

SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

Part XII. A Synthesis of 7-O-Methyl-Ethers of Hydroxy Flavones

BY N. NARASIMHACHARI AND T. R. SESHADRI, F.A.Sc.

(From the Department of Chemistry, Delhi University, Delhi)

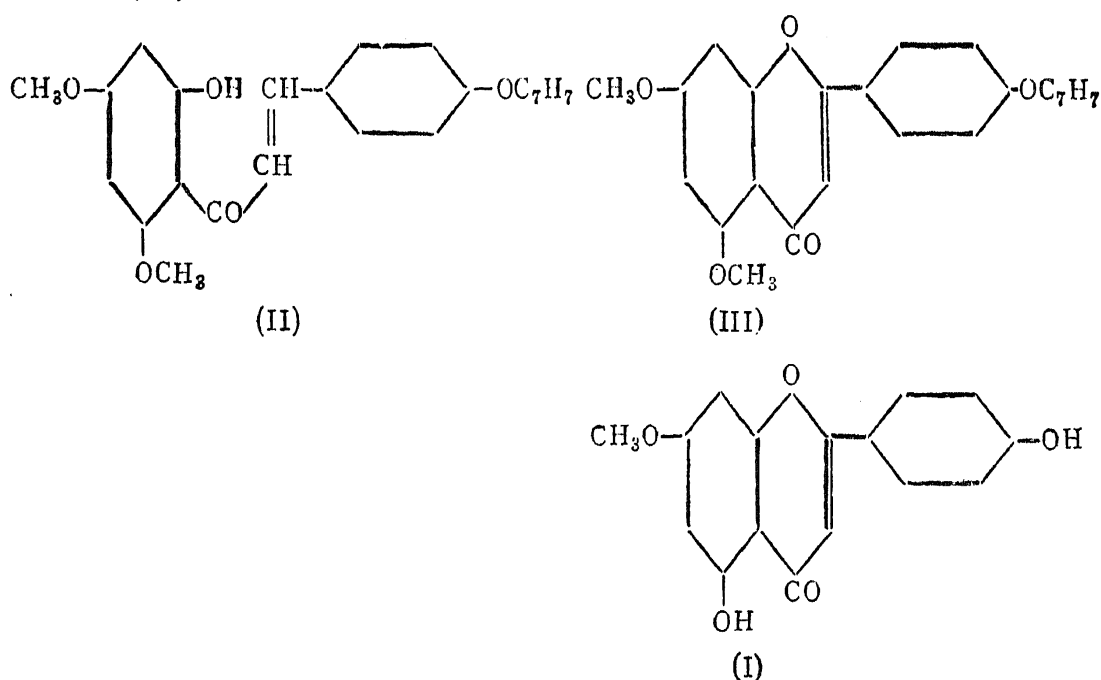
Received April 10, 1950

PARTIAL methyl ethers of flavones and flavonols are found to occur widely in nature and a large number of them are 7-methyl ethers, the 7-position being very frequently subjected to methylation analogous to glucoside formation. Based on past work a few methods could be suggested for the synthesis of these 7-methyl ethers. (1) Direct synthesis (Allan-Robinson) from the appropriate components has been employed by Kuhn and Low¹ for obtaining rhamnetin. But it has not been more widely adopted in view of inherent difficulties; the yields are very discouraging in the preparation of flavone derivatives. (2) Partial methylation of hydroxy flavones has been successful only in the case of chrysin to yield tectochrysin.² (3) On the other hand partial demethylation of more fully methylated methyl ethers which are readily obtained in synthesis has been more successfully adopted (tectochrysin and genkwanin; izalpinin and rhamnocitrin^{3,7}). For this purpose several reagents have been employed; aluminium chloride, aluminium bromide and hydrobromic acid under suitable conditions hydrolyse ether groups in the 5 and 3 positions. In certain cases where demethylation of 5 and 8 positions are involved nitric acid could also be employed.⁴ It forms a quinone which could subsequently be reduced to the quinol, *e.g.*, isowogonin.

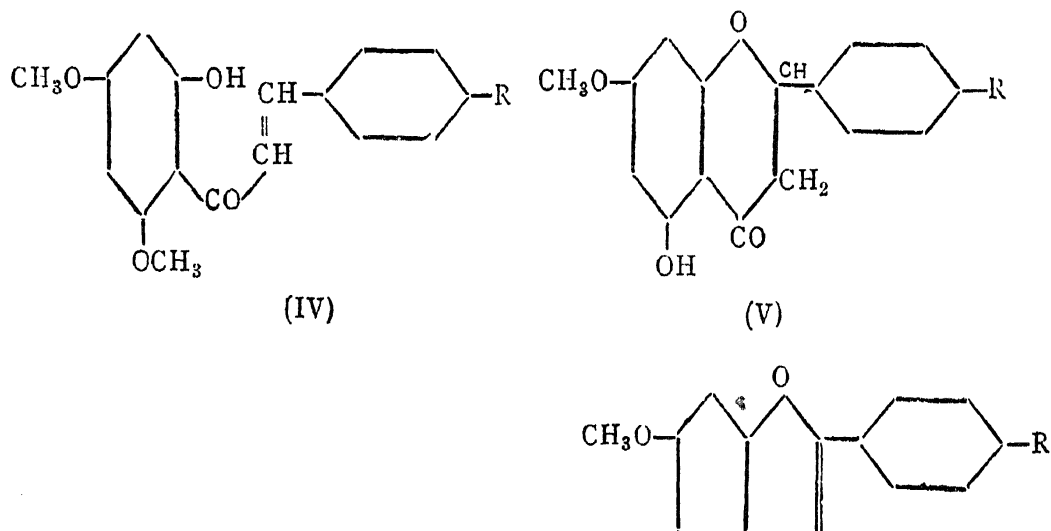
As already mentioned the above methods are successful only in simpler cases, but fail in the preparation of more complex types. The discovery of new methods which are suitable for such cases should mean valuable addition to technique. One such suggested itself as the result of our recent work. It consists in making the 7-methyl ether of the corresponding flavanone and subsequently oxidising it to the flavone. In our studies on the partial demethylation of chalcones⁵ it was shown that by employing hydrobromic acid (48%) at 100° it is possible to prepare hydroxy flavanone 7-methyl ethers. In a subsequent paper on the iodine oxidation of flavanones⁶ the conversion of these into corresponding flavones has been described. The two put together provide a new and convenient method for the synthesis of

7-methyl ethers of hydroxy flavones. As a typical example the case of genkwanin (I) is described in the following para:

Genkwanin (I) which is the 7-methyl ether of apigenin was first synthesised by Mahal and Venkataraman⁷ by the dehydrogenation of 2-hydroxy-4:6-dimethoxy-4'-benzyloxy chalcone (II) with selenium dioxide and by the subsequent debenzoylation and partial demethylation of the resulting flavone (III).

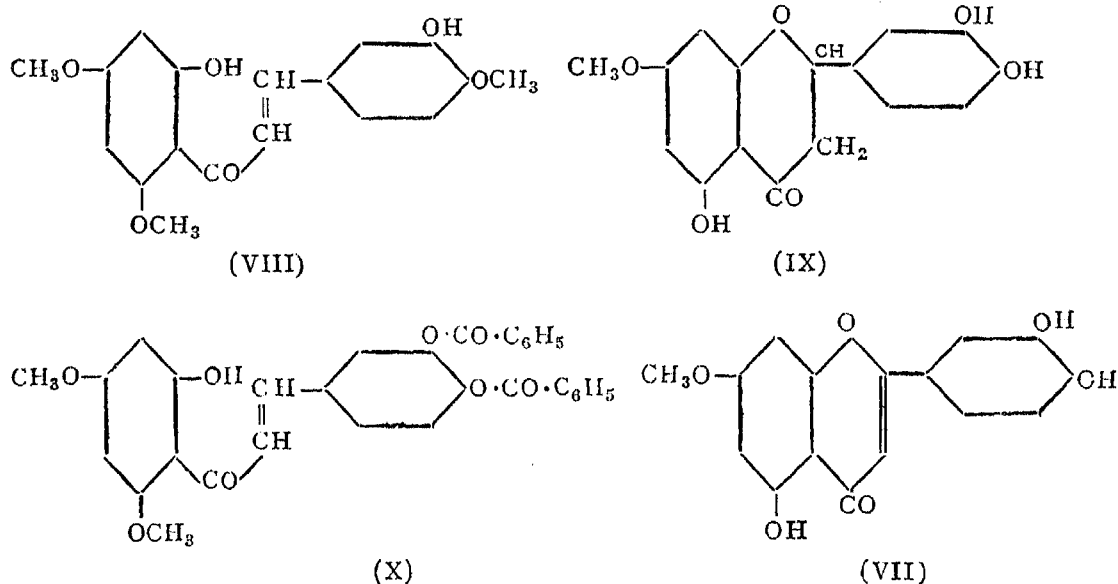


The new method consists in making sakuranetin (V, R=OH) from 2-hydroxy 4:6:4'-trimethoxy chalcone (IV, R=OCH₃), by heating it with hydrobromic acid⁵ and subsequently dehydrogenating the resulting sakuranetin with iodine.⁸ The yields are good. This method has now been extended to closely related flavones. Tectochrysin (VI, R=H) is now made from



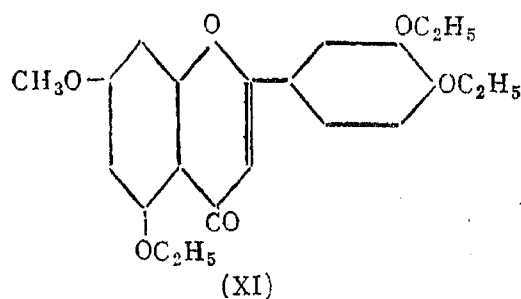
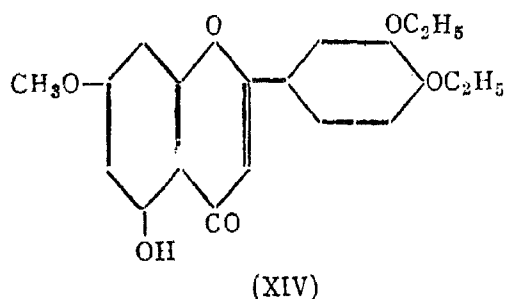
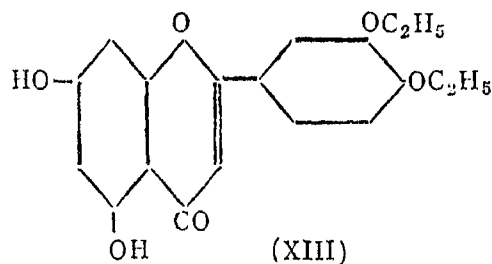
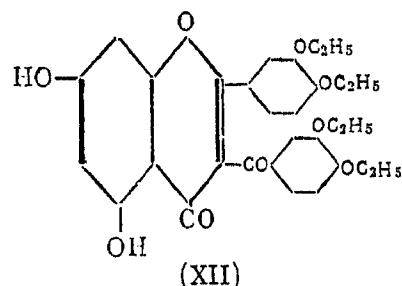
2-hydroxy-4:6-dimethoxy chalcone (IV, R = H), the intermediate stage being 5-hydroxy-7-methoxy flavanone (V, R = H).

7-Methyl ether of luteolin (VII) is an example of a flavone methyl ether which is rather difficult to prepare by using the other methods. Diller and Kostanecki⁹ obtained in the course of their demethylation of luteolin-5:7:3'-trimethyl-4'-ethyl ether besides luteolin, a by-product melting at 270°. They considered it to be the 7-methyl ether but the point does not seem to have been adequately investigated. The 7-methyl ether is readily obtained by the new procedure. For this purpose 2-hydroxy-4:6-dimethoxy acetophenone is condensed with isovanillin in presence of alkali. The resulting chalcone (VIII) yields readily 7-O-methyl eriodictyol (IX) on treatment with hydrobromic acid. Subsequent dehydrogenation with iodine proceeds smoothly to produce 7-O-methyl luteolin (VII). As a variation the condensation of phloracetophenone dimethyl ether with the dibenzoate of protocatechuic aldehyde has also been effected in the presence of hydrogen chloride in ethyl acetate solution.¹⁰ The resulting chalcone (X) undergoes both demethylation and debenzoylation with hydrobromic acid to yield 7-O-methyl eriodictyol (IX). Of the two methods the use of isovanillin is more convenient. The melting point of 7-O-methyl luteolin thus obtained is found to be 258–60°.



Though the 7-methyl ethers of eriodictyol and luteolin have not so far been isolated from natural products their occurrence seems to be possible. They correspond to rhamnetin in the flavonol series. Recently Ferguson *et al.*¹¹ considered that the muscle inhibiting compound in lucerne was luteolin-7-methyl ether; it has been subsequently found to be a different flavone.¹² Further the melting point of our methyl ether of luteolin differs from that of

the demethylation experiments of Diller and Kostanecki.⁹ For these reasons it was felt necessary to confirm the constitution of the synthetic material; the flavone methyl ether has therefore been fully ethylated using ethyl sulphate. The product is found to be identical with 7-methoxy-5:3'-4'-tri-ethoxy flavone (XI) which has been independently synthesised in the following manner. Phloracetophenone is condensed with the anhydride and sodium salt of diethyl protocatechuic acid (Allan-Robinson). The major product appears to be the 3-acyl derivative (XII) which is hydrolysed to luteolin-3':4'-diethyl ether (XIII). This is subsequently subjected to partial methylation in 7-position (XIV) and final ethylation in the 5-position to yield the required product (XI).



EXPERIMENTAL

Tectochrysin (VI, R = H)

The preparation of 5-hydroxy-7-methoxy flavanone (V, R=H) has already been reported.⁵ It (0.5 g.) was dissolved in alcohol, sodium acetate (2 g.) added and the solution boiled. To this a boiling solution of iodine (0.5 g.) in alcohol was added with shaking. Iodine was rapidly decolourised and in the end there was a permanent colour due to iodine. On cooling, the flavone crystallised out. It was filtered and recrystallised from alcohol when it separated out in the form of pale brown shining needles melting at 165-6°. The mixed melting point with an authentic sample of tectochrysin² was undepressed. Some more of tectochrysin could be obtained by concentrating the alcoholic solution and crystallising the product from alcohol. Yield, 0.35 g.

2:3'-Dihydroxy-4:6:4'-trimethoxy chalkone (VIII)

A mixture of 2-hydroxy 4:6-dimethoxy acetophenone (2 g.) and isovanillin (2.5 g.) was dissolved in alcohol (70 c.c.) and potassium hydroxide

(5 g. in 5 c.c. water) added to it with cooling under the tap. The solution was then kept corked for 48 hours at room temperature. It was then diluted with water (200 c.c.), cooled and acidified with hydrochloric acid. The precipitated solid was filtered and washed twice with sodium bicarbonate solution to remove the isovanillic acid present in it. On crystallising it from alcohol 2:3'-dihydroxy-4:6:4'-trimethoxy chalkone (VIII) separated in the form of bright yellow rectangular prisms melting at 193–4°. It gave a deep brown colour with ferric chloride in alcoholic solution and dissolved readily in sodium hydroxide solution. Its alcoholic solution gave no colour with magnesium and hydrochloric acid. (Found: C, 65.2; H, 5.5; $C_{18}H_{18}O_6$ requires C, 65.5; H, 5.5%.)

7-O-Methyl-eriodictyol (7-methoxy-5:3':4'-trihydroxy flavanone) (IX)

The above chalkone (1 g.) was dissolved in glacial acetic acid (5 c.c.) and treated with a saturated solution of hydrobromic acid in acetic acid (10 c.c.). The mixture was then heated on a boiling water-bath for 1½ hours, cooled and diluted with water and left in the refrigerator overnight. The solid that separated was filtered and washed with water. It was crystallised first from ethyl acetate-petroleum ether mixture and then from alcohol. It finally came out in the form of colourless needles melting at 215°. It gave a green colour with ferric chloride in alcoholic solution and a blue colour with concentrated nitric acid. On reduction with magnesium and hydrochloric acid in alcoholic solution it developed a bright scarlet colour. Some more of it could be obtained by ether-extracting the aqueous solution and evaporating the ether, after washing with aqueous sodium bicarbonate. Yield, 0.4 g. (Found: C, 61.9; H, 4.9; OCH_3 , 10.3; $C_{16}H_{14}O_6$, $\frac{1}{2}H_2O$ requires C, 61.7; H, 4.8; OCH_3 , 10.0%. Loss on drying: 3.3; $C_{16}H_{14}O_6$, $\frac{1}{2}H_2O$ requires 2.9%.)

7-O-Methyl luteolin (VII)

7-O-Methyl eriodictyol (0.5 g.) was treated with sodium acetate (2 g.) and iodine (0.5 g.) in alcoholic solution as described earlier. 7-O-Methyl luteolin crystallised from alcohol in the form of small yellow prisms melting at 258–60°. Its alcoholic solution gave a green colour with ferric chloride and a red colour with magnesium and hydrochloric acid. (Found: C, 63.8; H, 4.0; OCH_3 , 10.7; $C_{16}H_{12}O_6$ requires C, 64.0; H, 4.0; OCH_3 , 10.3%.)

2-Hydroxy-4:6-dimethoxy-3':4'-dibenzoyloxy-chalkone (X)

A solution of phloracetophenone-4:6-dimethyl ether (1 g.) and dibenzoate of protocatechuic aldehyde (1.8 g.) in dry ethyl acetate was cooled in

ice, saturated with dry hydrogen chloride gas for 2 hours, and kept at 0° for 24 hours. Ethyl acetate was then distilled under reduced pressure. The solid that was left behind was crystallised from excess of alcohol when it was obtained in the form of pale brownish yellow prisms melting at 168–70°. It gave a reddish brown colour with ferric chloride in alcoholic solution. Yield, 0.6 g. (Found: C, 70.6; H, 4.3; C₃₁H₂₄O₈ requires C, 71.0; H, 4.5%.)

7-O-Methyl-eriodictyol

The above chalkone (1 g.) was dissolved in glacial acetic acid (7 c.c.) and a saturated solution of hydrogen bromide in glacial acetic acid (15 c.c.) added to it. The mixture was heated on a water-bath for 1 hour and after cooling, was diluted with water and left in the ice-chest overnight. The solid that separated was filtered and washed twice with aqueous sodium bicarbonate and then with water. When crystallised twice from alcohol (animal charcoal) it came out in the form of colourless needles melting at 215–16°. It gave a green colour with ferric chloride in alcohol and a blue colour with conc. nitric acid. On reduction with magnesium and hydrochloric acid it developed a scarlet red colour. It agreed in all its properties with the sample described earlier and the mixed melting point was undepressed.

5:7-Dihydroxy-3':4'-diethoxy flavone (XIII)

Phloracetophenone (3 g.), diethyl protocatechuic anhydride (25 g.) and the sodium salt of diethyl protocatechuic acid (5 g.) were intimately mixed and heated for 3 hours at 180–90° under reduced pressure. The product was refluxed with alcoholic potash (6 g. in 75 c.c.) for 20 minutes, alcohol removed under reduced pressure, the residue dissolved in water and carbon dioxide passed through it. The 3-acyl derivative that separated was filtered and washed with water. It crystallised from alcohol in the form of brownish yellow prisms melting at 190° (decomp.). It was hydrolysed by refluxing with aqueous sodium carbonate (5%, 100 c.c.) for 2 hours. The carbonate solution was cooled and acidified with hydrochloric acid. The solid that separated was filtered and washed with sodium bicarbonate solution to remove the acid formed (solution A). The remaining flavone crystallised from ethyl acetate-alcohol mixture in the form of colourless short rectangular prisms melting at 250–52°. Its alcoholic solution gave a reddish violet colour with ferric chloride and a bright red colour with magnesium and hydrochloric acid. It dissolved readily in aqueous sodium carbonate. (Found: C, 66.6; H, 5.4; C₁₉H₁₈O₆ requires C, 66.7; H, 5.3%.) The sodium bicarbonate solution (A) on acidification gave diethyl protocatechuic acid (m.p. and mixed m.p. 165–6°).

Partial methylation

The above flavone (0.5 g.) was refluxed for 6 hours with dimethyl sulphate (0.15 g.) and anhydrous potassium carbonate (0.5 g.) in acetone solution (40 c.c.). It was then filtered and the residue washed with acetone. The acetone filtrate was then evaporated and the product crystallised. 5-Hydroxy-7-methoxy-3':4'-diethoxy-flavone (XIV) crystallised from alcohol in the form of colourless prisms and needles melting at 155–6°. (Found: C, 66.9; H, 5.7; $C_{20}H_{20}O_6$ requires C, 67.4; H, 5.6%.) It gave a brown colour with ferric chloride in alcoholic solution and was sparingly soluble in aqueous sodium hydroxide.

Ethylation

The above flavone (XIV) (0.3 g.) was ethylated with excess of diethyl sulphate (0.4 c.c.) and anhydrous potassium carbonate by refluxing in acetone solution for 24 hours. 7-O-Methyl-triethyl luteolin (XI) crystallised from alcohol in fine colourless needles melting at 162–3°. It gave no colour with ferric chloride in alcoholic solution and was insoluble in aqueous sodium hydroxide. (Found: C, 68.4; H, 6.5; $C_{24}H_{26}O_2$ requires C, 68.7; H, 6.3%.)

Ethylation of 7-O-methyl luteolin

The synthetic sample of 7-O-methyl luteolin (0.2 g.) was ethylated by refluxing it for 24 hours with excess of diethyl sulphate (0.5 g.) and anhydrous potassium carbonate (2 g.) in acetone solution. The product crystallised from alcohol as colourless needles melting at 162–3°. It agreed in all its properties with 7-O-methyl-triethyl luteolin described above and mixed melting point was undepressed.

SUMMARY

A general method for the synthesis of the 7-methyl ethers of hydroxy flavones is described using as examples (1) tectochrysin, (2) genkwanin and (3) 7-O-methyl luteolin. It consists in preparing the corresponding 7-O-methyl flavanone and oxidising it with iodine. 7-O-Methyl eriodictyol is now made from (a) 2:3'-dihydroxy-4:6:4'-trimethoxy chalcone and (b) 2-hydroxy-4:6-dimethoxy-3':4'-dibenzoyloxy chalcone by treatment with hydrobromic acid. Iodine oxidation of it yields (3). The constitution of this product is confirmed by fully ethylating it and showing that the triethyl ether is identical with 7-methoxy-5:3':4'-triethoxy flavone.

REFERENCES

1. Kuhn and Low .. *Chem. Abs.*, 1945, 3285.
2. Piccard .. *Ber.*, 1873, 6, 884.
Rao, Rao and Seshadri .. *Proc. Ind. Acad. Sci.*, A, 1947, 25, 430.
3. Gulati and Venkataraman .. *J.C.S.*, 1936, 267.
Rao and Seshadri .. *Proc. Ind. Acad. Sci.*, A, 1945, 22, 383 and *J.C.S.*,
1947, 122.
4. Rao, Rao and Seshadri .. *Proc. Ind. Acad. Sci.*, A, 1947, 25, 431.
5. Narasimhachari and Seshadri .. *Ibid.*, 1949, 29, 265.
6. ————— .. *Ibid.*, 1949, 30, 151.
7. Mahal and Venkataraman .. *J.C.S.*, 1936, 569.
8. Narasimhachari and Seshadri .. *Proc. Ind. Acad. Sci.*, A, 1949, 30, 271.
9. Diller and Kostanecki .. *Ber.*, 1901, 1449.
10. Russel and Todd .. *J.C.S.*, 1934, 218.
11. Ferguson *et al.* .. *Nature*, 1949, 163, 606.
12. Ferguson .. Private communication.