[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF WISCONSIN]

Studies on 4-Hydroxycoumarins. XIII. The Mechanism for the Reaction of 4-Hydroxycoumarin with Aliphatic Acid Chlorides[1]

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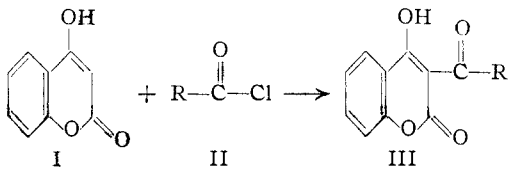
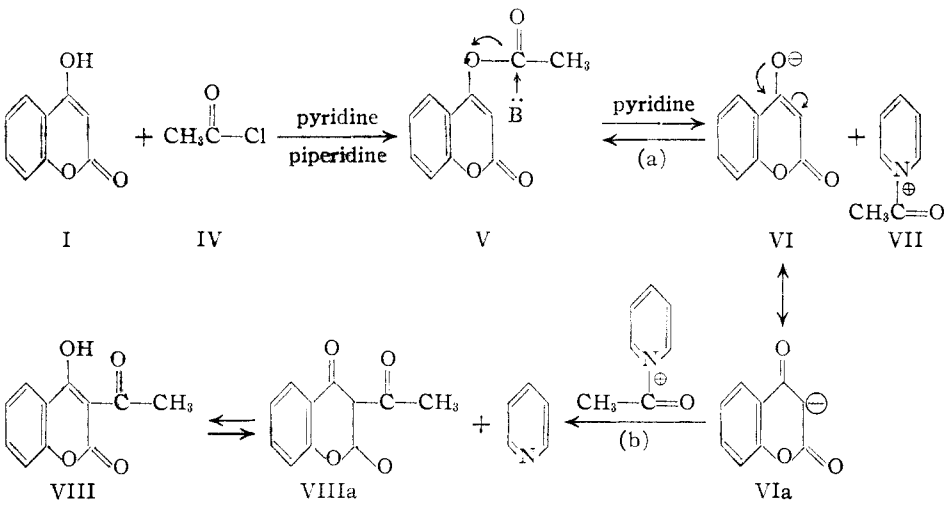
The reaction between 4-hydroxycoumarin (I) and acetyl chloride (IV) to yield 3-acetyl-4-hydroxycoumarin (VIII) has been studied. The mechanism proposed whereby VIII is formed is as follows. Acetyl chloride reacts irreversibly with 4-hydroxycoumarin in the presence of pyridine and piperidine to yield 4-acetoxycoumarin (V). A nucleophilic attack of pyridine on the carbonyl of the ester group reversibly cleaves this compound to yield the anion of 4-hydroxycoumarin (VI) and the acetylpyridinium cation (VII). This latter moiety further reacts with a different resonance form of the 4-hydroxycoumarin anion (VIa) to yield, after enolization, 3-acetyl-4-hydroxycoumarin.

Ukita, *et al.*,[2] have shown recently that 4-hydroxycoumarin (I) reacted with aliphatic acid chlorides (II) in the presence of dry pyridine, containing a catalytic amount of piperidine,[3] to yield the corresponding 3-acyl-4-hydroxycoumarin (III).



I II III

On examination of this reaction, using acetyl chloride (IV) as the aliphatic acid chloride, we have deduced a mechanism which is indicated below.



I IV V VI VII

VIII VIIIa VIa

The experimental observations were as follows: (1) Interaction of 4-hydroxycoumarin (I) and acetyl chloride (IV) in the presence of pyridine and piperidine yielded 3-acetyl-4-hydroxycoumarin (VIII) in 60% yield. (2) 4-Acetoxycoumarin (V) rearranged in the presence of pyridine and piperidine, under the conditions of the above mentioned reaction, to yield 3-acetyl-4-hydroxycoumarin in 60% yield. (3) After the reaction had proceeded for one minute at 0°, 4-acetoxycoumarin may be isolated in 78% yield by the interaction of 4-hydroxycoumarin and acetyl chloride in pyridine and piperidine. (4) In the same manner, the reaction between 4-hydroxycoumarin in pyridine and piperidine (present as the anion VI) and acetylpyridinium chloride (present as the cation VII) yielded 4-acetoxycoumarin in 70% yield. (5) The repetition of experiment (4) under the conditions indicated in observation (1) yielded 3-acetyl-4-hydroxycoumarin in 59% yield. (6) Upon allowing a solution of 3-acetyl-4-hydroxycoumarin in pyridine and piperidine to react under the conditions indicated in (1), above, no 4-hydroxycoumarin was obtained, but only 3-acetyl-4-hydroxycoumarin was recovered. (7) On the attempted reaction between 4-methoxycoumarin (IX) and acetyl chloride in pyridine and piperidine, only 4-methoxycoumarin was recovered, with no 3-acetyl-4-methoxycoumarin (X) being obtained.

With reference to the experimental observations listed above and to the outlined reaction mechanism, the following conclusions can be drawn. From (1) and (2), it was concluded that 4-acetoxycoumarin was an intermediate in this reaction, especially since the final product, 3-acetyl-4-hydroxycoumarin, was obtained in the same yield whether the reaction was conducted with 4-hydroxycoumarin and acetyl chloride or with 4-acetoxycoumarin. The fact that 4-acetoxycoumarin may be isolated from the reaction mixture involving 4-hydroxycoumarin and acetyl chloride, as indicated in observation (3), supported this conclusion.

That reaction (a) was reversible is indicated by the following. 4-Acetoxycoumarin may be isolated from the interaction of 4-hydroxycoumarin and acetyl chloride as well as from 4-hydroxycoumarin (as the anion) and acetylpyridinium chloride

(1) Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

(2) T. Ukita, S. Nojima and M. Matsumoto, THIS JOURNAL, **72**, 5143 (1950).

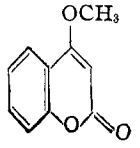
(3) Ukita, *et al.*,[2] used catalytic amounts of piperidine in their preparation of 3-acyl-4-hydroxycoumarins, thus it was also included here. Although no study on the usefulness of this reagent was conducted, it was inadvertently omitted in one of the experiments and the yield of 3-acetyl-4-hydroxycoumarin was the same as that in which piperidine was present. It is thus suggested that piperidine serves no useful purpose and probably immediately forms the amide with acetyl chloride.

(as the cation) under the same conditions and in approximately the same yield. Furthermore, this reversible reaction was rapid, requiring about one minute at 0° (observations 3 and 4). Moreover, it should be noted that reaction (b) was relatively slow, requiring 48 hours at 37° for the optimum yield of 3-acetyl-4-hydroxycoumarin.[2] The slow step in this reaction is probably the formation of the carbanion VIa.

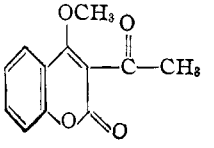
Evidence that 4-hydroxycoumarin (as the anion) and acetylpyridinium chloride (as the cation) are intermediates in the suggested mechanism was shown by the following. The interaction of VI and VII yielded 3-acetyl-4-hydroxycoumarin under the same conditions and in the same yield as for the reaction between 4-hydroxycoumarin and acetyl chloride (observation 5).

Since no 4-hydroxycoumarin could be obtained from 3-acetyl-4-hydroxycoumarin under the conditions outlined in observation (6) above, the reaction (b) was probably not reversible.

As indicated in observation (7), the interaction of 4-methoxycoumarin (IX) with acetyl chloride yielded no 3-acetyl-4-hydroxycoumarin (X). This indicated that direct C-acylation probably does not take place in the case of 4-hydroxycoumarin, and



IX



X

that the isolation of 4-acetoxycoumarin, together with the above mentioned observations, were not artifacts. However, it should be borne in mind that the degree of electron repulsion in the case of 4-methoxycoumarin (which would activate the 3-position[4] and lead to direct C-acylation) is less than that of 4-hydroxycoumarin and its anion.

From these observations, then, it was concluded that the suggested mechanism for the reaction between 4-hydroxycoumarin and aliphatic acid chlorides to yield the corresponding 3-acyl-4-hydroxycoumarins was valid. Recently, King and Ingold[5] suggested the term "excited state" to describe the high energy state of acetylene. It would appear to us that this term might be appropriately applied to the resonance form VIa of the 4-hydroxycoumarin molecule in preference to "resonance hybrid" or "canonical form."

It is of interest to compare this reaction mechanism with that proposed by Hauser, *et al.*[6] for the acylation of ketone enol acetates with acetic anhydride, catalyzed by boron trifluoride, to form β-diketones. In both, the acetylcarbonium ion is proposed.

(4) The 3-position of 4-hydroxycoumarin is activated by the hydroxyl group as indicated by R. C. Elderfield, "Heterocyclic Compounds," Vol. 2, p. 192, John Wiley and Sons, Inc., New York, N. Y., 1951.

(5) G. W. King and C. K. Ingold, *Nature*, **169**, 1101 (1952).

(6) C. R. Hauser, F. C. Frostick, Jr., and E. H. Man, THIS JOURNAL, **74**, 3231 (1952).

Experimental

3-Acetyl-4-hydroxycoumarin (VIII).—(a) To an ice-cold solution of 4-hydroxycoumarin (1.0 g.) in anhydrous pyridine (8 ml.) containing piperidine (one drop), there was added acetyl chloride (0.7 ml.). The mixture was kept at 37° for 48 hours. The resulting solution was poured into ice and dilute hydrochloric acid to yield 3-acetyl-4-hydroxycoumarin (0.77 g., 60%). On recrystallization from ethanol–water, the melting point and mixed melting point with an authentic sample of 3-acetyl-4-hydroxycoumarin was 134–136°.

(b) 4-Acetoxycoumarin (2.0 g.) was dissolved in anhydrous pyridine (20 ml.) containing piperidine (2 drops). After allowing the reaction to proceed at 37° for 48 hours, it was poured into ice and dilute hydrochloric acid. The yield of 3-acetyl-4-hydroxycoumarin was 1.2 g. (60%).

(c) To an ice-cold solution of 4-hydroxycoumarin (1.0 g.) in pyridine (8 ml.) containing piperidine (one drop) was added acetylpyridinium chloride[7] (1.5 g.). After allowing the reaction to proceed at 37° for 48 hours, it was poured into ice and dilute hydrochloric acid. The voluminous precipitate was steam distilled to yield 3-acetyl-4-hydroxycoumarin (0.75 g., 59%).

4-Acetoxycoumarin (V).—(a) A stock supply of 4-acetoxycoumarin was prepared by the Chattaway procedure.[8] To a solution of 4-hydroxycoumarin (30 g.) in 10% sodium hydroxide solution (100 ml.) was added crushed ice (100 g.) and acetic anhydride (60 ml.). The mixture was shaken vigorously for about one minute, filtered, washed with cold water (the product was very readily hydrolyzed by sodium hydroxide solution or hot water) and dried. The product was recrystallized from absolute ethanol. The yield of 4-acetoxycoumarin was 38 g. (100%). The melting point and mixed melting point with an authentic sample of 4-acetoxycoumarin was 109–110°.

(b) To an ice-cold solution of 4-hydroxycoumarin (1.0 g.) in pyridine (8 ml.) containing piperidine (one drop) was added acetyl chloride (0.7 ml.). After shaking for one minute, the mixture was poured into ice and dilute hydrochloric acid to yield a voluminous white precipitate. The initial melting point of 105–110° was raised to 108–110° by recrystallization from absolute ethanol. A mixed melting point with an authentic sample of 4-acetoxycoumarin was undepressed.

(c) To an ice-cold solution of 4-hydroxycoumarin (1.0 g.) in dry pyridine (8 ml.) containing piperidine (one drop) was added acetylpyridinium chloride (1.5 g.). Thereafter, the reaction mixture was treated as in (b) above to yield 4-acetoxycoumarin (0.9 g., 70%).

Attempted Conversion of 3-Acetyl-4-hydroxycoumarin (VIII) to 4-Hydroxycoumarin.—3-Acetyl-4-hydroxycoumarin (10.0 g.) was dissolved in anhydrous pyridine (80 ml.) containing piperidine (8 drops). This solution was kept at 37° for 48 hours. Steam distillation of the product, precipitated as before with ice and dilute hydrochloric acid, yielded only 3-acetyl-4-hydroxycoumarin (9.6 g.). No 4-hydroxycoumarin was recovered in the residue from the steam distillation.

Attempted Preparation of 3-Acetyl-4-methoxycoumarin (X).—To an ice-cold solution of 4-methoxycoumarin (1.0 g.) in anhydrous pyridine (10 ml.) containing piperidine (one drop) was added acetyl chloride (1.0 ml.). The mixture, after standing at 37° for 48 hours, was poured into ice and dilute hydrochloric acid to yield an amorphous brown mass. On recrystallization of this from water, there was obtained 4-methoxycoumarin (0.8 g.). The melting point and mixed melting point with an authentic sample was 123–125°.

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(7) Acetylpyridinium chloride was prepared in essentially the same manner as outlined by H. Adkins and Q. E. Thompson, *ibid.*, **71**, 2242 (1949).

(8) F. D. Chattaway, *J. Chem. Soc.*, 2495 (1931).