

LACTAM ACETALS.

XIV.* IONIZATION CONSTANTS OF

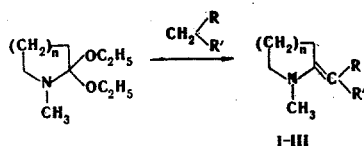
1-METHYL-2-METHYLENEPYRROLIDINES

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A number of 1-methyl-2-(2'-substituted methylene)pyrrolidines were synthesized, and their ionization constants in nitromethane were measured. The ΔpK_c values obtained were compared with the corresponding values for their six- and seven-membered analogs. The increased basicity of enamines with six-membered rings is apparently due to the strain that develops in the cations of the five- and seven-membered enamines during the formation of an endocyclic $C = N^+$ bond.

The aim of the present research was a comparison of the ionization constants of 1-methyl-2-(2'-substituted methylene)pyrrolidines (I), piperidines (II) [2], and hexahydroazepines (III) [2] and a discussion of the dependence of the basicities of the indicated enamines on the size of the saturated azaheterocycle. The synthesis of I was accomplished by reaction of N-methyl-2-pyrrolidone diethylacetal with compounds containing active methylene or methyl groups:



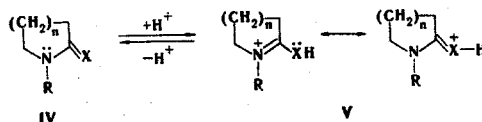
Ia-f n=1, IIa-f n=2; IIIa-f n=3; I-IIIa R=COC₆H₅, R'=H; b R=C₆H₄NO₂-p, R'=H; c R=NO₂, R'=H; d R=CN, R'=C₆H₅; e R=R'=COOC₂H₅; f R=R'=COOCH₃

As in the case of enamines II and III, a satisfactory correlation, expressed by the following equation, exists between the ΔpK_a values (in CH₃NO₂) of Ia-f and the summation of the σ_i constants:

$$\Delta pK_a = 1.57 + 11.29 \sum \sigma_i; r = 0.989, S = 0.26,$$

and special calculations showed that the ρ_R value in the equation $\Delta pK_a = \Delta pK_a^0 + \rho_i \sigma_i + \rho_R \sigma_R$ is statistically reliably indistinguishable from zero also for enamines of the pyrrolidine series (I) [2].

The ΔpK_a values of Ia-f and their six- (IIa-f) and seven-membered (IIIa-f) analogs are presented in Table 1. The fact that enamines IIa-f are the strongest bases in the series under consideration is in general agreement with the data on the change in the basic properties in lactams [3] (IV, X = O) and amidines [1] (IV, X = NR) as a function of the ring size.



n=1-3, X=O, NR'

*See [1] for communication XIII.

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TABLE 1. Ionization Constants (in CH_3NO_2) of 1-Methyl-2-(2'-substituted methylene)Pyrrolidines, Piperidines, and Hexahydroazepines (I-III)

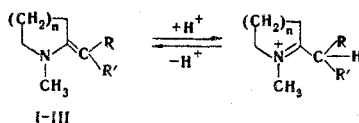
No.	R	R'	$\Sigma\sigma_i^*$	$\Delta pK_a (\text{CH}_3\text{NO}_2) \dagger$		
				n=1	n=2	n=3
1	$\text{C}_6\text{H}_5\text{CO}$	H	0,285	4,68	3,02	4,02
2	$p\text{-NO}_2\text{C}_6\text{H}_5\text{CO}$	H	0,404	6,40	4,76	5,06
3	NO_2	H	0,60	8,65	6,85	7,91
4	CN	C_6H_5	0,66	8,75	7,01	8,75
5	COOC_2H_5	COOC_2H_5	0,42	6,15	4,05	5,63
6	COOCH_3	COOCH_3	0,42	6,28	—	—

$$* \Sigma\sigma_i = \sigma_i\text{R} + \sigma_i\text{R}'.$$

$\dagger pK_a (\text{CH}_3\text{NO}_2) = pK_a$ of diphenylguanidine - pK of the enamine (in nitromethane).

This was explained for lactams by the high degree of conjugation of the unshared pair of electrons of the nitrogen atom with the exocyclic carbonyl group, which has a stronger effect in the charged protonated form (V) than in the ground state [3]. This also leads to higher basicities of the six-membered lactams and amidines as compared with their five- and seven-membered analogs.

The PMR-spectral data show that the protonation of enamines I, like the protonation of enamines II-III, proceeds at the exocyclic β -carbon atom; the definite similarity in the compounds under consideration (lactams, amidines, and enamines) consists in this. However, the difference consists in the fact that the exocyclic grouping in the protonated form of enamines is not conjugated with the $\text{C} = \text{N}^+$ bond.



If it is assumed that the increased stabilization of the cation due to conjugation is the only factor that insures the higher basicity of six-membered lactams and amidines, the reverse order of decreasing basicity, i.e., $5 > 7 > 6$, should be observed for enamines, inasmuch as stabilization of the ground state by conjugation will be highest for the six-membered ring (conjugation is absent in the protonated form). However, the order of decreasing basicity in the series of enamines is the same as in the series of lactams and amidines: $6 > 7 > 5$ (see Table 1). Consequently, there are additional factors responsible for the increased basicities of six-membered compounds, during the protonation of which an endocyclic $\text{C} = \text{N}^+$ bond develops. It has been demonstrated [4] that the free energy of activation of cis-trans isomerization about the enamine $\text{C} = \text{C}$ bond is appreciably lower for six-membered enamines than for the corresponding five- and seven-membered analogs. Considering that the principal factor that determines the rate of isomerization is the energy of the transition state rather than that of the ground state [4, 5], it might have been concluded that the presence of an endocyclic double bond in the transition state is more favorable for six-membered rings than for seven- and five-membered rings. This is in agreement with the data for cyclic olefins with rings of different sizes [6].

The differences in the basicities of enamines discussed in the present paper are also in agreement with this assumption. It might be assumed that the chief factor that insures the high basicity of piperidine derivatives is not stabilization of the cations due to conjugation but rather the strain that develops in five- and seven-membered rings during the development of an endocyclic $\text{C} = \text{N}^+$ bond. Destabilization of the cations due to this strain also leads to a decrease in the basicities of five- and seven-membered compounds as compared with the basicities of six-membered compounds.

In those cases in which the formation of a cation is not associated with the development of an endocyclic $\text{C} = \text{N}^+$ bond, differences in the basicities as a function of the ring size are practically absent (the pK_a values of pyrrolidine and piperidine [7] are 11.27 and 11.22, respectively).

EXPERIMENTAL METHOD

The ionization constants in nitromethane were measured with an LPU-01 potentiometer [8]. Enamines Id-f have been previously described [4]. Compounds Ia-c were obtained by the method in [9]: Ia, with bp 185° (3 mm), was obtained on 60% yield. Found: C 77.5; H 7.6; N 7.1%. $\text{C}_{13}\text{H}_{15}\text{NO}$. Calculated: C 77.6;

H 7.5; N 7.0% compound Ib, with mp 150-151° (from alcohol), was obtained in 76% yield. Found: C 63.0; H 5.5; N 11.0%. $C_{13}H_{14}N_2O_2$. Calculated: C 63.4; H 5.7; N 11.4%. Compound Ic, with mp 158-158.5 (water) was obtained in 62% yield. Found: 51.0; H 7.2; N 20.0%. $C_8H_{10}N_2O_2$. Calculated: C 50.7; H 7.0; N 19.7%.

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