

FLAVONOLS: DIRECT NEW SYNTHESIS OF 6-HYDROXY-FLAVONOLS

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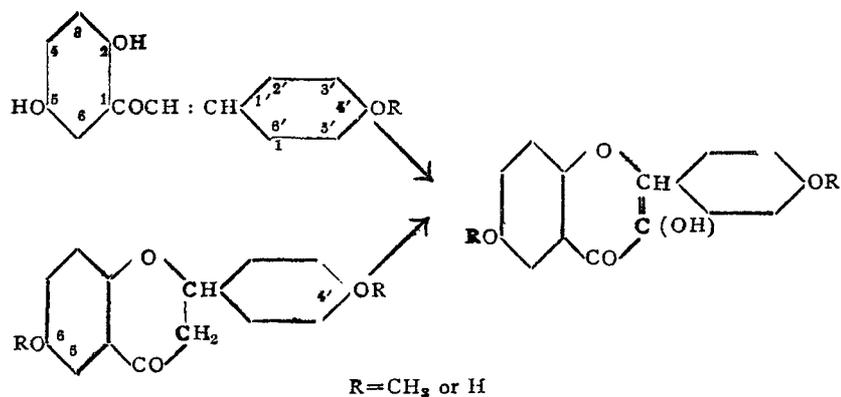
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SEVERAL investigators have done a large amount of work on flavonols containing resorcinol and phloroglucinol nuclei. However, the flavonols containing quinol nucleus have not received so much attention. Kostanecki and coworkers¹ synthesised a number of 6-hydroxy-flavonols from the corresponding methoxy-flavanones by subjecting them to amylnitrite reaction, subsequent hydrolysis and demethylation.

Among the methods which have been described for the synthesis of hydroxy-flavonols, the oxidation of *O*-hydroxy-chalkones by means of alkaline hydrogen peroxide—Algar and Flynn² method has been successfully applied by several investigators notably by Oyamada,³ Murakami and Irie.⁴ However, Geissman and Fukushima⁵ found that the chalkones derived from phloracetophenone dimethyl ether with anisaldehyde, benzaldehyde and veratraldehyde, etc., gave on Algar-Flynn oxidation predominantly the benzalcoumaranones instead of the expected flavonols. They attributed this abnormal behaviour to the presence of 6-methoxy group in the chalkone used.

Recently Anand, Iyer and Venkataraman⁶ have found that the Algar-Flynn oxidation of *O*-hydroxy-chalkones to flavonols by means of alkaline hydrogen peroxide is applicable to chalkones with a hydroxyl group at 4' irrespective of the presence of OMe at 6. Thus they have been able to synthesise rhamnazin-5-methyl ether from 2-hydroxy-4-6-dimethoxy-phenyl-4'-hydroxy-3'-methoxy-styryl-ketone in one step.

In continuation with our work on chalkones and flavanones derived from quinacetophenone⁷ we have applied the Algar-Flynn oxidation for synthesis of 6-hydroxy-flavonols directly from the hydroxy-chalkones. The reaction was found to be smooth and no other products like benzal-coumaranones could be isolated. 6-Hydroxy-flavonols have now been made directly from 2:5-dihydroxy-, 2:5:2'-trihydroxy-, 2:5:4'-trihydroxy-chalkones as well as from 6:4'-dimethoxy- and 6:3'-dihydroxy-flavanones. They all agree with the compounds prepared by Kostanecki and his coworkers.



Thus it is obvious that the presence of OH or OCH₃ group in 5-position in the quinacetophenone nucleus as well as hydroxy group in the styryl part of the chalcone does not affect the normal course of the oxidation. It is interesting to point out that in all the cases the hydroxy-flavonols were obtained directly in good yield. The 6-hydroxy-flavonols described here dissolve in concentrated sulphuric acid with greenish yellow fluorescence and in alkali with greenish yellow colouration. With alcoholic ferric chloride, they give greenish red colour.

EXPERIMENTAL

6-Hydroxy-flavonol

To an ice-cold red solution of 2:5-dihydroxy chalcone (1.0 g.) in sodium hydroxide (30 c.c.: 5 per cent.) and methyl alcohol (20 c.c.) was gradually added hydrogen peroxide (8 c.c.: 18 per cent.) with shaking and cooling in ice-bath. The mixture was kept in ice-bath for 2 hours and then left overnight at room temperature. The colour of the solution changed from dark red to pale yellow. It was mixed with ice (200 g.) and acidified with dilute sulphuric acid (2 N). A pale yellow solid separated which was crystallised from dilute alcohol, pale yellow needles, m.p. 234°. Yield = 0.5 g. (approximately 50%). Kostanecki and Lampe¹ give the same melting point.

The acetyl derivative prepared by sodium acetate-acetic anhydride method, crystallised from dilute alcohol, colourless lustrous needles, m.p. 195°. Kostanecki and Lampe¹ record the same melting point (Found: C, 67.3; H, 4.0. Calculated for C₁₉H₁₄O₆: C, 67.45; H, 4.1 per cent.)

6:2'-Dihydroxy-flavonol

2:5:2'-Trihydroxy-chalcone (1 g.) was subjected to hydrogen peroxide (5 c.c.: 18 per cent.) oxidation as in the previous case and the pale yellow solid obtained on similar treatment as before was crystallised from dilute

alcohol, long colourless needles, m.p. 243°. Yield = 0.45 g. Kostanecki and Katschalowsky¹ give the same melting point.

The *methyl ether*: 6:2'-Dihydroxy flavonol (0.5 g.) in methyl alcohol (20 c.c.) was methylated by dimethyl sulphate (4 c.c.) and sodium hydroxide (20 c.c.: 8 per cent.). The mixture was heated on water-bath for 2 hours when the methyl alcohol evaporated and an insoluble brownish yellow solid separated. It was collected and crystallised from methyl alcohol, yellow prismatic needles, m.p. 187°. Kostanecki and Katschalowsky¹ give the same melting point (Found: C, 68.2; H, 4.6. Calculated for C₁₇H₁₄O₅: C, 68.4; H, 4.7 per cent.).

6:4'-Dihydroxy-flavonol

2:5:4'-Trihydroxy-chalkone (1 g.) was oxidised as in the previous cases by means of hydrogen peroxide (8 c.c.: 18 per cent.). The pale yellow solid isolated as usual was crystallised from methyl alcohol, pale yellow short needles. It did not melt upto 300°. Yield = 0.3 g. (Found: C, 66.5; H, 3.6. Calculated for C₁₅H₁₀O₅: C, 66.7; H, 3.7 per cent.).

The *acetyl derivative* prepared as before, crystallised from dilute alcohol, colourless flat needles, m.p. 169°. Kostanecki and Stoppani¹ give the same melting point (Found: C, 63.4; H, 4.1. Calculated for C₂₁H₁₆O₈: C, 63.6; H, 4.0 per cent.).

6:3'-Dihydroxy-flavonol

6:3'-Dihydroxy-flavanone was treated with hydrogen peroxide (4 c.c.: 18 per cent.) in ice-bath and the flavonol isolated as before. It crystallised from alcohol, colourless needles, m.p. 300°. Yield = 0.5 g. Kostanecki and Ottmann¹ record the same melting point.

The *acetyl derivative* was prepared as before, crystallised from dilute alcohol, colourless needles, m.p. 126°. Kostanecki and Ottmann¹ record the same melting point (Found: C, 63.5; H, 4.2. Calculated for C₂₁H₁₆O₈: C, 53.6; H, 4.0 per cent.).

6:4'-Dimethoxy-flavonol

6:4'-Dimethoxy-flavanone (0.5 g.) was oxidised as before by using hydrogen peroxide (20 c.c.: 8 per cent.) and sodium hydroxide (10 c.c.: 16 per cent.) in methyl alcohol or acetone (50 c.c.) in the usual manner keeping the reaction mixture in ice-bath for 3 hours and then for two days at room temperature. The flavonol was isolated as before and crystallised from methyl alcohol, pale yellow needles, m.p. 185°. Yield = 0.4 g. Kostanecki and Stoppani¹ give the same melting point.

The acetyl derivative prepared as before, crystallised from dilute alcohol, colourless needles, m.p. 131–32° (Found: C, 67.0; H, 4.6. $C_{19}H_{16}O_6$ requires: C, 67.1; H, 4.7 per cent.).

SUMMARY

The synthesis of 6-hydroxy-flavonols has been effected by the Algar and Flynn oxidation of 2:5-dihydroxy-, 2:5:2'-trihydroxy-, 2:5:4'-trihydroxy-chalkones and 6:3'-dihydroxy- and 6:4'-dimethoxy-flavanones by means of alkaline hydrogen peroxide. The flavonols obtained have been characterised by preparing their acetyl or methoxy derivatives. It is interesting to note that free hydroxyl group in either nucleus of the chalkone molecule does not lead to complications during the oxidation, the flavonols being obtained in good yield.

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