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ENAMINES.

8.* POLAROGRAPHIC STUDY OF THE REACTIONS OF A NUMBER OF ENAMINO KETONES WITH NUCLEOPHILIC REAGENTS

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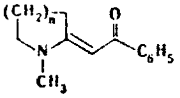
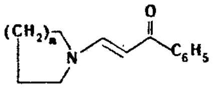
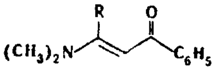
The hydrolysis and hydrazinolysis of cyclic enamino ketones of the pyrrolidine, piperidine, and hexahydroazepine series, as well as their noncyclic analogs, were investigated. It is shown that these processes have several principles in common. A bell-shaped dependence of k_{obs} on the pH of the medium is characteristic for hydrolysis; the reaction of the enamino ketones with hydrazine hydrate in absolute ethanol is accelerated in the presence of p-toluenesulfonic acid. It is shown that the rates of hydrolysis and hydrazinolysis depend on the size of the saturated azaheteroring and change in the order 6 > 5 > 7. A possible mechanism for the processes in which the slow step is C-protonation and(or) attack by the nucleophilic reagent in the "enamine" α position is discussed.

The reactions of enamino ketones with nucleophilic reagents at the present time constitute an extremely promising and convenient approach to the synthesis of various classes of heterocyclic compounds [2-5]. We have previously [1, 6] used polarography to investigate the hydrolysis of cyclic enamino ketones Ia-c, which was selected as a model reaction for the study of the reaction of these compounds (or their cations) with nucleophilic partners.


Ia-c


IIa-c


IIIa,b

I a n=1; b n=2; c n=3; III a R=H; b R=CH$_3$

It was recently demonstrated by PMR spectroscopy that the behavior of enamino ketones Ia-c and their noncyclic analog IIIb with respect to protonating agents differs substantially from the behavior (under the same conditions) of enamino ketones of a different type (IIa-c, IIIa) in which a CH$_2$ link or a CH$_3$ group is absent in the "enamine" α position [7].

In conformity with this, the aim of the present research was to investigate the dependence of the rate of hydrolysis of enamino ketones IIa-c and IIIa on the properties of the medium and the ring size and to compare data on the hydrolysis of two series of enamino ketones (Ia-c, IIIb and IIa-c, IIIa). In addition, in the present paper we compare the results of a study of the hydrolysis with data on the heterocyclization of IIa-c and IIIa (in the case of the synthesis of 3-phenylpyrazole by the reaction of these enamino ketones with hydrazine). The dependence of the hydrolysis of enamino ketone IIIa on the pH is presented in Fig. 1. It is apparent from Fig. 1 that the general form of the observed dependence corresponds to the results previously obtained for other enamino ketones [1, 6]. The curve has a bell-shaped

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*See [1] for Communication 7.

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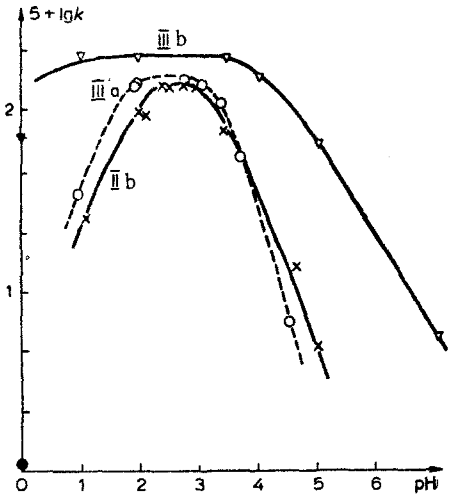

Fig. 1. Dependence of the hydrolysis of enamino ketones IIb, IIIa, and IIIb on the pH of the medium at 25°C in 10% ethanol at an ionic strength (NaCl) of 0.1 (▼ and ● pertain to the values obtained in 1 N HCl).

form: it passes through a maximum, and the rate of hydrolysis decreases sharply in strongly acidic ($pH < 1$) or weakly acidic ($pH > 5$) media. A similar dependence of the rate constant

TABLE 1. Dependence of the Rate of Hydrolysis of the Enamino Ketones on the pH in Aqueous Solutions (50°C, 10% by volume ethanol, ionic strength 0.1)

pH	IIb	IIa	IIc
	$k \cdot 10^4$ sec^{-1}		
1,0	30	4,9	2,1
2,0	88	27,0	5,4
3,0	160	32,0	4,3
4,4	15,0	5,1	1,3
5,1	1,9	—	0,24
13,0	0,91	0,61	0,10

TABLE 2. Dependence of the Observed First-Order Rate Constants for the Hydrolysis of the Enamino Ketones on the pH of the Medium and the Buffer Solution Concentration [25°C, 10% by volume ethanol, ionic strength 1.0 (NaCl)]

Compound	$k \cdot 10^3$ sec^{-1}			
	pH 2.5, glycine buffer		pH 4.6, acetate buffer	
	1,0 M	0,01 M	1,0 M	0,01 M
IIb*	1,47±0,32	1,48±0,20	0,37; 0,34	0,14; 0,15
IIIa	1,4; 1,6	0,93; 0,84	0,316±0,034	0,070±0,011
IIIb	2,71±0,65	1,34; 1,46	7,5±2,7	0,71; 0,79

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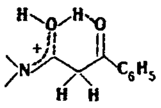
*In a 0.1 mole/liter glycine buffer with an ionic strength of 0.1, $k = (1.45 \pm 0.18) \cdot 10^{-3}$ sec^{-1}.

(k_{obs}) on the pH is observed for the other investigated compounds (IIa-c, IIIb) (Fig. 1 and Tables 1 and 2). It also follows from these data that a distinct dependence of the rate of hydrolysis on the concentration of the buffer solution is observed for the investigated compounds and for enamino ketones of the I type (see the k_{obs} values for enamino ketones IIb and IIIa at pH 4.6 in Table 2), and this indicates the existence of general catalysis in the hydrolysis process. This in turn implies that proton transfer occurs in rate-determining step of the hydrolysis of the amino ketones. It also follows from the data in Table 2 that there is a definite dependence of the rate of hydrolysis on the size of the saturated ring; the order in this case is somewhat unusual, viz., $6 > 5 > 7$. Either the order $6 > 7 > 5$ or the order $5 > 7 > 6$ is observed in other cases (for example, see [8]). Finally, attention should be directed to the fact that the "bell" of the dependence of the hydrolysis of IIIa on the pH differs in form from the curve for enamino ketone IIIb; the latter has a plateau at pH 1-3.5 (Fig. 1). A similar picture is also observed when one compares the profiles of these dependences for IIc and Ic.

A prerequisite for the interpretation of the results was the fact that the enamino ketones of the two types indicated above behave differently with respect to protonating agents under identical conditions: Compounds of the first group (Ia-c, IIIb) are protonated at the β-carbon atom, while N- and O-protonation, as previously demonstrated [7] by means of the PMR spectra, is characteristic for compounds of the second group (IIa-c, IIIa). It should be noted that the polarograms of enamino ketones IIa-c and IIIa contain waves that correspond to the reduction of the N- and O-protonated forms: For example, $E_{1/2} = -0.78$ and -0.88 relative to a saturated calomel electrode for IIIa in 1 N HCl, while $E_{1/2} = -0.91$ V for β-methoxy-β-phenylvinylmethylene-N,N-dimethylimmonium methylsulfate (a model of the O-protonated form) under the same conditions (see [9]). In addition, there are data [6, 10] that show that the addition of water cannot take place to an appreciable extent at the α-carbon atom of the N- or O-protonated forms. Consequently, the overall scheme of the hydrolysis of enamino ketones IIa-c and IIIa should include "reprotonation" with the formation of an immonium cation of the C-protonated form.

An increase in the rate of hydrolysis, which is evidently associated with an increase in the rate of C-protonation, is observed on the right-hand branch of the "bell" (pH 3-6) for IIIa,b (Fig. 1), just as for other enamino ketones I and II, as the acidity is increased; k_{obs} for IIIb $\gg$ k_{obs} for IIIa, since IIIb is more inclined to undergo C-protonation [7]. There are plateaus where k_{obs} is independent of the pH at the apexes of the "bells" of the dependence of the hydrolysis of these compounds on the pH. It may be assumed that the presence of such plateaus is associated with a change in the rate-determining step and that in this pH region the rates of C-protonation and subsequent attack by water (hydration) are close to one another. One might have suppose that the independence of k_{obs} on the pH indicates hydration as the rate-determining step; however, at the apexes of the "bells" we observe a slight (actually smaller than on the right-hand branch of the "bell") dependence of k_{obs} on the buffer concentration. Let us note that this sort of dependence is absent at the apex of the "bell" for enamino ketone IIb and that in this case the plateau is probably determined by the rate-determining step, viz., the addition of water. It is apparent from Fig. 1 that the plateau on the curve for enamino ketone IIIb occupies a broader pH range than for IIb and IIIa. The fact that the plateau for the compounds of the first group is expressed considerably more distinctly is explained by the fact that the rate of C-protonation for them is substantially higher than for compounds of the second group (II, IIIa). A change in the rate-determining step is therefore observed in those media in which for the second group of compounds C-protonation is the slow step in the hydrolysis process.


IV

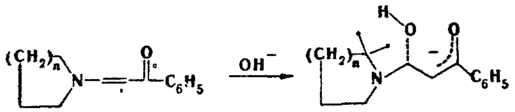
In those cases in which the slow step is hydration, the change in the hybridization of the ring nitrogen atom from sp^2 to sp^3, which is most favorable for six-membered compounds [8], should be taken into account for transition state IV. At the same time, the steric hindrance due to overlapping of the α, α' protons of the hexahydroazepine ring and the N substituent in complex IV is responsible for the anomalously low rate of hydrolysis of seven-membered enamino ketone IIc. Thus each of the C-protonation and hydration processes at various pH values to a greater or lesser extent may determine the rate of the process: At

TABLE 3. Dependence of the Observed First-Order Rate Constants for the Reaction of the Enamino Ketones (E) with Hydrazine Hydrate on the Ring Size and the Amount of Added p-Toluenesulfonic Acid (TsOH) (50°C, absolute ethanol, hydrazine hydrate concn. 0.6 mole/liter)

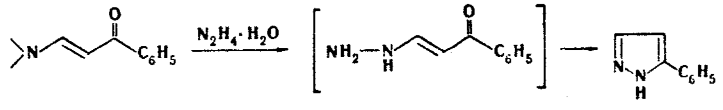
$\frac{[TsOH]}{[E]}$	IIa	IIb	IIc	IIIa
	$k \cdot 10^4$ sec^{-1}			
—	4,5; 4,8	12; 16	1,4; 1,8	11,2; 10,6
5	21	—	—	—

higher pH values the rate of hydrolysis depends to a greater extent on the rate of C-protonation, while at lower pH values it depends to a greater extent on the rate of hydration (compare with the data for other enamines [11] and enamino ketones [1]).

In an alkaline medium (see Table 1) the order of the decrease in the rate of hydrolysis in the series of investigated cyclic enamino ketones remains unchanged: Six-membered IIb is hydrolyzed at the highest rate, while seven-membered enamino ketone IIc is hydrolyzed at the lowest rate. Taking into account the above-stated considerations regarding steric hindrance in the case of attack on the "enamine" α position when a seven-membered ring is present, this order corresponds to the ideas that follow from the concept of I strain [8]. In fact, in this case the rate-determining step is evidently attack by the hydroxide anion, during which rehybridization of the α-carbon atom and the nitrogen atom of the enamino ketones ($sp^2 \rightarrow sp^3$) occurs. This change in the hybridization leads to steric interaction of the N-substituent and the ring α protons for the five- and seven-membered compounds (this interaction is not manifested for the six-membered compound in the "chain" conformation). The relatively high stability of the transition state for six-membered enamino ketone IIb and, correspondingly, the increase in the rate of its hydrolysis as compared with five- and seven-membered IIa,c follow from this.



The results of hydrolysis were compared with the data that we obtained during a study of the reaction of enamino ketones IIa-c and IIIa with hydrazine hydrate (Table 3). The fact that the rate of formation of pyrazole V depends distinctly on the size of the ring and that this dependence has the same order as hydrolysis (the reaction becomes slower in the order IIb > IIa > IIc) makes it possible to propose that the slow step in the process is attack by hydrazine on the α position of the enamino ketone. It is apparent from Table 3 that the rate of the reaction increases markedly when TsOH is added.



V

Thus the hydrolysis and hydrazinolysis have several principles in common; consequently, a study of the hydrolysis of enamino ketones is an important component and a good model for the study of other reactions of compounds of this type with nucleophilic reagents.

EXPERIMENTAL

The methods used to make the kinetic measurements and carry out the polarographic study were basically described in [1, 6]. The kinetics of the hydrolysis and hydrazinolysis processes were recorded from the decrease in the wave of the enamino ketone in the course of three to ten transformation half-periods. The reaction of the enamino ketones with hydrazine hydrate were carried out in a thermostatted cell with a minimal volume of the gas phase; a sample of the reaction mass was transferred to a buffer solution with pH 11, 12, or 13, and polarography was carried out at a standard temperature of 25°C. The reaction was close to first order in the enamino ketone in all cases. The first-order rate constant was calculated by the method of least squares from the equation

$$\ln(i-i_\infty)=\ln(i_0-i_\infty)-k\cdot t,$$

where i_0 and i are the limiting current of the enamino ketone, and i_∞ is the current of the base electrolyte. Special methods of treatment of the kinetic curves (Guggenheim and Mangelsdorf [12]) were also used.

3-Phenylpyrazole (V). A mixture of 3 g (17 mmole) of enamino ketone IIIa, 1.6 g (32 mmole) of hydrazine hydrate, and 30 ml of absolute ethanol was refluxed for 2 h (with polarographic monitoring). Workup gave 2.3 g (94%) of V with mp 77-78°C (mp 78 and 79°C [13]).

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