NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XIX. A New Synthesis of Robinetin and Kanugin

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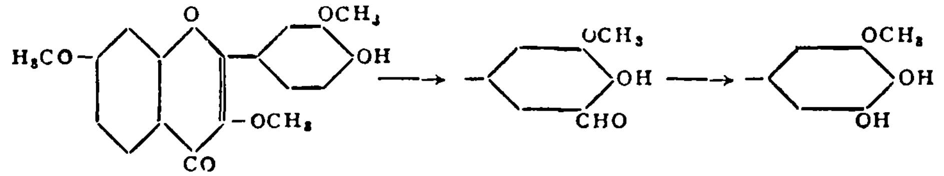
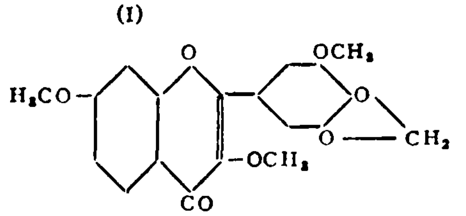
In Part XVI[1] was described a typical case of ortho oxidation in the side phenyl nucleus which consisted in the conversion of O-tetramethyl quercetin into myricetin. As further support for the multi-stage theory of ortho-oxidation the closely analogous case of robinetin has now been studied and it has been prepared from fisetin trimethyl ether (I). Further an important synthetic advantage of this method is the preparation of methylene ethers and this is illustrated by the synthesis of kanugin, a derivative of robinetin occurring in the root and stem barks of *Pongamia glabra.*[2]

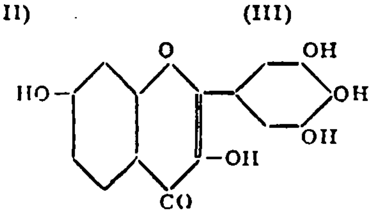
The abovementioned fisetin trimethyl ether (I) does not give any appreciable yield of the oxidation product with alkaline persulphate. But it condenses with hexamine to form the corresponding 5'-aldehyde (II) in good yields which subsequently undergoes oxidation with hydrogen peroxide to the catechol (III). These compounds have the expected properties and reactions. Methylenation of the catechol (III) yields kanugin (IV) and demethylation robinetin itself (V).



(I) (II) (III)



(IV)



(V)

Experimental

3 : 7 : 3'-*Trimethoxy-4'-hydroxy flavone* (*I*)

ω : 4-Dimethoxy-2-hydroxy acetophenone (2 g.) was condensed with the anhydride (10 g.) and the potassium salt (4 g.) of benzoyl vanillic acid by heating at 180° under reduced pressure for four hours. The product was refluxed with 10% aqueous alcoholic potash (65 c.c.) for 20 minutes. Alcohol was then removed under reduced pressure and water (100 c.c.) added to dissolve the residue. The yellow solution was filtered and the filtrate saturated with carbon dioxide. The flavone separated out as a brownish yellow solid. When crystallised from alcohol, it was obtained as yellow elongated rectangular prisms melting at 173–4°. Yield, 1 g. It did not develop any marked colour with alcoholic ferric chloride. It easily dissolved in aqueous alkali. (Found: C, 65·1; H, 5·3; $C_{8}H_{16}O_6$ requires C, 64·8; H, 5·0%.)

3: 7: 3′-*Trimethoxy*-4′-*hydroxy flavone*-5′-*aldehyde* (*II*)

The above flavone (0·5 g.) was heated with glacial acetic acid (6 c.c.) and hexamine (2 g.) over a boiling water-bath for six hours. The solution which was yellow at first turned deep brown towards the end. At the end of six hours, hydrochloric acid (1: 1; 6 c.c.) was added to the solution while still hot. After ten minutes water (10 c.c.) was added and the mixture left overnight. A bright yellow crystalline solid separated out (0·3 g.). It was crystallised first from alcohol and then from ethyl acetate when it was obtained in the form of pale yellow flat needles melting at 180–81°. Yield, 0·2 g. It was sparingly soluble in aqueous alkali giving a bright yellow solution. In dilute alcoholic solutions the aldehyde gave an immediate pale brown colour with ferric chloride ; in concentrated solutions, the initial colour was deep bluish green which slowly faded to brown. There was no precipitate with alcoholic neutral lead acetate for several hours. (Found: C, 63·6; H, 4·8; $C_{19}H_{16}O_7$ requires C, 64·0; H, 4·5%.)

3; 7: 3′-*Trimethoxy*-4′: 5′-*dihydroxy flavone* (*III*)

The above aldehyde (II) (0·25 g.) was dissolved in N/2 sodium hydroxide (2 c.c.) and treated with 6% hydrogen peroxide (0·6 c.c.) dropwise with vigorous shaking and occasional cooling in ice water. The solution was then kept at ordinary temperature. Within an hour the yellow solution became turbid. A few drops of pyridine were therefore added to clear up the turbidity. After three hours, the solution was acidified and the precipitated flavone filtered (0·2 g.). It was crystallised twice from alcohol when the dihydroxy flavone was obtained in the form of pale yellow small rectangular prisms melting at 199–200°. Yield, 0·15 g. The alcoholic solution of the substance was very pale yellow. It gave a deep olive green colour with a drop of ferric chloride solution, an immediate yellow precipitate with neutral lead acetate and a deep red colour with a drop of aqueous sodium hydroxide. (Found: C, 62·6; H, 4·9; $C_{18}H_{16}O_7$ requires C, 62·8; H, 4·7%.)

3 : 7 : 3′-*Trimethoxy*-4′ : 5′-*methylenedioxy flavone*: *Kanugin* (*IV*)

The dihydroxy flavone (85 mg.) was refluxed in anhydrous acetone solution (25 c.c.) with methylene sulphate (0·2 g.) and anhydrous potassium carbonate (1·0 g.) for 12 hours. At first the solution was clear yellow which gradually faded to pale yellowish brown in the course of four to five hours. The colour of the solution then began to deepen gradually and at the end of twelve hours it was deep yellowish brown. After the removal of acetone, water was added to the residue and extracted with ether. The ethereal extract was washed with 5% aqueous alkali twice and then with water. It was then evaporated to dryness and the residue crystallised from alcohol using a small quantity of animal charcoal. The methylene ether, kanugin, crystallised out as colourless rectangular plates melting at 204–5°. It did not depress the melting point of an authentic sample of kanugin and exhibited all the reactions.[3]

3 : 7 : 3′ : 4′ : 5′-*Pentahydroxy flavone*: *Robinetin* (*V*)

A solution of the dihydroxy flavone (III) (0·1 g.) in acetic anhydride (2 c.c.) was treated with hydriodic acid (d. 1·7; 4 c.c.) and refluxed for an hour and a half. The solution was then poured into water (30 c.c.) and decolourised by passing sulphur dioxide. It was saturated with sodium chloride and extracted with ether repeatedly. The ether extract was evaporated and the residue crystallised twice from aqueous ethyl alcohol. It was obtained as yellow rectangular plates melting at 320–25° (decomp.). Identity was established by direct comparison with an authentic sample of robinetin; the characteristic colour reactions were found to be identical.

SUMMARY

The trimethyl ether of fisetin with a free hydroxyl group in 4′-position yields the 5′-aldehyde readily by the action of hexamine. Subsequent oxidation with hydrogen peroxide gives rise to good yields of robinetin trimethyl ether. Its methylenation leads to the synthesis of kanugin and demethylation to the formation of robinetin. This constitutes another example of the two stage ortho-oxidation of the side phenyl nucleus of the flavonols.

REFERENCES

1.	Rao and Seshadri	.. *Proc. Ind. Acad. Sci.*, A., 1948, **28**, 210.
2.	Rangaswami, Rao and Seshadri	*Ibid.*, 1942, **16**, 319 ; 1943, **17**, 20 ; 1946, **23**, 60.
3.	Rao and Seshadri	.. *Ibid.*, 1946, **23**, 147.
4.	Rajagopalan, *et al.*	.. *Ibid.*, 1946, **23**, 62.