

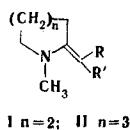
## LACTAM ACETALS

VIII.\* IONIZATION CONSTANTS OF SUBSTITUTED  
1-METHYL-2-METHYLENEPIPERIDINESV. G. Granik, I. V. Persianova,  
and Yu. N. Sheinker

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The dependence of  $\Delta pK_a$  (in nitromethane) and  $\Sigma \sigma_I$  of methylene-group-substituted 1-methyl-2-methylenepiperidines is expressed by the equation  $\Delta pK_a = -0.41 + 11.8 \Sigma \sigma_I$ . The basicities of tertiary enamines are more than five orders of magnitude greater than the basicities of the corresponding secondary enamines.

A number of enamines — substituted 1-methyl-2-methylenepiperidines (Ia-i) and -hexahydroazepines (IIa-i) — were previously synthesized by the reaction of N-methyl-2-piperidine diethyl acetals and N-methylcaprolactam [1-3] with compounds having active methylene (or methyl) groups.



A comparison of the basicities† of identically substituted representatives of both series (see Table 1) shows that the enamines of the piperidine series (I) are 0.5 to one order of magnitude more basic than the corresponding seven-membered analogs (II). These data are extremely similar to the results obtained in

\* See [1] for communication VII.

† The ionization constants were measured with an LPU-01 potentiometer (with nitromethane as the solvent) by the method in [4].

TABLE 1.  $\Delta pK_a$  ( $\text{CH}_3\text{NO}_2$ )\* Values of Substituted 2-Methylenepiperidines and -hexahydroazepines (I, II)

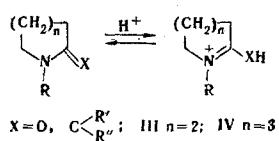
Compound index	R	R'	$\Delta pK_a$ ( $\text{CH}_3\text{NO}_2$ )	
			I	II
a	H	$\text{NO}_2$	6.85	7.91
b	CN	$\text{CONH}_2$	9.40	10.18
c	H	CN	6.48	6.90
d	H	$\text{COC}_6\text{H}_5$	3.02	4.02
e	H	$\text{COC}_6\text{H}_4\text{NO}_2-p$	4.76	5.06
f	H	$\text{COC}_6\text{H}_4\text{OCH}_3-p$	2.80	3.77
g	CN	$\text{C}_6\text{H}_5$	7.01	8.75
h	$\text{COOC}_2\text{H}_5$	$\text{COOC}_2\text{H}_5$	4.05	5.53
i	H	$\text{COC}_6\text{H}_4\text{NO}_2-m$	4.57	—
j	$\text{C}_6\text{H}_5$	$\text{COOCH}_3$	—	2.77
k	$\text{C}_6\text{H}_5$	$\text{COOC}_2\text{H}_5$	—	2.52
l	$\text{COCH}_3$	$\text{COCH}_3$	—	3.00

\*  $\Delta pK_a$  ( $\text{CH}_3\text{NO}_2$ ) = ( $pK_a$  of diphenylguanidine) — ( $pK_a$  of the enamine) [in nitromethane]. The error in the determination of  $\Delta pK_a$  does not exceed 0.1 pK unit.

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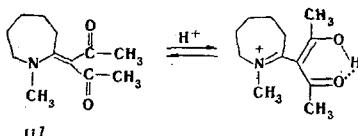
a measurement of the basicities of lactams: in this case also, 2-piperidone is  $\sim 0.4$   $pK_a$  unit more basic than caprolactam [5]. There is evidently a definite analogy between these two cases, inasmuch as protonation of both enamines [6] and lactams [5] proceeds at the exocyclic carbon and oxygen atoms, respectively.



The data available in the literature [5] make it possible to assume that the best conditions for amide conjugation are realized in 2-piperidone derivatives. Similar relationships apparently should also exist for the corresponding enamines.

The results obtained made it possible to study the character of transmission of the electronic effect of a substituent to the reaction center, which in this case is the  $\beta$ -carbon atom of the enamines.

It has been shown [6] that the  $\Delta pK_a$  values of enamines IIa-*l* cannot be satisfactorily correlated with the  $\sigma_I$  and  $\sigma_R$  constants. A more detailed examination of the results obtained showed that II*l* has an anomalously high basicity, which can be explained by substantial stabilization of the O-protonated form of V due to hydrogen bonding\*:



A comparison of the  $\Delta pK_a$  ( $\text{CH}_3\text{NO}_2$ ) values of enamines Ia-k with the  $\Sigma \sigma_I$  constants showed that the relationship between these values is expressed by the equation

$$\Delta p K_a = -0.91 + 14.1 \Sigma \sigma_L; \quad r = 0.958, \quad s = 0.79.$$

Correlation with respect to the equation  $\Delta pK_a = \Delta pK_a^0 + \rho_I \Sigma \sigma_I + \rho_R \Sigma \sigma_R$  gives the following parameters:  $\rho_I = 14.12$ ,  $\rho_R = 0.581$ ,  $\Delta pK_a^0 = -0.99$ ,  $r = 0.963$ , and  $s = 0.77$ . In order to ascertain the significance of the magnitude of  $\rho_R$ , we calculated the partial coefficient of correlation  $r_{xz}/y$ , where  $x = \sigma_I$ ,  $y = \sigma_R$ , and  $z = \Delta pK_a$ , the value of which (0.34) makes it possible to consider the  $\Delta pK_a$  and  $\sigma_R$  values to be mutually independent [8, 9]. It hence follows that  $\rho_R$  is statistically reliably indistinguishable from zero.

Similarly, for the  $\Delta pK_a$  ( $\text{CH}_3\text{NO}_2$ ) values of Ia-i and the  $\Sigma\sigma_I$  constants† the equation has the form

$$\Delta_B K_a \equiv -0.41 + 11.8 \Sigma \sigma_L; \; r = 0.986, \; s = 0.38.$$

Calculation of the multiple correlation gives in this case the equation  $\Delta pK_a = -0.799 + 12.58\Sigma\sigma_I - 0.27\Sigma\sigma_R$ , for which  $r_{xz/y} = -0.11$ ; this makes it possible to consider  $\Delta pK_a$  and  $\sigma_R$  to be mutually independent.

In examining these equations one's attention is drawn to the extremely large values of the standard deviations; this makes it impossible to consider the correlations obtained to be completely satisfactory.‡ Nevertheless, it can be asserted that the inductive effect makes the primary contribution to the interaction of the substituent with the reaction center.

In the measurement of the ionization constants of enamines one should bear in mind that the measured constant corresponds to the sum of the contributions of C- and N-protonation (equilibrium between A and B) \*\* although C-protonation, which is responsible for the high basicity of enamines as a conse-

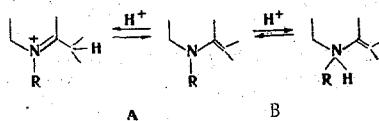
\* Acetylacetone in nonaqueous solvents is a tautomeric mixture with predominance of the enol [7]. Consequently it can be expected that in the case of enamine *III* the O-protonated form rather than the C-protonated form (as is usually the case) will be the more stable form thermodynamically.

† The constant for the  $m\text{-O}_2\text{NC}_6\text{H}_4\text{CO}$  group calculated by the method in [10] and the equations presented in [6] is 0.395. The  $\sigma_D$  constant (0.136) was obtained by this same method.

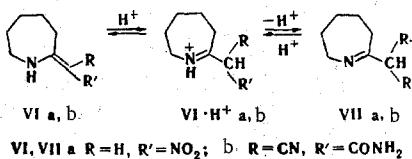
† However, one should point out the inaccuracy of the  $\sigma$  constants used for the analysis, a portion of which were obtained by computation [6, 10].

\*\* In the case of enamino ketones, one must also take into account the possibility of O-protonation.

quence of the formation in this case of the thermodynamically more stable cation [11, 12], is the predominant process.

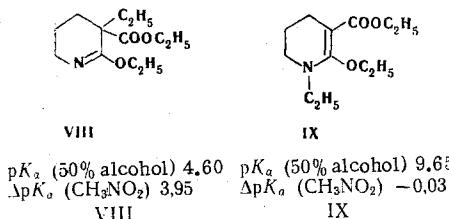


In this connection, it seems of interest to compare the results of measurements of  $\Delta pK_a$  ( $\text{CH}_3\text{NO}_2$ ) for tertiary (IIa, b) and secondary (VIa, b) [1, 13] enamines. It was found that the basicities of enamines VIa, b are lower by five orders of magnitude than the basicities of enamines IIa, b; of course, this cannot in any way be associated with the weak electron-donor effect of the methyl group. This strange, at first glance, phenomenon can be explained by an examination of the equilibria that occur during the protonation of the indicated enamines:



As seen from the schemes presented above,\* the primary difference between enamines IIa, b and VIa, b consists in the fact that substantially more stable immonium cations IVa, b are formed in the protonation of the former (deprotonation requires cleavage of the C-H bond). In the second case (VIa, b), the imine  $\rightleftharpoons$  immonium cation (VII  $\rightleftharpoons$  VI  $\cdot$  H<sup>+</sup>) equilibrium makes the primary contribution to the effective ionization constant. However, inasmuch as the ground states of II and VI in both cases are energetically extremely close, it is clear that the considerably greater stability of cation IV as compared with VI  $\cdot$  H<sup>+</sup> leads to substantially greater basicity of tertiary amines II as compared with secondary amines VI. The fact that primarily C-protonation takes place in the case of secondary enamines is confirmed by the PMR spectra of IVa in concentrated H<sub>2</sub>SO<sub>4</sub>.

The above interpretation is in good agreement with the fact that when the basicities of 3-ethyl-3-carbethoxy-O-ethylvalerolactim (imine) (VIII) and 1-ethyl-2-ethoxy-3-carbethoxy-1,4,5,6-tetrahydropyridine (enamine) (IX) were compared, the latter proved to be four to five orders of magnitude more basic [14, 15].



It is completely clear that the comparison of the ionization constants of secondary and tertiary enamines corresponds approximately to a comparison of tertiary enamines with imines (compare the equilibria  $\text{Ia},\text{b} \rightleftharpoons \text{IVa},\text{b}$  and  $\text{VIIa},\text{b} \rightleftharpoons \text{VI} \cdot \text{H}^{\text{+}}\text{a},\text{b}$ ).

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\* For simplicity in both cases, the equilibria associated with N-protonation were disregarded.

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