NEW SYNTHESIS OF TAMARAXETIN, ALPINONE AND IZALPININ

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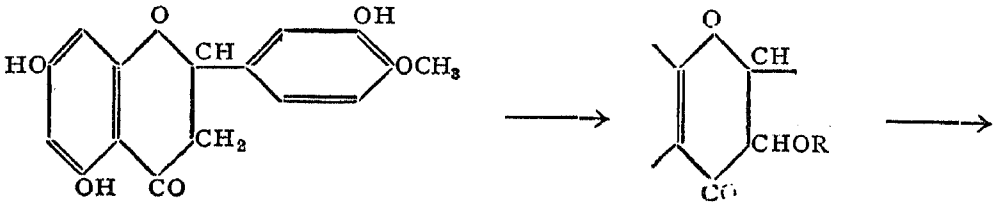
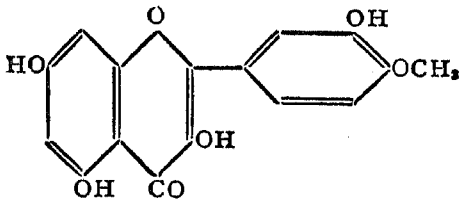
New methods of synthesis have been developed recently for the preparation of 3-hydroxy flavanones and since these compounds can be readily converted into the corresponding flavonols, they eventually provide more convenient methods of preparing naturally occurring flavonols also. As a typical example could be taken the synthesis of tamaraxetin (I) which is the 4'-mono-methyl ether of quercetin. Its earlier synthesis by Gupta and Seshadri,[1] using the well established method of Allan and Robinson, is rather tedious involving a number of steps. The alternative route now examined starts with hesperetin (II) which can be readily made from commercially available hesperidin.[2] Using iodine and silver acetate,[3] it can be conveniently converted into 3-acetoxy-hesperetin (III) which on subsequent hydrolysis gives 3-hydroxy-hesperetin (IV) in good yields. Subsequent dehydrogenation with iodine and potassium acetate in glacial acetic acid yields the flavonol tamaraxetin (I).



II

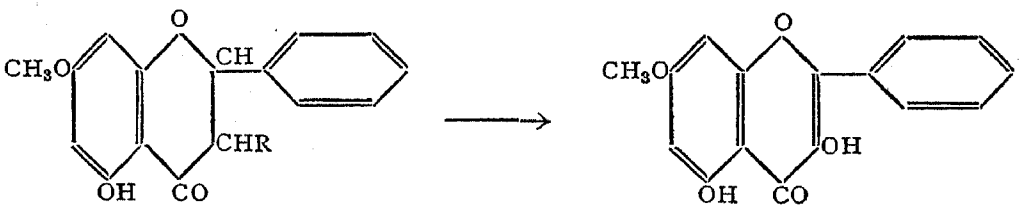
III, R=Ac.
IV, R=H.



I

The constitution of alpinone has been conclusively established[4,5] as 7-O-methyl pinobanksin (V). It is found to occur along with izalpinin (VI)

in the seeds of *Alpinia japonica*,[6] and these two are obviously related. It has been recently suggested[7] that the simpler flavanone structure represents an earlier stage in biogenesis and others involve further stages of oxidation. The feasibility of this scheme as a laboratory process has now been worked out. 5-Hydroxy-7-methoxy-flavanone (pinostrobin of pine heart-woods VII) which is conveniently obtained by partial demethylation[8] of the corresponding dimethoxy compound has been subjected to Fenton's oxidation[9] to yield alpinone (V). The alternative method used in the earlier case (iodine and silver acetate) is not suitable since, as is general with methyl ethers, here also the reaction stops with the stage of the 3-iodo-compound.[3] Alpinone (V) thus prepared could be dehydrogenated by iodine and potassium acetate to izalpinin (VI).



V. R=OH
VII, R=H

VI

EXPERIMENTAL

3-Acetoxy-hesperetin (III).—This was made earlier by Goel, Narasimhachari and Seshadri.[10] The modification of the general method recently described[3] gives better yields of the purer product. To hesperetin (1 g.) dissolved in absolute alcohol (30 c.c.) was added silver acetate (2 g.) and iodine (0·85 g.) in absolute alcohol (25 c.c.) at room temperature during a period of one hour with vigorous shaking. The mixture was then refluxed for two hours and the silver salt filtered off. Alcohol was then evaporated and the brown oily mass which solidified on cooling, was crystallised from ethyl acetate light petroleum mixture yielding aggregates of pale yellow tiny prisms (0·65 g.), m.p. 146–47°, agreeing with the m.p. given earlier by Goel, Narasimhachari and Seshadri.[11] It gave a violet colour with alcoholic ferric chloride.

3-Hydroxy-hesperetin (IV).—Earlier[10] the hydrolysis of the acetate was carried out by means of alkali; this has been found to give impure products owing to the formation of the corresponding benzyl coumaranone also. Hence acid hydrolysis has now been adopted. 3-Acetoxy-hesperetin (0·5 g.) was boiled with alcoholic hydrochloric acid (50 c.c., 1 : 1) for half an hour. Alcohol was removed under reduced pressure and ice added. The solid that separated was filtered, washed free of acid, dried in a vacuum desiccator

and crystallised from ethyl acetate light petroleum mixture yielding tiny prisms (0·3 g.), m.p. 200–201°, agreeing with the record of Zemplen and Bognar.[11] It gave a violet colour with alcoholic ferric chloride and was easily soluble in sodium carbonate. Its alcoholic solution gave a deep red colour with magnesium and hydrochloric acid and a pink colour with zinc and hydrochloric acid.

5 : 7 : 3′-*Trihydroxy*-4′-*methoxy flavonol* (*Tamaraxetin I*).—The above compound (0·2 g.) was dissolved in glacial acetic acid (6 c.c.) and fused potassium acetate (1 g.) added. The mixture was refluxed in an oil-bath and to the boiling solution iodine (0·16 g.) in glacial acetic acid (3 c.c.) was added dropwise during the course of an hour. The refluxing was continued for another hour, acetic acid removed under reduced pressure and sulphur dioxide water (50 c.c.) added to the residue. The solid thus obtained was filtered, washed with water and dried in a vacuum desiccator. It was first crystallised from ethyl acetate petroleum ether mixture and then from ethyl alcohol when tamaraxetin (0·12 g.) separated as golden yellow rectangular prisms, m.p. 260°, alone or mixed with an authentic sample earlier prepared by Gupta and Seshadri.[1]

Tamaraxetin tetra-acetate was prepared by the acetic anhydride pyridine method; it crystallised from alcohol as prismatic needles and rods, m.p. 203–04°.

3 : 5-*Dihydroxy*-7-*methoxy flavanone* (*Alpinone V*).—A suspension of finely powdered 5-hydroxy-7-methoxy flavanone (1 g.) in sulphuric acid (100 c.c., 2 N) was cooled in ice, vigorously stirred and hydrogen peroxide (5 vol., 80 c.c.) and ferrous sulphate solution (2%, 75 c.c.) were run in simultaneously during one hour. The mixture was allowed to stand for an hour and then extracted repeatedly with ether and the extract evaporated yielding a yellow solid. It was dissolved in alcohol (60 c.c.), a saturated solution of basic lead acetate (150 c.c.) added and the mixture allowed to stand overnight. A crystalline yellow lead salt separated (700 mg.) which was filtered, finely powdered and suspended in warm alcohol. Hydrogen sulphide was passed till the solution was saturated and the lead sulphide possibly containing some undecomposed lead salt was filtered off. This process was repeated twice again using the sulphide precipitate to ensure complete decomposition and complete recovery of the hydroxylated product. The total filtrate was evaporated to dryness when a pale yellow solid remained. It was first crystallised from ethyl acetate and light petroleum ether and then from methanol yielding colourless needles, m.p. 182–83°, agreeing with m.p. recorded earlier by Gripenberg[12] (Found: C, 67·1%; H, 4·8%;

$C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%). It gave a reddish purple colour with alcoholic ferric chloride and a greenish indigo colour with conc. nitric acid. It developed a red colour with alcoholic magnesium and hydrochloric acid and a pink colour with zinc and hydrochloric acid.

3 : 5-*Dihydroxy-7-methoxy flavone* (*Izalpinin VI*).—To a solution of alpinone (V) (100 mg.) in glacial acetic acid (10 c.c.) was added fused potassium acetate (0·5 g.) and iodine (100 mg.) in glacial acetic acid (5 c.c.). The mixture was refluxed for 2 hours, acetic acid removed under reduced pressure and sulphur dioxide water added. The brownish yellow solid was filtered and dried in a vacuum desiccator. It was first purified by disolution in ethyl acetate and precipitation of the coloured impurities by controlled addition of light-petroleum and finally crystallised from alcohol yielding yellow needles (40 mg.), m.p. 195–96°. It agreed in its m.p. and colour reactions with izalpinin synthesised earlier by Rao and Seshadri.[13]

The diacetate of the above sample was prepared by the acetic anhydride-pyridine method; it crystallised from alcohol to give colourless needles, m.p. 172–73°. Rao and Seshadri[13] reported the same m.p. for izalpinin diacetate.

SUMMARY

A new and convenient method for the synthesis of tamaraxetin uses hesperetin. By the action of iodine and silver acetate, it is converted into 3-acetoxy-hesperetin and eventually into 3-hydroxy-hesperetin which undergoes dehydrogenation by means of iodine and potassium acetate to yield tamaraxetin.

5-Hydroxy-7-methoxy-flavanone (pinostrobin) is converted into alpinone by Fenton's oxidation and subsequent dehydrogenation yields izalpinin.

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