SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

Part XXV. Isomerisation of 5 : 7 : 8-Hydroxy Flavanones

By Ishwar-Dass, N. Narasimhachari and T. R. Seshadri, F.A.Sc.

(From the Department of Chemistry, Delhi University)

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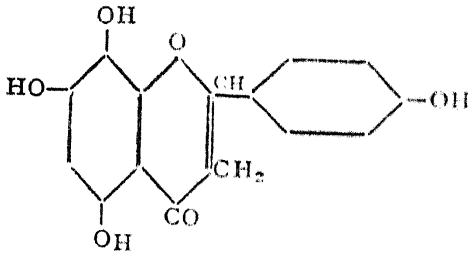
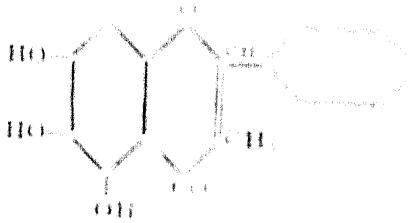
Experiments using flavones and chromones have shown that 5 : 7 : 8-trihydroxy or methoxy derivatives undergo isomeric change into the corresponding 5 : 6 : 7-substituted isomers when boiled with hydriodic acid (for a discussion see Mukerjee *et al.*).[1] The change is prevented when a substituent such as hydroxyl or phenyl is present in the 3-position.[2] This kind of isomeric change has not been studied in detail in the case of flavanones. It has however been recorded that carthamidin (5 : 7 : 8 : 4′-tetrahydroxy flavanone) (I) undergoes change into isocarthamidin (5 : 6 : 7 : 4′-tetrahydroxy flavanone) (II) even when heated with water in a sealed tube in the presence of animal charcoal.[3]



I

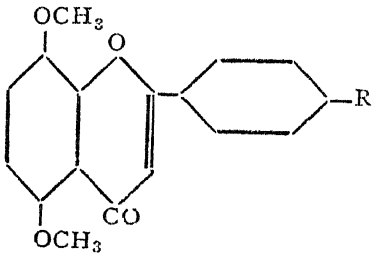


II

When dealing with the flavanones or the corresponding chalcones hydriodic acid cannot be used as a demethylating agent since it produces besides demethylation profuse decomposition which has not yet been understood. Aluminium chloride has been used successfully for partial as well as complete demethylation and with this reagent no isomeric change is brought about. Its action on methoxy flavanones is very similar to that on methoxy flavones. Regarding partial demethylation it has been used in nitrobenzene solution for the preferential demethylation of the 5-hydroxyl group of flavanones by Rao and Seshadri.[4] The synthesis of norwogonin (5 : 7 : 8-trihydroxyflavone) by the demethylation of its 5 : 8-dimethyl ether by Shah, Mehta and Wheeler[5] would indicate that the 8-methoxyl in flavanones can undergo easy removal. Its capacity to effect complete demethylation is

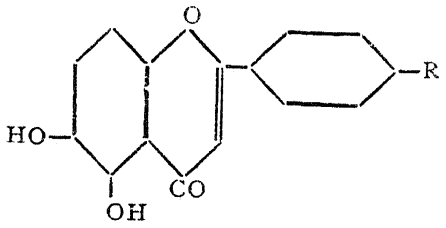
benzene solution without causing isomeric change has been employed for the synthesis of carthamidin and isocarthamidin.[6]

Hydrobromic acid has also been used for the demethylation of chalkones and flavanones. In this case the products are flavanones and the 7-methoxyl is invariably left out unaffected; this has been utilised for the convenient synthesis of sakuranetin and the 7-methyl ether of eriodictyol.[7] This reagent is known to cause isomerisation in the flavones, examples being the conversion of primetin dimethyl ether (III *a*) to 5:6-dihydroxy flavone (IV *a*) and 5:8:4′-trimethoxy flavone (III *b*) to 5:6:4′-trihydroxy flavone (IV *b*).[8]



a, R=H
b, R=OCH_3

III

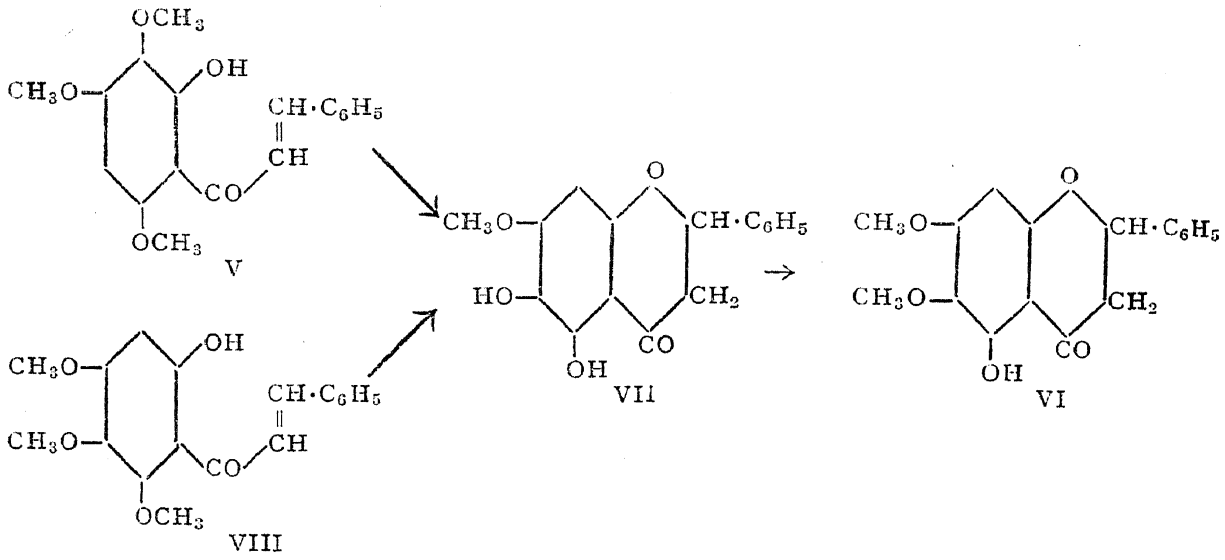


a, R=H
b, R=OH

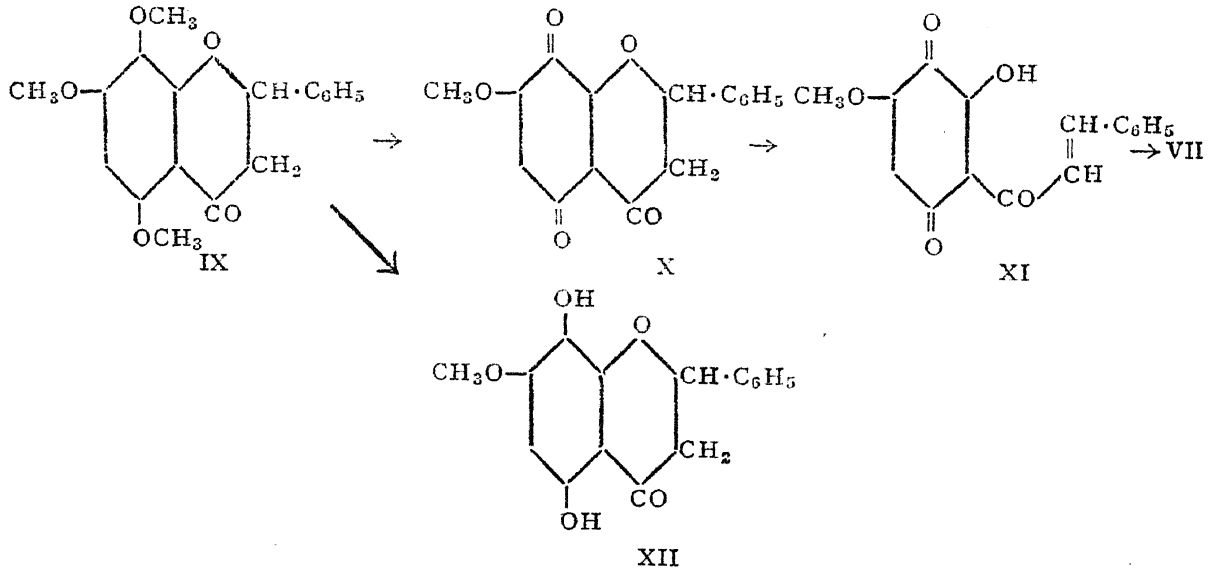
IV

For the purpose of the present study as the simplest suitable example 2-hydroxy-3:4:6-trimethoxy chalkone (V) has been employed. By the action of hydrobromic acid a product (A) is obtained which is a monomethyl ether and which does not give the reactions expected for 7-methoxy-5:8-dihydroxy flavanone. On the other hand, it gives a green colour with ferric chloride changing to brown and does not react with *p*-benzoquinone. It would appear therefore that during the demethylation isomeric change has also taken place. The product could undergo partial methylation and form a dimethoxy compound (B) giving characteristic reactions for the presence of a 5-hydroxyl group. The constitution of (A) has been established by preparing 7-methoxy-5:6-dihydroxy flavanone (VII) by the treatment of 2-hydroxy-4:5:6-trimethoxy chalkone (VIII) with hydrobromic acid; the constitution of B is then represented by VI.

In order to further confirm the constitution of the demethylation product (A) attempts have been made to prepare 7-methoxy-5:8-dihydroxy flavanone adopting a different route. For this purpose 5:7:8-trimethoxy flavanone (IX) is subjected to oxidative demethylation with nitric acid[9] and 7-methoxy-5:8-quinoflavanone (X) obtained. But when it is reduced using sodium hydrosulphite the product is again found to be identical with 7-methoxy-5:6-dihydroxy flavanone (VII). These experiments indicate the readiness with which ring isomeric change takes place in the flavanone series in alkaline medium. It is interesting to note that the product is not a mixture



and the isomeric change is complete. In this connection may be mentioned the results of Rao and Seshadri[10] who reduced 2-hydroxy-4-methoxy-3: 6-quino-chalkone (XI) with sodium hydrosulphite and obtained 7-methoxy-5: 6-dihydroxy flavanone (VII) as the only product. These results are explicable on the basis that the conversion of the quinoflavanone to the corresponding quino-chalkone is quite easy and the *o*-hydroxyl group which is part of the quinol system is more reactive than the other.



7-Methoxy-5: 8-dihydroxy flavanone (XII) could however be successfully prepared by the demethylation of 5: 7: 8-trimethoxy flavanone (IX) using anhydrous aluminium chloride in nitrobenzene solution. This reagent has been used earlier in the demethylation of the 8-position of flavones.[5]

The product agreed in its properties with those of a 5: 8-dihydroxy compound. It dissolved readily in aqueous sodium carbonate, gave a green colour changing to deep red with ferric chloride and a positive *p*-benzoquinone reaction. It was different from the demethylation product (A) described earlier.

Experimental

7-Methoxy-5: 6-dihydroxy flavanone (VII):—

(A) *By the demethylation of 2-hydroxy-3: 4: 6-trimethoxy chalkone (V):*

2-Hydroxy-3: 4: 6-trimethoxy chalkone[9] (0·8 g.) was dissolved in glacial acetic acid (5 c.c.) and the solution treated with a saturated solution of hydrogen bromide in glacial acetic acid (8 c.c.). After leaving at room temperature for two hours it was heated on a boiling water-bath for one hour, then cooled and diluted with water (40 c.c.). The brown solid that separated was filtered, washed with water and crystallised from acetone-petroleum ether mixture. On recrystallising from methyl acetate it separated as pale yellow tiny prisms melting at 248–49° (decomp.). When the aqueous filtrate was neutralised with aqueous alkali it gave some more of the same product which was crystallised from methyl acetate. It gave a green colour with ferric chloride in alcoholic solution changing to brown with excess of the reagent. It developed no colour with *p*-benzoquinone in alcoholic solution (Found: C, 67·1; H, 4·5; $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·2%). Yield 0·4 g.

Partial methylation (6: 7-dimethoxy-5-hydroxy flavanone) (VI).—The above dihydroxy flavanone (0·27 g.) was refluxed in acetone solution with dimethyl sulphate (0·11 c.c.) and anhydrous potassium carbonate (0·5 g.) for six hours. On filtering and distilling off acetone a pale yellow solid separated. It crystallised from acetone as pale yellow rectangular prisms melting at 230–32°. It gave a red colour with ferric chloride and was sparingly soluble in aqueous sodium hydroxide (Found: C, 67·5; H, 5·4; $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%).

(B) *By the demethylation of 2-hydroxy-4: 5: 6-trimethoxy chalkone (VIII).*—2-Hydroxy-4: 5: 6-trimethoxy chalkone[6] (1·0 g.) was demethylated with hydrobromic acid under exactly the same conditions as used in the previous experiment. On working up the product and crystallising first from acetone-petrol mixture and finally from methyl acetate it was obtained in the form of pale yellow tiny prisms melting at 248–49° (decomp.). It agreed in its properties with 7-methoxy 5: 6-dihydroxy flavanone described in experiment (A) and the mixed melting point was not depressed.

On partial methylation with 1 mole of dimethyl sulphate and potassium carbonate in dry acetone solution, the dihydroxy compound yielded a monomethyl ether which crystallised from alcohol as pale yellow rectangular prisms melting at 230–32°. It was identical with 5-hydroxy-6: 7-dimethoxy flavanone and the mixed melting point with the sample obtained in the previous experiment was undepressed.

7-Methoxy-5: 8-quinoflavanone (X):—

Nitric acid (10 c.c.; d, 1·2) was added to finely powdered 5: 7: 8-trimethoxy flavanone[6] (0·5 g.) cooled in ice water with shaking. During the course of five minutes the solid changed colour and slowly turned to a yellowish red semi-solid mass. The temperature was kept at 20° for 15 minutes and the clear supernatant liquid decanted. On adding ice-cold water to the semi-solid residue it solidified. It was filtered, washed repeatedly with water and dried. It crystallised from benzene as orange red long prismatic needles melting at 182–4°. It gave no colour with ferric chloride in alcoholic solution (Found: C, 67·8; H, 4·5; $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·2%).

Reduction (5: 6-Dihydroxy-7-methoxy flavanone) (VII).—To a suspension of 7-methoxy-5: 8-quinoflavanone (0·2 g.) in water (10 c.c.) was added a solution of sodium hydrosulphite (2·0 g.) in water (10 c.c.) and the mixture boiled for 3 minutes. The original orange-red colour of the quinone changed to pale yellow. After cooling, the solid was filtered and washed with water. It crystallised from methyl acetate as pale yellow tiny prisms melting at 248–49° (decomp.). It gave a green colour with ferric chloride changing to brown with excess of the reagent. It was therefore identical in its reactions with 7-methoxy-5: 6-dihydroxy flavanone and mixed melting points with the two samples described earlier were undepressed.

In another experiment the same reduction was carried out with sodium hydrosulphite in presence of sodium carbonate with the same result.

7-Methoxy-5: 8-dihydroxy flavanone (XII):—

5: 7: 8-Trimethoxy flavanone[6] (0·6 g.) and anhydrous aluminium chloride (2·0 g.) were dissolved in dry nitrobenzene (10 c.c.) and the mixture refluxed over a water-bath for two hours. After allowing it to cool, petroleum ether was added to precipitate the complex. The supernatant liquid was decanted and the residue washed with petroleum ether repeatedly to remove nitrobenzene. The aluminium chloride complex was treated with ice and hydrochloric acid (20 c.c.). The last traces of nitrobenzene were removed by passing in steam. The pale-brown solid that separated was filtered and

washed with water. It was taken up in acetone and the dark coloured solution was treated with petroleum ether till there was turbidity which on allowing to stand cleared up depositing a sticky mass. The clear solution was decanted off, treated with more petrol and warmed to get a clear solution. The solvent was completely distilled off and the residue was crystallised from a mixture of absolute alcohol and petroleum ether from which it separated as pale yellow aggregates of stout prismatic needles melting at 133–4°. It gave a green colour with ferric chloride in alcoholic solution changing to deep red. It gave a red colour with *p*-benzoquinone in alcoholic solution. It dissolved completely in aqueous sodium carbonate (Found: C, 67·6; H, 4·6; $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·2%).

Summary

Heating 2-hydroxy-3:4:6-trimethoxy-chalkone with hydrobromic acid yields instead of the expected 7-methoxy-5:8-dihydroxy flavanone, the isomeric 7-methoxy-5:6-dihydroxy flavanone. The same product is obtained by the partial demethylation of 2-hydroxy-4:5:6-trimethoxy chalkone. Attempts to prepare 5:8-dihydroxy-7-methoxy flavanone by the reduction of the corresponding quinone again resulted in the formation of the isomeric 7-methoxy-5:6-dihydroxy flavanone. The 5:8-dihydroxy compound has been obtained by the partial demethylation of 5:7:8-trimethoxy flavanone by means of aluminium chloride in nitrobenzene solution.

References

1. Mukerjee *et al.* .. *Proc. Ind. Acad. Sci.*, 1953, **37A**, 127.
2. Seshadri *et al.* .. *Ibid.*, 1950, **32A**, 250.
   Narasimhachari *et al.* .. *Ibid.*, 1952, **35A**, 46.
3. Kuroda .. *J.C.S.*, 1930, 752.
4. Rao and Seshadri .. *Proc. Ind. Acad. Sci.*, 1946, **23A**, 213.
5. Shah, Mehta and Wheeler .. *J.C.S.*, 1938, 1555.
6. Sastri *et al.* .. *Proc. Ind. Acad. Sci.*, 1949. **29A**, 464.
7. Narasimhachari and Seshadri .. *Ibid.*, 1949, **29A**, 265; 1950, **32A**, 17.
8. Baker *et al.* .. *J.C.S.*, 1939, 1922; 1940, 1370.
9. Rao and Seshadri . *Proc. Ind. Acad. Sci.*, 1948, **27A**, 385.
10. ———— .. *Ibid.*, 1952, **36A**, 130.