

NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

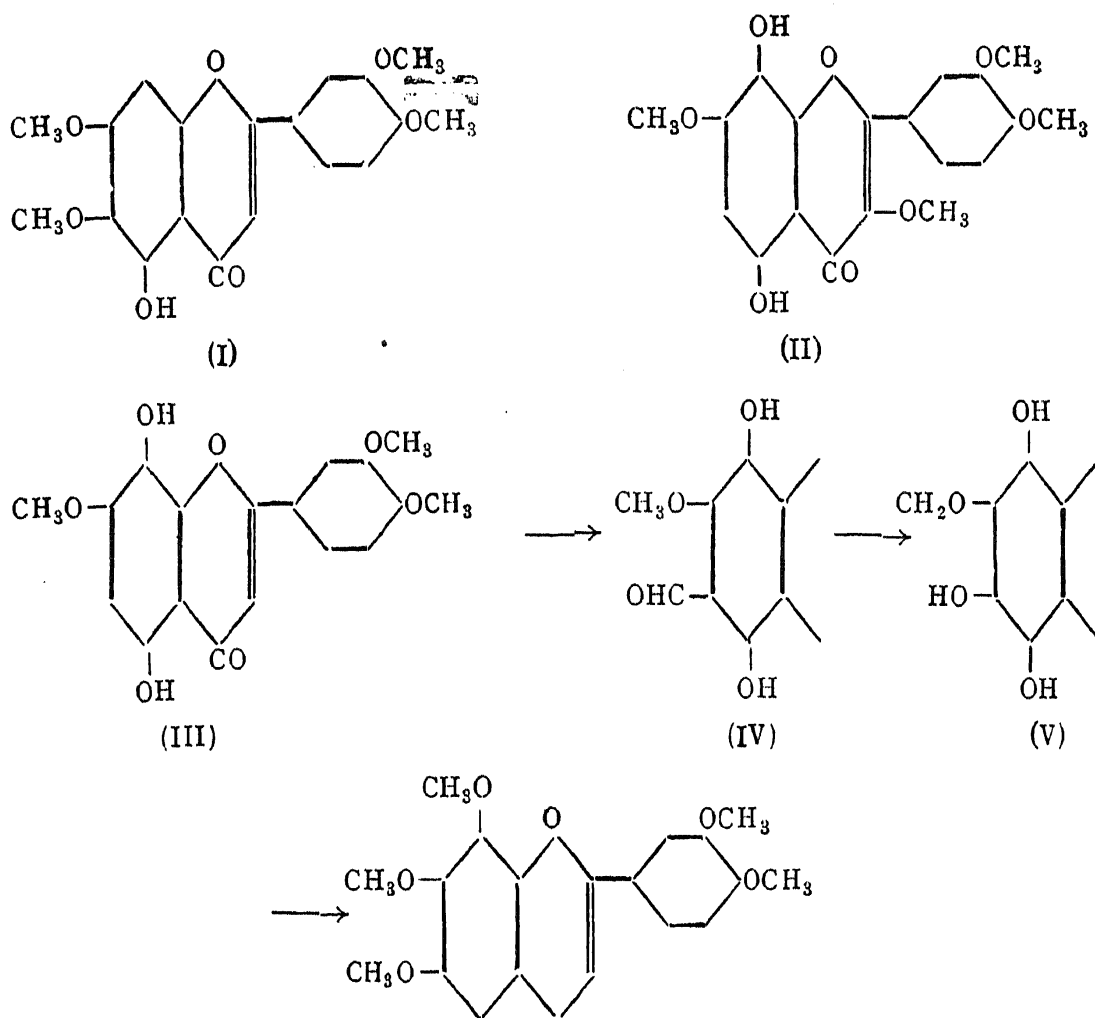
Part XXI. Another Synthesis of Nobiletin

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IN Part XI¹ was reported a synthesis of nobiletin involving the *p*-oxidation of 5-hydroxy-6:7:3':4'-tetramethoxy flavone (I) using alkaline persulphate. More recently was explored successfully the alternative route of ortho-oxidation in the 6-position using as typical example the conversion of the gossypetin derivative (II) into 6:8-dihydroxy quercetin.² The two stage process of ortho-oxidation was used. This method has now been applied to the synthesis of nobiletin, the analogous member of the flavone group.



5:8-Dihydroxy-7:3':4'-trimethoxy flavone (III) required for this purpose was recently described by Rao, Seshadri and Viswanadham.³ Its condensation with hexamine takes place satisfactorily yielding the corresponding 6-aldehyde (IV). Subsequent oxidation with hydrogen peroxide also proceeds well, the resulting compound (V) being a useful partial methyl ether of non-nobiletin. Further methylation yields nobiletin (VI) which is identical with samples obtained by earlier methods.

EXPERIMENTAL

5:8-Dihydroxy-7:3':4'-trimethoxy flavone-6-aldehyde (IV)

5:8-Dihydroxy-7:3':4'-trimethoxy flavone (III) was prepared according to the method of Rao, Seshadri and Viswanadham.³ It (2 g.) was dissolved in glacial acetic acid (25 c.c.) and hexamine (6 g.) was added to the yellow solution. The mixture was gently refluxed for 6 hours, a mixture (10 c.c.) of equal volumes of fuming hydrochloric acid and water added and refluxing continued for another 15 minutes. The dark red solution was diluted, saturated with sodium chloride and the aldehyde extracted with a large volume of ether. On distilling off the ether, a yellow solid was obtained which crystallised from alcohol-acetic acid mixture as yellow prisms melting at 262–4°; yield, 0.6 g. The compound dissolved in aqueous sodium hydroxide with a yellow colour and gave a brown-red colour with ferric chloride in alcoholic solution. (Found: C, 61.6; H, 4.4; $C_{19}H_{16}O_8$ requires C, 61.3; and H, 4.3%). The dinitrophenyl hydrazone was prepared and was found to melt at 253–5°.

5:6:8-Trihydroxy-7:3':4'-trimethoxy flavone (V)

The above aldehyde (1 g.) was dissolved in a mixture of 2 N sodium hydroxide (6 c.c.) and pyridine (5 c.c.) and the yellow solution was treated with 6% hydrogen peroxide (4 c.c.) in small quantities while cooling in ice-water. The mixture was occasionally shaken during half-an-hour, then acidified with dilute hydrochloric acid, and extracted with ether. The solid left behind after removing the solvent was crystallised from rectified spirit when it was obtained as bright yellow rectangular rods melting at 271–2°; yield, 0.5 g. It gave a deep reddish brown colour with alcoholic ferric chloride. (Found: C, 60.2; H, 4.6; $C_{18}H_{16}O_8$ requires C, 60.0; and H, 4.4%).

Nobiletin

The trihydroxy compound was completely methylated in acetone solution using excess of dimethyl sulphate in the presence of anhydrous potassium carbonate. The product crystallised from methyl alcohol as pale yellow

needles melting at 132–3° and was identical in all respects with a sample of nobiletin prepared earlier.¹

A correction

In the earlier paper,¹ the melting point of 5:6:7:3':4'-pentamethoxy flavone was reported as 142–43° and the sample was considered to contain half a molecule of water of crystallisation. Subsequently it has been found that in this case there was an error owing to the incomplete deacylation in the 3-position of the Allan-Robinson condensation product when boiling for half an hour with 5% aqueous sodium carbonate was used. Boiling for two hours seems to be necessary. Using this modification the penta-methyl ether is found to crystallise from alcohol as colourless needles melting at 172–3°. (Found: C, 64.7; H, 5.7; C₂₀H₂₀O₇ requires C, 64.5; H, 5.4%.)

SUMMARY

A new synthesis of nobilein has been achieved employing the two stage process of ortho-oxidation. 5:8-Dihydroxy-7:3':4'-trimethoxy flavone (III) is condensed with hexamine to yield the 6-aldehyde (IV) which undergoes smooth oxidation with hydrogen peroxide to 7:3':4'-trimethyl ether (V) of nornobiletin. Final methylation of (V) produces nobiletin (VI).

REFERENCES

1. Murthi and Seshadri .. *Proc. Ind. Acad. Sci., A*, 1948, 27, 217.
2. ————— .. *Ibid.*, 1949, 29, 221.
3. Rao, Seshadri and Viswanadham .. *Ibid.*, 1949, 29, 72.