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THE MECHANISM[1] OF WARFARIN[2] FORMATION FROM 4-HYDROXYCOUMARIN AND β-ANILINOBENZYLACETONE. EVIDENCE FOR SCHIFF BASE INTERMEDIATES SHOWING ENHANCED REACTIVITY IN THE MICHAEL REACTION

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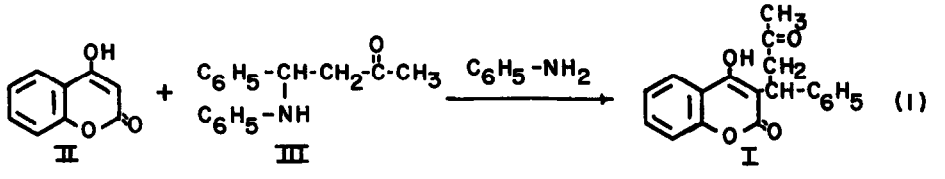
PREVIOUS kinetic studies[3] have shown that the formation of warfarin (I) from 4-hydroxycoumarin (II) and β-anilinobenzylacetone (III) in the presence of aniline (reaction 1) is more rapid (ca. double at equivalent concentrations)



(I)

than its formation from 4-hydroxycoumarin and benzalacetone (IV) in the presence of aniline (reaction 2).

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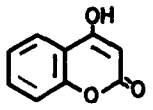
[1] In the Japanese Patent Court demandant Toko Chemical Co., Ltd., Tokyo, Japan, for H. Naruke "on the scope of right of patent number 195, 040 held by Wisconsin Alumni Research Foundation, Madison 5, Wisconsin, Trial No. 380/1953" dated October 26, 1953, it is asserted that the formation of warfarin from 4-hydroxycoumarin and β-anilinobenzylacetone is a direct (S_N2) reaction.

[2] The chemical name 3-(α-acetonylbenzyl)-4-hydroxycoumarin is the systematic name selected by Chemical Abstracts for the anticoagulant warfarin.

[3] C.H. Schroeder, Tien-Hui Lin, E.L. King and K.P. Link, Abstracts of Papers, the 136th Meeting of the American Chemical Society, Atlantic City, New Jersey, September 13-18, 1959, p. 109-p.



+ C_6H_5-CH=CH-C(=O)-CH_3 (IV) $\xrightarrow{C_6H_5NH_2}$ I (2)

These results supported the conclusion that the usual mechanism of the Robinson modification[4a,b] of the Michael reaction is not operative. That is, (a) the elimination of aniline from β-anilinobenzylacetone to give benzalacetone and (b) the condensation of benzalacetone with 4-hydroxycoumarin to give warfarin, occurs only to a minor extent.

The first clue on the role of aniline in reaction 1 was obtained when it was found that tertiary amines (e.g. triethylamine, triethylenediamine,[5] pyridine) are poor catalysts for the formation of warfarin in this reaction. This similarity to the well-known Knoevenagel condensation in which tertiary amines are less effective as catalysts suggested like mechanisms.

Reactive Intermediates

It has been proposed[6 - 9a] on the basis of kinetic evidence that the active species in the Knoevenagel reaction is a condensation product of the

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4a F.J. McQuillin and R. Robinson, J. Chem. Soc. 1097 (1938); b For a discussion of this method and a review of the Michael reaction see E. Bergmann, D. Ginsburg and R. Pappo in R. Adams, Organic Reactions Vol. 10, Chapter 3. John Wiley, New York (1959); c Ibid. pp. 207, 241.

5 DABCO-grade 1,4-diazo [2.2.2] bicyclooctane was obtained from Houdry Process Corp., Philadelphia, Pa.

6 E. Knoevenagel, Ber. Dtsch. Chem. Ges. 31, 2596 (1898).

7 F.H. Westheimer and H. Cohen, J. Amer. Chem. Soc. 60, 90 (1938).

8 T.I. Crowell and D.W. Peck, J. Amer. Chem. Soc. 75, 1075 (1953).

9a C.K. Ingold, Structure and Mechanism in Organic Chemistry p. 685 Cornell University Press, Ithaca, N.Y. (1953); b Ibid. p. 694.

primary or secondary amine with the carbonyl group. Therefore, in an effort to extend and test this proposal the anils of β-anilinobenzylacetone and of benzalacetone were prepared.

β-Anilinobenzylacetone anil (m.p. 135°, infrared spectrum: N-H, 2.95 μ; -C=N-, 6.02 μ. (Found: C, 83.5; H, 7.2. Calc. for $C_{22}H_{22}N_2$: C, 84.0; H, 7.0)) was obtained in low yield by heating a mixture of aniline and β-anilinobenzylacetone. This anil can be more readily obtained by the azeotropic distillation of water from a reaction mixture containing either benzalacetone or β-anilinobenzylacetone, aniline and an acid catalyst whose acidity (pK'a) in comparable systems is essentially in the range of acetic acid (i.e. 4-hydroxycoumarin, warfarin, dihydroresorcinol, barbituric acid, lawsone, ascorbic acid, certain ion exchange resins, etc.).

Benzalacetone anil (m.p. 108-110°, infrared spectrum -C=N- of an α,β-unsaturated system,[10] 6.15 μ. (Found: C, 86.9; H, 6.7. Calc. for $C_{16}H_{15}N$: C, 86.9; H, 6.8) was also obtained in low yield from these reaction mixtures.

The role of the two anils as intermediates in the formation of warfarin in reaction 1 is demonstrated by yield comparison studies. Benzalacetone, β-anilinobenzylacetone, β-anilinobenzylacetone anil and benzalacetone anil were each allowed to react with 4-hydroxycoumarin under similar conditions. The results are given in Table 1.

These results show that β-anilinobenzylacetone anil and benzalacetone anil react with 4-hydroxycoumarin to form warfarin much more rapidly than either β-anilinobenzylacetone or benzalacetone.

Although the degree of enhanced reactivity of the Schiff base system must await a thorough kinetic analysis, it can be said that the ethylenic

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[10] H.R. Nace and E.P. Goldberg, J. Amer. Chem. Soc. 75, 3646 (1953).

Schiff base benzalacetone anil and the Schiff base β-anilinobenzylacetone anil show substantial increased reactivity. These Schiff base systems react at least 25 times faster than the β-anilinobenzylacetone-aniline system and at least 50 times faster than the benzalacetone-aniline system.

TABLE 1[a].

Formation of warfarin from 4-hydroxycoumarin[b] plus acceptors related to benzalacetone

Acceptor	Acceptor (moles/l.)	Aniline (moles/l.)	Warfarin (% yield)
$C_6H_5-CH=CH-\overset{O}{\overset{\|}{C}}-CH_3$	0.117	0.234	Less than 4[c]
$C_6H_5-\underset{C_6H_5-NH}{\underset{\|}{CH}}-CH_2-\overset{O}{\overset{\|}{C}}-CH_3$	0.117	0.117	Less than 4[d]
$C_6H_5-\underset{C_6H_5-NH}{\underset{\|}{CH}}-CH_2-\underset{N-C_6H_5}{\underset{\|}{C}}-CH_3$	0.117	none	76
$C_6H_5-CH=CH-\underset{N-C_6H_5}{\underset{\|}{C}}-CH_3$	0.117	0.117	72
$C_6H_5-CH=CH-\underset{N-C_6H_5}{\underset{\|}{C}}-CH_3$	0.117	none	71
$C_6H_5CH=CH-\overset{O}{\overset{\|}{C}}-CH_3$	0.175	0.350	17
$C_6H_5\underset{C_6H_5NH}{\underset{\|}{CH}}-CH_2-\overset{O}{\overset{\|}{C}}-CH_3$	0.175	0.175	25

[a] Each reaction took place in refluxing dioxane for 60 min. These conditions were the same as those used in the kinetic studies.[3]

[b] The initial concentration of 4-hydroxycoumarin (moles/l.) was equal to the initial concentration of the acceptor in each case.

[c] On the basis of the rate law[3] a 3% yield of warfarin can be calculated for these conditions.

[d] This yield was estimated to be one half that of part c or 1.5%.[3]

An overall mechanism consistent with the above results and the kinetics[3,11] is given. The acid HX in the scheme is provided by the Michael donor 4-hydroxycoumarin (pKa 4.1). A non-donor acid such as acetic acid can be used to catalyze this reaction.

The mechanism provides a reasonable rationalization for the function of the Knoevenagel type catalysts when they are used in the Michael reaction with α,β-unsaturated carbonyl acceptors (or their Mannich base precursors).[9b]

It is noteworthy that the reaction of benzalacetone anil with 4-hydroxycoumarin appears to be the first example of a Michael reaction initially involving the open-chain conjugated system of the type $-\overset{|}{C}=C-C=N-$.[4b,c] (See also Adams and Reifschneider).[12]

In Situ Formation of the $-\overset{|}{C}=C-C=N-$ System

Additional evidence is provided for the above mechanism by a comparison of the catalytic effect of aniline with the tertiary bases dimethylaniline and triethylamine in the reaction of benzalacetone and 4-hydroxycoumarin to form warfarin (reaction 2). The data are in Table 2.

With dimethylaniline (a weak base of comparable strength to that of aniline) the yield is very low, while triethylamine a much stronger base

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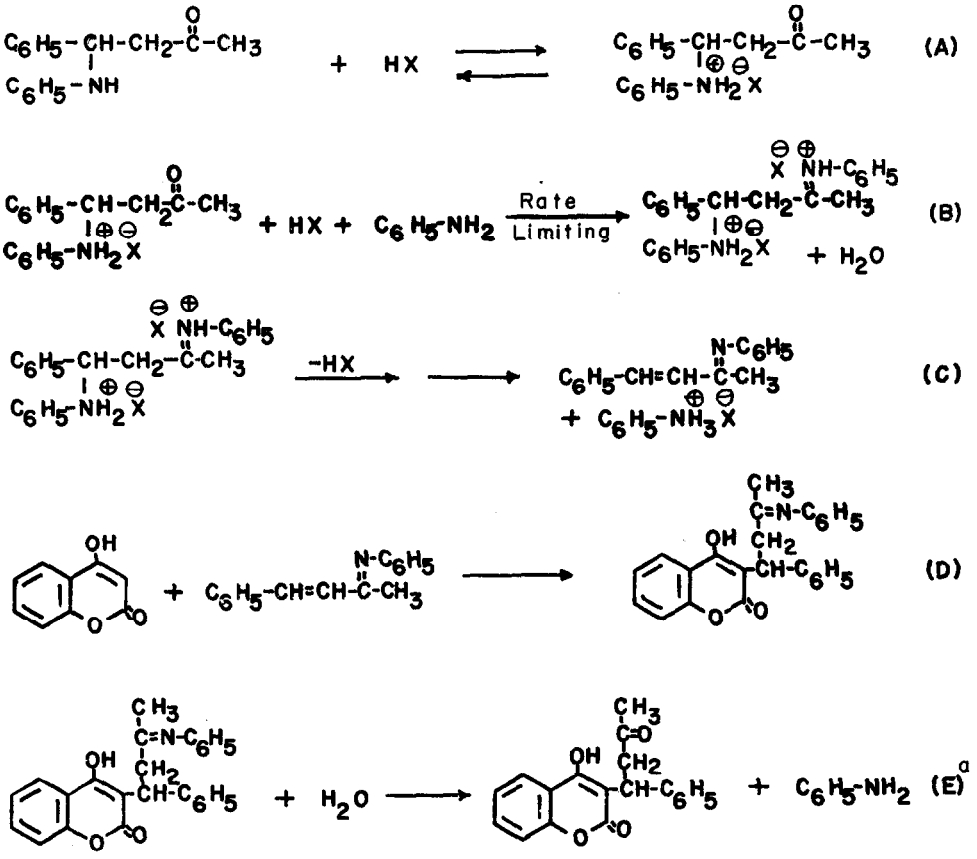
11 Kinetic studies have shown that reaction 1 is second order with respect to 4-hydroxycoumarin and first order with respect to both β-anilinobenzylacetone and aniline. These details will appear in a journal of the American Chemical Society.[3]

12 R. Adams and W. Reifschneider, Bull Soc. Chim. Fr. 49 (1958). The words are (bottom of column right) "Aliphatic molecules containing the $\overset{|}{C}=C-C=N-$ conjugation do not undergo 1,4-addition of active methylene compounds loc.cit. (57)." The emphasis is ours.



[a] At present it is not known whether step (E) occurs chiefly in the reaction mixture or during the isolation procedure.

catalyzes the formation of warfarin though to a lesser extent than aniline. It is well accepted that the role of triethylamine in the Michael reaction is that of a general base catalyst which removes the proton from the Michael donor and the activity of such a catalyst is a function of its base strength.[4b] Since aniline (a weak base) is more effective than triethylamine an alternate pathway is indicated. This suggests that in the presence of aniline benzalacetone anil is formed in situ which reacts with 4-hydroxycoumarin to

TABLE 2[a].

The catalytic effect of aniline and the tertiary bases dimethylaniline and triethylamine in the production of warfarin from 4-hydroxycoumarin and benzalacetone

Base	Base (moles/l.)	Benzalacetone (moles/l.)	4-Hydroxy-coumarin (moles/l.)	Warfarin (% yield)
Aniline	0.67	0.67	1.0	94
Dimethylaniline	0.67	0.67	1.0	less than 4
Aniline	0.315	0.315	0.315	37
Triethylamine	0.315	0.315	0.315	19

[a] Each reaction was done in refluxing dioxane for 60 minutes.

form warfarin.

The scope of the above mechanism as it applies to the Michael reaction is now under investigation here.

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