LACTAM ACETALS

XIII.* IONIZATION CONSTANTS AND SPECTRAL PROPERTIES OF N-METHYL-2-ARYLIMINOLACTAMS

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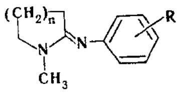
UDC 547.749 : 543.422.25.4.6 : 541.132

The UV, IR, and PMR spectra of N-methyl-2-aryliminolactams and their salts were examined. The ionization constants of the investigated amidines in aqueous alcohol depend substantially on the ring size (the basicities fall in the order 6 > 7 > 5). On the basis of the correlation dependences of the pK_a values of the amidines and the Hammett σ constants it is shown that the π electrons of the benzene ring are conjugated both with the C=N bond and with the p electrons of the exocyclic nitrogen atom. The angles of rotation of the benzene ring with respect to the C=N bond were calculated.

The aim of the present research was to study the physicochemical properties of 1-methyl-2-aryliminopyrrolidines (Ia-e), piperidines (IIa-e), and hexahydroazepines (IIIa-i) (Table 1), which were synthesized by reaction of lactam acetals [2] with aromatic amines.



I-III

I—III $n=1—3$; a $R=p\text{-}OCH_3$; b $R=p\text{-}CH_3$; c $R=H$; d $R=p\text{-}Cl$; e $R=n\text{-}NO_2$; f $R=$ $=p\text{-}COOC_2H_5$; g $R=p\text{-}COCH_3$; h $R=m\text{-}NO_2$; i $R=m\text{-}F$; j $R=p\text{-}SO_2NH_2$

The character of the UV spectra of amidines I-III depends substantially both on the type of substituent in the benzene ring and on the size of the saturated nitrogen heteroring (Figs. 1 and 2). Moreover, the spectra of II and III are similar to one another and differ substantially from the spectra of amidines I of the pyrrolidine series (these differences become smaller when electron-acceptor substituents are present). Similarly, the absorption bands of the C=N bonds in the IR spectra of amidines II and III lie at 1600-1612 cm^{-1}, while for the analogous I compounds these bands are shifted appreciably to the high-frequency region (1630-1640 cm^{-1}). Differences in the IR and UV spectra of five-membered rings of this sort are also characteristic for the corresponding lactams [3] and are probably due to partial weakening of the "amidine" (or amide) conjugation in the pyrrolidone derivatives. A certain shift of the absorption maximum to the shortwave region on passing from dioxane to protogenic solvents is observed in the UV spectra of amidines I-III (see Fig. 3), while the spectra in aqueous solutions, for example, for Ia, IIa, and IIIa, practically coincide completely with the spectra of these compounds in 0.1 N HCl. The indicated changes in the spectra are apparently associated with ionization of the compounds. In fact, according to the pK_a data (see below) and the pH values of the solutions, these amidines are practically completely ionized in 50% alcohol (the degree of ionization is 98-99%).

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* See [1] for communication XII.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1220-1225, September, 1974. Original article submitted February 7, 1974.

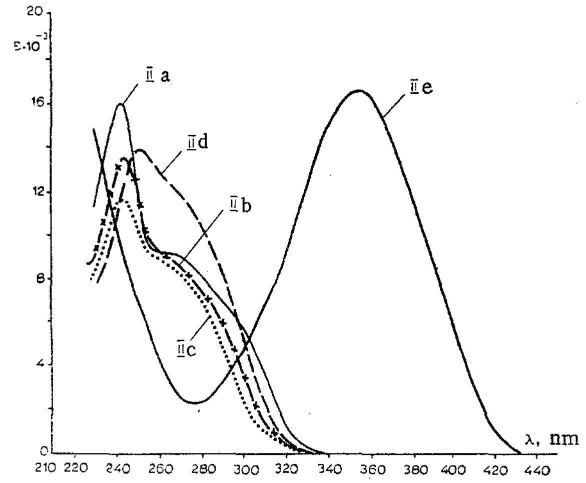


Fig. 1. UV spectra of N-methyl-2-aryliminopiperidines (IIa-e) in dioxane.

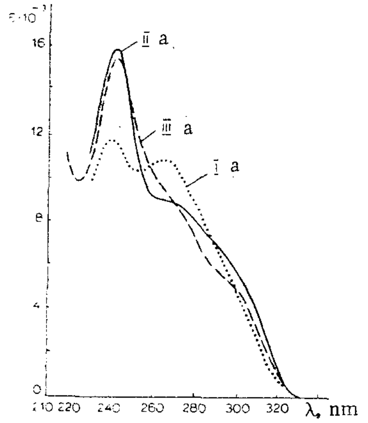


Fig. 2

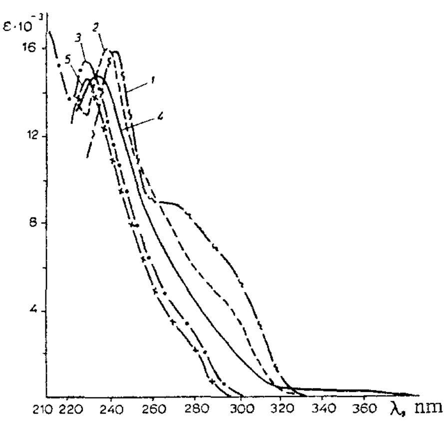
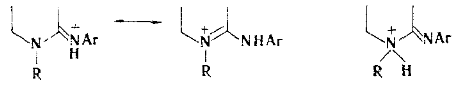


Fig. 3

Fig. 2. UV spectra of N-methyl-2-(4-methoxyphenyl)pyrrolidine (Ia), -piperidine (IIa), and -hexahydroazepine (IIIa) in dioxane.

Fig. 3. UV spectra of IIa in various solvents: 1) dioxane; 2) 0.1 N NaOH; 3) 0.1 N HCl; 4) alcohol; 5) 90% alcohol.

It is known [4-6] that amidines are protonated at the imine nitrogen atom to give a cation (A) that is stabilized by resonance (in contrast to thermodynamically less stable cation B).



A B

Comparison of the IR and PMR spectra of amidines I-III and their salts indicates that in our case a proton also adds to the exocyclic nitrogen atom. Thus, in agreement with the results obtained in [4], a shift of the absorption of the C=N group of 25-40 cm^{-1} (which is characteristic for the development of a $C=\overset{+}{N}$ group) is observed in the IR spectra on passing from amidines Id, IId, and IIId to their hydrochlorides. As one should have expected, a weak-field shift of the signals of all of the protons is observed in the PMR spectra of the salts of these amidines as compared with the free bases. If it is assumed that structure B with a localized positive charge on the cyclic nitrogen atom is realized during protonation, the weak-field shift of the signals of the protons of the $N-CH_3$ and $N-CH_2$ groups should be considerably greater than the shift of the signals of the ortho protons of the substituted amidine ring. In fact (see Table 2), the $\Delta\delta$ values of the signals of these groups are close to one another, and in the case of amidines II and III the weak-field shift of the signals of the ortho protons of the benzene ring even exceeds the analogous shifts of the signals

TABLE 1. N-Methyl-2-aryliminolactams

Compound	Temp., °C	Reac. time, h	mp (crystallization solvent) or bp (mm)	n_D^{20}	Empirical formula	Found, % C	Found, % H	Found, % N	Calc., % C	Calc., % H	Calc., % N	Yield, %
Ib	60	1	120—121 (3)	1,5794	$C_{12}H_{16}N_2$	76,6	8,5		76,6	8,5		60
Ic	20	4	117—118 (4)	1,5850	$C_{11}H_{14}N_2$	75,9	8,2		75,8	8,1		40
Id	60	1	140—141 (3)	1,5991	$C_{11}H_{13}N_2Cl$	63,4	6,2		63,3	6,2		45
Ie	60	1,5	70—71 (hexane)		$C_{11}H_{13}N_3O_2$	60,4	6,0	19,2	60,3	5,9	19,2	82
IIb	50	1,5	134—135 (5)	1,5758	$C_{13}H_{18}N_2$	77,3	9,0		77,2	8,9		75
IIc	50	1,5	144—145 (5)	1,5875	$C_{13}H_{16}N_2$	76,6	8,6		76,6	8,5		82
IId	40	2	153—154 (4)	1,5966	$C_{12}H_{15}N_2Cl$	64,8	6,8		64,7	6,7		80
IIe	60	1	72—73 (hexane)		$C_{12}H_{15}N_3O_2$	61,8	6,5		61,8	6.4		87
IIIe	20	1	107—109 (heptane)		$C_{13}H_{17}N_3O_2$	63,2	6,8	16.8	63,2	6,8	17,0	100
IIIf	60	3	198—200 (3)		$C_{16}H_{22}N_2O_2$	70,1	8,2	10,3	70,1	8,0	10,2	91
IIIg	60	3	190—192 (3) 101—102 (petroleum ether)		$C_{15}H_{20}N_2O$	73,3	8,5	11,3	73,8	8,2	11.5	86
IIIh	35	5	194—195 (1)		$C_{13}H_{17}N_3O_2$	63,2	7,0	16,8	63,2	6,9	17,0	86
IIIi*	20	3	177,0—177,5 (acetone)		$C_{13}H_{17}N_2F\cdot HCl$	60.9	7,1	11,2	60,8	7,0	10.9	76
IIIj†	20	2	239—240 (alcohol)		$C_{13}H_{19}N_3O_2$	55,4	6,8	15,2	55,5	6,8	15,0	54

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* These data are for the hydrochloride. Found, %: 7.5. Calculated, %: F 7.4.

† Found, %: S 11.2. Calculated, %: S 11.4.

TABLE 2. Data from the PMR Spectra of Amidines Id, IId, and IIId and Their Hydrochlorides

Compound	δ_0 for aryl ring protons, ppm	$\Delta\delta$, ppm	δ_{CH_2-N}, ppm	$\Delta\delta$, ppm	δ_{CH_3-N}, ppm	$\Delta\delta$, ppm	δ_3 CH_2, ppm	$\Delta\delta$, ppm
Id	6,75	0,57	3,35	0,47	2,93	0,6	2,35	0,58
Id·HCl	7,32		3.82		3,53		2.93	
IId	6,63	0,7	3,22	0,33	2,97	0,63	2,2	0,27
IId·HCl	7,33		3,55		3.6		2,47	
IIId	6,60	0,72	3,35	0,38	3,07	0,56	2,38	0,34
IIId·HCl	7,32		3,73		3,63		2,72	

TABLE 3. pK_a Values (50% Ethanol) for 1-Methyl-2-aryliminopyrrolidines (I), -piperidines (II), and -hexahydroazepines (III)

R	$n=3$	$n=2$	$n=1$
H	8,91	9,28	8,73
p-CH_3	9,44	9,61	9,13
p-OCH_3	9,61	9,86	9,23
p-Cl	8,12	8,69	8,12
p-NO_2	6,31	6,96	6,41
m-NO_2	6,90		
m-F	7,89		
p-COOEt	7,44		
p-$COCH_3$	7,21		

of the protons of the N$-$CH$_3$ and N$-$CH$_2$ groups; this is in agreement with the type A representation of the structure of the cation.

The electronic interaction of substituents with the protonation center was investigated by a study of the correlation dependence of the ionization constants of the investigated amidines (Table 3) with Hammett σ constants. The correlation of the pK_a values of IIIa-d, h, i, which do not have substituents that are capable of direct polar conjugation, with the σ constants is expressed by the equation

$$pK_a = 8.88 - 286\sigma \ (\gamma 0.998,\ S_0\ 0.076). \qquad (1)$$

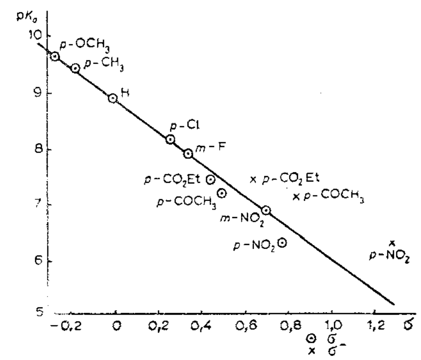


Fig. 4. Dependence of the pK_a values of N-methyl-2-aryliminohexahydroazepines (IIIa-i) on the σ constants.

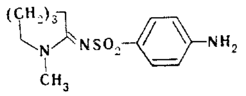
As seen from Fig. 4, points corresponding to amidines IIIe-g do not fit the line of this dependence, and the basicities of these amidines are lower than the values calculated from Eq. (1). This indicates the existence of a contribution of direct polar conjugation to the interaction between the electron-acceptor substituents (p-NO_2, p-$COCH_3$, and p-$COOC_2H_5$) and the p electrons of the exocyclic nitrogen, which is the reaction center. On the other hand, when σ^- constants are used for the indicated substituents, the corresponding points proved to lie above the line corresponding to Eq. (1) (Fig. 4), i.e., the effect of direct polar conjugation is realized only partially. Consequently, the phenyl ring in the investigated amidines does not lie in the plane of the C=N bond but rather is turned at a certain angle in such a manner that its π electrons are simultaneously in conjugation with both the π electrons of the C=N bond and the p electrons of the nitrogen atom. Similar rotation of the benzene ring was previously observed in an investigation of azomethines (for example, see [7, 8]). It also follows from construction of molecular models (Dreiding and Stuart–Briegleb) that the presence of a benzene ring in the place of the C=N bond leads to pronounced steric interactions, and transoid orientation of the aryl ring with respect to the $N-CH_3$ group is most probable. The data obtained from the correlation make it possible to calculate σ_{eff} for the p-NO_2, p-$COOC_2H_5$, and p-$COCH_3$ groups, and the equation [9]

$$\mathrm{Cos}^2\,\theta = \frac{\sigma_{eff} - \sigma}{\sigma^- - \sigma}$$

was used to calculate the angles of rotation of the phenyl ring, which proved to be 60, 61, and 63°, respectively. Inasmuch as this angle is practically independent of the electron-acceptor strength of the substituents, it might be assumed that this sort of rotation of the aryl ring is also characteristic for other amidines of the hexahydroazepine series.

A similar calculation for the pyrrolidine and piperidine amidines (disregarding the points for p-nitro derivatives Ie and IIe) leads to the equation $pK_a = 8.68 - 2.3\sigma$ (r 0.99, S_0 0.077) and $pK_a = 9.24 - 2.3\sigma$ (r 0.99, S_0 0.037), respectively. The angles of rotation (θ), which proved to be 49° for Ie and 50° for IIe, were calculated from these equations and formula (2).

It should be noted that an attempt to obtain amidine IIIj, which contains a sulfamido group in the para position, was unsuccessful. Just as in the reaction of lactim ethers with sulfanilamide [10], the reaction in this case took place at the sulfamido group to give an acylamidine (IV):



IV

Evidence in favor of the sulfanilamide structure of IV is its markedly depressed basicity as compared with the basicities of amidines III (for IV, $pK_a < 2$). The above direction of the reaction is understandable if one takes into account the fact that the 1-methyl-2-alkoxy-7H,3,4,5,6-hexahydroazepinium cation and the alkoxide anion [11], which strips a proton from the sulfanilamide group, are in equilibrium with the acetals in solution. The reaction then proceeds at the anionic SO_2NH^- center.

As seen from Table 3, the basicities of the investigated amidines depend on the ring size. Piperidine derivatives II have the highest pK_a values; this is due to the high stabilization of cation A in six-membered amidines, as was previously shown [3] in a comparison of the basicities of butyro-, valero-, and caprolactams.

EXPERIMENTAL

The IR spectra of mineral-oil suspensions and $CHCl_3$ solutions of the compounds were recorded with a Perkin-Elmer 457 spectrometer. The UV spectra of solutions of the compounds in dioxane, 95% hexane–5% dioxane, alcohol, aqueous alcohol mixtures, and aqueous and alcoholic 0.1 N HCl and 0.1 N NaOH were recorded with an EPS-3 spectrophotometer. The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The basicity constants were calculated from the curves of potentiometric titration of 0.001 M solutions of the substances in 50% (by volume) ethanol [12]. The pH values were measured with a PHM-26 pH-meter with glass (G 222B) and calomel electrodes (Radiometer, Denmark). A total of two to three titrations were made for each compound, and eight to nine constants were examined in the region of 15-85% neutralization. The standard error in the determination of the basicity constants did not exceed 0.05 pK_a units.

1-Methyl-2-(p-toluidylimino)pyrrolidone (Ib). A 4.5-g (26 mmole) sample of N-methylpyrrolidone diethylacetal was added to 2.7 g (26 mmole) of p-toluidine in 20 ml of dry chloroform, and the mixture was stirred at 60° for 1 h. The solvent was then evaporated, and the residue was distilled. The yield of amidine Ib with bp 120-121° (3 mm) was 2.9 g (60%). Compounds Ib-e, IIb-e, and IIIe-i (see Table 1) were similarly synthesized from the appropriate acetals. Compounds Ia, IIa, and IIIa-d were previously described.

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