

HETEROCYCLIC COMPOUNDS.

Part V. Synthesis of 2-Methyl-6-ethyl-7-hydroxy-chromone and Its Derivatives.

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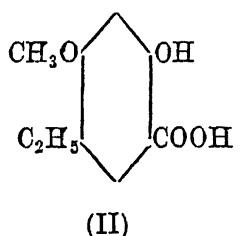
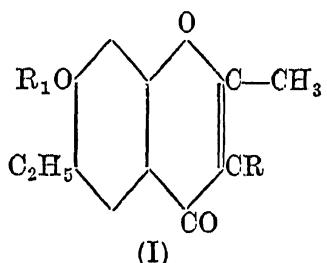
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THE vigorous acylation of *o*-hydroxy-acetophenones¹ provides a useful method for the synthesis of chromones containing substituents in various positions, and this method has been subjected to a critical investigation by various investigators² to determine the factors leading to the formation of coumarins and chromones. Robinson and co-workers³ have utilised this method to synthesise the naturally occurring flavones and flavonols. The only attempt to utilise the Kostanecki Reaction for the synthesis of chromones containing alkyl groups in the benzene nucleus is that of Wittig, Baugert, and Richter⁴ who acetylated 2-aceto-4-methyl-, 2-aceto-6-methyl-, 2-aceto-5-methyl-, and 2-aceto-3:5-dimethyl-phenols. These types of flavones, flavanones and flavonols derive additional interest from the fact that matteucinol,⁵ as well as another colouring matter isolated from *Matteuccia orientalis* are flavanones containing dimethylated benzene nucleus.

The present communication deals with the application of the Kostanecki Reaction to 2:4-dihydroxy-5-ethylacetophenone which readily gave 7-acetoxy-6-ethyl-3-acetyl-2-methylchromone (I, $R = R_1 = \text{CH}_3 - \text{CO}$) with acetic anhydride in the presence of anhydrous sodium acetate, while 7-hydroxy-6-ethyl-2-methylchromone (I, $R = R_1 = \text{H}$) was obtained from it by the usual method. Dilute alkali hydrolysed this chromone to 2:4-dihydroxy-5-ethylacetophenone, but 2-hydroxy-4-methoxy-5-ethylbenzoic acid (II) was obtained by the hydrolysis of its methyl ether (I, $R = \text{H}$, $R_1 = \text{CH}_3$). This acid was also obtained by the action of potassium bicarbonate on 4-ethylresorcinol⁶ and subsequent methylation. The chromone structure of (I) is thus proved beyond doubt.



We are busy synthesising the flavones and flavonols from this as well as similarly related ketones.

Experimental.

7-Acetoxy-6-ethyl-3-acetyl-2-methylchromone.—A mixture of 2:4-dihydroxy-5-ethylacetophenone (10 g.), anhydrous sodium acetate (20 g.) and acetic anhydride (50 c.c.) was heated in an oil-bath at 170–180° for ten hours. The solid obtained by pouring the contents into water was collected, and crystallised from dilute alcohol when long, silky needles melting at 138°, were obtained (5 g.). [Found : C, 66.4 ; H, 5.7 ; $C_{16}H_{16}O_5$ requires C, 66.6 ; H, 5.6 per cent.]

The alcoholic mother-liquor furnished more of the same compound after removal of the solvent, and extraction of the original ketone with dilute alkali from the ethereal solution of the residue. *7-Hydroxy-6-ethyl-3-acetyl-2-methylchromone* was obtained by shaking the acetoxy derivative with dilute ammonia for one hour, and acidifying the filtered solution with concentrated hydrochloric acid. It crystallised from dilute alcohol in thick, rhombic plates (m.p. 193°). [Found : C, 68.0 ; H, 5.8 ; $C_{14}H_{14}O_4$ requires C, 68.3 ; H, 5.7 per cent.]

Its alcoholic solution gave no coloration with ferric chloride, and dissolved in concentrated sulphuric acid with a yellow colour. *The methylether*, obtained by methylating its solution in alkali with dimethyl sulphate crystallised from hexane in plates (m.p. 158°). [Found : C, 69.0 ; H, 6.3 ; $C_{15}H_{16}O_4$ requires C, 69.2 ; H, 6.2 per cent.]

7-Hydroxy-6-ethyl-2-methylchromone was obtained by heating the solution of the chromone (1.5 g.) in 5 per cent. sodium carbonate (20 c.c.) for one hour on a sand-bath under reflux. The chromone obtained by acidifying the filtered alkaline solution crystallised from dilute alcohol in rhombic plates (m.p. 204°). [Found : C, 70.5 ; H, 6.1 ; $C_{12}H_{12}O_3$ requires C, 70.6 ; H, 5.9 per cent.]

The chromone dissolved in concentrated sulphuric acid with a yellow colour and its alcoholic solution did not give any coloration with ferric chloride.

The methylether obtained in the usual manner with dimethyl sulphate crystallised from hexane in plates (m.p. 90°). [Found : C, 71.3 ; H, 6.5 ; $C_{13}H_{14}O_3$ requires C, 71.6 ; H, 6.4 per cent.]

The acetyl derivative obtained by heating the chromone (0.5 g.) with acetic anhydride (3 c.c.) and a few drops of pyridine crystallised from dilute alcohol in fine needles (m.p. 99°). [Found : C, 68.1 ; H, 5.9 ; $C_{14}H_{14}O_4$ requires C, 68.3 ; H, 5.7 per cent.]

Hydrolysis of 7-hydroxy-6-ethyl-2-methylchromone with alkali and formation of 2:4-dihydroxy-5-ethyl-acetophenone.—The solution of the chromone (0.5 g.) in normal caustic soda solution (10 c.c.) was heated on a sand-bath under reflux for two hours. The cooled solution was diluted with water, filtered and acidified with concentrated HCl. The solid thus obtained was dried and crystallised from benzene when flat plates (m.p. 118°) were obtained. This was identified as 2:4-dihydroxy-5-ethylacetophenone by comparison with an authentic specimen.

Hydrolysis of 7-methoxy-6-ethyl-2-methylchromone with alkali and formation of 5-ethyl-4-methoxy-2-hydroxybenzoic acid.—A suspension of the methyl-ether (0.5 g.) in normal caustic soda solution (10 c.c.) was heated on a sand-bath under reflux for two hours. The solid obtained by acidifying the cooled solution with dilute HCl and purified through sodium bicarbonate, crystallised from dilute alcohol in thick, prismatic needles (m.p. 192°). [Found : C, 61.3 ; H, 6.2 ; $C_{10}H_{12}O_4$ requires C, 61.2 ; H, 6.1 per cent.]

Its aqueous solution gave violet coloration with ferric chloride, while the alcoholic solution gave bluish black colour with the same reagent.

2:4-Dimethoxy-5-ethylbenzoic acid was obtained by methylating the acid (0.5 g.) with three lots of dimethyl sulphate (2 c.c.) each and warming on the water-bath for half an hour. After purification through sodium bicarbonate, it crystallised from dilute alcohol in plates (m.p. 126°). Its alcoholic solution did not give any coloration with ferric chloride. [Found : C, 62.7 ; H, 6.7 ; $C_{11}H_{14}O_4$ requires C, 62.9 ; H, 6.7 per cent.]

Synthesis of 2:4-dihydroxy-5-ethylbenzoic acid.—We are indebted to Dr. R. C. Shah of the Royal Institute of Science, Bombay, for the detailed information regarding this preparation (Unpublished work).

A solution of 4-ethyl-resorcinol (5 g.) in anhydrous potassium bicarbonate (25 g.) and water (50 c.c.) was heated on a sand-bath for two hours. The cooled solution was diluted with water, filtered and acidified with concentrated HCl. The acid crystallised from hot water in silky needles (m.p. 188°) (yield 70 per cent.). [Found : C, 59.1 ; H, 5.6 ; $C_9H_{10}O_4$ requires C, 59.3 ; H, 5.5 per cent.]

Its aqueous solution gave bluish black coloration with ferric chloride.

Synthesis of 5-ethyl-4-methoxy-2-hydroxybenzoic acid.—The above dihydroxy acid (1 g.) was dissolved in normal alkali (10 c.c.) and dimethyl sulphate (3 c.c.) was gradually added with constant shaking. After half an hour, the acid was obtained by acidification with dilute HCl, and crystallised from dilute alcohol when thick, prismatic needles (m.p. 192°) were obtained. The melting point was not depressed by admixture with

the specimen obtained by the alkaline hydrolysis of 7-methoxy-6-ethyl-2-methylchromone. Further methylation of this acid gave the dimethoxy acid (m.p. 126°), identical with the specimen prepared from the chromone.

Summary.

7-Acetoxy-6-ethyl-3-acetyl-2-methylchromone has been prepared by the application of the Kostanecki Reaction to 2: 4-dihydroxy-5-ethylacetophenone. The various derivatives of this chromone have been also described.

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