

SELECTIVE DEMETHYLATION OF THE 5-METHOXYL GROUP IN FLAVANONES AND SYNTHESIS OF DIHYDROWOGONIN

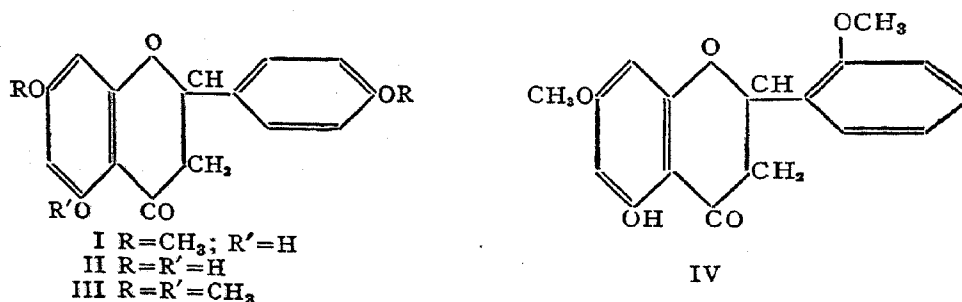
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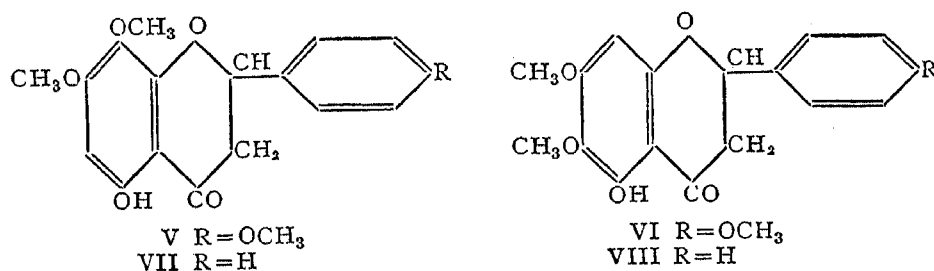
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A CONVENIENT method was needed for the exclusive demethylation of the 5-methoxyl group in flavanones. Aluminium chloride in nitrobenzene and hydrobromic acid which are satisfactory in simpler cases are not suitable for more complex flavanones because they can demethylate other positions also; further, hydrobromic acid can bring about ring isomeric change. Aqueous hydrochloric acid, which has been used in the case of furanochromones¹ and isoflavones,² has not been successful in the partial demethylation of flavanones. On the other hand, aluminium chloride in dry ethereal solution serves the purpose very well and gives good yields. By means of this reagent a number of representative methoxy flavanones have now been converted into the corresponding 5-hydroxy compounds. This reagent was earlier used by Baker and Simmonds³ for the preparation of 5-hydroxy-8:4'-dimethoxy flavone, and has not so far been employed in the flavanone series.

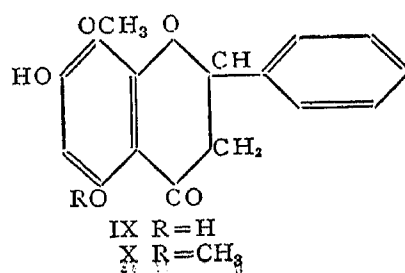
The reagent was first tested in simple cases for the preparation of known compounds. 5-Hydroxy flavanone⁴ is smoothly prepared by the demethylation of 5-methoxy flavanone. The product is found to be identical with the sample obtained by the action of hydrobromic acid on 2-hydroxy-6-methoxy chalcone whereby demethylation and ring closure are known to take place.⁵ 5-Hydroxy-7-methoxy flavanone was prepared earlier from 5:7-dimethoxyflavanone by demethylation with aluminium chloride and nitrobenzene⁶; aluminium chloride in ether is much better. Naringenin dimethyl ether⁷ (I) originally obtained by the partial methylation of naringenin (II) with diazomethane is also formed easily from the trimethyl ether (III) by the partial demethylation. Under this category comes citronetin methyl ether also⁸ (IV).



For the study of carthamidin (5:7:8:4'-tetrahydroxy flavanone) and isocarthamidin (5:6:7:4'-tetrahydroxy flavanone) and the recently discovered dihydrowogonin⁹ (5:7-dihydroxy-8-methoxy flavanone), convenient derivatives, which can be used for comparison, are the partial methyl ethers with only the 5-hydroxyl group left free. They are usually made by carrying out the partial methylation of the natural hydroxy flavanones with diazomethane or with restricted quantities of dimethyl sulphate. Authentic samples of synthetic compounds can now be easily obtained for comparison by the partial demethylation of synthetic methyl ethers using aluminium chloride in ether solution. As typical examples, carthamidin trimethyl ether (5-hydroxy-7:8:4'-trimethoxy flavanone, V), isocarthamidin trimethyl ether (5-hydroxy-6:7:4'-trimethoxy flavanone, VI), dihydrowogonin monomethyl ether (5-hydroxy-7:8-dimethoxy flavanone, VII) and also 5-hydroxy-6:7-dimethoxy flavanone (VIII) have been prepared by partial demethylation.



The method can be conveniently used also for the preparation of certain naturally occurring flavanones. As an example, the synthesis of dihydrowogonin⁹ (IX) has now been carried out. For this purpose 7-hydroxy-5:8-dimethoxy flavanone (X) has been prepared by the condensation of 2:4-dihydroxy-3:6-dimethoxy acetophenone¹⁰ and benzaldehyde and subsequent ring closure. This undergoes smooth demethylation with aluminium chloride in ether and the product is found to be identical with dihydrowogonin (IX), isolated from *Prunus avium* by Mentzer *et al.*,⁹ in all its properties and reactions except optical activity. The partial methyl ether (7-methyl ether) of the synthetic compound has been made by means of diazomethane and is found to be identical with a similar sample prepared from natural dihydro-



wogonin¹¹ and also with the synthetic 5-hydroxy-7:8-dimethoxy flavanone (VII) mentioned earlier. These observations confirm that there has been no isomeric change during the demethylation in ether solution.

Recently Chopin *et al.*¹² condensed iretol with cinnamoyl chloride in the presence of aluminium chloride and could isolate the isomeric dihydro-oxylin from the product. They proved the presence of dihydrowogonin in the more soluble fractions by chromatography. Our method is quite convenient for the synthesis of dihydrowogonin.

EXPERIMENTAL

General method of selective demethylation of the 5-methoxyl group

The 5-methoxy flavanone is dissolved or suspended as very fine powder in anhydrous ether, powdered anhydrous aluminium chloride added in excess and the mixture stirred for ten minutes and kept at room temperature for about twenty-four hours. Ether is then distilled off and the aluminium chloride complex decomposed with ice-cold hydrochloric acid which is subsequently warmed if necessary for half an hour to complete the decomposition. The solid that separates is filtered and washed with water and crystallised from a suitable solvent.

5-Hydroxy flavanone.—(a) Demethylation of 5-methoxy flavanone as given above yielded a product which crystallised from alcohol yielding colourless broad rectangular plates, m.p. 63–64° (Found: C, 74.6; H, 5.0; $C_{15}H_{12}O_3$ requires C, 75.0; H, 5.0%). It gives a deep reddish violet colour with ferric chloride in alcoholic solution and with concentrated nitric acid a permanent green solution. Though the properties and analysis agree with the previous description of 5-hydroxy flavanone,⁴ the melting point observed now is considerably lower. The earlier sample was not available, and the earlier method does not give consistent results. However, demethylation of 2-hydroxy-6-methoxy chalcone as given below yielded the same product, m.p. 63–64°, and hence there was no doubt about the correctness of the present sample.

(b) *Demethylation of 2-hydroxy-6-methoxy chalcone with hydrobromic acid.*—The chalcone (0.5 g.) was treated with a saturated solution of hydrobromic acid in acetic acid (10 c.c.) and the red solution heated on a boiling water-bath for two hours. It was then diluted with water (50 c.c.) when a dark brown semi-solid separated. This was ether extracted, the extract washed with cold aqueous sodium carbonate (2%) and dried over anhydrous sodium sulphate. The solvent was distilled off and the residue crystallised from ethyl acetate-petroleum ether mixture and then from methanol. It

separated as colourless broad rectangular plates, m.p. 63–64°, undepressed by admixture with the sample from (a).

5-Hydroxy-7-methoxy flavanone

The product obtained by the demethylation of 5:7-dimethoxy flavanone with aluminium chloride crystallised from alcohol as colourless prisms, m.p. 100–01°, undepressed by an authentic sample of 5-hydroxy-7-methoxy flavanone.⁶ It gave a red colour with ferric chloride in alcoholic solution and a green colour with concentrated nitric acid which rapidly changed to blue.

5-Hydroxy-7:4'-dimethoxy flavanone (Naringenin dimethyl ether)

This was prepared in a similar way from 5:7:4'-trimethoxy flavanone. It crystallised from ethyl acetate as colourless long rectangular prisms, m.p. 120–22°, either alone or with naringenin 7:4' dimethyl ether.⁷ It gave a red colour with ferric chloride in alcoholic solution and a blue colour with concentrated nitric acid. It developed a brilliant purple colour with magnesium and hydrochloric acid.

5-Hydroxy-7:2'-dimethoxy flavanone (Citronetin monomethyl ether)

5:7:2'-Trimethoxy flavanone underwent smooth demethylation and the product crystallised from ethyl acetate-petroleum ether mixture and then from absolute alcohol as colourless rectangular tablets, m.p. 91–92° either alone or with an authentic sample of citronetin monomethyl ether.⁸ It gave a wine red colour with ferric chloride and a deep blue colour with concentrated nitric acid. It developed a pink colour with magnesium and hydrochloric acid.

5-Hydroxy-7:8-dimethoxy flavanone

5:7:8-Trimethoxy flavanone was subjected to selective demethylation and in this case the product was extracted with benzene and the benzene layer washed with hydrochloric acid and then with water. It was dried over anhydrous sodium sulphate, the solvent distilled off and the residue crystallised from methanol yielding colourless rectangular prisms melting at 98–99°. The substance gave a green colouration with ferric chloride in alcoholic solution. With concentrated nitric acid it developed an orange red colour (Found: C, 68.6; H, 5.0; $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%).

5-Hydroxy-7:8:4'-trimethoxy flavanone (Carthamidin trimethyl ether)

This was obtained by the general method from 5:7:8:4'-tetramethoxy flavanone. It crystallised from methanol as pale yellow broad and thin

plates melting at 137–38°. Its alcoholic solution gave a greenish brown colour with ferric chloride and a magenta colour with magnesium and hydrochloric acid. With concentrated nitric acid it developed an orange colour (Found: C, 64.4; H, 5.7; $C_{18}H_{18}O_6$ requires C, 65.4; H, 5.4%).

5-Hydroxy-6 : 7-dimethoxy flavanone

This resulted from the demethylation of 5 : 6 : 7-trimethoxy flavanone and crystallised from alcohol as colourless rectangular plates, m.p. 148–50°. It gave a red colour with ferric chloride in alcoholic solution changing with excess to greenish brown. With concentrated nitric acid, it developed a wine red colouration (Found: C, 67.7; H, 5.4; $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%).

5-Hydroxy-6 : 7 : 4'-trimethoxy flavanone (Isocarthamidin trimethyl ether)

This was obtained in good yield from 5 : 6 : 7 : 4'-tetramethoxy flavanone and it crystallised from alcohol as pale yellow rectangular prisms, m.p. 132–33°. It gave a reddish violet colour with alcoholic ferric chloride changing gradually to green. With concentrated nitric acid it developed an orange red colour, and with magnesium and hydrochloric acid a purple colour (Found: C, 64.8; H, 5.5; $C_{18}H_{18}O_6$ requires C, 65.4; H, 5.4%).

7-Hydroxy-5 : 8-dimethoxy flavanone

To a solution of 2 : 4-dihydroxy-3 : 6-dimethoxy acetophenone¹⁰ (0.5 g.) in alcohol (5 c.c.), benzaldehyde (redistilled; 0.3 g.) in alcohol (2 c.c.) and saturated alcoholic potash (5 c.c.) were added and the mixture kept at room temperature (25° C.) for 48 hours. It was then diluted with 30 c.c. of water and ether extracted to remove unchanged aldehyde. The aqueous solution on acidification deposited a brown oil which soon solidified on stirring to an yellow-brown solid. It was macerated with sodium bicarbonate solution, filtered and the residue crystallised from ethyl acetate yielding very pale yellow large rectangular prisms, m.p. 185–86°. Yield 0.3 g. (Found: C, 67.9; H, 5.9; $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%). There was no change when it was heated with alcoholic sulphuric acid and it should therefore be the flavanone.

5 : 7-Dihydroxy-8-methoxy flavanone (Dihydrowogonin)

7-Hydroxy-5 : 8-dimethoxy flavanone (0.15 g.), ether (5 c.c.) and anhydrous aluminium chloride (0.5 g.) were stirred for 12 hours using magnetic stirrer and the mixture allowed to stand at room temperature (25° C.) for 36 hours. Ether was distilled off and the brownish aluminium chloride complex decomposed with ice-cold hydrochloric acid (1 : 1) and the decom-

position completed by warming on a water-bath to 45° C. The pale yellow product was extracted with benzene, and the benzene layer washed with dilute hydrochloric acid and then with water, dried and concentrated when the flavanone crystallised out. Recrystallisation from benzene yielded rectangular tablets, m.p. 147–48°, undepressed by admixture with the natural sample of dihydrowogonin (m.p. 148°) (yield 0.1 g.) (Found: C, 66.9; H, 5.4; OCH₃, 10.8. C₁₆H₁₄O₅ requires C, 67.1; H, 4.9; 1 OCH₃, 10.8%).

It gave a pinkish brown colour with ferric chloride, a red colour with concentrated nitric acid and an yellow-orange colour with magnesium and hydrochloric acid agreeing with the behaviour of natural dihydrowogonin.

Dihydrowogonin monomethyl ether

Synthetic dihydrowogonin (0.05 g.) was dissolved in ether (10 c.c.) and a solution of diazomethane in ether (1.5 moles) was added. This mixture was left in the refrigerator overnight, ether distilled off and the yellow residue crystallised from methyl alcohol yielding long rectangular prisms, m.p. 98°, undepressed by admixture with the same methyl ether similarly prepared from natural dihydrowogonin¹¹ and also with 5-hydroxy-7:8-dimethoxy flavanone already described.

We convey our thanks to Prof. C. Mentzer and Dr. J. Chopin for the gift of natural dihydrowogonin and its 7-methyl ether.

SUMMARY

Anhydrous aluminium chloride in ether solution is found to be a convenient reagent for the selective demethylation of the 5-position of methoxy flavanones and these 5-hydroxy compounds can serve as standard derivatives for comparison. A number of typical compounds are reported, the most important being naringenin dimethyl ether, citronetin monomethyl ether and carthamidin and isocarthamidin trimethyl ethers. The method has been employed for the synthesis of dihydrowogonin which has been recently isolated. This involves the preparation and partial demethylation of 7-hydroxy-5:8-dimethoxy flavanone.

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