

METHYLATION OF HYDROXY FLAVONOLS USING METHYL IODIDE AND POTASSIUM CARBONATE

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It is well known that the chief difficulties in the methylation of hydroxy flavonols are (1) their ready oxidisability in alkaline solutions, (2) the resistance offered to methylation by the hydroxyl group in position 5 and (3) the possibility of nuclear methylation. The process has been carried out in the past by treatment with (a) diazomethane, (b) methyl iodide and alkali and (c) dimethyl sulphate and alkali, and it has been noticed that irrespective of the nature of the methylating agent used, the methylation of the hydroxyl group in position 5 could not be easily effected, and where complete methylation took place, the yield was poor. Recently it has been shown by Rao and Seshadri¹ that it is possible to produce complete methylation of these compounds with satisfactory yields by treatment of their acetyl derivatives in acetone solution with dimethyl sulphate and alkali.

The use of methyl iodide and potassium carbonate as an alternative method seemed to offer good scope for effecting complete methylation of the important naturally occurring flavonols. It has been found to be quite useful in several cases where other methods failed to serve. The complete methylation of benzoyl phloroglucinaldehyde,² hesperidin³ and naringin⁴ may be quoted as important examples. Its scope has, therefore, been examined now employing quercetin, herbacetin and gossypetin.

Quercetin undergoes complete methylation whilst herbacetin and gossypetin yield partially methylated compounds which are, however, definite individuals. The tetramethyl herbacetin that is obtained as the sole product is identical with 3:7:8:4'-tetramethyl ether prepared by Rangaswami, Rao and Seshadri by the action of diazomethane on the flavonol.⁵ The pentamethyl gossypetin produced now is found to be identical with the sample obtained by the treatment of gossypetin with diazomethane. Since the hydroxyl group in position 5 is the one which is generally found to be most refractory, the product is here represented as 3:7:8:3':4'-pentamethyl gossypetin and this is also in accordance with the properties of the compound. Thus the action of methyl iodide and potassium carbonate on the naturally occurring flavonols seems to be similar to that of diazomethane used in

large excess, as exemplified in the cases of herbacetin,⁵ gossypetin and quercetin,^{6,7} though the last substance is said to yield the partially methylated product also under certain conditions.^{6,8}

Experimental

3:5:7:3':4'-Pentamethyl quercetin.—Quercetin (0.5 g.) was dissolved in dry acetone (50 c.c.) and anhydrous potassium carbonate (2 g.) and methyl iodide (about 5 g.) were added to the solution. The mixture was then refluxed on a water-bath for about 60 hours, adding a small quantity of methyl iodide every day to make up for the loss of the reagent through evaporation. At the end of the period, the solvent and the excess of the methyl iodide were distilled off and water was added to the residue to dissolve the potassium salts, when the methyl ether separated out. It was filtered, washed with a little water and recrystallised from dilute alcohol. It came down as pale yellow needles melting at 150–51° and the yield was 0.45 g. [Found in the sample dried at 120°: OCH₃, 41.2; C₁₅H₅O₂ (OCH₃)₅ requires OCH₃, 41.6%.] It was insoluble in dilute alkalis, gave no colour with ferric chloride and was otherwise identical with the pentamethyl quercetin obtained by other methods.

3:7:8:4'-Tetramethyl herbacetin.—The same procedure as above was followed for the methylation of herbacetin also. The final product on crystallisation from alcohol was obtained as pale yellow rectangular plates, and the yield was 0.4 g. from 0.5 g. of herbacetin. The methyl ether shrank and sintered at 115–20° (dehydration) and melted completely at 158–60°. [Found in the sample dried at 120°: OCH₃, 34.6; C₁₅H₅O₂ (OH) (OCH₃)₄ requires OCH₃, 34.8%.] In all its properties it resembled 3:7:8:4'-tetramethyl herbacetin. It dissolved in concentrated hydrochloric acid and sodium hydroxide to form yellow solutions, and its alcoholic solution gave a beautiful green colour with ferric chloride. The identity of the two samples was established by taking the mixed melting point of the anhydrous materials.

3:7:8:3':4'-Pentamethyl gossypetin.—The methylation of gossypetin was carried out as in the two previous cases, and a pentamethyl gossypetin crystallising with five molecules of water was obtained. [Found in the air-dried material: C, 50.0; H, 4.4; OCH₃, 32.1; and loss on drying 18.8%; C₁₅H₄O₂ (OH) (OCH₃)₅, 5 H₂O requires C, 50.2; H, 4.2; OCH₃ 32.1 and loss of H₂O on drying 18.8%. Found in the specimen dried at 120° for two hours: OCH₃, 39.9; C₁₅H₄O₂ (OH) (OCH₃)₅ requires OCH₃, 39.9%.] It crystallised from dilute alcohol as pale yellow needles, and the yield was 0.4 g. from 0.5 g. of the flavonol. It shrank and sintered from 110 to 115° (dehydration) and melted completely at 166–68°. If the heating was rapid,

the melting took place at 143–45°. The substance easily lost all the water of crystallisation when heated at 120° for about two hours, and the anhydrous material melted at 166–68°. It dissolved in concentrated hydrochloric acid and sodium hydroxide forming yellow solutions and in alcoholic solution it gave a light green coloration with ferric chloride. In all these properties it agreed with the pentamethyl gossypetin prepared by the action of diazomethane on the flavonol.⁹

Gossypetin (0.5 g.) was dissolved in excess of anhydrous methyl alcohol (150 c.c.) and treated at room temperature with an ethereal solution of diazomethane (4 g.) in small quantities according to the procedure adopted for the methylation of herbacetin.⁵ After the reaction was over, the alcohol and ether were distilled off, when a pale yellow sticky solid was left. It was purified by crystallisation from aqueous alcohol twice (using a little animal charcoal) and finally from acetic acid. It was obtained as fine needles, melting at 166–68° after dehydration. The two samples of pentamethyl gossypetin as obtained from the flavonol by the action of methyl iodide and potassium carbonate on the one hand and diazomethane on the other were found to be identical and the mixed melting point of the anhydrous materials was undepressed.

Summary

By the action of methyl iodide and potassium carbonate, quercetin underwent complete methylation, while herbacetin and gossypetin yielded 3:7:8:4'-tetramethyl ether and 3:7:8:3':4'-pentamethyl ether respectively. This reagent, therefore, resembles diazomethane in the methylation of the naturally occurring flavonols.

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