferric chloride (Found: C, 63·8; H, 6·3; $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1%).

2 : 3-*Dimethyl*-5 : 7 : 8-*trihydroxy chromone* (*II a*)

To a solution of 2 : 3-dimethyl-5 : 7 : 8-trimethoxy chromone (0·95 g.) in dry benzene (15 c.c.), was added anhydrous aluminium chloride (2 g.) and the mixture was heated under reflux for two hours. The solvent was then distilled off and the residual aluminium chloride complex was cooled and decomposed by cautiously adding pieces of ice and concentrated hydrochloric acid (6 c.c.). The resulting yellow powder was filtered, washed with a little ether and crystallised from a mixture of ethyl acetate and alcohol when the trihydroxy-dimethyl chromone separated as thick yellow rhombic prisms melting at 243-44°. Yield 0·7 g. With ferric chloride in alcoholic solution, it gave a deep green colour which changed to brown with excess of the reagent. It dissolved in aqueous sodium carbonate (5%) to give a deep pink solution which changed quickly to yellow and then faded (Found: C, 59·1; H, 4·4; $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%).

2-*Hydroxy*-4 : 6-*dimethoxy propiophenone* (*IV*)

This was prepared earlier by Canter, Curd and Robertson[7] by the Hoesch reaction using phloroglucinol dimethyl ether and propio-nitrile. For the present work the Friedel Crafts reaction was carried out as given below.

To a solution of anhydrous aluminium chloride (68 g.) in dry ether (300 c.c.) cooled to 0°, was added with stirring, phloroglucinol trimethyl ether[8] (34 g.), followed by propionyl chloride (23 c.c.) during one and a half hours, the temperature being maintained at 0°. After 48 hours, the aluminium chloride complex was decomposed with the addition of pieces of ice and concentrated hydrochloric acid (70 c.c.). The ether was then distilled off and the hot aqueous solution extracted with benzene. Extraction of the benzene solution with aqueous alkali and subsequent acidification gave the hydroxy dimethoxy ketone. It crystallised from alcohol as colourless elongated plates melting at 111°. Yield 30 g. Canter *et al.*[7] give same m.p. It gave a blue colour with nitric acid.

The benzene solution left after extraction with alkali was washed with water and evaporated. The residue crystallised from alcohol as pale yellow long thick rectangular rods melting at 136-37°. It was evidently 2 : 4 : 6-trimethoxy propiophenone. It did not give any colour with alcoholic ferric chloride (Found: C, 64·7; H, 7·3; $C_{12}H_{16}O_4$ requires C, 64·3; H, 7·1%).

2 : 5-*Dihydroxy*-4 : 6-*dimethoxy propiophenone* (*V*)

2-Hydroxy-4 : 6-dimethoxy propiophenone (12 g.) was dissolved in aqueous sodium hydroxide (11 g. in 80 c.c. of water) and to this stirred solution, maintained at 15–17°, was added dropwise a solution of potassium persulphate (19 g.) in water (350 c.c.) in the course of 5 hours. It was set aside and after 36 hours acidified to congo red with concentrated hydrochloric acid. The precipitated solid (2 g.) consisting of the unreacted material was filtered off and the filtrate extracted twice with ether. Norit (6 g.) and sodium bisulphite (5 g.) were then added, the mixture stirred well and filtered. The residual charcoal was washed with water. The filtrate was heated on a boiling water-bath to remove dissolved ether and to the hot solution was added concentrated hydrochloric acid (150 c.c.) with stirring. On allowing the clear deep red solution to cool, bright shining crystals of the dihydroxy compound separated. A further quantity came out on cooling the mixture to 0°. These crystals were filtered off. Some more of the substance was obtained by ether extraction of the aqueous mother liquors. When crystallised from alcohol twice, it came out as bright yellow irregular prisms melting at 120–21°. Yield 4·0 g. With ferric chloride in alcoholic solution, it gave a transient green colour which quickly faded. Addition of more of the reagent gave a permanent orange red solution. It dissolved in aqueous sodium hydroxide to give a bright yellow solution which fades slowly in the cold, but quickly on heating. It gave a red colour with concentrated nitric acid and with concentrated sulphuric acid produced a yellow colour changing to orange and then to violet brown on warming (Found: C, 58·4; H, 5·8; $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%).

Sastri and Seshadri[9] recorded that with alcoholic ferric chloride, 2:5-dihydroxy-4:6-dimethoxy acetophenone gives a transient green colour changing to brown and its solution in aqueous sodium hydroxide is yellow at first and then changes to reddish brown. A pure sample of this ketone is now found to exhibit the same colour reactions as recorded for 2:5-dihydroxy-4:6-dimethoxy propiophenone above.

2-*Hydroxy*-4:5:6-*trimethoxy propiophenone* (*VI a*)

A solution of 2:5-dihydroxy-4:6-dimethoxy propiophenone (3·75 g.) in dry benzene (200 c.c.) was mixed with dimethyl sulphate (1·9 c.c.) and anhydrous potassium carbonate (5 g.) and the mixture refluxed for 12 hours. Water (100 c.c.) was then added to the hot mixture. The potassium salts dissolved on vigorous shaking. The aqueous layer was drawn off and the benzene solution extracted with aqueous sodium carbonate (10%). It was then extracted with aqueous sodium hydroxide (10%) repeatedly and the combined alkaline extract cooled to 0° and acidified. 2-Hydroxy-4:5:6-trimethoxy propiophenone was precipitated as an oil. It was extracted with ether and the ether extract dried over anhydrous sodium sulphate and the solvent evaporated. The oil that was left did not solidify and hence was employed directly for the diketone condensation.

2-*Hydroxy*-4 : 5 : 6-*trimethoxy-α-acetyl propiophenone* (*VI b*)

2-Hydroxy-4 : 5 : 6-trimethoxy propiophenone (1·7 g.) was condensed with sodium (2 g.) and ethyl acetate (20 c.c.) in the same way as the isomeric 2-hydroxy-3 : 4 : 6-trimethoxy propiophenone (I *a*) described earlier. The diketone crystallised from ethyl acetate as colourless rectangular plates melting at 204–6°. Yield 0·5 g. It gave a deep bluish green colour with ferric chloride in alcoholic solution (Found: C, 59·7; H, 6·0; $C_{14}H_{18}O_6$ requires C, 59·6; H, 6·4%).

2 : 3-*Dimethyl*-5 : 6 : 7-*trimethoxy chromone* (*III b*)

To a solution of the above diketone (0·2 g.) in alcohol (5 c.c.), concentrated sulphuric acid (2 drops) was added and the mixture refluxed for 10 minutes. It was concentrated and diluted with water and allowed to cool. The trimethoxy chromone which separated was filtered and crystallised from very dilute alcohol. It was obtained as long narrow colourless rectangular plates melting at 135–135·5° (Found: C, 64·0; H, 6·4; $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1%).

2 : 3-*Dimethyl*-5 : 6 : 7-*trihydroxy chromone* (*III a*)

2 : 3-Dimethyl-5 : 7 : 8-trimethoxy chromone (II *b*) (1 g.) was dissolved in acetic anhydride (15 c.c.) and to the solution, cooled to 0°, hydriodic acid (20 c.c., d. 1·7) was added cautiously. The mixture was refluxed for 2 hours at 140° on an oil-bath. It was then cooled and diluted with aqueous sodium sulphite. The reddish brown powder that had seaparated after three hours was filtered, washed with water, dried and crystallised from a mixture of absolute alcohol and ethyl acetate. The trihydroxy chromone separated as long colourless needles and rectangular rods melting at 230–31°. Yield 0·7 g. It was sparingly soluble in ethyl acetate. With ferric chloride in alcoholic solution, it gave a deep bluish green colour which was unchanged on further addition of the reagent. It dissolved in aqueous sodium carbonate (5%) to give a pale green solution (Found in a sample dried at 110° in vacuuo: C, 59·5; H, 4·8; $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%).

Remethylation

The above demethylated product (0·52 g.) was dissolved in dry acetone (50 c.c.) and treated with dimethyl sulphate (0·92 c.c., 4 moles) and potassium carbonate (4 g.). The mixture was refluxed on a water-bath for 8 hours. The solvent was then distilled off and water was added to the residue. The resulting clear solution on standing for two days, deposited big crystals. These were filtered off and crystallised from very dilute alcohol. The methyl ether was obtained in the form of long narrow colourless rectangular plates melting at 135–135·5°, alone or when mixed with 2:3-dimethyl-5:6:7-trimethoxy chromone (III *b*) described earlier. Yield 0·4 g.

SUMMARY

When boiled with hydriodic acid, 2:3-dimethyl-5:7:8-trimethoxy chromone undergoes besides demethylation, isomeric change also, yielding 2:3-dimethyl-5:6:7-trihydroxy chromone, thus showing that a free hydrogen atom in the 3-position is not essential for this isomeric change to take place and that the nature of the substituent is also important. For purposes of comparison, 2:3-dimethyl-5:7:8-trihydroxy chromone has been obtained by demethylation of the above trimethyl ether with aluminium chloride and 2:3-dimethyl-5:6:7-trimethoxy chromone by independent synthesis using nuclear oxidation as a stage.

REFERENCES

1. Sastri and Seshadri .. *Proc. Ind. Acad. Sci.*, 1946, **24 A**, 243.
2. Rao, Seshadri and Viswanadam .. *Ibid,*, 1949, **29 A**, 72.
3. Chakravorty, Mukerjee, Murty and Seshadri *Ibid.*, 1952, **35 A**, 34.
4. Narasimhachari, Row and Seshadri *Ibid.*, 1952, **35 A**, 46.
5. Seshadri, Varadarajan and Venkateswarlu *Ibid.*, 1950, **32 A**, 250.
6. Bargellini .. *Gazetta*, 1915, **45** (i), 87.
7. Canter, Curd and Robertson .. *J. C. S.*, 1931, 1245.
8. Aghoramurty, Narasimhachari and Seshadri *Proc. Ind. Acad. Sci.*, 1951, **33 A**, 257.
9. Sastri and Seshadri .. *Ibid.*, 1946, **23 A**, 267.