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


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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 furanochromones\(^1\) 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 Simmonds\(^3\) 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 flavanone\(^4\) 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 nitrobenzene\(^6\); aluminium chloride in ether is much better. Naringenin dimethyl ether\(^7\) (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 also\(^8\) (IV).

\[\text{RO} \quad \text{CH} \quad \text{OR} \quad \text{CH}_3\]

\[\text{CH}_3 \quad \text{OH} \quad \text{CO} \quad \text{OCH}_3\]

\[\text{I} \quad R=\text{CH}_3; \quad R'=\text{H}\]
\[\text{II} \quad R=R'=\text{H}\]
\[\text{III} \quad R=R'=\text{CH}_3\]

\[\text{IV}\]
Demethylation of 5-Methoxyl Group in Flavanones

For the study of carthamidin (5:7:8:4'-tetrahydroxy flavanone) and isocarthamidin (5:6:7:4'-tetrahydroxy flavanone) and the recently discovered dihydrowogonin\(^9\) (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-6:7:8-dimethoxy flavanone, VII) and also 5-hydroxy-6:7-dimethoxy flavanone (VIII) have been prepared by partial demethylation.

\[ \text{V} \quad R=\text{OCH}_3 \\
\text{VII} \quad R=\text{H} \\
\text{VI} \quad R=\text{OCH}_3 \\
\text{VIII} \quad R=\text{H} \]

The method can be conveniently used also for the preparation of certain naturally occurring flavanones. As an example, the synthesis of dihydrowogonin\(^9\) (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 acetophenone\(^{10}\) 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 dihydrowogonin (IX), isolated from Prunus avium by Mentzer et al.,\(^9\).