

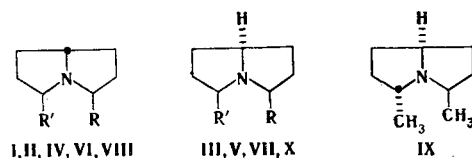
21.* BASICITIES, STEREOCHEMISTRY, AND ^1H and ^{13}C NMR SPECTRA OF
PYRROLIZIDINE AND ITS HOMOLOGS IN AQUEOUS AND AQUEOUS ACETONITRILE
SOLUTIONS. PREDICTION OF THE pK_a VALUE OF *trans*-FUSED PYRROLIZIDINEI. V. Antipova, V. V. Negrebetskii,
and I. M. Skvortsov

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The basicities of pyrrolizidine and its homologs in aqueous and aqueous acetonitrile solutions at 25°C were determined. It is shown that among 3-alkylpyrrolizidines, the isomers with *cis* configurations have higher pK_a values than the isomers with *trans* configurations. On the basis of a comparative study of the ^1H and ^{13}C NMR spectra it was concluded that *cis*-3,8-H-*cis*-5,8-H-3,5-dimethylpyrrolizidine in aqueous solutions exists chiefly in the *trans*-fused form, whereas conformationally heterogeneous pyrrolizidines with primarily *cis*-fused rings experience a shift of the equilibrium to favor an increase in the *cis*-fused conformations when a nonpolar solvent is replaced by a polar solvent. The basicity of the *trans*-fused conformation of pyrrolizidine is predicted on the basis of the data obtained.

The high basicities of pyrrolizidines have been recently demonstrated [2-4]; an attempt has been made to explain this property [3, 4], and it has been pointed out that in series of saturated amines with a tertiary nitrogen atom pyrrolizidine and 3-methylpyrrolizidines are among the most strongly basic compounds [4].

In the present communication we present data on the pK_a values and from the ^1H and ^{13}C NMR spectra of pyrrolizidines I-X [5] in polar solvents and discuss the relationship between the strengths of the bases and the peculiarities of the stereochemistry in the examined group of compounds.



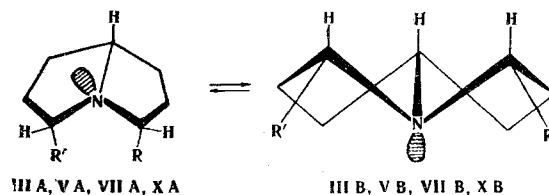
I $\text{R}=\text{R}'=\text{H}$; II, III $\text{R}=\text{CH}_3$, $\text{R}'=\text{H}$; IV, V $\text{R}=\textit{i}\text{-C}_4\text{H}_9$, $\text{R}'=\text{H}$; VI, VII $\text{R}=\textit{t}\text{-C}_4\text{H}_9$, $\text{R}'=\text{H}$;
VIII, X $\text{R}=\text{R}'=\text{CH}_3$

Pyrrolizidine (I) and 3-methylpyrrolizidines II and III are quite soluble in water, whereas the solubilities of 3,5-dimethylpyrrolizidines VIII-X are relatively low but sufficient for the determination of the pK_a values of these bases in aqueous solutions. 3-Isobutyl- (IV, V) and 3-*tert*-butylpyrrolizidines (VI, VII) are only slightly soluble in water, and the pK_a values were therefore determined in acetonitrile-water (7:3) for comparison of the basicities of all of the pyrrolizidines obtained. Data on the basicities of pyrrolizidines I-X are presented in Table 1.

The basicities of *cis* isomers III, V, VII, and IX are higher than the basicities of *trans* isomers II, IV, VI, and VIII in both aqueous and aqueous acetonitrile solutions (except for the pair of IX and X epimers). It is known that pyrrolizidines I and II [6], VI [7, 8], and VIII [8, 9] exist virtually completely in *cis*-fused forms in nonpolar solvents and in pure liquid form. On the basis of the results in [6, 7, 9], the general principles of the stereo-

chemistry of pyrrolizidines, and data on the chemical shifts of the 8-H protons in nonpolar solvents (Table 2), it may be assumed that base IV will also exist in similar conformations in nonpolar inert solvents.

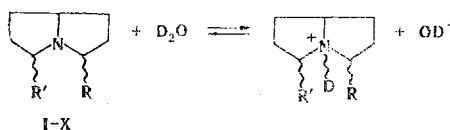
According to the data in [6], III exists primarily in cis-fused forms (IIIA); however, the presence of the trans-fused IIIB conformation is reflected in the PMR [6] and ^{13}C NMR [10] spectra. Pyrrolizidine homolog V will also evidently be conformationally heterogeneous with respect to the type of ring fusion; as in the case of base III, the cis-fused conformations (VA) will be the dominant forms.



The transition from a less polar solvent to a more polar solvent gives rise to a shift of the conformational equilibrium to favor the conformer with a larger dipole moment [11]. According to calculations, the trans-fused conformations of pyrrolizidines have lower dipole moments than the cis-fused conformations [5], and replacement of the nonpolar cyclopentane (ϵ 1.965 [12])* by polar solvents — water (ϵ 81.0 [13]), acetonitrile (ϵ 37.5 [12]), or mixtures of these solvents — will consequently promote an even more pronounced preponderance of the cis-fused conformations over the trans-fused conformations in the case of III, V, and IX. In addition, we took into account the fact that the ability of pyrrolizidines to form a hydrogen bond with H_2O or D_2O is a powerful factor that affects the conformational equilibrium [14]. Since the basicities of cis-fused pyrrolizidines are higher than the basicities of trans-fused pyrrolizidines, the effect of the formation of an H bond promotes [15] a shift of the equilibrium to favor the cis-fused conformations.

Thus both of the factors presented above, which affect the change in the conformational equilibrium, act in the same direction, and in polar solvents pyrrolizidines I-VI, VIII, and IX can be regarded as a conformationally monotypic group of compounds with dominant cis ring fusion. Hence the higher basicities of cis isomers III, V, and IX as compared with trans isomers II, IV, and VIII are understandable if one bears in mind the fact that steric hindrance to solvation lowers the basicity [16]. In the former the alkyl substituent in the 3 position is trans-oriented with respect to the unshared electron pair of the nitrogen atom, and steric hindrance to solvation of the nitrogen atom is therefore smaller than in the case of the latter, which have a mutual cis orientation of the unshared electron pair and the alkyl group. The effect of shielding with respect to solvation on the pK_a values is displayed most prominently in the case of VI, which has a branched substituent adjacent to the nitrogen atom.

A shift of the signal of the 8-H protons to weak field when cyclopentane is replaced by D_2O or $\text{CD}_3\text{CN}-\text{D}_2\text{O}$ is displayed in the PMR spectra of pyrrolizidines I-VI and IX (Table 2). This effect can be explained by partial deuteration of the nitrogen atom when the compounds are dissolved in these solvents. As a result of reversible chemical reaction with the solvent one observes a strongly alkaline reaction of aqueous solutions of pyrrolizidines and the development of a certain surplus positive charge on nitrogen, which gives rise to deshielding of the protons attached to the α -carbon atoms. The $\Delta\delta$ values, which are surpassed by the values on the order of 0.68–1.06 ppm that are characteristic for complete protonation of pyrrolizidine [6], indicate the partial character of protonation (deuteration). The concept of the partial deuteration of the nitrogen atom when the compounds are dissolved in D_2O is also confirmed by data on the change in the chemical shifts of the ^{13}C



*The dielectric constants of the solvents are the values at 20°C.

TABLE 1. pK_a Values of Pyrrolizidines I-X in Aqueous and Aqueous Acetonitrile Solutions and ΔpK_a Values* of the Epimers at 25°C

| Compound | Aqueous solution | | Aqueous acetonitrile (7:3) solution | |
|----------|------------------|---------------|-------------------------------------|---------------|
| | pK_a | ΔpK_a | pK_a | ΔpK_a |
| I | 11,67±0,04 | — | 10,61±0,01 | — |
| II | 11,63±0,06 | 0,26 | 10,45±0,01 | 0,29 |
| III | 11,89±0,06 | | 10,74±0,02 | |
| IV | | 0,31 | 10,41±0,01 | 0,31 |
| V | | | 10,72±0,01 | |
| VI | | | 10,21±0,01 | |
| VII | | 0,30 | 10,51±0,01 | 0,30 |
| VIII | 11,47±0,05 | | 10,49±0,01 | |
| IX | 11,74±0,06 | 0,27 | 10,80±0,02 | 0,31 |
| X | 10,28±0,10 | -1,46 | 9,37±0,01 | -1,43 |

*The ΔpK_a value is the difference between the pK_a values of the cis and trans isomers.

TABLE 2. Chemical Shifts of the 8-H Protons, Changes in Their Values on Passing from a Nonpolar Solvent to Polar Solvents, and $\Delta\Delta\delta$ Values of the Epimers^a

| Compound | δ_{8-H} , ppm | | | $\Delta\delta^b$, ppm | $\Delta\Delta\delta^c$, ppm | $\Delta\delta^d$, ppm | $\Delta\Delta\delta^c$, ppm |
|----------|----------------------|------------------|---|------------------------|------------------------------|------------------------|------------------------------|
| | cyclopentane | D ₂ O | CD ₃ CN-D ₂ O (7:3) | | | | |
| I | 3,36 | 3,50 | 3,43 | -0,14 | — | -0,07 | — |
| II | 3,45 | 3,55 | 3,48 | -0,10 | — | -0,03 | — |
| III | 3,22 | 3,55 | 3,45 | -0,33 | 0,23 | -0,23 | 0,20 |
| IV | 3,43 | 3,74 | 3,46 | -0,31 | 0,17 | -0,03 | 0,13 |
| V | 3,27 | 3,75 | 3,43 | -0,48 | | -0,16 | |
| VI | 3,32 | | 3,48 | | | -0,16 | |
| VII | ≤2,95 | | ≤3,26 | | | | |
| VIII | 3,59 | 3,64 | 3,56 | -0,05 | 0,07 | +0,03 | 0,07 |
| IX | 3,52 | 3,64 | 3,56 | -0,12 | | -0,04 | |
| X | <2,9 | <3,1 | <2,9 | | | | |

^aThe concentrations of I-X in solution in cyclopentane and CD₃CN-D₂O were 1.3 and 0.2 mole/liter, respectively. Compounds I-III were investigated in the form of solutions in D₂O (0.2 mole/liter). In view of the low solubilities of bases IV-X in D₂O, we used saturated (at room temperature) solutions of them. The "-" and "+" signs indicate, respectively, shifts of the signals to weak and strong fields.

^b $\Delta\delta = \delta(C_5H_{10}) - \delta(D_2O)$. ^c $\Delta\Delta\delta = \Delta\delta(\text{trans isomer}) - \Delta\delta(\text{cis isomer})$.

^d $\Delta\delta = \delta(C_5H_{10}) - \delta(CD_3CN, D_2O)$.

nuclei of pyrrolizidines I-III on passing from cyclopentane to D₂O (Table 3); a shift of the signals of most of the carbon atoms to strong field is observed, which is in agreement with the greater tendency for shielding of the carbon atoms under the influence of protonation of the nitrogen atom in cyclic and two-ring tertiary amines [17, 18].

Upon closer examination of the $\Delta\delta$ values it is observed that cis isomers III, V, and IX under the influence of a polar solvent experience a more pronounced shift of the signal of the 8-H proton to weak field than the corresponding trans isomers II, IV, and VIII. We assume that this difference in the epimers on passing from cyclopentane to water, as well as to CD₃CN-D₂O, in the ¹H NMR spectra (Table 2) and the changes in the chemical shifts of the 8-C, 2-C, and 3-C atoms in the ¹³C NMR spectra (Table 3) indicate a shift in the conformational equilibrium to favor the cis-fused forms as a result of a change in the solvents. In fact, it is known that an increase in the fraction of the trans-fused conformation of pyrrolizidines leads to a diamagnetic shift of the signal of the 8-H proton in the PMR spectra [6, 7, 9], a paramagnetic shift of the signals of the 8-C and 2-C atoms, and a diamagnetic shift of the 3-C signal in the ¹³C NMR spectra [10].

The shift of the signals of the 8-H protons ($\Delta\delta$) of cis isomers III, V, and IX induced by polar solvents exceeds the analogous shift of the signals of the 8-H protons of trans iso-

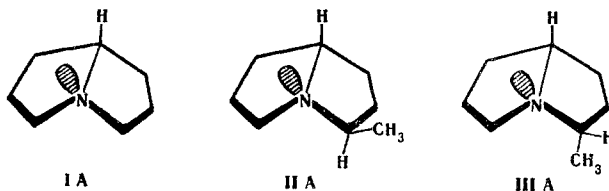
mers II, IV, and VIII by 0.23-0.07 ppm in D₂O and by 0.20-0.07 ppm in CD₃CN-D₂O (see Table 2). Data from the ¹³C NMR spectra are in agreement with the adopted scheme of the shift of the conformational equilibrium under the influence of a polar solvent (Table 3). In the series of pyrrolizidines I-III the maximum shift of the 2-C and 8-C signals (the $\Delta\Delta\delta$ values of the epimers are, respectively, -0.40 and -0.59 ppm) to strong field under the influence of D₂O is observed for base III. At the same time, a more pronounced shift of the signal of the 3-C atom to weak field ($\Delta\Delta\delta = 0.26$ ppm) is observed for isomer III than for isomer II.

We realize that in each individual case the magnitude of the recorded effect of the shift of the signal under the influence of a polar solvent is an approximate value, since various standards in various solvents were used in the case of the proton spectra. However, in the recording of the ¹³C NMR spectra the effects of various solvents on the chemical shifts of the atoms of the investigated compound and the standard may differ, and the caution expressed in [18] in this connection therefore remains in force in our case. However, the set of compatible data makes it possible to hope that we will observe an effect of an increase in the fraction of cis-fused forms in III, V, and IX on passing from solutions in nonpolar solvents to solutions in polar solvents.

Unfortunately, a comparison of the PMR spectra of solutions of pyrrolizidine VII in cyclopentane, D₂O, and mixtures of CD₃CN with D₂O does not make it possible to form a judgment regarding the direction of the change in the VIIA \rightleftharpoons VIIB conformational equilibrium on passing from an inert solvent to polar solvents.

In the series of examined pyrrolizidines X has a basicity that differs markedly from the basicities of the other compounds and is close to the basicities of such typically trans-fused 1-aza two-ring systems as indolizidine [19] ($pK_a 10.15 \pm 0.05$) [4] and quinolizidine [19] ($pK_a 10.19 \pm 0.07$) [20]. We therefore proposed that base X in aqueous and aqueous acetonitrile solutions, just as in the pure liquid form [8, 9] and in nonpolar solvents, exists primarily in the trans-fused XB form. This concept is supported by a comparison of the PMR spectra of isomers VIII (cis ring fusion) and X in benzene* and D₂O (Fig. 1); see [9] for the assignment of the signals. The spectrum of X in D₂O has the same character of the spectrum of X in benzene but differs substantially from the spectra of base VIII in benzene and D₂O. The complexity of the PMR spectrum of X excludes its interpretation from first-order considerations. One can only note that the transition from cyclopentane to D₂O gives rise to a shift of the lower boundary of the spectrum to weak field of ~0.2 ppm, which is due to partial deuteration of the base.

By examining the primarily cis-fused pyrrolizidines I-III, VIII, and IX it can be seen that the rule of additivity of the contribution of the effects of substituents to the basicities [21] is obeyed satisfactorily for them. By comparing the pK_a values in water and CH₃CN-H₂O for bases I-III and taking into account the fact that these values pertain exclusively to the cis-fused IA-III A conformations we find the ΔpK_a increments of the methyl groups in the 3 position.



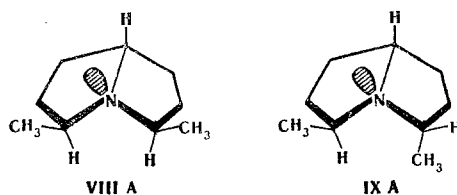
For the exo-methyl group $\Delta pK_a = -0.04$ (H₂O) and -0.16 (CH₃CN-H₂O), whereas the ΔpK_a values of the endo-methyl group are $+0.21$ and $+0.13$, respectively. Hence from the additive scheme for the cis-fused VIIIA and IXA conformations one can calculate the pK_a values by two and three methods proceeding alternately from data on the pK_a values of pyrrolizidines I-III. Since VIII and IX are primarily cis-fused compounds, the values obtained can be ascribed to the isomers themselves. The experimental and calculated pK_a values of these compounds are presented in Table 4.

*Benzene was used as the nonpolar solvent for demonstration of the spectra, since in the case of cyclopentane a significant portion of the spectrum is overlapped by resonance absorption of the protons of the solvent.

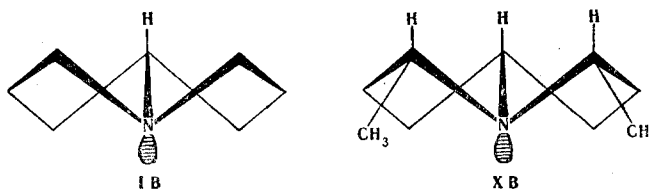
TABLE 3. ^{13}C Chemical Shifts of I-III in Cyclopentane and D_2O and Differences in the Chemical Shifts of the Signals [$\Delta\delta = \delta(\text{C}_5\text{H}_{10}) - \delta(\text{D}_2\text{O})$]

| Com- pound | Sol- vent | Concn., % | Chemical shift relative to dioxane, ppm ($\Delta\delta$, ppm) ^a | | | | | | | |
|---------------|---------------------------|--------------|--|-------------------|-------------------|-------------------|-------------------|-------------------|------------------|---------------|
| | | | 1-C | 2-C | 3-C | 5-C | 6-C | 7-C | 8-C | CH_3 |
| I | C_5H_{10} | 9.7 | -34.15 | -41.06 | -11.71 | -11.71 | -41.06 | -34.15 | -2.59 | — |
| | D_2O | 5.7 | -34.78 (+0.63) | -41.08 (+0.02) | -12.51 (+0.80) | -12.51 (+0.80) | -41.08 (+0.02) | -34.78 (+0.63) | -2.40 (-0.19) | — |
| II | C_5H_{10} | 9.7 | -34.37 ^b | -30.64 | -4.53 | -13.65 | -c | -33.78 | -2.00 | -45.86 |
| | D_2O | 6.0 | -35.23 (+1.28) | -31.92 (-0.18) | -4.35 (+0.63) | -14.28 (+0.63) | -41.71 | -34.50 (+0.04) | -2.04 (+1.84) | -47.70 |
| III | C_5H_{10} | 9.7 | -34.42 | -35.23 | -9.55 | -21.00 | -c | -35.07 | -2.00 | -50.34 |
| | D_2O | 6.0 | -34.28 (+1.68) | -36.91 (-0.44) | -9.11 (+0.17) | -21.17 (+0.17) | -41.08 | -35.18 (+0.63) | -2.63 (+1.17) | -51.51 |

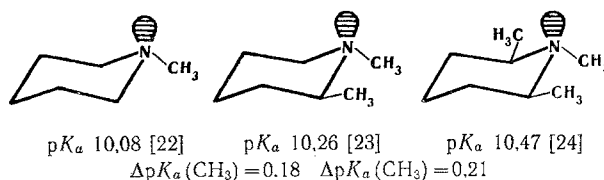
^aThe "+" and "-" signs denote, respectively, shifts of the signals to strong and weak fields on passing from cyclopentane to D_2O . ^bThe chemical shifts of the signals with their hypothetical assignment are given in italics. ^cThe signal is overlapped by the signal of the solvent.



Using the idea of the additivity of the contribution of substituents to the basicities of amines [21] and taking into account the fact that X exists virtually completely in the trans-fused XB form one may attempt to estimate the pK_a value of the trans-fused conformation of pyrrolizidine (IB).



The computational scheme is simple: $\text{pK}_a(\text{IB}) = \text{pK}_a(\text{X}) - 2\Delta\text{pK}_a(\text{CH}_3)$. It is apparent that among the known $\Delta\text{pK}_a(\text{CH}_3)$ values the most suitable value for the pseudoequatorial methyl groups in the XB conformation will be the value for the equatorial methyl group attached to the α -carbon atom. This value can be derived from data on the basicities of 1-methyl-, 1,2-dimethyl-, and 1,2,6-trimethylpiperidines:



The average value of the increment for the pseudoequatorial methyl group is 0.20. Hence for IB we obtain $\text{pK}_a = 10.28 - 2 \cdot (0.20) = 9.88$. Since X may contain a certain amount of the cis-fused XA form, which makes the basicity somewhat too high, $\text{pK}_a(\text{XB}) \leq 10.28$, and $\text{pK}_a(\text{IB}) \leq 9.9$.

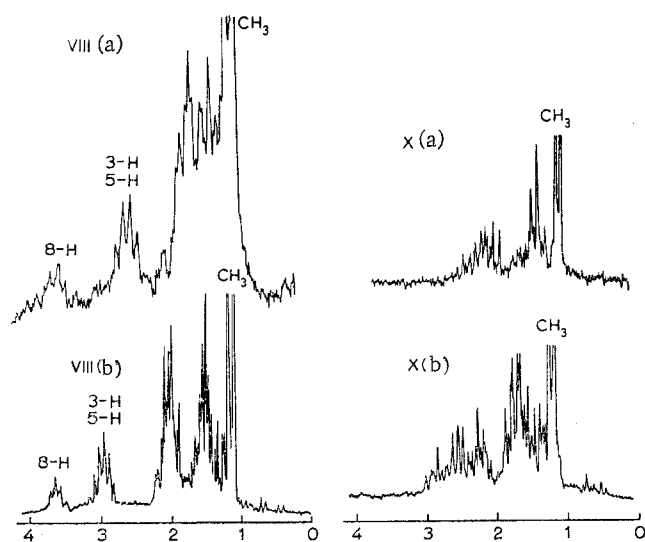


Fig. 1. PMR spectra of VIII and X in benzene (a) and D₂O (b): VIII(a) indicates recording at 60 MHz, and VIII(b), X(a), and X(b) indicate recording at 90 MHz.

TABLE 4. Experimental and Calculated pK_a Values of Pyrrolizidines VIII and IX

| Compound | pK _a | | | |
|----------|------------------------------|-------|---|-------|
| | solution in H ₂ O | | solution in CH ₃ CN-H ₂ O | |
| | found | calc. | found | calc. |
| VIII | 11,47 | 11,59 | 10,49 | 10,29 |
| IX | 11,74 | 11,84 | 10,80 | 10,58 |

With respect to their basicities isomers VIII and X (ΔpK_a 1.19) and IX and X (ΔpK_a 1.46) and conformers IA and IB ($\Delta pK_a \geq 1.8$) differ rather strikingly, in our opinion. Such a sharp drop in the pK_a values of these isomers and conformers is due, on the one hand, to the increased basicities of the cis-fused pyrrolizidines [2-4]. The trans-fused IB and XB forms do not have the exceptional steric accessibility of the nitrogen atom of the cis-fused pyrrolizidines and, on the other hand, have geometrical conditions for partial delocalization of the unshared electron pair of the nitrogen atom via the mechanism in [25]. It is possible that the angular strain of trans-fused pyrrolizidines also makes a certain contribution to the decrease in the pK_a values. As a result, the basicity of the IB conformer turns out to be somewhat lower than the basicities of the structurally related indolizidine [4] and quinolizidine [20].

EXPERIMENTAL

The ¹H NMR spectra of solutions of I-X in cyclopentane [with hexamethyldisiloxane (HMDS) as the internal standard], of I-III in D₂O [with sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as the internal standard], and of I-X in CD₃CN-D₂O (7:3) (with HMDS as the internal standard) were recorded with Perkin-Elmer R-12 (60 MHz), Hitachi-Perkin-Elmer R 20 (60 MHz), and Bruker HX-90E (90 MHz) spectrometers. The PMR spectra of solutions of IV-X in D₂O (with DSS as the internal standard) were recorded with a Bruker HX-90E spectrometer (90 MHz) under pulse conditions with subsequent Fourier transformation (4 K per 600 Hz). The signal of the D₂O solvent was used for stabilization of the resonance conditions with respect to ²H. The chemical shifts were rescaled relative to tetramethylsilane (TMS) and are given on the δ scale.

The ¹³C NMR spectra of solutions of I-III in cyclopentane and D₂O were obtained with a Bruker HX-90E spectrometer (22.63 MHz) under conditions of ¹³C-¹H spin coupling and pulse operation with subsequent Fourier transformation. Dioxane served as the internal standard. The resonance conditions were stabilized with respect to the deuterium nuclei in D₂O. The accuracy in the measurement of the ¹³C chemical shifts was ± 0.05 ppm.

The pK_a values were determined potentiometrically by titration with a pH-340 spectrometer at 25°C. In the experiments with a mixed solvent a solution of acetonitrile and water with a volume ratio of the components of 7:3 was used. A 0.1 N solution of HCl in a mixture with the same composition was used as the titrating agent. The experimental procedures and processing of the results of the measurements were carried out by methods similar to those described in [4].

Pyrrolizidines I-X were prepared by known methods [5].

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