LACTAM AND ACID AMIDE ACETALS

57.* SYNTHESIS, PROTONATION, AND ACID-BASE PROPERTIES OF CONDENSED DERIVATIVES OF 4-OXO-1,4-DIHYDRO-1,8-NAPHTHYRIDINE

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UDC 547.836'834'75:541.132:543.422

A number of 4-oxo-1,4-dihydro-1,8-naphthyridine derivatives that differ with respect to the sizes of the aza- and carbocycles were synthesized by the reaction of 3-amino-4-ethoxycarbonyl-5,6-dihydro-7H-pyrindine and 3-amino-4-ethoxycarbonyl-5,6,7,8-tetrahydroisoquinoline with N,N-dimethylacetamide diethylacetal and N-methylbutyrolactam, N-methylvalerolactam, and N-methylcaprolactam diethylacetals and subsequent cyclization of the intermediate amidines. It was established by UV and ^1H and ^{13}C NMR spectroscopy that the protonation of these compounds takes place at the exocyclic oxygen atom. The dependence of the ionization constants of the compounds obtained in 70% DMFA on the size of the saturated cyclic fragments of the molecules was established.

It is known [2] that aromatic and heterocyclic compounds that have amino and ethoxycarbonyl groups in adjacent positions react readily with N,N-dimethylacetamide diethylacetal (I) and N-methylbutyrolactam diethylacetal (IIa), N-methylvalerolactam diethylacetal (IIb), and N-methylcaprolactam diethylacetal (IIc) to give the corresponding amidines which, upon heating under acid- or base-catalysis conditions, undergo cyclization to condensed compounds that contain a 2-(substituted amino)-4-oxo-pyridine ring as a fragment. In the present research as starting compounds for the synthesis of heterotricyclic and heterotetracyclic systems of this type we used the previously synthesized 3-amino-4-cyano-5,6-dihydro-7H-pyrindine (IIIa) and 3-amino-4-cyano-5,6,7,8-tetrahydroisoquinoline (IIIb). Concentrated HBr has been previously used [3] for saponification of the cyano group in IIIa, b. However, this method is preparatively inconvenient, since it requires prolonged heating and does not ensure sufficiently high yields of the corresponding amino acids (IVa was obtained in 56% yield, and IVb was obtained in 30% yield). It is more convenient to use the method that we developed [4] for the hydrolysis of the cyano group in sulfuric acid. As in the case of 2-oxo-3-cyano derivatives [4], the yields of the hydrolysis products depended on the sulfuric acid concentration; the optimal sulfuric acid concentration proved to be 60% H_2SO_4 – in this case the yield of 3-amino-4-carboxy-5,6-dihydro-7H-pyrindine (IVa) was 93%, while the yield of 3-amino-4-carboxy-5,6,7,8-tetrahydroisoquinoline (IVb) was 59% (amide V was also isolated in 7% yield). Refluxing in ethanol in the presence of a large excess of concentrated H_2SO_4 (10–13 moles per mole of the amino acid) is optimal for the esterification of acids IVa, b. The reaction of the resulting esters VIa, b with acetal I was carried out by refluxing in toluene, and the course of the process was followed from the disappearance of the signals of the NH_2 group in the IR spectra. Under these conditions we could not expose differences in the reactivities of VIa, b – condensation with the formation of the corresponding amidines proceeds smoothly and in a short time (15–20 min). The ease of cyclization of amidines VIIa, b (without isolation of them in pure form) in butanol in the presence of sodium butoxide, as a result of which tricyclic naphthyridines VIIIa, b are formed, depends on the size of the condensed carbocycle – the increase in the intensity of the longwave absorption maximum (at 334 nm), which corresponds to the naphthyridine system, in the UV spectra for isoquinoline derivative VIIb during its conversion to tricycle VIIIb takes place ~1.5 times faster than for the process VIIa → VIIIa.

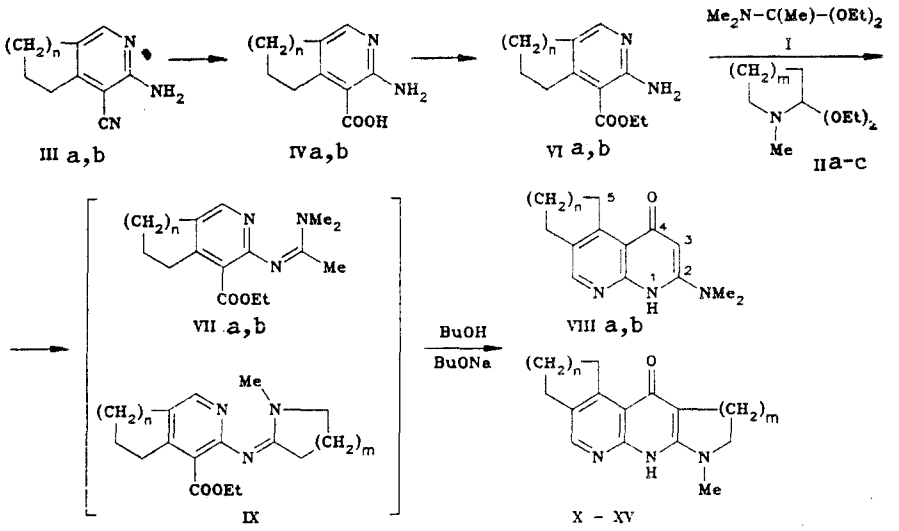
*See [1] for Communication 56.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 643–651, May, 1990. Original article submitted August 10, 1988.

0009-3122/90/2605-0544$12.50

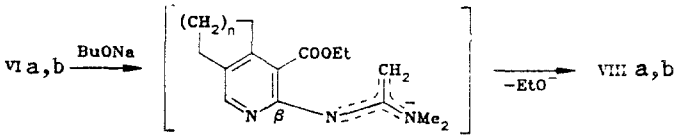
TABLE 1. Physical Constants, Yields, and Ionization Constants of the Synthesized Compounds

Compound	Empirical formula	T_{mp}, °C	Crystallization solvent	pK_a		Yield, %
				addition of a proton	splitting out of a proton	
IVa		>300	AcOH—H_2O, 3:2			94
IVb		>300	AcOH—H_2O, 3:2			59
V	$C_{10}H_{13}N_3O$	219...220	Ethanol—water (1:1)			7
VIa		158...160				85
VIb	$C_{12}H_{16}N_2O_2$	82...84	Hexane			54
VIIIa	$C_{13}H_{15}N_3O \cdot HCl \cdot H_2O$	280	2-Propanol	5,87±0,05	11,83±0,03	65
VIIIb	$C_{14}H_{17}N_3O$	256...258	DMF	5,86±0,03	11,87±0,05	73
X	$C_{14}H_{15}N_3O \cdot HCl \cdot 1{,}5H_2O$	>300	2-Propanol	6,57±0,07	11,34±0,07	78
XI	$C_{15}H_{17}N_3O \cdot HCl \cdot H_2O$	246	2-Propanol	5,77±0,06	11,95±0.05	70
XII	$C_{16}H_{19}N_3O$	203...205	Ethyl acetate	5,33±0,06	12,34±0,07	64
XIII	$C_{15}H_{17}N_3O \cdot HCl \cdot 0{,}5H_2O$	>300	2-Propanol	6,30±0,05	11,57±0,06	61
XIV	$C_{16}H_{19}N_3O \cdot HCl \cdot 2H_2O$	236...238	2-Propanol	5,35±0,07	11,92±0,06	63
XV	$C_{17}H_{21}N_3O \cdot HCl$	213...215	2-Propanol	4,94±0,04	11,89±0,07	69
XVI	$C_{13}H_{14}N_3Cl$	190...192	Ethyl acetate			53
XVII	$C_{15}H_{19}N_3O$	172...174	2-Propanol—H_2O (1:4)	6,51±0,07		97



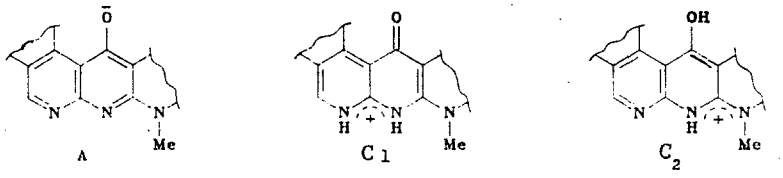
IIa $m=1$, b $m=2$, c $m=3$; III, IV, VI, VIIa $n=1$, b $n=2$; X—XII $n=1$, XIII—XV $n=2$; X—XV $m=1 \ldots 3$

Although the interpretation of these data is difficult and requires a special quantitative investigation, it has been previously shown [5] that 3-amino-5,6-dihydro-7H-pyrindine derivatives have higher basicities than the corresponding 3-amino-5,6,7,8-tetrahydroisoquinoline derivatives; this was explained on the basis of the Finnegan–Streitweiser concept proceeding from the assumption of higher electron density on the atoms of the aromatic ring that are located in the β position relative to the strained, annelated, five-membered ring. Measurement of the ionization constants of amino esters VIa, b in 50% ethanol showed that this principle is retained and that the pK_a of VIa is 5.32 ± 0.07, as compared with 4.88 ± 0.06 for VIb. It is possible that an increase in the electron density in the 3 position of the pyrindine derivative hinders splitting out of a proton from the C–CH_3 group in VIIa and thereby slows down the cyclization of pyrindine derivative VIIa as compared with hydrogenated isoquinoline VIIb.



The reaction of derivatives VIa, b with lactam acetals IIa–c and subsequent cyclization of intermediate amidines IX under the conditions described above lead smoothly to tetracyclic naphthyridine derivatives X–XV in satisfactory yields.

We have previously investigated the acid-base properties of 4-quinolone derivatives and a number of their aza analogs that are condensed with pyrolidine, piperidine, and hexahydroazepine rings [5, 6]. In developing these investigations in the present research, we studied the effect of the size of the condensed saturated rings on the acid-base properties of the newly synthesized tri- and tetracyclic 1,4-dihydro-4-oxonaphthyridine derivatives VIIIa, b and X–XV. For this, we measured the ionization constants of these compounds in 70% DMF (Table 1). Since all of the compounds contain one anionic center, the pK_a values found for the acidic ionization pertain to splitting out of a proton from the nitrogen atom of the pyridone fragment to give an anion of the A type. The protonation of VIIIa, b and X–XV can take place at the pyridine nitrogen atom or at the exocyclic oxygen atom (cations C_1 and C_2, respectively).



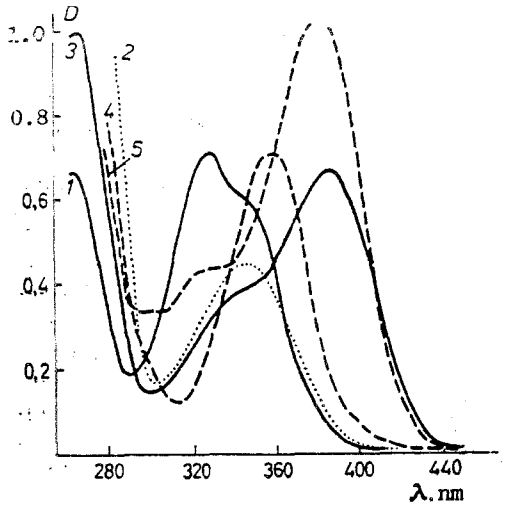
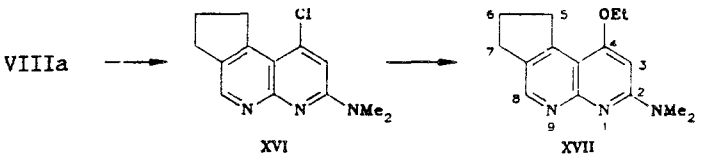


Fig. 1. UV spectra of XII and XVII in 70% aqueous DMF: 1) neutral molecule (pH 8.4); 2) anion (pH 13.9); 3) cation (pH 3.17) of XII; 4) neutral molecule (pH 8.2); 5) cation (pH 3.8) of XVII.

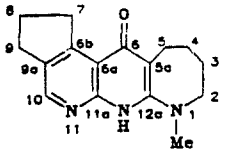
The closeness of the range of changes in the ionization constants corresponding to the addition of a proton (pK_a 4.9–6.6, Table 1) to the range of pK_a values in the corresponding 4-quinoline derivatives (5.0–5.6), as well as the complete analogy in the change in the IR spectra of the crystals on passing from the bases to the corresponding hydrochlorides, made it possible to assume that the protonation of all of the investigated compounds takes place at the same center, viz., the carbonyl oxygen atom. The significant deshielding of the 3-H proton vis-a-vis the small change in the chemical shift of the proton in the 8(9) position that is observed in the PMR spectra of VIIIa,b upon protonation constitutes evidence in favor of the cation C_2 structure. For VIIIa (in d_6-DMSO and CF_3COOH, respectively) 5.36 and 6.60 ppm (3-H), 8.32 and 8.48 ppm (8-H); for VIIIb: 5.25 and 6.59 ppm (3-H), 8.15 and 8.48 ppm (9-H). To prove the structure of cation C_2 we also studied the UV spectra and the ^{13}C NMR spectra of the neutral and charged forms of XII.

Two $\pi \rightarrow \pi^*$ transitions can be isolated in the UV spectrum of the neutral XII molecule (see Fig. 1) >260 nm. A low-energy transition (λ_{max} ~ 345 nm) is observed in the form of a shoulder on the longwave wing of the more-intense band with an absorption maximum at 333.5 nm (ε 13,480). Splitting out of a proton is accompanied by a bathochromic shift ($\Delta\lambda$ = 12.5 nm) and a decrease in the absorption intensity (ε 9134). Similar changes in the spectrum are observed in the deprotonation of 4-pyridone [7]. For a more accurate interpretation of the UV spectral data we used the reaction of tricycle VIIIa with phosphorus oxychloride to synthesize chloro derivative XVI, from which we obtained ethoxy derivative XVII, which is a model compound for a study of the protonation and deprotonation of the tri- and tetracyclic systems under investigation.

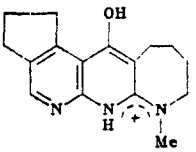


An appreciable similarity is observed when one compares the spectra of anion XII^- and model compound XVII; this is in good agreement with structure A, which corresponds to localization of the negative charge primarily on the oxygen atom. It is known that the spectra of neutral 4-pyridone and 4-methoxypyridine molecules differ considerably, while the spectra of their cations are essentially similar [7]. Similar results were obtained in a comparison of the spectra of the neutral molecules and cations of the investigated and model compounds XII and XVII. Protonation of XVII should take place at the $N_{(1)}$ atom with the formation of a cation of the amidinium type. This is in agreement with the ionization constant of XVII (pK_a 6.51), which under identical conditions exceeds by 0.61 of a pK_a unit the ionization constant of the corresponding oxo analog VIIIa, which adds a proton at the other center. In addition to this, the chemical shifts of the 3-H and 8-H protons in the PMR spectrum of cation $XVII^+$ in CF_3COOH (6.37 and 8.44 ppm) are close to the corresponding values in the spectra of cations $VIIIa^+$ and $VIIIb^+$.

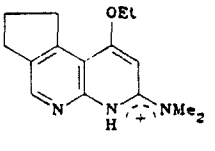
On passing from the neutral XVII molecule to the amidinium structure of the $XVII^+$ cation the low-energy transition in the UV spectrum is shifted 27 nm to the longwave region (see Fig. 1). The large bathochromic shift of the longwave band ($\Delta\lambda$ = ~43 nm) corresponds to transition from the pyridone structure of the neutral XII molecule to the amidinium structure of the cation of the C_2 type; the spectra of the two cations (XII^+ and $XVII^+$) are similar both with respect to the positions and the relative intensities of the observed absorption bands. These data correspond completely to protonation of the investigated compounds at the carbonyl oxygen atom.



XII



XII$^+$



XVII$^+$

An independent confirmation of this conclusion was obtained in a study of the ^{13}C NMR spectra of base XII measured in neutral (d_6-DMSO) and acidic (DCOOD) media. In the case of complete suppression of the spin-spin coupling (SSC) with the protons 16 signals are observed in the spectra. The weak-field (177.6 ppm) signal of the carbonyl $C_{(6)}$ atom (t, $^3J_{65}$ ~3 Hz), a doublet of $C_{(10)}$ singlets (146.7 ppm, $^1J_{CH}$ = 176.5 Hz), and a $C_{(11a)}$ doublet with $^3J_{11a10}$ = 12 Hz (in pyridine the corresponding constant $^3J_{2,6}$ = 11.2 Hz [8], in isoquinoline $^3J_{13}$ = 10.5 Hz, $^3J_{31}$ = 12.5 Hz [9]) are readily identified in the ^{13}C monoresonance spectrum of the neutral molecule in the aromatic region. On the basis of a comparison with the spectral parameters of 4-pyridones [10] and 1,8-naphthyridines [11, 12] the singlet (splitting <1 Hz) at 115.3 ppm and a triplet at 107.7 ppm ($^2J_{5a5}$ = 6 Hz) were assigned to the $C_{(6a)}$ and $C_{(5a)}$ atoms, respectively. The signals at 155.6, 154.9, and 135.7 ppm, which have a more complex fine structure, belong to the $C_{(12a)}$, $C_{(6b)}$, and $C_{(9a)}$ atoms. Signals of the N-methyl group (qt, 39.6 ppm, $^1J_{CH}$ = 136 Hz, $^3J_{CH_3,2\text{-}H}$ = 3.5 Hz) and the $C_{(2)}$ atom in the α position relative to this group (tm, 52.7 ppm, $^1J_{CH}$ = 135.5 Hz) can be unequivocally assigned in the region characteristic for sp^3 carbon atoms. The preliminary assignment of the signals of the remaining carbon atoms of the saturated fragments was made on the basis of the character of the multiplicity of the components of the triplets and the direct ^{13}C–^1H constants. The triplets at 36.4, 29.7, and 25.8 ppm with constants $^1J_{CH}$ = 131–133 Hz were assigned to the carbon atoms in the 5, 7, and 9 positions. The strong-field $C_{(3)}$, $C_{(4)}$, and $C_{(8)}$ triplets (26.3, 24.9, and 23.0 ppm) are characterized by smaller $^1J_{CH}$ constants (125–127 Hz) and have a more complex fine structure of the signals due to SSC with the protons of the two adjacent methylene groups.

In the spectrum of cation XII$^+$ all of the signals, with the exception of the $C_{(12a)}$ signal, are shifted ~1.5 ppm to strong field relative to the positions of the corresponding signals in the spectrum of the neutral molecule. Despite the significant increase in the direct ^{13}C–^1H constant in the α position relative to $N_{(11)}$ ($^1J_{1010\text{-}H}$ = 187.3 Hz) and the small decrease in the $^3J_{11a10}$ constant (10 Hz), the increase in the shielding of the $C_{(6a)}$, $C_{(9a)}$, and $C_{(6b)}$ atoms, which are in the β and γ positions relative to $N_{(11)}$, does not correspond to the addition of a proton to this center [13]. In addition to this, the significant strong-field shift of the $C_{(6)}$ signal to the region that is typical for phenolic carbon atoms (156.2 ppm) is a characteristic sign of protonation of pyridones at the carbonyl oxygen atom [10]. The observed change in the chemical shifts and the increase in the direct ^{13}C–^1H constants of the methylene $C_{(2)}$ and N-methyl carbon atoms (Δ^1J = 5.3 and 5.5 Hz) constitute evidence for delocalization of the positive charge primarily within the limits of the amidine $N_{(12)}C_{(12a)}N_{(1)}$ grouping. The increase in the $^1J_{CH}$ constant of the methylidyne $C_{(10)}$ atom is evidently due to the high inductive effect of the charged amidine fragment. The significant strong-field shifts of the signals of the $C_{(3)}$–$C_{(9)}$ atoms, which are remote from the cationic center ($\Delta\delta$ = 4–7 ppm), may be associated with a change in the geometry of the saturated fragments of cation XII$^+$ due to redistribution of the bond orders in the heteroaromatic two-ring system.

Measurement of the ionization constants showed that in the series of compounds VIIIa, b, and X–XV (Table 1) the relative basicity and acidity depend in a regular way on the size of the saturated fragments of the molecules. On the basis of the information set forth in [5, 6] this dependence can be explained by a change in the spatial accessibility of the polar groupings of the cationic and anionic forms for solvation. In fact, the size of the saturated N-methylated heteroring, which creates greater steric hindrance to solvation as compared with the carbocyclic fragment, has the predominant effect on the acid-base properties of the investigated compounds. An increase in the size of the aza heteroring in X–XII and XIII–XV from m = 1 to m = 3 leads to a successive decrease in the basicity: regardless of the size of the carbocycle, dehydropyrrole derivatives X and XIII have the greatest basicity, while tetrahydroazepine derivatives XII and XV have the lowest basicity (ΔpK_a 1.24–1.36). The size of the condensed carbocyclic ring has a substantially weaker effect on the relative basicities of the examined compounds. On passing from cyclopentene derivatives X–XII to cyclohexene derivatives XIII–XV, depending on the size of the saturated azo heteroring, the basicity decreases by 0.39–0.47 of a pK_a unit. The steric factor of the carbocycle may hinder solvation of the hydroxy group of the cation, but it evidently has virtually no effect on the spatially remote charged amidine fragment. In the case of the absence of a substituent in the 3 position of the pyridone fragment in VIIIa, b replacement of the five-membered carbocycle by a six-membered carbocycle does not affect the ionization constant.

The relative acidities of X–XV, just like the basicities, depend chiefly on the size of the saturated aza heteroring, although the observed effects are relatively small. Thus, the basicity decreases by 1.63 orders of magnitude on passing from X to XV (i.e., from the least bulky to the most bulky tetracycle) while the acidity decreases by 0.65 of an order of magnitude.

TABLE 2. Spectral Characteristics of VIII and X–XVII

Compound	IR spectrum, cm^{-1}			M+	PMR spectrum, ppm*
	NH	C=O	C=N		
VIIIa	3400	1645	1570, 1530	229	2,18 (2H, m, 6-H); 2,95 (2H, m, 7-H); 3,31 (6H, s, NMe_2); 3,53 (2H, m, 5-H); 6,49 (1H, s, 3-H); 8,45 (1H, s, 8-H)
VIIIb	3450	1620	1580, 1530	243	1,5...2,0 (4H, m, 6-, 7-H); 2,6...3,0 (2H, m, 8-H); 3,32 (6H, s, NMe_2); 3,44...3,80 (2H, m, 5H); 6,55 (1H, s, 3-H); 8,42 (1H, s, 9-H)
X	3450	1660, 1620	1570	241	2,25 (2H, m, 6-H); 3,0 (4H, m, 2,7-H); 3,25 (3H, s, NMe); 3,6 (2H, m, 5-H); 4,0 (2H, t, 3-H); 8,34 (1H, s, 8-H)
XI	3450	1630	1600, 1530	255	1,9 (2H, m, 3-H); 2,27 (2H, m, 7-H); 2,7 (2H, m, 8-H); 3,02 (2H, m, 6-H); 3,39 (3H, s, NMe); 3,65 (4H, m, 4-H); 8,42 (1H, s, 9-H)
XII	3400	1640	1600, 1530	283	1,9 (4H, m, 3-, 4-H); 2,26 (2H, m, 8-H); 2,83 (2H, m, 9-H), 8,4 (1H, s, 10-H)
XIII	3400	1670	1570, 1530	255	1,75 (4H, m, 6-, 7-H); 2,82 (2H, m, 8-H); 3,2 (5H: m, NMe, 2-H); 3,6 (2H, m, 5-H); 4,1 (2H, t, 3-H); 8,4 (1H, s, 10-H)
XIV	3450	1640	1600, 1550	269	1,7 (4H, m, 7-, 8-H); 2,05 (2H, m, 3-H); 2,8 (4H, m, 6-, 9-H); 3,37 (3H, s, NMe); 3,62 (4H, m, 2-, 4-H); 8,36 (1H, s, 10-H)
XV	3400	1640	1600, 1530	283	1,93 (4H, m, 3-, 4-H); 2,26 (2H, m, 8-H); 2,83 (2H, m, 9-H); 3,07 (2H, m, 7-H); 3,36 (3H, s, NMe); 3,7 (4H, m, 2-, 5-H); 8,4 (1H, s, 10-H)
XVI	—	1650	—	247	2,15 (2H, m, 6-H); 2,87 (2H, m, 7-H); 3,15 (5H, s, 8-H, NMe_2); 3,55 (2H, m, 5-H); 7,21 (1H, s, 3-H); 8,31 (1H, s, 10-H)
XVII	—	—	—	257	1,40 (3H, t, OCH_2CH_3); 2,10 (2H, m, 8-H); 2,95 (2H, m, 9-H); 3,37 (2H, m, 7-H); 3,34 (6H, s, NMe_2); 4,27 (2H, q, OCH_2CH_3); 6,31 (1H, s 3-H); 8,39 (1H, s, 10-H)

*The PMR spectra of VIIIa, XVI, and XVII were recorded in DCOOD, while the PMR spectra of VIIIb and X–XV were recorded in CF_3COOD.

The greater effect of the size of the condensed fragments on the basicity than on the acidity can be explained by the fact that the cationic form (C_2), in contrast to the anionic form (A), contains two labile protons (NH, OH), which are capable of forming strong hydrogen bonds with the solvent molecules. Consequently, one might assume that the solvation effect makes a significantly greater contribution to stabilization of the cationic forms than to stabilization of the anionic forms.

EXPERIMENTAL

The ionization constants were determined by potentiometric titration with a Radiometer PHM-26 pH meter with glass (G 2222 B) and calomel (K 4112) electrodes (tuning with respect to aqueous buffer standards with a reproducibility of no less than 0.05 of a pH unit) in 70% aqueous DMF at 25 ± 0.02°C at a concentration of $1 \cdot 10^{-3}$ mole/liter. We used aqueous 0.1 N NaOH and 0.1 N HCl solutions as the titrants.

The UV spectra of 10^{-5} M solutions of the substances in 70% aqueous DMF were recorded with a Specord M-40 spectrophotometer. The ^{13}C NMR spectra were recorded with a Bruker CXP-200 spectrometer (50.3 MHz); the scanning width was 12 kHz, the pulse duration was 20 μsec (60°), the data-sampling time was 1 sec, the time lag between pulses was 10 sec, and the number of passes ranged from 1600 to 4000, depending on the concentration of the investigated substance in the sample. In recording the spectra without suppression of the ^{13}C–^1H SSC to improve the signal/noise ratio we used saturation of the ^1H nuclei during the time lag between pulses. The PMR spectra were recorded with a Tesla BS-497 spectrometer (80 MHz). The mass spectra were obtained with a Varian MAT-112 spectrometer with direct introduction of the samples into the ion source; the temperature of the ionization chamber was 180°C, and the ionizing-electron energy was 70 eV. The melting points were determined with a heating stage of the Boetius type.

The spectral characteristics of VIIIa, b and X–XVII are presented in Table 2. The results of elementary analysis of V–XVII for C, H, N, Cl, and H_2O were in agreement with the calculated values.

3-Amino-4-carboxy-5,6,7,8-tetrahydroisoquinoline (IVb). A solution of 22.9 g (132 mmole) of 3-amino-4-cyano-5,6,7,8-tetrahydroisoquinoline (IIIb) in 227 ml of 58–60% H_2SO_4 was stirred for 5 h at 134–137°C, after which it was cooled and made alkaline to pH ~5 with 20% NaOH solution, and the resulting precipitate was removed by filtration.

3-Amino-4-carboxy-5,6-dinitro-7H-2-pyrindine (IVa). This compound was synthesized by the similar hydrolysis of 3-amino-4-cyano-5,6-dihydro-7H-2-pyrindine.

3-Amino-4-carbamido-5,6,7,8-tetrahydroisoquinoline (V). The mother liquor after filtration of IVb was made alkaline to pH ~9 with 20% NaOH solution, and the resulting precipitate was removed by filtration. IR spectrum: 3500, 3450, 3300, 3200 (NH_2); 1650 cm^{-1} (C=O); a band of C≡N vibrations was absent.

3-Amino-4-carbethoxy-5,6,7,8-tetrahydroisoquinoline (VIb). A mixture of 1 g (5.2 mmoles) of IVb, 10 ml of absolute alcohol, and 4 ml of concentrated H_2SO_4 (d = 1.84 g/cm^3) was refluxed for 12 h, after which it was evaporated. A saturated solution of Na_2CO_3 was added to the residue to pH ~9, and the resulting precipitate was removed by filtration.

3-Amino-4-carbethoxy-5,6-dihydro-7H-2-pyrindine (VIa). This compound was similarly synthesized from IVa.

2-N,N-Dimethylamino-4-oxo-5,6-tetramethylene-1,8-naphthyridine (VIIIb). A mixture of 1 g (4.5 mmoles) of VIb, 3 ml of N,N-dimethylacetamide diethylacetal, and 10 ml of dry toluene was refluxed for 1 h, after which it was evaporated. A solution of sodium butoxide (0.3 g of Na and 20 ml of butanol) was added to the residue, and the mixture was refluxed for 5 h. It was then evaporated, 10 ml of water was added to the residue, and the mixture was adjusted to pH 8-9 with 10% HCl and extracted with chloroform (four 40-ml portions). The combined chloroform extracts were dried with Na_2SO_4, filtered, and evaporated, the residue was triturated with ether, and the precipitate was removed by filtration.

Naphthyridines VIIIa and X–XV.* These compounds were similarly synthesized.

*Naphthyridines VIIIa, X, XIII, XI, and XIV crystallized on titration with ether; the ether was decanted, the oil was dissolved in the minimum amount of methylene chloride, and a solution of HCl in 2-propanol (0.4 g/ml) was added dropwise to the solution to pH ~1. The resulting precipitates of the corresponding hydrochlorides were removed by filtration.

2-N,N-Dimethylamino-4-chloro-5,6-trimethylene-1,8-naphthyridine (XVI). A mixture of 3 g (13 mmoles) of VIIIa, 1 g of triethylamine hydrochloride, and 20 ml of phosphorus oxychloride was refluxed for 3 h, after which the excess oxychloride was removed by vacuum distillation, 15 ml of water was added to the residue, and the aqueous mixture was made alkaline to pH 8-9 with 25% ammonium hydroxide. The mixture was extracted with chloroform (four 40-ml portions), and the combined chloroform extracts were dried with Na_2SO_4, filtered, and evaporated. The residue was refluxed with 90 ml of ethyl acetate and activated charcoal. The filtrate was cooled to –4°C and maintained at this temperature for 12 h, and the resulting precipitate was removed by filtration.

2-N,N-Dimethylamino-4-ethoxy-5,6-trimethylene-1,8-naphthyridine (XVII). A mixture of 1 g (4 mmoles) of XVI and sodium ethoxide (from 0.3 g of Na and 15 ml of absolute ethanol) was heated in an autoclave for 6 h at 150°C, after which the solvent was evaporated, and the residue was triturated with water. The resulting precipitate was removed by filtration.

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