# KINETIC CHARACTERISTICS OF THE RING–CHAIN TAUTOMERIC EQUILIBRIA OF 2,3,3-TRIMETHYL-1-ARYL-2-HYDROXY-5-PYRROLIDONES

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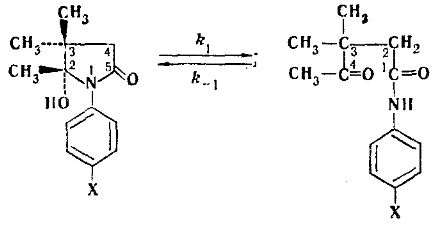
UDC 547.743.1'744'745:541.623:127:543.422.25

The kinetics of the ring–chain tautomeric equilibria of a number of p-substituted 2,3,3-trimethyl-1-aryl-2-hydroxy-5-pyrrolidones in 50% aqueous pyridine were studied by dynamic PMR spectroscopy, and the effect of substituents on the kinetic parameters of this process was determined. The free energies of activation ($\Delta G^{\neq}$) decrease regularly on passing from electron-donor to electron-acceptor substituents. A good correlation between $\Delta G^{\neq}$ and the $\sigma^+$ and $\sigma$ substituent constants is observed. On the basis of the data obtained, it was concluded that the rate-determining step in the process is detachment of a proton under the influence of the base to give the corresponding anion.

In a previous study [1] we used PMR spectroscopy to determine the equilibrium constants ($K_T$) and thermodynamic parameters of the ring–chain tautomeric equilibria of a series of p-substituted 2,3,3-trimethyl-1-aryl-2-hydroxy-5-pyrrolidones in 50% aqueous pyridine.

In the present research we used dynamic PMR spectroscopy [2] to study the kinetics of this process (see the scheme below) and determined the effect of substituent X in the benzene ring on the kinetic parameters. The literature contains very little data on the kinetics of ring–chain tautomeric transformations.



I II

a X = $N(C_2H_5)_2$; b X = $OCH_3$; c X = H; d X = Cl;
e X = Br; f X = COOH; g X = $COOCH_3$; h X = CN

Rate constants $k_1$ and $k_{-1}$, which correspond to the transformation from cyclic form I to open form II and vice versa ($k_1/k_{-1} = K_T$), were determined for 0.4 M solutions of I (or II) in 50% aqueous pyridine containing 0.032 M sodium bicarbonate. The addition of the bicarbonate, which serves as a catalyst for the tautomeric transformations, is necessary in orden to bring the rates of this process for all substituents into the range over which the effect of the substituent on the form of the lines of the PMR signals of one or both tautomeric forms becomes appreciable.*

Special experiments demonstrate that the presence of sodium bicarbonate (up to a concentration of 0.11 M) does not affect the equilibrium constants and the PMR-spectral parameters, whereas $k_1$ and $k_{-1}$ are linear functions of the bicarbonate concentration.

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*When sodium bicarbonate is absent, the I $\rightleftarrows$ II transformations of all of the investigated compounds at 0 to 100°C take place "slowly" on the PMR scale and do not affect the form of the lines.

All-Union Scientific-Research Vitamin Institute, Moscow 117246. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 758-763, June, 1978. Original article submitted July 5, 1977.

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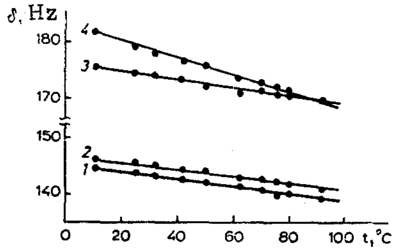

Fig. 1

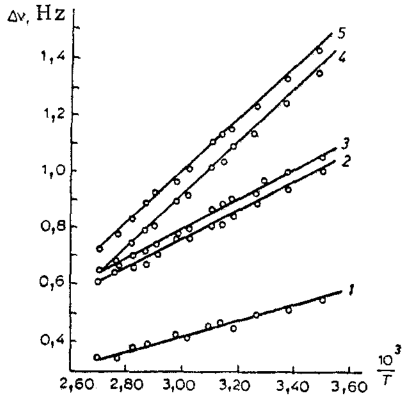

Fig. 2

Fig. 1. Temperature dependence of the chemical shifts (δ) of the protons of tautomeric forms Ia-IIa [X = $N(C_2H_5)_2$] in 50% aqueous pyridine: 1,3) δ values of the protons of the $CH_3CO$ and $2\text{-}CH_2$ groups in the open form (IIa); 2,4) δ values of the $4\text{-}CH_A$ and $4\text{-}CH_B$ protons in the cyclic form (Ia).

Fig. 2. Temperature dependence of the width of the lines (Δν) of the protons of tautomeric forms Ia-IIa [X = $N(C_2H_5)_2$] in 50% aqueous pyridine: 1) Δν of ethanol; 2,3) Δν values of the protons of the $CH_3CO$ and $2\text{-}CH_2$ groups in the open form (IIa); 4,5) Δν values of the $4\text{-}CH_A$ and $4\text{-}CH_B$ protons in the cyclic form (Ia).

It is known [3] that the temperature dependence of the chemical shifts (δ) and the line widths (Δν) of the signals of the protons of both tautomeric forms in the absence of tautomeric transformations may be a source of systematic error in calculations of the exchange processes by the dynamic NMR method. To eliminate this error we determined the dependences of δ on the temperature and Δν on the reciprocal temperature in a solvent that does not contain sodium carbonate for all of the investigated compounds. The graphs of the corresponding temperature depenedences for Ia-IIa and a sodium 2,2-dimethyl-2-silapentane-5-sulfonate standard are presented in Figs. 1 and 2. The constant ($^2J$) of geminal spin–spin coupling between the $4\text{-}CH_A$ and $4\text{-}CH_B$ protons in the cyclic tautomer did not change with the temperature, in agreement with the data in [4].

To obtain the kinetic characteristics of the tautomeric transformations we used an analysis of the overall form of the line, which presupposes computer calculation of the theoretical spectrum for the given kinetic parameters and comparison of the calculated spectrum with the observed spectrum. The best agreement between the two spectra is achieved by selection of the kinetic parameters. The $k_1$ and $k_{-1}$ rate constants were determined from the change in the overall form of the lines of the signals of two groups of protons: the methylene protons attached to the amide carbonyl group, which gives a system of the AB type in cyclic form I ($4\text{-}CH_A$ and $4\text{-}CH_B$) that is converted to a $2\text{-}CH_2$ singlet in the spectrum of form II, and the $2\text{-}CH_3$ protons in I, which are converted to protons of the $CH_3CO$ group in II (exchange between two singlets). The chemical shifts of these protons at 34°C in the absence of sodium bicarbonate are presented in [1].

The interconversion of the methylene groups represents exchange of two strongly coupled spin systems. The apparatus of the density matrix (ρ) of the system of spins within the framework of the formalism in [5, 6] as applied to intramolecular exchange was therefore used for the calculation of the theoretical signal of the absorption of this group of protons; in this case the equations for the nm elements of density matrices $\rho_I$ and $\rho_{II}$ (the subscripts pertain to forms I and II) have the following form within the approximation of the small magnitude of the radio-frequency field and under the condition of slow transmission (these two conditions are satisfied in the experiments under discussion):

$$\begin{gathered}(\rho_{II}^{nm}-\rho_{I}^{nm})/\tau_{I}+\rho_{I}^{nm}/T_2^{I}+\{\hat{H}_{I},\rho_{I}\}^{nm}=0,\\(\rho_{I}^{nm}-\rho_{II}^{nm})/\tau_{II}+\rho_{II}^{nm}/T_2^{II}+\{\hat{H}_{II},\rho_{II}\}^{nm}=0\end{gathered}\tag{1}$$

Here $\tau_I$ and $\tau_{II}$ are the lifetimes in the I and II states, respectively ($\tau_I = 1/k_1$ and $\tau_{II} = 1/k_{-1}$), $T_2^{I}$ and $T_2^{II}$ are the spin–spin relaxation times, and $\hat{H}_I$ and $\hat{H}_{II}$ are the

Hamiltonians of tautomeric forms I and II, which include Zeeman, spin–spin, and radio-frequency terms. The signal of the absorption is defined as the imaginary part of the expression

$$P_{I}(\rho_{I}^{12}+\rho_{I}^{13}+\rho_{I}^{24}+\rho_{I}^{34})+P_{II}(\rho_{II}^{12}+\rho_{II}^{13}+\rho_{II}^{24}+\rho_{II}^{34}), \qquad (2)$$

where $P_I$ and $P_{II}$ are the fraction of forms I and II, and $\tau_{II}/\tau_I = P_{II}/P_I = K_T$. Thus to find the signal of the absorption of the methylene groups one must solve a system of eight linear algebraic equations in complex form. The signal of the absorption of the methyl protons was determined from the known analytical expression [2] obtained in the solution of Block equations modified for the case of exchange.

In the procedure to find $k_{-1}$ and $k_1$ the iteration program,* which calculates the theoretical spectrum for predesignated initial lifetimes, compares the agreement between the theoretical and experimental spectra and calculates the $k_1$ and $k_{-1}$ values that ensure the best agreement between the two spectra. The coefficient of correlation between their points was selected as the criterion of coincidence of the two spectra. In the course of the calculation of the rate constants it was observed that in the case of $k_{-1}$ values greater than 100 $sec^{-1}$ ("fast exchange") the theoretical spectrum no longer adequately corresponds to the experimental spectrum in the region of the signals of the methylene groups but continues to satisfactorily describe the region of signals of the methyl groups. An additional exchange process evidently affects the form of the signals of the protons of the methylene groups beginning at these rates. Up to $k_{-1}$ values below 100 $sec^{-1}$ the calculation was therefore carried out for both the methyl and methylene protons, whereas it was performed only with respect to the methyl protons at higher rates. The following information provides evidence for the negligibly small effect of the second exchange process on the overall form of the line of the methyl protons at rates below 100 $sec^{-1}$. The rate constants obtained in the slow-exchange range (up to 30-40 $sec^{-1}$) from an independent treatment of the signals of the two groups coincide within the limits of experimental error, whereas at intermediate exchange rates (from 40 to 100 $sec^{-1}$) the ln $(k_1/T)$ and ln $(k_{-1}/T)$ values calculated from the signals of the methylene protons lie on the line of the direct dependence of these values on the reciprocal temperature drawn through the slow- and rapid-exchange points.

It was also observed that over the intermediate-exchange range the form of the spectrum in the range of the methylene protons is sensitive to the magnitude and sign of the constant ($^2J$) of spin–spin coupling between the protons of the 2-$CH_2$ group in tautomer II. It is not possible to determine the magnitude of this constant from the PMR spectrum in the absence of exchange, since the chemical shifts of both methylene protons in the II form are identical. However, in the intermediate-exchange rate the best agreement between the theoretical and experimental spectra and, consequently, the correlation coefficient between them depend on $^2J$, all other parameters being equal. For example, when the sign of $^2J$ changes for IIe at 50°C, the correlation coefficient decreases from 0.9 for –25 Hz to 0.8 for +25 Hz (in tautomer I the analogous constant is assumed to be negative). When the $^2J$ value changes from zero to –25 Hz, the correlation coefficient increases from 0.78 to 0.9; the correlation coefficient remains virtually unchanged as the constant decreases further (see Fig. 3). Thus the sign and limits of the latent spin–spin coupling constant (SSCC) can be determined by means of the dynamic NMR spectra. In connection with the fact that a correlation for the second exchange process is not introduced in the present research, the limits found for $^2J$ obviously cannot be regarded as the definitive values.

The enthalpies and entropies of activation for the transitions from the cyclic form to the open form and vice verse ($\Delta H_I^{\neq}$ and $\Delta S_I^{\neq}$ and $\Delta H_{II}^{\neq}$ and $\Delta S_{II}^{\neq}$, respectively; see Table 1) were obtained from the Eyring equation [7] from the experimental dependences of ln $(k_1/T)$ and ln $(k_{-1}/T)$ on $1/T$ (Fig. 4). The free energies of activation ($\Delta G_I^{\neq}$ and $\Delta G_{II}^{\neq}$) and the statistically averaged ln $(k_1/T)$ and ln $(k_{-1}/T)$ values were calculated from these values at 50°C. It is apparent from Table 1 that the $\Delta H_I^{\neq}$ values are larger than the $\Delta H_{II}^{\neq}$ values and that the $\Delta S_I^{\neq}$ values are larger than the $S_{II}^{\neq}$ values for all of the investigated compounds. The $\Delta S_I^{\neq}$ and $\Delta S_{II}^{\neq}$ values are positive for most of the compounds except those containing Br

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*The program was composed by L. Yu. Yuzefovich and Yu. V. Benderskii. The system of equations is solved by the Gauss method, and iteration is accomplished by the method of fastest descent.

Equilibria of p-Substituted Arylhydroxypyrrolidones Ia-h in 50% Aqueous Pyridine*

| X | $\Delta H_I^{\neq}$, kcal/mole | $\Delta H_{II}^{\neq}$, kcal/mole | $\Delta S_I^{\neq}$, eu | $\Delta S_{II}^{\neq}$, eu | $\Delta G_I^{\neq}$, kcal/mole | $\Delta G_{II}^{\neq}$, kcal/mole | $k_1$, sec$^{-1}$ | $k_{-1}$, sec$^{-1}$ |
|---|---|---|---|---|---|---|---|---|
| $N(C_2H_5)_2$ | 30,1±1,5 | 25,7±1,5 | 27,6±5,0 | 18,7±4,8 | 21,2 | 19,7 | 0,031 | 0,31 |
| $OCH_3$ | 24,6±1,0 | 19,3±1,0 | 14,2±3,2 | 2,7±3,0 | 20,0 | 18,4 | 0,19 | 2,34 |
| H | 23,9±0,3 | 19,1±0,3 | 20,9±0,8 | 8,7±0,8 | 17,1 | 16,3 | 14,2 | 54,6 |
| Cl | 24,7±1,2 | 18,7±0,9 | 23,5±3,8 | 7,8±2,7 | 17,1 | 16,2 | 18,0 | 75,9 |
| Br | 19,6±1,3 | 15,3±1,0 | 8,1±4,0 | −2,4±3,0 | 17,0 | 16,1 | 23,4 | 77,6 |
| COOH | 27,2±1,8 | 22,9±1,8 | 8,6±5,0 | 5,1±5,0 | 24,4 | 21,3 | 0,013 | 0,030 |
| $COOCH_3$ | 17,7±0,8 | 14,6±0,5 | 6,1±3,0 | −2,7±2,0 | 15,7 | 15,5 | 148,4 | 195,0 |
| CN | 21,1±0,9 | 17,9±0,8 | 18,9±2,6 | 11,3±2,6 | 15,0 | 14,3 | 478,6 | 512,9 |

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*The $\Delta G_I^{\neq}$, $\Delta G_{II}^{\neq}$, $k_{-1}$, and $k_1$ values were obtained at 50°C from regression lines.

and $COOCH_3$ substituents. From this it might be expected that as compared with the open tautomeric form, the transition state for the latter compounds has approximately the same or slightly less conformational freedom ($\Delta S_{II} \leq 0$). In general, the $\Delta H_I^{\neq}$ and $\Delta H_{II}^{\neq}$ values decrease on passing from electron-donor to electron-acceptor substituents. The same tendency, although it is less distinctly expressed, can also be traced for $\Delta S_I^{\neq}$ and $\Delta S_{II}^{\neq}$. The free energies of activation ($\Delta G_I^{\neq}$ and $\Delta G_{II}^{\neq}$) decrease regularly in the same order; this is in agreement with the decrease in the free energies ($\Delta G$) [1] and the principle of linearity of the free energies. The $\Delta S_I^{\neq}$ and $\Delta S_{II}^{\neq}$ values for the tautomeric system with a COOH substituent are close to the entropies of activation of other systems with acceptor substituents, but the $\Delta H_I^{\neq}$ and $\Delta H_{II}^{\neq}$ values are close to the corresponding values for systems with electron-donor substituents; this also determines the large barriers of the tautomeric transitions for this case. The nature of substituent X in the benzene ring has the greatest effect on the rate constants. Thus the $k_1$ values are increased by a factor of 15,000 on passing from the electron-donor substituent to an electron-acceptor substituent for the two extreme members of the series. For comparison, we note that $K_T$ increases only by 9.3 times.

A good correlation between the $\ln(k_{-1}/k_1^{\circ})$ and $\ln(k_1/k_1^{\circ})$ constants and the $\sigma$ substituent constants is observed ($k_1^{\circ}$ and $k_{-1}^{\circ}$ are the rate constants for X = H; the COOH substituent was disregarded in the correlation): for transition from the I form to the II form correlation coefficient r is 0.97, $\rho$ is 6.52 ± 0.74, and the sum (F) of the squares of the deviations of the experimental points from the regression line is 1.68; for the reverse transition r, $\rho$, and F are 0.98, 4.97 ± 0.49, and 1.58. Better correlation is observed when the $\sigma^+$ substituent constants are used: the r, $\rho$, and F values are 0.993, 4.68 ± 0.26, and 1.04 for the I → II transitions, as compared with 0.997, 3.56 ± 0.12, and 0.86 for the II → I transitions. The better correlation with the $\sigma^+$ substituent constants may be associated with the presence of a partial positive charge on the nitrogen atom because of the partial double bond characteristic for amides with the formation of the $-\overset{+}{N}{=}C{-}O^-$ structure (according to the data in [8], the fraction of this form reaches 40%) and the possibility of direct polar conjugation with electron-donor substituents. For comparison we note that the $\sigma^+$ constants also ensure better correlation with the equilibrium constants ($K_T$) [1].

The pronounced acceleration of the tautomeric transformations under the influence of bases and the observed character of the effect of substituent X on these transformations (the increase in the rate constants when electron-donor substituents are present and the decrease in the rate constants when electron-acceptor substituents are present) provide a basis for the assumption that the rate-determining step in the process is detachment of a proton. The scheme of the tautomeric transformation can be represented in the form

$$I \underset{k'_1}{\overset{k_1}{\rightleftarrows}} \left[ I^- \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} II^- \right] \underset{k_{-1}}{\overset{k'_{-1}}{\rightleftarrows}} II,$$

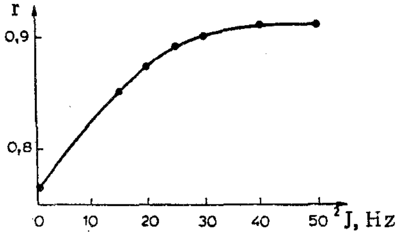


Fig. 3

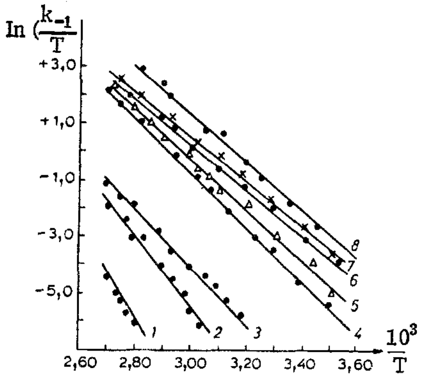


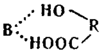
Fig. 4

Fig. 3. Dependence of the correlation coefficient (r) on the magnitude of the constant ($^2J$) of spin–spin coupling between the protons of the 2-$CH_2$ group of the IIe form (X = Br).

Fig. 4. Dependence of ln ($k_{-1}/T$) on the reciprocal temperature: 1) X = COOH, r = 0.990; 2) X = $N(C_2H_5)_2$, r = 0.990; 3) X = $OCH_3$, r = 0.994; 4) X = H, r = 0.999; 5) X = Cl, r = 0.989; 6) X = Br, r = 0.985; 7) X = $COOCH_3$, r = 0.993; 8) X = CN, r = 0.995.

where

$$k_1, k_{-1} \ll k'_1, k'_{-1}, k_2, k_{-2}.$$

The additional (in addition to the interaction with the hydroxyl or amide group) deactivating interaction of the basic catalyst with the carboxyl group of the tautomers (for example, of the  type) is a possible explanation of the anomalously low rate constants for the compound with a carboxyl substituent (see Table 1 and Fig. 4).

## EXPERIMENTAL

Arylhydroxypyrrolidones Ia-d and If-h were obtained by the method in [1]. 2,3,3-Trimethyl-1-(p-bromophenyl)-2-hydroxy-5-pyrrolidone (Ie)* was obtained in the same way as Id [1] from 6.9 g (0.04 mole) of p-bromoaniline and 8.1 g of 4-chloro-3,3,4-trimethyl-4-butanolide. The yield of product with mp 111-112°C was 9.2 g (77.5%). For the preparation of an analytically pure sample the substance was dissolved in chloroform and reprecipitated by the addition of hexane. Found: C 51.9; H 5.4; Br 26.9; N 5.0%. $C_{13}H_{16}BrNO_2$. Calculated: C 52.4; H 5.4; Br 26.8; N 4.7%. PMR spectrum in 50% pyridine: 3-$(CH_3)_2$ 1.24 (s, 3H) and 1.40 (s, 3H); 2-$CH_3$ 1.41 (s, 3H); 4-$CH_AH_B$ 2.40 (2.58), 2.90-3.08 (q, AB system, 4H, $J_{AB}$ = 17.1); $C_6H_4$ 7.3-7.9 ppm (m, 4H). The PMR spectra were recorded with a Hitachi-20A spectrometer (60 MHz); the concentration of Ie was 0.15 mole/liter, and the concentration of the remaining compounds was 0.4 mole/liter. A correlation for the change in the relative concentration of sodium bicarbonate as compared with solutions of the other compounds on the basis of the linear dependence of the bicarbonate concentration was introduced in the calculation of the rate constants and other values for Ie. A sodium 2,2-dimethyl-2-silapentane-5-sulfonate standard was used to exclude changes in the apparatus-induced line broadening. The temperature from 0 to 34°C were measured by means of a standard sample of methanol, and the temperatures from 34 to 100°C were measured by means of a standard sample of ethylene glycol. The temperature was measured before and after recording the dynamic PMR spectrum; the accuracy in maintaining the temperature at a constant reading was 0.5°C. All of the samples were first passed four times through a cycle of freezing, evacuation of the air, and filling of the ampul with argon. The ampuls containing the frozen samples were sealed *in vacuo*. During the recording to the necessary portion of the experimental spectra the signals were processed with an analog-digital transformer with a preset sampling time. The calculated spectrum was recorded on a perforated tape with a teletype and in this form was ready for calculation with a computer. In the calculation of the rate constants the parameters that characterize the change with temperature of the chemical shifts, line widths, and the populations of both tautomeric forms and the parameters that characterize the specific experiment (the frequencies

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*L. Ya. Denisov participated in the synthesis.

of the initial and final points of the portion of the spectrum selected for processing the temperature, and the initial lifetimes) were fixed. It was usually necessary to make three to four iterations to achieve the maximum correlation coefficient with an accuracy up to 0.003. The maximally available correlation coefficient depends markedly on the conditions under which the spectra are recorded: the phase tuning, the signal noise, etc. Points with correlation coefficients of no less than 0.85 were used in the subsequent calculations. Depending on the form of the spectrum, the number of points in the spectrum varied from 80 to 300. After iteration was completed, the correlation coefficients, rate constants, and ln (k/T) values were printed. The theoretical spectrum was also printed out for visual comparison.

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# RESEARCH ON 1-AZA TWO-RING COMPOUNDS.

# XVIII.* DETERMINATION OF THE CONFIGURATION OF 3-ALKYLPYRROLIZIDINES BY THE METHOD OF COMPETITIVE QUATERNIZATION. PROSPECTS FOR THE PREPARATIVE APPLICATION OF THE METHOD

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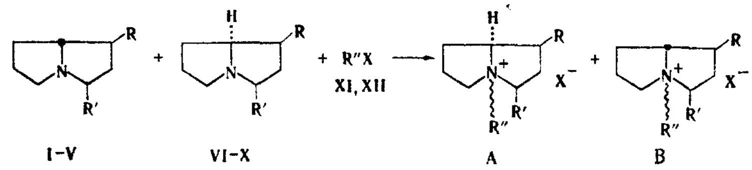
UDC 547.759.5:541.634

The applicability of competitive quaternization for the configurational assignment of isomers of 3-substituted pyrrolizidines is demonstrated. The method can be used for the preparative isolation of the isomer from mixtures.

A method for the determination of the configurations of 3-alkylpyrrolizidines in mixtures of the isomers has been developed in the case of 3-methylpyrrolizidine [2]. As a result of shielding of the free electron pair of the nitrogen atom in trans-3,8-H-3-methylpyrrolizidine (I), its N-alkylation proceeds at a lower rate than the N-alkylation of cis-3,8-H-3-methylpyrrolizidine (VI). It was assumed that any other groupings that have greater steric hindrance would give rise to an even greater difference in the rates of the reactions of the epimers, and the method was thus regarded as a general method.



I, VI R=H, R'=$CH_3$; II, VII R=H, R'=$i$-$C_3H_7$; III, VIII R=H, R'=$i$-$C_4H_9$; IV, IX R=H, R'=$t$-$C_4H_9$; V, X R=$CH_3$, R'=H; XI R''=$n$-$C_3H_7$, X=I; XII R''=$C_6H_5CH_2$, X=Cl

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*See [1] for communication XVII.

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