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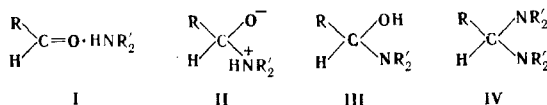
MECHANISM OF THE REACTION OF ALDEHYDES OF THE FURAN SERIES WITH SECONDARY AMINES IN METHANOL

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The reaction of 5-halofurfurals with piperidine and morpholine in methanol under various reaction conditions was investigated by means of spectrophotometry. The kinetics of the stepwise addition of the amine to the aldehyde function of the halofurfural were studied in the case of a dilute solution, while the conversion of the aldehyde to a 5-N,N-dialkylaminofurfurylidene-N,N-dialkylimmonium salt, for which two autocatalysis mechanisms were observed, was investigated in the case of a concentrated solution. Reaction intermediates, viz., 5-halofurfurylidene-N,N-bis(dialkylamines), were isolated preparatively and investigated.

Aldehydes of the furan series react with nitrogen bases that contain a primary amino group (phenylhydrazine [1, 2] and aniline [3]) with the intermediate formation of aminocarbinols, which subsequently lose water and are converted to the corresponding imines. The mechanism of the reaction of furfural derivatives with secondary amines has not been previously studied in detail. It is known [4] that furfural under mild conditions forms stable crystalline molecular compound I with morpholine; I undergoes disproportionation during storage to give the starting aldehyde and an aminal of the IV type. The latter can be obtained directly from the aldehyde by heating it with excess morpholine. Lidak and Giller [5] have investigated this reaction using ethyleneimine and piperidine, in addition to morpholine, as the bases and have expanded the number of aldehydes used. The reaction of the reagents in ethyl chloride at -40°C gave molecular complexes I in high yield, which retain the band of a carbonyl group in their IR spectra. In attempts to recrystallize them they were converted to aminals IV. Lidak and Giller [5] assumed the intermediate formation in this reaction of dipolar adducts II, which exist in equilibrium with aminocarbinols III.



5-Halofurfurals react with secondary amines to give ultimately products of substitution of both the aldehyde oxygen atom and the halogen atom by an amino group. This reaction is carried out preparatively in two variants — in one of them the aldehyde is converted to the corresponding Schiff base, which upon reaction with a secondary amine gives a 5-N,N-dialkylaminofurfurylidene-N,N-dialkylimmonium salt [6]; in the other variant the aldehyde is subjected directly to reaction with a secondary amine, and the same immonium salt is formed [7]. A study of the kinetics of the reaction [8-10] showed that nucleophilic attack by the amine at the aldehyde function and in the 5 position of the furan ring is involved in a complex manner. In a continuation of these studies we investigated the reaction of aldehydes of the furan series with secondary amines (piperidine and morpholine) in absolute methanol. By varying the concentrations of the reagents and by purposeful modification of the experimental method we found it possible to form a more valid judgment regarding the structures of the intermediates formed in this reaction and the reaction mechanism.

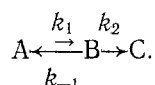
Kinetics of the Reaction in Dilute Solution

The electronic spectra of aldehydes of the furan series contain an intense band with an absorption maximum at 270-360 nm (its absorption depends on the nature of the substituent in

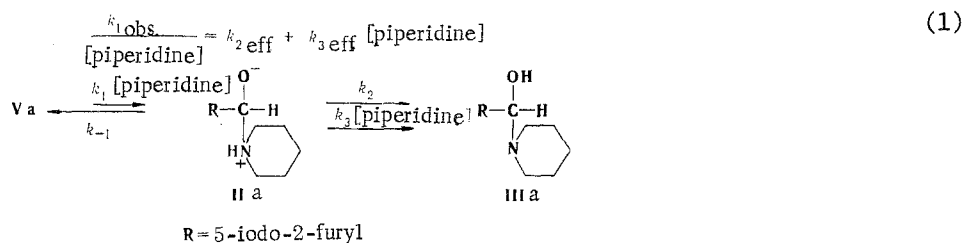
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the ring). Disruption of the carbonyl function or the furan system itself leads to disappearance of this band. The reactions of furan aldehydes with secondary amines are therefore conveniently studied by the method in [11], which makes it possible to carry out the process directly in the spectrophotometer cuvette at low ($\sim 10^{-4}$ mole/liter) concentrations of the substrate. The kinetics observed in this case were simplified for two reasons. First, excess amine ensures that the reaction is zero-order in the amine and that the overall order of all of the reactions in which the amine participates is decreased by unity; the true order in the amine was found in a series of experiments on the dependence of the pseudo first-order constant on the amine concentration. Second, at such a low substrate concentration and at a moderate temperature (35°C) processes involving exchange of the halogen atom in the furan ring by an amino group did not occur, the kinetics were not complicated by autocatalysis, and the initial steps in the process — reaction of the amine at the carbonyl group — could not be observed distinctly in great detail.

The reaction with piperidine was studied in the case of 5-nitrofurfural (Va). The kinetic curves of its reaction with the amine during variation of the piperidine concentration are presented in Fig. 1. All of the curves start from the same point, which corresponds to the initial concentration of aldehyde Va; this indicates the absence of any fast process that affects the spectral extinction of the substrate. An induction period, which on the semilogarithmic graph gives negative deviations from linearity for the first 2-3 min of the reaction, is noted on curves 1-3. This may constitute evidence for the formation of a highly reactive intermediate in conformity with the scheme:

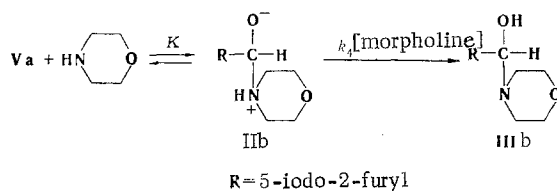


The induction period in this case corresponds to the time prior to the establishment of a steady-state concentration of intermediate B [12]. For simplification of the kinetics, curves 1-3 were treated in accordance with a first-order equation below the KL line. The semilogarithmic treatment of the family of curves in Fig. 1 is presented in Fig. 2a. The dependence of the constants calculated on the basis of this figure on the amine concentration (Fig. 2b) has curvilinear character and is rectified only in coordinates of $k_{\text{obs}}/[\text{piperidine}]$ and $[\text{piperidine}]$ (Fig. 2c). The line obtained cuts out a segment on the axis of ordinates, which usually constitutes evidence that the reaction proceeds via two parallel pathways — catalytic and noncatalytic [13] in conformity with Eq. (1) and the scheme:



The constants corresponding to Eq. (1) and calculated on the basis of Fig. 2c are $k_{2\text{eff}} = 0.12 \text{ sec}^{-1} \cdot \text{liter} \cdot \text{mole}^{-1}$ and $k_{3\text{eff}} = 0.52 \text{ sec}^{-1} \cdot \text{liter}^2 \cdot \text{mole}^{-2}$. The relationship between these effective constants and the elementary constants shown in the scheme can be obtained on the basis of the principle of steady-state character (for example, see [11]).

The reaction with morpholine proceeds as stepwise addition of the amine to the aldehyde group; however, the ratio of the constants of the individual steps differs here from the ratio in the case of piperidine, as a consequence of which the overall kinetic scheme undergoes a



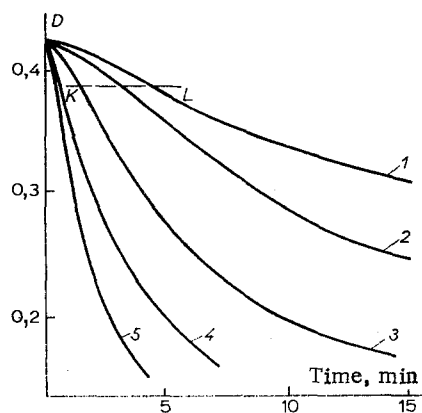


Fig. 1. Kinetics of the reaction of 5-iodofurfural with piperidine during variation of the piperidine concentration.

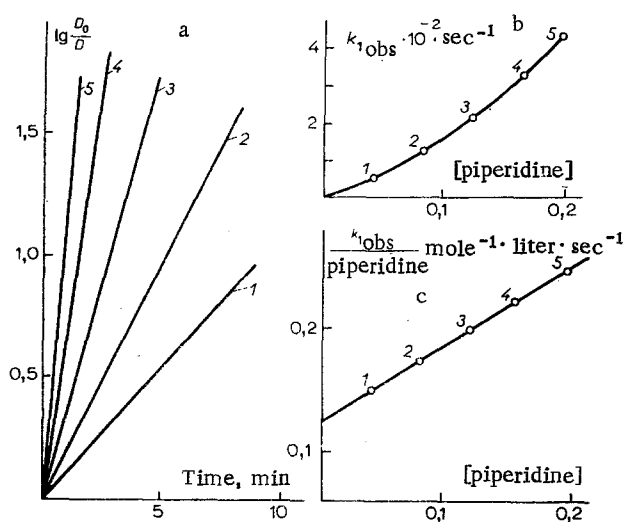


Fig. 2. Graphical treatment of the kinetic data of Fig. 1 (the numbers of the points correspond to the numbers of the curves in Fig. 1).

change in its form. In this reaction equilibrium is established instantaneously in the first step, and the concentration of the free aldehyde decreases in the presence of the amine, to a greater extent, the higher the concentration of the amine (Fig. 3).

The initial equilibrium value (D_e) of the optical density found by extrapolation of the kinetic curves (Fig. 3) was used to find equilibrium constant K . By replacing the equilibrium concentrations of the free aldehyde and adduct IIb by the spectral equivalents D_e and $D_0 - D_e$ we obtain:

$$k_1 D_e [\text{morpholine}] = k_{-1} (D_0 - D_e), K = \frac{k_1}{k_{-1}} = \frac{D_0 - D_e}{D_e [\text{morpholine}]},$$

$$\frac{D_0}{D_e} = 1 + K [\text{morpholine}] \quad (2)$$

Equation (2) was used to find K from the slope of the corresponding graph (Fig. 4). The K value for aldehyde Va is $0.74 \text{ liter} \cdot \text{mole}^{-1}$.

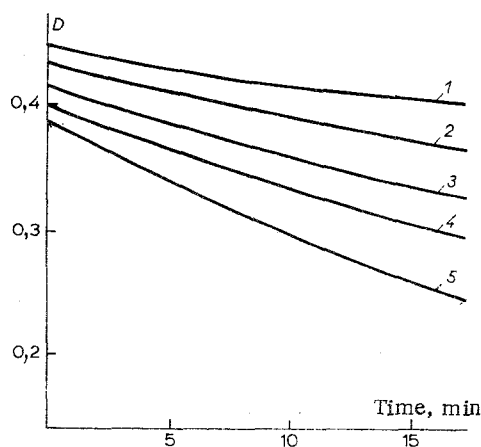


Fig. 3

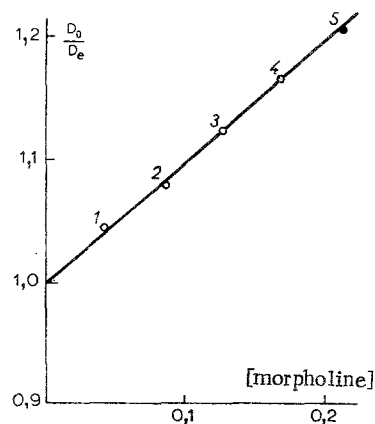


Fig. 4

Fig. 3. Kinetics of the reaction of 5-iodofurfural with morpholine during variation of the morpholine concentration.

Fig. 4. Graphical determination of the equilibrium constant of the first step of the reaction of 5-iodofurfural with morpholine (the numbers of the points correspond to the numbers of the curves in Fig. 3).

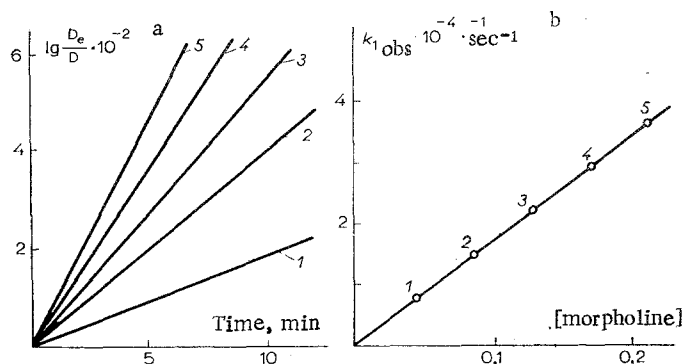


Fig. 5. Graphical treatment of the kinetic curves in Fig. 3.

It follows from Fig. 3 that the establishment of equilibrium in the first step is followed by conversion of adduct IIb to aminocarbinol IIIb. Semilogarithmic treatment of the curves in Fig. 3 (Fig. 5) showed that the reaction $Va \rightarrow IIIb$ is second-order overall and first-order in the amine and that it proceeds via a unique catalytic pathway in conformity with the equation

$$k_{1\text{obs}} = k_{2\text{eff}}[\text{morpholine}] \quad (3)$$

The corresponding second-order rate constant for aldehyde Va is $1.63 \cdot 10^{-3} \text{ sec}^{-1} \cdot \text{liter} \cdot \text{mole}^{-1}$.

Thus the "base-catalysis" scheme that describes the reaction of amines with activated unsaturated systems (for example, nucleophilic aromatic substitution [11]) is also acceptable for the description of the kinetics of the reaction of aldehydes of the furan series with secondary amines at the carbonyl group. An interesting detail is the modification of this scheme as the amine is varied: It is either "compressed" into one observable step $V \rightarrow III$, and "base catalysis" is then observed owing to second-order of the reaction in amine and the overall third kinetic order of the reaction, or it is "dispersed" into two kinetically independent steps — rapid establishment of equilibrium, as in the case of ordinary titration of an acid by a base, with subsequent base-catalyzed transformation $II \rightarrow III$, which occurs in the background of this equilibrium.

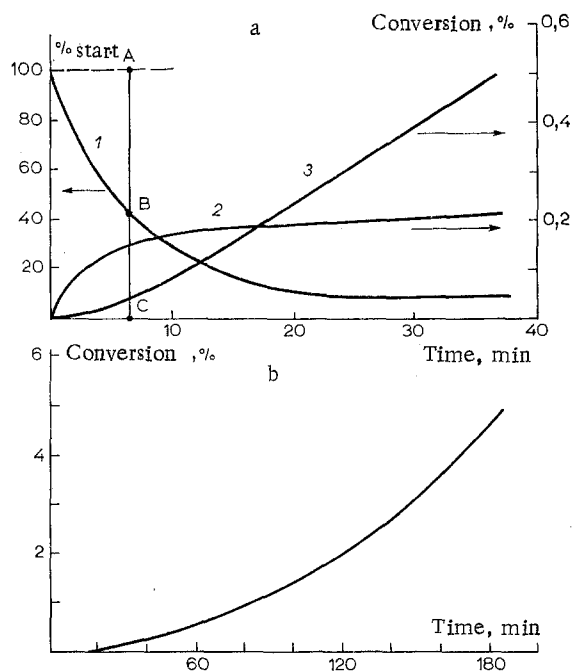


Fig. 6. Kinetics of the reaction of 5-iodofurfural with piperidine (explained in the text).

Reaction Intermediates

The data presented above confirm the well-known fact that secondary amines add stepwise to the carbonyl group of aldehydes. In the spectrum of the reaction mixture during kinetic measurements we observed directly only the starting aldehyde; the assumption of the existence of adduct II and aminocarbinol III was made on the basis of an analysis of the kinetic data. In fact, the high reversibility of reaction $V \rightleftharpoons II$ and the possibility of the amine-catalyzed transformation $II \rightarrow III$ raise no doubts — this interpretation of the reactions of aldehydes with amines is generally accepted [12, 13]. Proceeding from this we assumed [8, 9] that aminocarbinol III is an important chief product in the reactions of aldehydes of the furan series with secondary amines, is relatively stable, and therefore accumulates in high concentrations and that under acid-catalysis conditions it leads to immonium salts VI, which ensure subsequent substitution of halogen. This prediction was not confirmed. It is known [4, 5] that of all of the intermediates of the reactions of furfurals with secondary amines only the aminal of the IV type is relatively stable. Moreover, in [7] it was noted that 5-halofurfurals react with secondary amines in concentrated alcohol solutions to give crystalline adducts with unknown structures, which were converted, without isolation, to final product VIII by heating. We checked these data and found that aminals of 5-halofurfurals of the IV type, which can be isolated in crystalline form, are formed in the initial step of this reaction in quantitative yields. The structure of aminals IV was confirmed by the results of analysis and PMR spectral data; an aldehyde band is not observed in their electronic spectra, and carbonyl extinction is absent in their IR spectra.

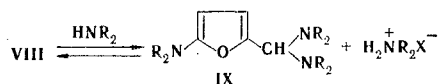
Thus it has been reliably shown that aminals IV are intermediates in the reaction of 5-halofurfurals with secondary amines. It is apparent that aminocarbinols III, as a consequence of the high "inner" nucleophilicity of the amino group, are inclined to undergo conversion to hydroxides, which rapidly add amine and give aminals IV. Similar noncatalytic splitting out of a hydroxide ion from the intermediate aminocarbinol has been noted by do Amaral and Moscovici [2] in the reaction of aldehydes of the furan series with phenylhydrazine. Whether this process occurs only in concentrated solution due to the effects of intermolecular interaction or also occurs in dilute solution but as a fast step that itself is not detected kinetically is difficult to confirm definitely. One thing is certain — none of the data, either preparative or kinetic, thus far obtained for the investigated reaction has taken the formation of this product into account, and the data therefore require serious refinement.

ing aldehyde and all of the unstable reaction products (I, II, or III) that decompose instantaneously when the mixture is diluted. It is not possible to distinguish them by the given method.

It is apparent from curve 3 that on the same kinetic segment the rate of formation of salt VIII gradually increases until it becomes steady (on the scale of Fig. 6a). This steady-state situation corresponds to the maximum amounts of aminal IV and the dialkylammonium salt in the mixture after bonding of the starting aldehyde is complete. Having been formed in two parallel reaction links, these products "connect" them by their interaction, thereby giving rise to a new reaction pathway: $IV \rightarrow VI \rightarrow VIII$.

Both the amine itself and aminal IV may act as the nucleophile in the halogen-substitution step. When the aminal is the nucleophile, with respect to its stoichiometry the process will appear to be "intramolecular" disproportionation of aminal IV catalyzed by salt VI.

Finally, the kinetics of the accumulation of salt VIII for more pronounced degrees of conversion — up to 5-6% — are presented in Fig. 6b. On this scale it is apparent that the reaction proceeds with autocatalytic acceleration. The general reason for autocatalysis consists in the accumulation in the reaction mixture of particles with acidic character due to the elimination of ionic halogen. The number of such particles would be maintained at a steady level if "aminolysis" of the immonium fragment of salt VIII did not occur. However, the electrophilicity of this fragment evidently is also precisely the reason for autocatalytic acceleration during the reaction. Salt VIII, by undergoing reversible conversion to the corresponding aminal, may furnish the reaction mixture with an acidic catalyst:



The function of salt VIII as a direct transmitter of an amino group from one aminal molecule to another, i.e., its catalytic role in the disproportionation of the aminal, is also not excluded:



EXPERIMENTAL

The kinetic measurements in dilute solution were made at 35°C by the method in [11]. The morpholine was dried with potassium hydroxide and distilled. The piperidine was dried by the method in [14] by refluxing and subsequent distillation over potassium metal.

The kinetic measurements in concentrated solutions were made by the following method. A solution of the 5-halofurfural and the secondary amine in absolute methanol (the substrate concentration was 0.6 mole/liter, and the reagent concentration was 1.5 moles/liter) was maintained at 35°C in a thermostat. Samples selected during the reaction were diluted with absolute propanol; several dilutions were simultaneously prepared (the spectral concentrations based on the starting aldehyde ranged from $3 \cdot 10^{-3}$ to $3 \cdot 10^{-5}$ mole/liter), and this made it possible to encompass the entire range of the change in the concentrations of the analyzed substances in the reaction mixture. The electronic spectra of standard substances — the starting aldehydes [16, 17], aldehydes VII, and immonium salts VIII [6, 7] — were first recorded over the entire range in propanol; their concentrations in the analyzed solutions were calculated from the Firordt formula [15].

5-Halofurfural Aminals (IV). A 0.015-mole sample of the secondary amine was added to a solution of 0.005 mole of the 5-halofurfural in 1 ml of absolute methanol, and the mixture was heated to the boiling point. It was then cooled and placed in a refrigerator to complete crystallization. The precipitated crystals were removed by filtration and washed on the filter with cold methanol. The products were obtained in ~80% yields.

Aminal IVa (X = I, NR₂ = piperidino) was obtained as snow-white crystals with mp 106-107°C that turned yellow during storage. PMR spectrum (in d₆-acetone): 6.5 (3-H), 6.1 (4-H), and 3.6 ppm (α-H). Found: C 48.0; H 6.3; N 7.6%. C₁₅H₂₃N₂O. Calculated: C 48.1; H 6.2; N 7.5%.

Aminal IVb (X = I, NR₂ = morpholino) was obtained as crystals with mp 240°C (dec.). Found: C 41.9; H 5.3; N 8.1%. C₁₃H₁₁IN₂O₃. Calculated: C 41.3; H 5.1; N 7.4%.

Aminal IVc (X = Br, NR₂ = piperidino) was obtained as crystals with mp 100°C.

Aminal IVd (X = Br, NR₂ = morpholino) was obtained as crystals with mp 220°C (dec.).

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STRUCTURE AND RING-CHAIN TAUTOMERISM OF 2-HYDROXY-5-METHYL-3,4-BENZOCINNAMALDEHYDE

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The previously undescribed 2-hydroxy-5-methyl-3,4-benzocinnamaldehyde was synthesized. A cyclic 2-hydroxy-2H-chromene structure in the crystalline state and in nonpolar solvents was established for it by IR, UV, and PMR spectroscopy. It is shown that transition to a polar solvent leads to the establishment of a tautomeric ring-chain equilibrium, the position of which is determined by the type of solvent.

We have previously shown that transition from 2-hydroxycinnamaldehyde and its imines, which exist exclusively in the benzoid tautomeric form in media with various polarities, to benzo-annelated systems, which are more inclined to undergo quinoidization, has a substantial effect on the structures of vinyls of o-hydroxy aldehydes and their derivatives [1]. Thus, 2-hydroxy-5,6-benzocinnamaldehyde and its imines in the crystalline state and in solutions in nonpolar solvents have a cyclic 2H-chromene structure, whereas a tautomeric ring-chain equilibrium is realized for them in polar media.

In order to further study prototropic transformations of this type we obtained the previously undescribed 2-hydroxy-5-methyl-3,4-benzocinnamaldehyde (Ia). The synthesis was ac-

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