Methylation of Hydroxy-Flavonols

(*Quercetin, Gossypetin and Herbacetin*)

THE complete methylation of flavonols by the ordinary methods using dimethyl sulphate or methyl iodide is difficult since many of the substances undergo oxidation very readily in the presence of alkali. Diazomethane does not effect complete methylation in several cases. It has recently been shown by us[1,2] that methylation of all the free phenolic hydroxyl groups in glucosides of the flavonols can be indirectly brought about by treatment of the acetyl derivatives with dimethyl sulphate and alkali in acetone medium. We have now examined the suitability of this new method for methylating the flavonols themselves.

The methylation of quercetin through its acetyl derivative with dimethyl sulphate and alkali in methyl alcoholic solution was originally attempted by Cohn and Freudenberg[3] and as a result the completely methylated derivative, along with the partially methylated one (3:7:3′:4′-tetramethyl compound) was isolated. Acetone as solvent seems to possess a specific influence in promoting the methylation of the hydroxyl group in position 5. It has

now been found that *penta*-acetyl quercetin, when methylated with dimethyl sulphate and alkali as described already in one of our previous publications using acetone as solvent,[1] gives rise to the pentamethyl ether exclusively, and the yield is almost quantitative.

The hexamethyl ether of gossypetin was prepared by Perkin[4] through a laborious process by treating the flavonol with excess of methyl iodide and methyl alcoholic potash during two days. Besides the formation of other substances (probably partially methylated compounds) the nature of which Perkin could not characterise for want of sufficient material, the yield of the hexamethyl ether was not satisfactory. The action of diazomethane upon the flavonol does not produce the completely methylated ether, but a substance which melts at 166–68° and crystallises with five molecules of water. This substance is still under investigation. The hexamethyl ether can, however, be conveniently prepared by an application of the new method of methylation starting with the acetyl derivative. Hexamethyl gossypetin melting at 170–72° is obtained in very good yields.

We have recently shown that diazomethane does not completely methylate herbacetin,[5] and that the tetramethyl ether produced thereby (3:7:8:4′-tetramethyl herbacetin) undergoes further methylation with dimethyl sulphate and alkali in acetone medium to yield *O*-pentamethyl herbacetin melting at 156–58°. The pentamethyl ether has now been readily obtained by treating *penta*-acetyl herbacetin in acetone solution with dimethyl sulphate and alkali.

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[1] Suryaprakasa Rao and Seshadri, *Proc. Ind. Acad. Sci.*, (A), 1939, **9**, 177.
[2] —— ——, *ibid.*, 1939, **9**, 365.
[3] Cohn and Freudenberg, *Ann.*, 1923, **433**, 230.
[4] Perkin, *J.C.S.*, 1913, 650.
[5] Rangaswami, Suryaprakasa Rao and Seshadri, *Proc. Ind. Acad. Sci.*, (A), 1939, **9**, 133.