

CONSTITUTION OF NARINGIN

The Position of the Sugar Group

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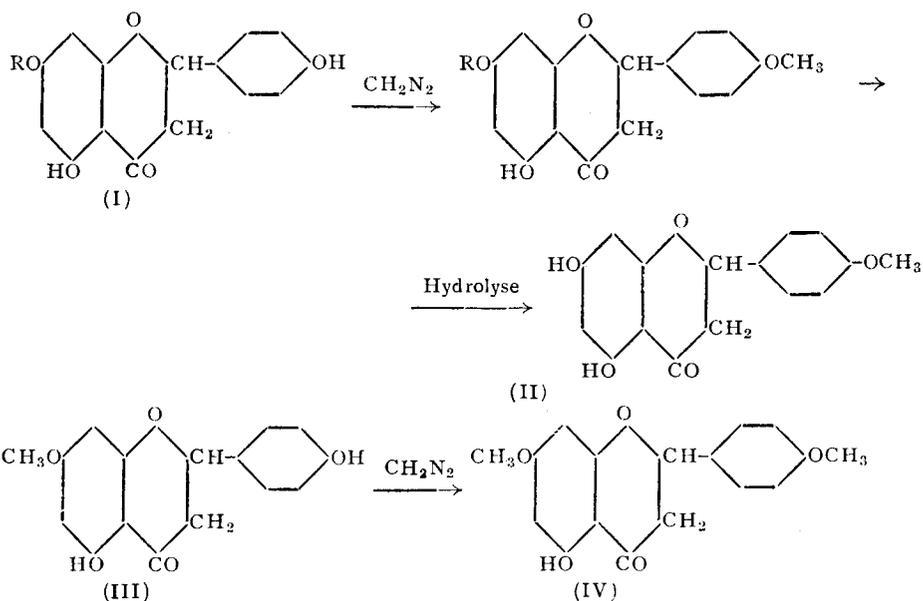
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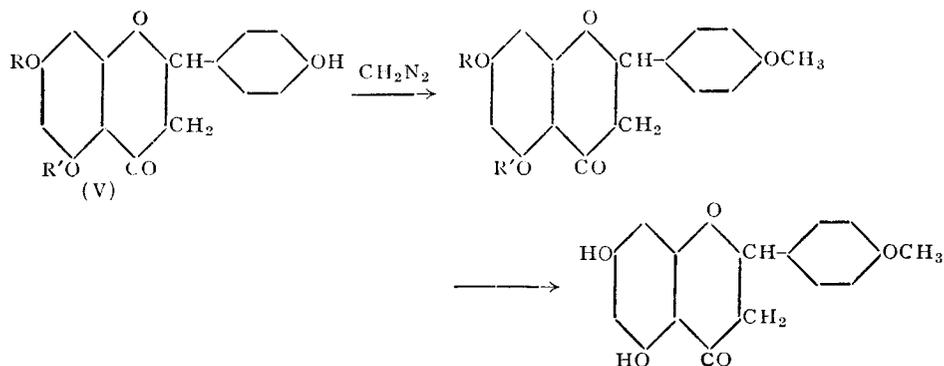
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THE crystalline bitter principle, naringin was first isolated in 1866 by de Vry in Java from grape fruit blossoms. Recently it has been produced in large quantities from grape fruit residues. In the course of our work on the chemistry of Indian fruits we have prepared naringin from the peels and rags of the pamparapanas fruit (*Citrus paradisi*). When anhydrous the substance has the composition $C_{27}H_{32}O_{14}$ and on hydrolysis with acids gives rise to an aglucone called naringenin along with a molecule of glucose and a molecule of rhamnose. Naringenin has the formula $C_{15}H_{12}O_5$. Though at first it was thought to be a chalkone¹ it was finally proved to have the constitution of 5:7:4'-trihydroxyflavanone (I, R = H) by Asahina and Inubuse² in 1928. This was confirmed subsequently by its synthesis by Shinoda and Sato³ by condensing phloroglucinol with the ethyl carbonate of *p*-coumaric acid in the presence of aluminium chloride.

An attempt was made by Asahina and Inubuse⁴ to locate the position of the sugars in the molecule of naringin. On heating the substance with barium hydroxide for 12 hours in an atmosphere of hydrogen it was found to yield *p*-hydroxy-benzaldehyde and a glycoside of phloracetophenone. The latter on further hydrolysis with dilute sulphuric acid yielded phloracetophenone, glucose and rhamnose. By the action of diazomethane on naringin a syrupy substance was obtained which on hydrolysis gave a monomethyl ether of naringenin known as *iso*-sakuranetin (II). It was therefore clear that the sugar residues were present in the benzopyrone portion of the molecule. Though there was no definite experimental evidence that they existed as a disaccharose unit, Asahina and Inubuse made this assumption from general considerations and concluded that the rhamnoglucose unit was present in position 7. Since it was known that position 5 is resistant to methylation under these conditions the formation of *iso*-sakuranetin was explained according to the scheme given below (R = sugar group):



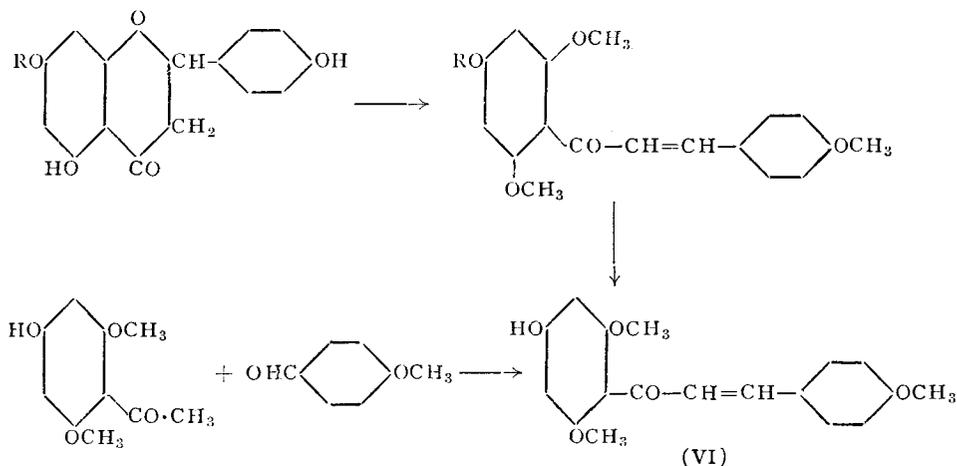
In this connection the similarity between naringin and sakuranetin (III) is noteworthy, since the latter undergoes monomethylation in position 4' only to give 4':7-dimethyl ether of naringenin (IV). But the experimental results of Asahina and Inubuse could equally satisfactorily be explained if two monosaccharose units should occupy positions 5 and 7 in naringin as in (V). The indefiniteness of the above results was due to the fact that the reagent diazomethane is not capable of methylating all the free phenolic hydroxyl groups present in the flavanone glycoside.



With a view to definitely establish the final constitution of naringin a successful attempt has now been made to methylate it completely using methyl iodide and potassium carbonate in acetone medium. It was found by King and Robertson⁵ that hesperidin which is a glycoside of the flavanone

hesperitin underwent complete methylation of the phenolic hydroxyl groups under these conditions though many of the hydroxyl groups of the sugar portion remained unaffected. At the same time the flavanone ring had opened out to form the corresponding chalcone. On the other hand, Lal⁶ noticed in connection with butrin that the opening of the pyrone ring took place only partially giving rise to two methylated products.

On methylating naringin by the above method and hydrolysing the product using alcoholic hydrochloric acid a brown solid was obtained which after repeated purification yielded a pale yellow crystalline compound melting at 206–7°. It was homogeneous and did not produce a red colour on reduction with magnesium and hydrochloric acid showing thereby the absence of the pyrone ring.^{7,8} Hence it was obvious that the pyrone ring had opened out completely during the methylation. The final product had the composition $C_{18}H_{18}O_5$ and contained three methoxyl groups. Its identity with 2 : 6 : 4'-trimethoxy-4-hydroxychalcone (VI) was proved by comparison with a synthetic sample of the chalcone. For this synthesis 2 : 6-O-dimethylphloroacetophenone prepared according to the method of Canter *et al.*,⁹ was condensed with anisaldehyde by the improved procedure recently described by Nadkarni and Wheeler.¹⁰ The transformations are represented below :



As a consequence of these experiments it is definitely established that in naringin there exists a disaccharide grouping attached to position 7 (Formula I, $R = C_{12}H_{21}O_9$). In this respect it is similar to the related compound hesperidin.

Experimental

Methylation of Naringin and Preparation of 2 : 6 : 4'-Trimethoxy-4-hydroxy-chalcone.—A suspension of naringin (5 g.) and anhydrous potassium carbonate

(5 g.) in a mixture of dry acetone (100 c.c.) and methyl iodide (10 c.c.) was heated under reflux on a water-bath. At the end of 30 hours further quantities of methyl iodide (10 c.c.) and potassium carbonate (5 g.) were added and the heating continued for another 30 hours. After cooling, the solution was filtered from inorganic salts and evaporated in a vacuum. A brown syrup was obtained and this was hydrolysed by refluxing with about 80 c.c. of alcoholic hydrochloric acid containing 5% of hydrogen chloride for 2 hours. The mixture was cooled, diluted with water (500 c.c.) and set aside. The brown precipitate which separated was filtered on the following day and washed several times with water. On repeated crystallisation from ethyl alcohol pale yellow glistening micaceous plates of the chalkone melting at 206° to 207° were obtained. (Found: C, 68.9; H 6.1; — OCH₃ 29.1; C₁₈H₁₈O₅ requires C 68.8; H 5.7; — OCH₃ 29.6%.) It did not produce a red colour with a reducing mixture of magnesium and hydrochloric acid thereby showing the absence of any flavanone structure. It was moderately soluble in pure alcohol and rather sparingly in 50% alcohol and the alcoholic solution did not give any characteristic colour with ferric chloride or lead acetate. It was readily soluble in cold dilute alkali giving a yellow solution from which it was re-precipitated on the addition of acids. A mixed melting point with the sample synthesised as below showed them to be identical.

2 : 6-0-Dimethyl-phloracetophenone was prepared from phloracetophenone by the method of Canter *et al.* (*loc. cit.*) It crystallised from methyl alcohol in slender prisms melting at 186° to 187°.

Synthesis of 2 : 6 : 4'-Trimethoxy-4-hydroxychalkone.—A solution of the above ketone (0.5 g.) and anisaldehyde (0.5 g.) in alcohol (3 c.c.) was treated at 0° with an ice-cold solution of potassium hydroxide (5 g. in 4 c.c. of water) and left out of contact with air for 4 days with occasional shaking. The mixture was then diluted with water (15 c.c.) and acidified with dilute hydrochloric acid, the temperature being maintained below 5°. A yellow solid separated which after filtration and washing with water was crystallised from aqueous alcohol (yield almost quantitative). A small quantity of a grey powder which was less soluble than the main portion was rejected. A repetition of the crystallisation gave the chalkone as pale yellow needles and micaceous plates melting at 204° to 205° (mixed m.p. 205° to 207°) and possessing all the properties of the sample prepared from naringin. (Found: OCH₃ 26.2, loss on drying at 140°, 10.0; C₁₈H₁₈O₅.2H₂O requires — OCH₃ 26.6, loss on drying 10.3%. Found in the dehydrated specimen: C 68.9; H 6.0 C₁₈H₁₈O₅ requires C 68.8, H 5.7%.) The sample had a tendency to lose its water of hydration on crystallisation from anhydrous alcohol.

Summary

Methylation of naringin by means of methyl iodide and potassium carbonate in acetone medium opens out the pyrone ring and methylates all the phenolic hydroxyl groups. The product on hydrolysis yields 2 : 6 : 4'-trimethoxy-4-hydroxychalkone. It is therefore concluded that in naringin the sugars, glucose and rhamnose exist as a disaccharide unit attached to position 7.

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