SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

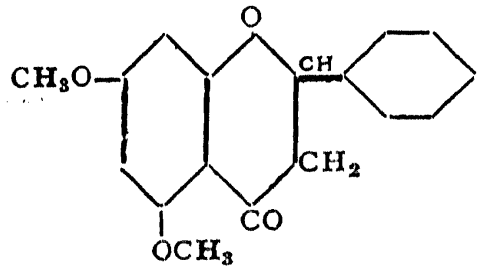
Part IX. Partial Demethylation of Chalkones : A Synthesis of Sakuranetin

BY N. NARASIMHACHARI AND T. R. SESHADRI

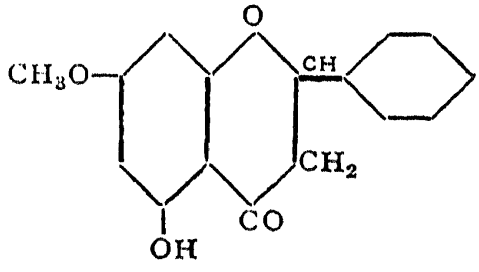
(From the Department of Chemistry, Andhra University, Waltair)

Received February 23, 1949

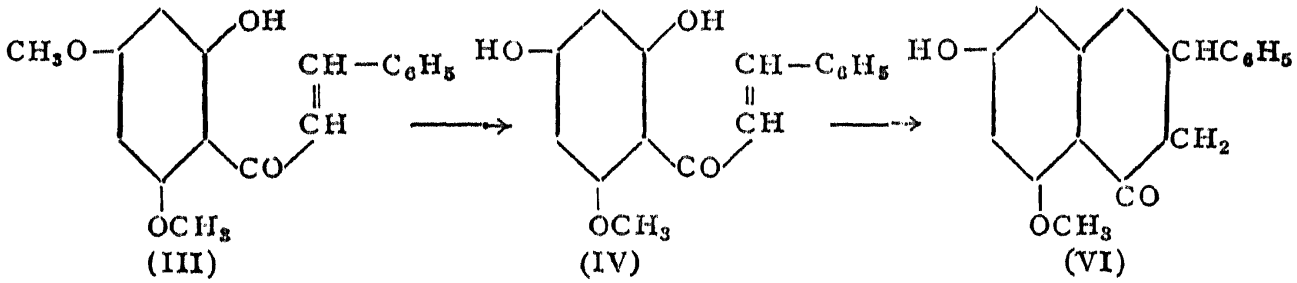
THE partial demethylation of 5 : 7-dimethoxy flavanone (I) using anhydrous aluminium chloride in nitrobenzene solution was described earlier in connection with the study of the constitution of alpinetin.[1] The 5-position underwent demethylation and 5-hydroxy-7-methoxy flavanone (II) was obtained. When the corresponding chalkone, 2-hydroxy-4 : 6-dimethoxy chalkone (III), was employed for this demethylation, it underwent demethylation in the 4-position analogous to the behaviour of the simpler acetophenone trimethyl ether (V)[2] which yields 6-O-methyl-phloroacetophenone (V*a*). The constitution of the product (IV) is supported by its properties and is fully confirmed by its synthesis using 2 : 4-dihydroxy-6-methoxy acetophenone (V *a*) and benzaldehyde. On cyclisation it yields 7-hydroxy-5-methoxy flavanone (VI) which has not been prepared before.



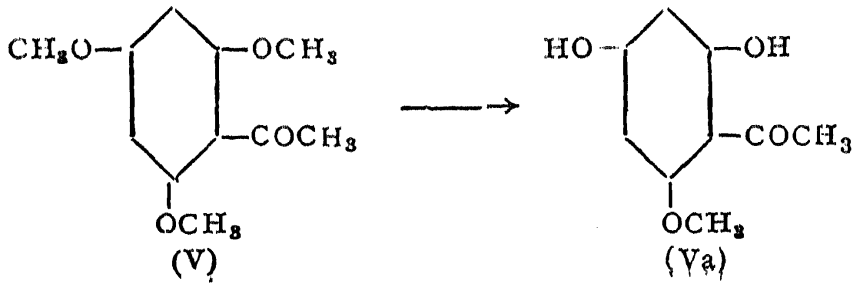
(I)



(II)



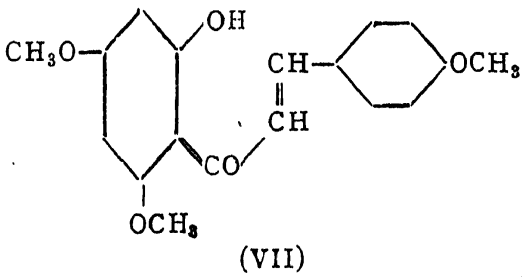
(III) (IV) (VI)



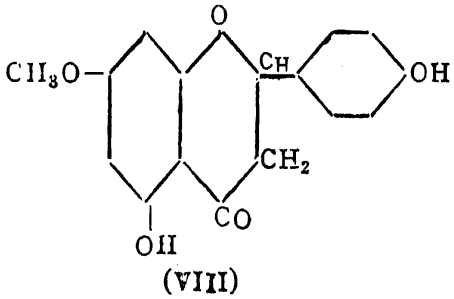
(V) (Va)

The use of hydrobromic acid for this partial demethylation of the chalkone (III) gave rise to very different results. The product was found to be 7-methoxy-5-hydroxy-flavanone (II). Its formation could be explained only on the basis that flavanone ring closure takes place first with subsequent facile demethylation in the 5-position of the flavanone (I) almost to the complete exclusion of the alternative course of change mentioned above. This difference is obviously due to the capacity of hydrobromic acid to bring about flavanone conversion readily. The reaction takes place with equal facility by means of hydrobromic acid in aqueous or in acetic acid solution. It thus represents a simplification in the synthesis of the flavanone (II).

The partial demethylation using hydrobromic acid was next applied to the higher member of the chalkone series, 2-hydroxy-4: 6: 4′-trimethoxy chalkone (VII). In this case the product was found to be a monomethyl ether identical in every respect with sakuranetin (VIII), the 7-methyl ether of naringenin.[3] Obviously besides the 5-methoxyl group, the methoxyl in the 4′-position of the flavanone skeleton had also suffered demethylation. The identity of the product was confirmed by comparison with a sample of sakuranetin obtained from *Prunus puddum*.[4] This naturally occurring monomethyl ether of naringenin was originally prepared synthetically by methylating naringenin with 1 mole of diazomethane.[5] Our attempts to carry out this partial methylation using 1 mole of dimethyl sulphate in the presence of potassium carbonate in acetone solution has not been successful.[6] The product was found to be a mixture which was difficult to separate. The above method of partial demethylation seems to be the most convenient one for the synthesis of this naturally occurring substance.



(VII)



(VIII)

Experimental

Demethylation with aluminium chloride

Preparation of 2: 4-*dihydroxy*-6-*methoxy chalkone* (*IV*).—(i) To a solution of 2-hydroxy-4: 6-dimethoxy-chalkone[7] (0·5 g.) in benzene (10 c.c.), anhydrous aluminium chloride (1·0 g.) was added and the mixture refluxed on a water-bath for 1 hour. Benzene was then distilled off and the aluminium chloride complex treated with ice and hydrochloric acid when a solid separated out. It was filtered and washed with water. It crystallised from

alcohol as yellow tiny prisms melting at 140–42°. It gave a dark brown colour with ferric chloride in alcoholic solution and dissolved in cold aqueous sodium carbonate. It was identical with a synthetic sample of 2:4-dihydroxy-6-methoxy chalkone described below. (Found: C, 71·8; H, 5·3; $C_{16}H_{14}O_4$ requires C, 71·9; H, 5·2%).

(ii) The condensation of 2:4-dihydroxy-6-methoxy acetophenone with benzaldehyde in alkali was carried out and the product was worked up as in similar cases.[6] 2:4-Dihydroxy-6-methoxy chalkone crystallised from alcohol in the form of short prisms melting at 140–2°. The mixed melting point with the sample described above was undepressed. The colour reactions of the two samples were identical.

Preparation of 5-methoxy-7-hydroxy flavanone (VI).—The above dihydroxy-monomethoxy chalkone (0·5 g.) was refluxed in alcoholic sulphuric acid solution (25 c.c., 4%) for 24 hours. Alcohol was then removed under reduced pressure, the residue diluted with water (25 c.c.) and the solid product filtered. The resulting chalkone-flavanone mixture was separated by fractional crystallisation from benzene-petroleum ether mixture in which the flavanone was more soluble. 5-Methoxy-7-hydroxy flavanone crystallised from petroleum ether as colourless prisms melting at 126–7°. It gave no colour with alcoholic ferric chloride and readily dissolved in cold aqueous sodium hydroxide (Found: C, 71·4; H, 5·1; $C_{16}H_{14}O_4$ requires C, 71·9; H, 5·2%).

Demethylation with hydrobromic acid

Preparation of 5-hydroxy-7-methoxy flavanone (II).—(i) 2-Hydroxy-4:6-dimethoxy chalkone (0·5 g.) was treated with a saturated solution of hydrobromic acid in acetic acid (10 c.c.) and the red solution heated on a boiling water-bath for 2 hours. It was then diluted with water (50 c.c.) when a pale brown solid separated out. It crystallised from alcohol as colourless prisms melting at 100–1°. It gave a green colour with ferric chloride in alcoholic solution and a deep blue colour with concentrated nitric acid. It was sparingly soluble in cold aqueous alkali. It was identical with the sample obtained by partial demethylation of 5:7-dimethoxy flavanone with aluminium chloride.[1] Yield, 0·3 g.

(ii) To a solution of the chalkone (0·3 g.) in glacial acetic acid (2 c.c.) aqueous hydrobromic acid (5 c.c., 40%) was added and the mixture heated at 110° on an oil-bath for 2 hours. On cooling and diluting with water 5-hydroxy-7-methoxy flavanone separated as a pale brown solid. It crystallised from alcohol in the form of colourless prisms and melted at 100–1° alone or in admixture with the sample obtained above.

Synthesis of sakuranetin (VIII).—2-Hydroxy-4: 6: 4′-trimethoxy chalkone[8] (0·5 g.) was treated as above with a solution of hydrogen bromide in acetic acid (10 c.c.) and the mixture heated on a boiling water-bath for 2 hours. The solution was then diluted and the solid product filtered and washed. It crystallised from alcohol as colourless prismatic needles and melted at 152–4°. It gave a deep violet red colour with alcoholic ferric chloride and a deep indigo blue colour with concentrated nitric acid. On reduction with magnesium and hydrochloric acid in alcohol the compound developed a scarlet red colour. It was identical in all its properties with sakuranetin and the mixed melting point with an authentic sample of sakuranetin obtained from the bark of *Prunus puddum*[4] was undepressed. (Found: C, 67·5; H, 4·6; OCH_3, 10·7; $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9; OCH_3, 10·8%).

Summary

Partial demethylation of 2-hydroxy-4: 6-dimethoxy chalkone with aluminium chloride yields 2: 4-dihydroxy-6-methoxychalkone which could be cyclised to 5-methoxy-7-hydroxy-flavanone. The use of hydrobromic acid for the demethylation produces directly 5-hydroxy-7-methoxy flavanone due to initial ring closure and subsequent demethylation in the 5-position of the flavanone. When this reagent acts on 2-hydroxy-4: 6: 4′-trimethoxy chalkone sakuranetin, the naturally occurring monomethyl ether of naringenin is produced.

References

1. Rao and Seshadri .. *Proc. Ind. Acad. Sci.* A, 1946, **23**. 213.
2. Gulati and Venkataraman .. *J. C. S.*, 1936, 267.
3. Asahina, Shinoda and Inubuse .. *J. Pharm. Soc.*, Japan, 1927, **47**, 133.
   Shinoda and Sato .. *Ibid.*, 1928, **48**, 220.
4. Chakravarti, *et al.* .. *J. I. C. S.*, 1948, **25**, 329.
5. Shinoda and Sato .. *J. Pharm. Soc.*, Japan, 1928, **48**, 933.
6. Narasimhachari and Seshadri .. *Proc. Ind. Acad. Sci.* A, 1948, **27**, 223.
7. Shinoda .. *J. Pharm. Soc.*, Japan, 1928, **48**, 214.
8. Kostanecki and Tambor .. *Ber.*, 1904, 792.