KINETICS AND MECHANISM OF THE REACTION OF 5-BROMO-2- CARBONYL DERIVATIVES OF FURAN WITH AMINES

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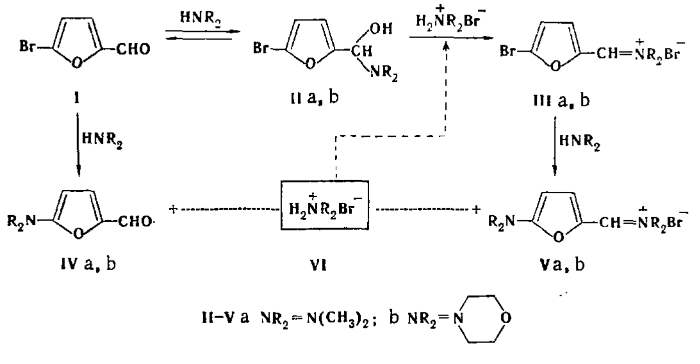
The kinetics of exchange of bromine in 5-bromo-2-carbonyl derivatives of furan by dimethylamino and morpholino groups was studied. The reaction is kinetically complicated for 5-bromofurfural (I) – aldehyde I initially reacts simultaneously at both the carbonyl group to give the aminocarbinol and at the bromine atom with exchange by an amino group. The accumulation of the ammonium salt in the latter reaction leads to the development of an autocatalytic reaction, the product of which is 5-N,N-dialkylaminofurfurylidene-N,N-dialkylammonium bromide. Amines react with the ketones without complications; the second-order rate constants are presented. The rate of exchange decreases in the order CHO > COC_6H_5 > $COCH=CHC_6H_5$ > $COCH_3$ > $CH=CHCOC_6H_5$.

The reaction of aldehydes with nitrogen bases, which takes place through the intermediate formation of aminocarbinols, has been well studied [1, 2]. Furfural and its derivatives react with amines similarly. Furfural reacts with secondary amines to give a 1:1 complex, which subsequently undergoes arrangement to an aminocarbinol [3]. The kinetics of the reaction of furfural and its 5-substituted derivatives with phenylhydrazine have also been studied [4], and it has been shown that it proceeds in conformity with the stepwise scheme of Jenks [2]. However, one should take into account the fact that the carbonyl group is an activator (although of moderate strength) of aromatic nucleophilic substitution [5-7]. The presence of a "good" leaving group in the 5 position of the furan ring therefore creates the possibility of superimposition of two parallel pathways of nucleophilic attack – at the carbonyl group and in the ring 5 position [8]. In earlier research [9] we observed a similar unusual mechanism in the reaction of 5-halofurfurals with secondary amines. In order to compare the behavior in this reaction of aldehydes and ketones, we investigated the reaction with secondary amines of a more extensive series of 5-halo-2-carbonyl derivatives of furan.



In comparison with [9], the method used to analyze the reaction mixtures was also modified: In addition to determination of the ionic halogen, the mixture was analyzed spectrophtometrically during the reaction; this made it possible to formulate a more nearly complete concept of the mechanism of the process.

In order to determine the percentages of the components from the spectral data, we first obtained the characteristics of both starting aldehyde I [in ethanol λ_{max} 283 nm (log ε 4.24] and of the possible products –

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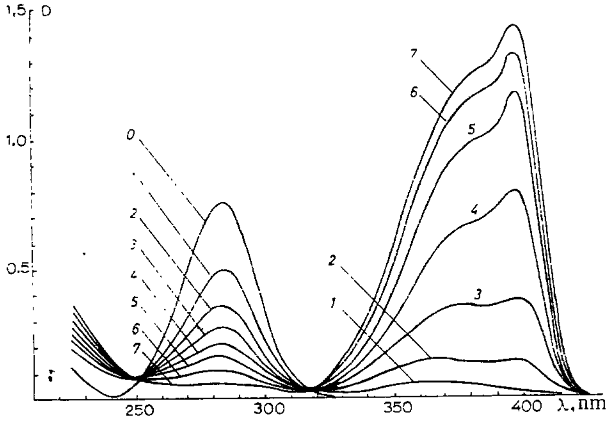

Fig. 1

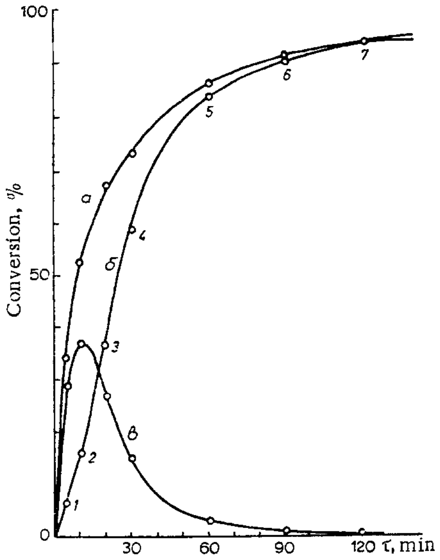

Fig. 2

Fig. 1. Spectra of the reaction mixture for the reaction of I with dimethylamine (the numbers on the curve correspond to the numbers of the points in Figs. 2 and 3).

Fig. 2. Theoretical yields of product with respect to the consumption of I (a), accumulation of ionic halogen (b), and change in the aminocarbinol II concentration (c) in the reaction of I with dimethylamine.

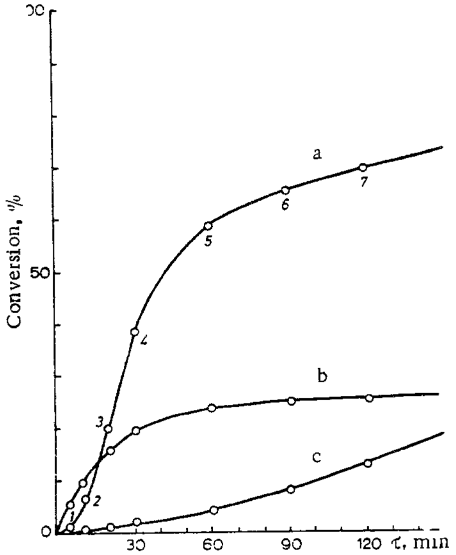

Fig. 3

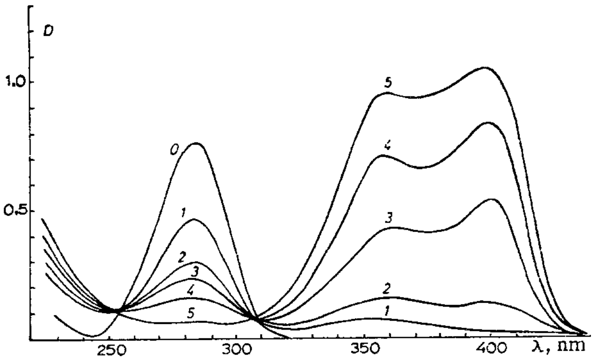

Fig. 4

Fig. 3. Kinetics of the accumulation of quaternary salt V (a), amino aldehyde IV (b), and quaternary salt III (c) in the reaction of I with dimethylamine.

Fig. 4. Spectra of the reaction mixture for the reaction of I with morpholine (the numbers on the curves correspond to the numbers of the points in Figs. 5 and 6).

amino aldehydes IVa [λ_{max} 361 nm (log ε 4.51)] and IVb [λ_{max} 356 nm (log ε 4.60)] and quaternary salts Va [λ_{max} 396 nm (log ε 4.68)] and Vb [λ_{max} 402 nm (log ε 4.59)].

The change in the spectrum of the reaction mixture in the reaction of aldehyde I with dimethylamine is shown in Fig. 1, and data on the percentage halogen in the reaction mixture are presented in Fig. 2 (curve b).

A comparison of curves a and b in Fig. 2 showed that the spectrally determined consumption of aldehyde I at the start of the reaction exceeds the yield of ionic halogen; this indicates accumulation of aminocarbinol IIa in the reaction (curve c). The spectrum of the mixture in the longwave region constitutes evidence that

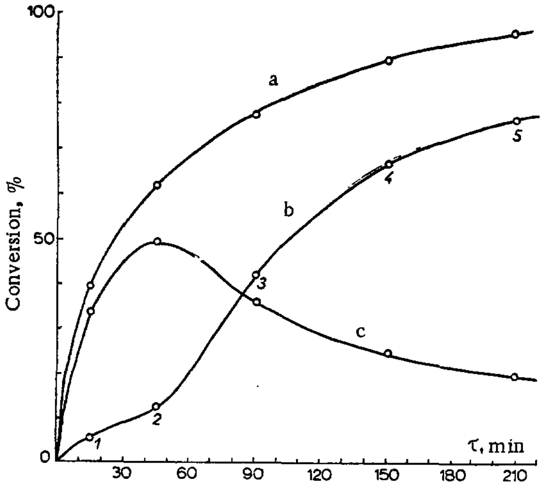

Fig. 5

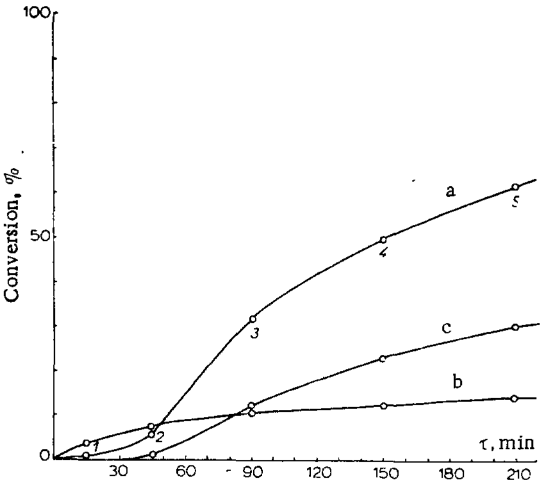

Fig. 6

Fig. 5. Theoretical yield of the product with respect to the consumption of I (a), accumulation of ionic halogen (b), and change in the aminocarbinol II concentration (c) in the reaction with morpholine.

Fig. 6. Kinetics of the accumulation of quaternary salt V (a), amino aldehyde IV (b), and quaternary salt III (c) in the reaction of I with morpholine.

amino aldehyde IVa predominates in the first samples. Consequently, until the aldehyde I content in the reaction mixture is high, nucleophilic exchange of bromine to give IVa (curve b in Fig. 3) proceeds at an appreciable rate. However, dimethylammonium hydrobromide VI is liberated in this reaction, and its accumulation affects the subsequent course of the reaction. The percentage of aminocarbinol IIa drops sharply (Fig. 2, curve c) as a result of its conversion to salt IIIa. The activating effect of the immonium group ensures rapid nucleophilic substitution of halogen in salt IIIa by a dimethylamino group, and salt Va therefore begins to accumulate rapidly in the reaction mixture after a short induction period (Fig. 3, curve a). However, the bromine exchange in the free aldehyde (to give amino aldehyde IVa) is slowed down because of the decrease in aldehyde I concentration; its rate at the end of the reaction drops to practically zero. Thus this reaction has complex autocatalytic character, and its catalyst is ammonium salt VI; an unusual "triggering mechanism" – the formation of salt VI in the reaction of aldehyde I with dimethylamine – operates at the start of the reaction. Salt VI is subsequently formed principally by bromine exchange in IIIa.

Another peculiarity of this reaction was observed during an analysis of the change in the optical density of solution at 350 nm for later samples (beginning with $\tau = 30$ min). Here we observed a sharper increase in the density that could not be ascribed to any of the products that we studied as "references" (IVa or Va). We explain this phenomenon by accumulation of salt IIIa at the end of the reaction as a result of a decrease in the percentage of dimethylamine in the mixture and, consequently, a decrease in the overall rate of exchange of bromine in IIIa by an amino group (Fig. 3, curve c).*

Similar results were obtained in the reaction of aldehyde I with morpholine (Figs. 4-6), except that the entire process had slower character because of the decrease in the basicity of the nucleophile. Some of the features of the reaction therefore show up more distinctly in this case – for example, a distinct transition from bromine exchange in free aldehyde I to autocatalytic bromine exchange in salt IIIb (which, as seen from curve c in Fig. 6, accumulates in considerable concentrations) can be observed on curve b in Fig. 5. On the whole, however, the reaction mechanisms for the two investigated amines are analogous.

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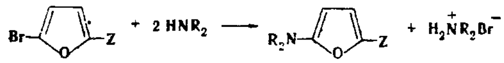
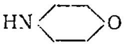
*We found the percentage of product IIIa (since it is not described and its optical properties are unknown) starting from the following considerations. In analogy with the similarly constructed 5-bromo-2-nitrofuran, it may be assumed that IIIa will absorb at 340-360 nm but will be transparent at ~400 nm. We therefore determined the percentage of Va on the basis of the optical density at 396 nm (Fig. 3, curve a); the overall percentage of Va and IVa was adjusted to the percentage of ionic halogen in the mixture (Fig. 2, curve b), and the percentage of IVa was found from the difference (Fig. 3, curve b). The surplus increase in the density referred to IIIa (Fig. 3, curve c) was determined after appropriate conversion with respect to the optical density at 356 nm. A similar calculation was performed for the reaction with morpholine.

TABLE 1. Second-Order Rate Constants ($k_2 \cdot 10^{-4}$ liter • mole^{-1}sec^{-1}) for the Reaction



HNR_2	Z				
	$-CHO$	$-COCH_3$	$-COC_6H_5$	$-COCH=CHC_6H_5$	$-CH=CH-COC_6H_5$
$HN(CH_3)_2$	7.9	0,69	2.77	2.00	0,19
	1.6	0,13	0.48	0,39	0.032
Δ lg *k*	0.69	0,72	0,76	0,71	0,77

The quantitative analysis of such complex reactions by simple integral methods is impossible, and we therefore restricted ourselves within the framework of this research to determination of the second-order rate constant for bromine exchange in free aldehyde I by a differential method for $\tau = 0$ (from the results of kinetic curve b in Fig. 3 and curve b in Fig. 6). These data are presented in Table 1.

For comparison under the same conditions, we studied the kinetics of exchange of bromine by an amino group in furan ketones. It is known from preparative data [10, 11] that furan ketones react readily with secondary amines to give the corresponding exchange products in which the carbonyl group is retained. The kinetic results confirmed that the reaction proceeds here without complication and is subject to a second-order equation. The corresponding second-order rate constants are presented in Table 1.

It is evident from the data in Table 1 that the reaction in all cases is slowed down by a factor of approximately five (Δ log k$\approx$0.7) on passing from dimethylamine to morpholine. this corresponds to an increase in the free activation energy of 1 kcal/mole (the fraction in $\Delta\Delta G^{\neq}$ due to the basicity of the amine and the steric peculiarities of the transition state). The effect of group Z on the reaction rate corresponds to the analogous activating effect of substituents in SN_2Ar reactions. Thus Miller [5] arranged the carbonyl substituents in the following order of weakening of the activating effect: $CHO > COC_6H_5 > COCH_3$. We also observed a similar substituent order in our case. It is apparent that the sharp decrease in the rate on passing from the aldehyde to the ketone cannot be explained only by the electronic effect of the methyl group – its steric effect, which hinders conjugation of the keto group with the ring and "compression" of the system during the formation of the intermediate σ complex, is more likely manifested here. When a phenyl group is introduced adjacent to the carbonyl group, this complex, on the other hand, will be stabilized due to both the acceptor properties of the phenyl group and particularly due to conjugation of the phenyl group with the exocyclic double bond developing in the complex. Removal of the phenyl group from the carbonyl group by the introduction of a double bond slightly reduces the rate, but removal of the activating carbonyl group from furan reduces the rate constant by a factor of 10. We have already noted [12] the similar deactivating effect of the double bond when it is introduced between an activating grouping and the halofuran ring.

EXPERIMENTAL

The preparations used in this research were obtained in accordance with the following literature sources: 5-bromofurfural [13], 5-bromo-2-acetylfuran [14], 5-bromo-2-furyl phenyl ketone [15], 5-bromofurfurylideneacetophenone and benzylidene-5-bromo-2-acetofuran [16], and aldehydes IVa and IVb and quaternary salts Va and Vb [17].

The kinetics of the reaction in 96.5% ethanol at 50° were studied. The substrate concentration was 0.1 M, and the reagent concentration was 0.3 M; the reaction mixture was analyzed for ionic halogen by the method in [9]. A certain portion of the reaction mixture was diluted with ethanol to a concentration of $4.3 \cdot 10^{-5}$ (with allowance for the starting substrate concentration) and analyzed with an SF-4A spectrophotometer.

The spectrophotometric data for the reaction of aldehyde I with amines were treated by an additive scheme [18]. The second-order rate constants were calculated graphically by the semilogarithmic method [19]

$$k_2 = \frac{2.303}{\tau(b-2a)} \lg \frac{a(b-2x)}{b(a-x)},$$

where a is the starting substrate concentration, b is the starting reagent concentration, and x is the concentration of the reaction product at time τ.

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SYNTHESIS OF γ-DIHYDROPYRONES AND β-DIHYDROFURANONES ON THE BASIS OF ACETYLENIC γ- AND δ-KETO ALCOHOLS AND ACETALS OF γ- AND δ-FORMYL ALCOHOLS

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Acetylenic γ- and δ-keto alcohols and acetals of acetylenic γ- and δ-keto alcohols and acetals of acetylenic γ- and δ-formyl alcohols undergo cyclization to γ-dihydropyrones and β-dihydrofuranones under the influence of acids.

Acetals (I) of acetylenic δ-hydroxy aldehydes [1] are potential sources of the corresponding δ-hydroxy aldehydes – they are converted to γ-pyrones (V) when the acetal protective group is removed by acidic reagents. It was found that this transformation is also common to other acetylenic carbonyl-containing compounds – γ- and δ-keto alcohols (II) and acetals (I) of acetylenic γ-formyl alcohols, which are converted, respectively, to γ-dihydropyrones (V) and β-dihydrofuranones (VII). This opens up a method for the preparation of compounds that have repellent properties. Thus 2,2-dimethyl-5-phenyl-4,5-dihydrofuran-3-one (VIIh) is a natural repellent.

The transformations found in this research can be explained by hydration of the triple bond of the above-indicated compounds to give hydroxydicarbonyl compounds (IV), which undergo cyclization with the loss of a water molecule to γ-pyrones V or β-furanones VII or are dehydrated to vinyl ketones or vinylketo aldehydes

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