SYNTHESIS OF 7-HYDROXY-5-METHYLCOUMARIN

By K. Ranganatha Rao and T. R. Seshadri

(From the Department of Chemistry, Andhra University, Waltair)

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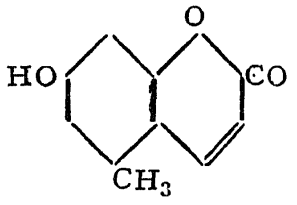
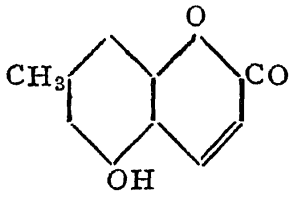
By the condensation of malic acid with orcinol Pechmann and Welsh[1] obtained a compound to which they assigned the formula of 7-hydroxy-5-methylcoumarin (I) from its similarity with umbelliferone. This was supported by alkali fission of the product whereby orcylic aldehyde was formed. Subsequently Pechmann and Cohen[2] effected the condensation of ethyl acetoacetate with orcinol and the resulting substance was given the constitution of 7-hydroxy-4 : 5-dimethylcoumarin (III) from considerations of analogy. This compound was later investigated by Dey[3] who definitely proved that it was 5-hydroxy-4 : 7-dimethylcoumarin (IV). As a result of this work there has been a tendency to regard the malic acid condensation product also as a 5-hydroxy-coumarin derivative[4] (II). The synthesis of 5-hydroxy-7-methylcoumarin (II) starting from ethyl hæmatommate has been described in a recent communication from these laboratories.[5] This compound is very different from the one obtained by Pechmann and Welsh; its solutions in alkali and in sulphuric acid are deep yellow in colour without fluorescence. Consequently the product of the condensation of orcinol and malic acid should be 7-hydroxy-5-methylcoumarin (I). However strict proof of its purity and individuality has been lacking. This is particularly important in view of the alternative ways in which orcinol can react. Though certain derivatives of 7-hydroxy-5-methylcoumarin have been obtained[6,7] the parent compound itself has not been produced synthetically by unambiguous methods. Attempt



I



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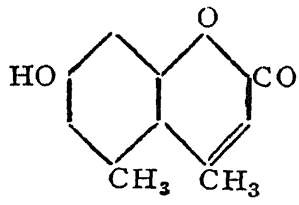

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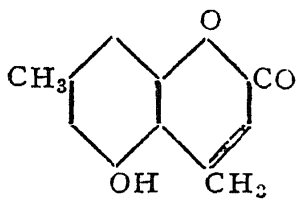

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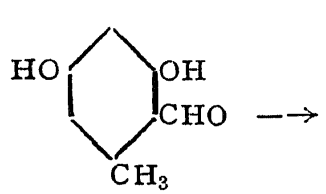

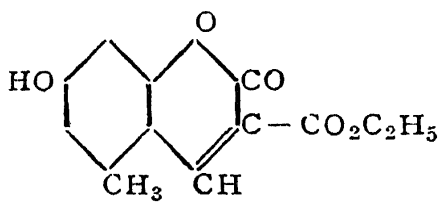

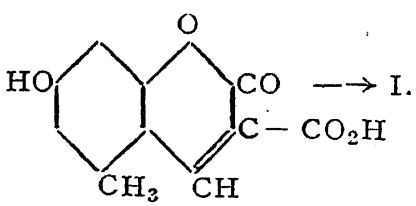

I.

has, therefore, been made now to prepare it from orcylic aldehyde which has been condensed with diethyl malonate. The coumarincarboxylic ester (V) thereby obtained has been hydrolysed to the carboxylic acid (VI) and finally decarboxylated to yield 7-hydroxy-5-methylcoumarin (I). This is identical in every respect with the coumarin obtained from orcinol and malic acid by the method of Pechmann.

Thus it is clear that orcinol behaves in two different ways in regard to its nuclear reactivity when forming coumarins in the presence of sulphuric acid as the condensing agent. With ethyl acetoacetate the γ-position between the two phenolic hydroxyl groups is the reactive centre whereas when malic acid is employed the β-position becomes reactive. And as far as one could judge from the existing data, the γ-position seems to be reactive to the complete exclusion of the β- and *vice versa*. The recent discovery of Desai and Vakil that in the case of Friedel and Crafts reaction orcinol exhibits simultaneous reactivity of the two positions may here be mentioned.[8]

Experimental

7-Hydroxy-5-methyl-3-carbethoxy-coumarin.—Orcylic aldehyde required for this synthesis was prepared by a modification of the method of Gattermann[9] using zinc cyanide. Orcinol (6 g.), dry ether (100 c.c.) and zinc cyanide (15 g.) were placed in a three-necked flask which was provided with a stirrer, a condenser and an inlet for dry hydrogen chloride. The mixture was saturated with the gas; during this process cooling with ice was employed and gentle stirring was kept up. The zinc salt gradually disappeared and the aldimine hydrochloride separated first as a thick oil which slowly solidified (45 minutes). The current of hydrogen chloride was continued for 4 hours. The flask was then sealed and kept in an ice chest for 2 days, at the end of which the solid was collected, washed with ether and decomposed by heating with water. When recrystallised from alcohol, orcylic aldehyde was obtained as colourless needles melting at 182–83°, the yield being 6·5 g.

The above aldehyde (1 g.) and malonic ester (2 g.) were intimately mixed and cooled in ice. To this piperidine (10 drops) was added and the mixture was allowed to stand for an hour in the ice-bath. Cooling was necessary since there was evolution of heat during the addition of piperidine and resin formation took place. The reaction was then allowed to proceed at room temperature for about 12 hours and the mixture was treated with a little dilute hydrochloric acid, cooling in ice being employed. The solid product was filtered, washed with water and recrystallised from alcohol when it yielded shining yellow needles melting at 193–94°. It dissolved in aqueous sodium hydroxide to produce an intense blue-violet

fluorescence. No colour was obtained with ferric chloride. It fluoresced remarkably blue even in neutral alcoholic solution. (Found: C, 58·7; H, 5·5; $C_{13}H_{12}O_5$, H_2O requires C, 58·6; H, 5·3%.)

7-Hydroxy-5-methyl-3-carboxy-coumarin.—The above ester (1 g.) was dissolved in 8% sodium hydroxide (20 c.c.) and allowed to stand for about 3 days. Excess of dilute hydrochloric acid was then carefully added, the mixture being cooled in ice. The precipitated acid was collected and was purified by dissolution in aqueous sodium carbonate and subsequent re-precipitation. Finally it was crystallised from alcohol when it yielded glistening yellow needles melting at 240° (decomp.). It dissolved in aqueous sodium hydroxide to exhibit an intense blue-violet fluorescence. No colour reaction was obtained with alcoholic ferric chloride. It fluoresced bright blue even in neutral alcoholic solution. (Found: C, 55·2; H, 4·5; $C_{11}H_8O_5$, H_2O requires C, 55·5; H, 4·2%.)

7-Hydroxy-5-methyl-coumarin.—The above acid (0·2 g.) was heated with quinoline (4 c.c.) and copper bronze (0·3 g.) for $\frac{3}{4}$ hour at 150–60° in an oil-bath. The mixture was treated with excess of ether and the solution quickly filtered. Ether was then distilled off; to the residue excess of dilute hydrochloric acid was added and the mixture repeatedly shaken with ether. The ether extract was washed free from acid with sodium bicarbonate solution and then evaporated. The resulting solid was washed with a little benzene to remove resin and crystallised from alcohol. It was obtained as pale yellow flat needles and tablets melting at 247–48°. It was insoluble in water, chloroform and benzene and readily soluble in alcohol, acetone and acetic acid. It gave no colour with alcoholic ferric chloride and its solutions in aqueous sodium hydroxide and in concentrated sulphuric acid were colourless exhibiting blue fluorescence. The coumarin obtained by Pechmann's method using orcinol and malic acid was found to be identical with this compound by a comparison of the properties and by the determination of the mixed-melting point; no depression was observed. (Found: C, 68·2; H, 4·9; $C_{10}H_8O_3$ requires C, 68·2; H, 4·5%.)

Summary

7-Hydroxy-5-methylcoumarin has been synthesised from orcylaldehyde by condensation with diethyl malonate and by subsequent removal of the carbethoxyl group. The compound obtained from orcinol and malic acid by the method of Pechmann has been shown to be identical with the above product and hence it is concluded that in this case orcinol exhibits reactivity of the β-position.

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