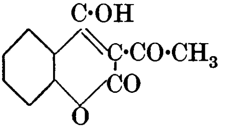
CCXIX.—*The Preparation of 4-Hydroxycoumarin Derivatives.*

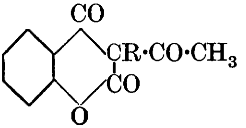
By ISIDOR MORRIS HEILBRON and DOUGLAS WILLIAM HILL.

THE hydroxycoumarins here described were prepared as a preliminary to the study of their action on aryl magnesium compounds, details of which will be furnished in subsequent papers. 4-Hydroxycoumarin (benzotetronic acid) was first described by Anschütz (*Annalen*, 1909, **367**, 169), who prepared it by condensing sodioacetoacetic ester with *o*-acetoxybenzoyl chloride in ethereal solution, followed by hydrolysis of the primarily isolated 3-acetyl-4-hydroxycoumarin (I). We have now obtained the substituted 3-methyl-, 3-benzoyl-, and 3-benzyl-4-hydroxycoumarins in good yield by this method. The 3-phenyl derivative has not been examined, as it has already been obtained by Pauly and Lockemann (*Ber.*, 1915, **48**, 28) by the intramolecular condensation of methyl *o*-phenylacetoxybenzoate in presence of sodium at 160°. Employing the α-substituted acetoacetic esters, we expected to obtain the acetyl derivatives (II) on removal of solvent from the condensation mixture; the products, however, were sodium salts, from which the acetyl-free hydroxycoumarins were obtained when their respective aqueous solutions were acidified.

(I.)



(II.)

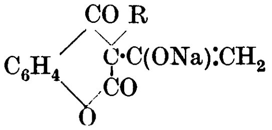


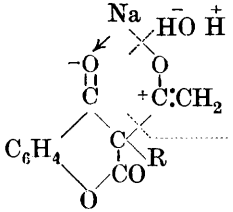
(R = CH_3, COPh, or CH_2Ph)

The extraordinarily ready elimination of acetyl is at first sight somewhat anomalous. It has been shown, however, by Widmann (*Ber.*, 1902, **35**, 1153) that 3-acetylcoumarin possesses strongly acidic properties, behaving as a typical pseudo-acid, and thus by analogy the sodium compounds now obtained may be similarly represented as still containing the acetyl intact in the molecule (III).

Although offering an explanation of the formation of sodium salts, this view in itself does not explain the subsequent ease with which the acetyl group is eliminated, for obviously precisely the same effect could occur with 3-acetyl-4-hydroxycoumarin, from which, however, the acetyl radical is by no means readily eliminated, requiring indeed several hours' heating with moderately concentrated potassium hydroxide solution for its removal.

(III.)





(IV.)

We submit, however, that a satisfactory interpretation of the observed facts can be arrived at by assuming that in the acetyl 3-substituted benzotetronic acids the simple enol does not exist as such, but that the sodium derivatives are present as co-ordinated salts (IV) only stable in non-aqueous media. Owing to the great tendency of the negatively charged oxygen of the carbonyl group to pass into the enolic state, as evidenced by the fact that benzotetronic acid itself is a strong acid, the chelated acetyl sodium compound is disrupted by water with formation of the free hydroxycoumarin. These changes obviously do not occur with the unsubstituted 3-acetylbenzotetronic acid, for here a free hydrogen atom is available for immediate formation of the isomeric coumarin form, and consequently this compound closely resembles 3-acetylcoumarin itself in stability.

Considerable difficulty was encountered in the methylation of these 4-hydroxycoumarins. This appears to be a general characteristic of this class of compounds, as similar difficulties were met with by Sonn (*Ber.*, 1917, **50**, 1292), who obtained only very small yields of 4 : 7-dimethoxycoumarin by the action of methyl sulphate upon the 4 : 7-dihydroxy-compound, the main product being 4-hydroxy-7-methoxycoumarin. We have now, however, prepared the dimethoxy-derivative in good yield by employing diazomethane.

EXPERIMENTAL.

4-*Hydroxy*-3-*methylcoumarin*.—Ethyl methylsodioacetoacetate (from 100 g. of the ester) in ether (600 c.c.) was treated with *o*-acetoxybenzoyl chloride (46 g.), prepared by the action of thionyl chloride upon *o*-acetoxybenzoic acid, and the mixture was heated under reflux on the water-bath for 18 hours. The resultant yellow solid was filtered off, well washed with ether, and dissolved in water, the solution was carefully neutralised with dilute sulphuric acid, and the semi-solid precipitate was crystallised repeatedly from dilute alcohol in presence of animal charcoal and finally from methyl alcohol, the *coumarin* being obtained in colourless needles, m. p. 230°, readily soluble in alcohol and somewhat sparingly soluble in ether and benzene (yield, 60%) (Found : C, 68·3 ; H, 4·8. $C_{10}H_8O_3$ requires C, 68·1 ; H, 4·6%).

4-*Methoxy*-3-*methylcoumarin* was prepared by heating the dry silver salt of the coumarin under reflux with a slight excess of methyl iodide. Silver iodide and the excess of methyl iodide were removed; the residual colourless oil slowly solidified and was then crystallised first from ether and finally from alcohol, the *methyl ether* separating in colourless needles, m. p. 89·5° (Found : C, 69·0 ; H, 5·4. $C_{11}H_{10}O_3$ requires C, 69·4 ; H, 5·3%).

4-*Hydroxy*-3-*benzylcoumarin*.—Ethyl benzylsodioacetoacetate, prepared by adding the ester (90 g.) to granulated sodium (9 g.) in xylene (90 c.c.), was boiled under reflux with *o*-acetoxybenzoyl chloride (50 g.) in ether (300 c.c.) for 24 hours. The resultant thick precipitate was filtered off and dissolved in water, and the solution rendered acid. The semi-solid mass was extracted with ether, the solution dried, and after removal of the ether the residue was crystallised from aqueous alcohol, from which the *coumarin* separated in colourless needles, m. p. 205° (Found : C, 76·1 ; H, 4·9. $C_{16}H_{12}O_3$ requires C, 76·2 ; H, 4·7%).

4-*Hydroxy*-3-*benzoylcoumarin* was prepared in a similar manner from ethyl α-benzoylsodioacetoacetate. The *coumarin* crystallised from 96% alcohol in colourless needles, m. p. 144°, readily soluble in alcohol, less soluble in benzene and ether. It is also readily soluble in sodium carbonate solution (Found : C, 71·8 ; H, 3·8. $C_{16}H_{10}O_4$ requires C, 72·1 ; H, 3·8%).

4-*Methoxycoumarin*.—(1) A solution containing 4-hydroxycoumarin (2 g.), acetone (200 c.c.), and aqueous potassium hydroxide (16 c.c. of 20%) was gently warmed and treated with methyl sulphate (2·5 g.), added in small quantities at a time. The mixture was boiled for an hour and the 4-*methoxy*-derivative was precipitated by dilution with water and separated from a small quantity of unchanged 4-hydroxycoumarin by addition of sodium carbonate in slight excess. It crystallised from water in colourless flakes, m. p. 124° (yield, 25%).

(2) Freshly prepared nitrosomethylurea (Werner, J., 1919, **115**, 1098) (25 g.), suspended in a solution of 4-hydroxycoumarin (10 g.) in acetone (100 c.c.), was very slowly treated with concentrated potassium hydroxide solution (17 g. in 12 c.c. of water), care being

taken to prevent the reaction becoming too violent. The *methoxycoumarin* was precipitated with water and crystallised as above (yield, 40%) (Found : C, 67·9; H, 4·5. $C_{10}H_8O_3$ requires C, 68·1; H, 4·6%).

4 : 7-Dihydroxycoumarin was prepared by a slight modification of Sonn's method (*loc. cit.*), ethyl cyanoacetate being employed in place of the free acid. A better yield of the coumarin was obtained by heating the ketimine under reflux with concentrated sulphuric acid (20 c.c.) and water (40 c.c.) for 3 hours. The ketimine gradually dissolved and after some time the ketone separated; it was recrystallised from hot water; m. p. 265° (yield, 80%).

4 : 7-*Dimethoxycoumarin.*—Sonn (*loc. cit.*) obtained this compound together with a large amount of 7-methoxy-4-hydroxycoumarin by the action of methyl sulphate upon 4 : 7-dihydroxycoumarin at 0°. On repeating this work it was found that the yield of alkali-insoluble product was almost negligible. Attempts to methylate the 4-hydroxy-group with methyl iodide and sodium ethoxide or silver oxide also failed. The dimethyl ether was finally obtained in good yield by passing diazomethane into a solution of 7-methoxy-4-hydroxycoumarin (7 g.) in absolute alcohol (150 c.c.); after remaining for 3 hours at room temperature, the solution was concentrated and the dimethoxycoumarin was precipitated by dilution with water, washed with dilute alkali solution to remove unchanged 7-methoxy-4-hydroxycoumarin, and recrystallised from boiling water. It formed colourless needles, m. p. 155—156°, identical with Sonn's product (yield, 85%).

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