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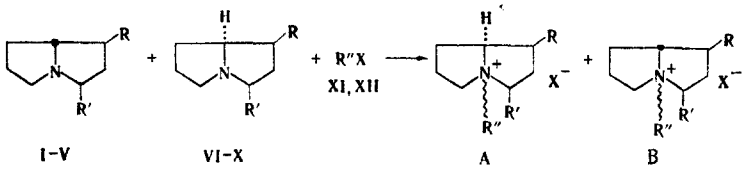
The applicability of competitive quaternization for the configurational assignment of isomers of 3-substituted pyrrolizidines is demonstrated. The method can be used for the preparative isolation of the isomer from mixtures.

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

*See [1] for communication XVII.

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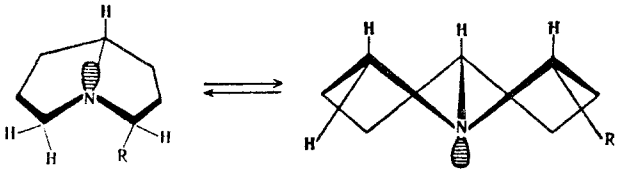
The conformational nonhomogeneity of cis isomers VI and IX, which consists in the fact that they contain both cis- (VIA and IXA) and trans-fused (VIB and IXB; for example, see [3]) forms in which the degree of shielding of the nitrogen atom is higher than in the former, was discovered in subsequent studies of the stereochemistry of pyrrolizidines.



VI A, IX A VI A, IX B

This fact was disregarded in the original scheme [2], in which cis fusion of the rings was assumed for both isomers. In this connection, the reliability of the application of the method of competitive quaternization for the solution of the problem of the stereochemistry of the epimeric 3-alkylpyrrolizidines required verification with compounds with known configurations.

We selected the isomeric 3-alkylpyrrolizidines I-IV and VI-IX, the configurations of which have been previously determined by the method of catalytic isomerization [4], for the investigation. The quaternization of the mixture of isomeric 3-alkylpyrrolizidines was carried out with n-propyl iodide (XI) in ether at room temperature. The change in the isomeric composition during the reaction was determined by gas–liquid chromatography (GLC) (Table 1).

Since the reaction rate depends on the concentrations of the starting reagents, in the case of unequal percentages of the epimers in the starting mixtures a state of the system in which the isomer ratio is 1:1 must be achieved for correct conclusions. In the case of a ratio of this magnitude and in the case of a lower percentage of one of the isomers in the starting mixture a decrease in its concentration during the reaction constitutes evidence for its higher reactivity and, consequently, its cis configuration. It follows from this that the configurational assignment with the aid of the described method can be made by means of mixtures of epimers of virtually any composition.

The reaction with n-propyl iodide proceeds extremely slowly in the case of a mixture of isomers IV and IX, apparently because of the pronounced shielding of the nitrogen atom by the tert-butyl group. The quaternization of these compounds was therefore carried out with methyl iodide. Observation of the course of the reaction showed that a very slow change in the isomeric composition occurs in the mixture of epimers IV and IX; however, the final result, as in the preceding cases, indicates that the cis isomer is more reactive than the trans isomer. Pure isomer IV remains in solution as a result of prolonged (for 5 months) reaction of a mixture of isomers IV and IX (in an initial ratio of 1:1) with CH_3I. With allowance for the weight of the precipitated quaternary salts of the A and B types it was found that ~11% of epimer IV underwent reaction, while all of epimer IX underwent reaction.

Competitive N-alkylation has been successfully used in the configurational assignment of 3-hydroxyalkylpyrrolizidines (for example, see [5]). Thus the method of competitive quaternization may be useful in the configurational assignment of other 3-substituted pyrrolizidines.

The substituent in 1-substituted pyrrolizidines is farther away from the reaction center, and one should apparently expect a smaller difference in the degree of shielding of the unshared electron pair of the nitrogen atom in the epimers. Nevertheless, the determination of the configurations of isomeric 1-methylpyrrolizidines by the method of competitive quaternization also was successful: trans isomer V reacts more slowly with n-propyl iodide than cis isomer X (Table 1).

The considerable difference in the reactivities of epimeric 3-alkylpyrrolizidines, the possibility of stopping the N-alkylation by the addition of acid, and the ease of the subsequent isolation of the base made the method a promising one in a preparative respect. The preparative merits of the method are lost in the case of isolation of isomer IV from a mixture of epimers IV and IX, and it can be understood that its application will be inefficient for the isolation of the trans isomer from a mixture of isomeric 3-tert-alkylpyrrolizidines. Examples of the isolation of the trans isomers have been described [5, 6]. The use of benzyl chloride as the alkyl halide makes it possible to obtain a salt of the A type in the first fractions of the precipitate; hydrogenolysis of this salt leads to the cis isomer. Isomer

TABLE 1. Change in the Isomeric Compositions of Mixtures of Epimeric 3-Alkylpyrrolizidines and 1-Methylpyrrolizidines as a Result of Reaction with n-Propyl Iodide

Mixture of isomers	Initial isomer ratio in the mixture, %		Reaction time, h	Final isomer ratio in the mixture	
	trans	cis		trans	cis
I and VI	36	64	20	100	0
II and VII	17	83	15	73	27
III and VIII	24	76	17	70	30
IV and IX*	50	50	72	78	22
V and X	46	54	8	88	12

*In the reaction with CH_3I.

VI was obtained in this way [6]. In the present research we isolated the latter from a mixture of epimers II and VII by this method.

EXPERIMENTAL

Chromatographic analysis was carried out with LKhM-8M and LKhM-8MD model 5 chromatographs with, respectively, thermal-conductivity and flame-ionization detectors. Triethanolamine [15% on silanized Chromaton N-AW-HMDS (0.20-0.25-mm particles)] was used as the stationary phase; the column was 2.9-m long, the inner diameter was 3 mm, the carrier-gas flow rate was 60 (hydrogen) or 40 ml/min (argon), and the thermostat temperature was 120°C (for I-III, V-VIII, and X) or 94°C (for IV and IX).

Quaternization of the pyrrolizidines was accomplished at room temperature and a reagent molar ratio of 1:2 (1:2.5 for a mixture of V and X) in a tenfold volume (with respect to the base) of ether.

Pyrrolizidines I, IV-VI, IX, and X were obtained by previously described methods [3, 7].

2-(3-Amino-4-methyl-1-pentyl)furan (XIII). A 610-ml rotating autoclave was charged with 55 g (0.34 mole) of furfurylidenemethyl isopropyl ketone [8], 120 ml of ammonia-saturated ethanol, and 8 g of Raney nickel [9]. The initial hydrogen pressure was 120 atm. The reaction was carried out at 70°C for 5 h, after which the catalyst was removed by filtration, the alcohol was removed from the filtrate by distillation, and amine XIII was tied up as the hydrochloride by the addition of a 15% HCl solution to pH 3-4. The solution was extracted with ether (the ether extracts were discarded), after which it was cooled and saturated with solid KOH. The base was separated, and the aqueous solution was extracted with ether. The ether extracts were combined with the separated base, and the resulting solution was dried with solid KOH. The ether was removed by distillation, and the residue was fractionated at reduced pressure to give 46 g (82%) of amine XIII with bp 100-101°C (12 mm), d_4^{20} 0.9438, and n_D^{20} 1.4752. Found: C 71.7; H 10.3; N 8.4%; MR_D 49.91. $C_{10}H_{17}NO$. Calculated: C 71.8; H 10.3; N 8.4%; MR_D 50.31.

2-(3-Acetamido-4-methyl-1-pentyl)furan (XIV). A mixture of 2.5 g (15 mmole) of amine XIII and 4.6 g (45 mmole) of acetic anhydride was heated on a boiling-water bath for 1 h, after which it was subjected to vacuum distillation to give 2.7 g (86%) of XIV as a colorless liquid that crystallized rapidly. The product had bp 164-165°C (3 mm) and mp 67-68°C (from benzene). Found: C 68.8; H 9.1; N 6.8%. $C_{12}H_{19}NO_2$. Calculated: C 68.9; H 9.2; N 6.7%.

3-Isopropyl-1,2-dihydropyrrolizine (XV). This compound was obtained by dehydration of amine XIII in a flow apparatus [3] at 360-380°C and a nitrogen flow rate through the reactor of 900-1000 ml/min. Aluminum oxide (GOST 8136-56) with a pour volume of 25 ml was used as the dehydration catalyst. A 19-g (0.11 mole) sample of amine XIII was passed over the catalyst in the course of 1.5 h. Ether (25 ml) and 15% HCl solutions were added to the catalyst up to pH 3-4, and the ether layer was separated, washed with water and sodium carbonate solution, and dried with solid KOH. Vacuum fractionation gave 8 g (47%) of XV with bp 91-92°C (17 mm), d_4^{20} 0.9448, and n_D^{20} 1.5051. Found: C 80.2; H 10.1; N 9.3%; MR_D 46.86. $C_{10}H_{15}N$. Calculated: C 80.5; H 10.1; N 9.4%; MR_D 46.99.

3-Isobutyl-1,2-dihydropyrrolizine (XVI). This compound was obtained in 46% yield by dehydration of 2-(3-amino-5-methyl-1-hexyl)furan [10] by the procedure used for XV and had bp 109-111°C (11 mm), d_4^{20} 0.9348, and n_D^{20} 1.5006. Found: C 80.6; H 10.3; N 8.4%; MR_D 51.41. $C_{11}H_{17}N$. Calculated: C 80.9; H 10.5; N 8.6%; MR_D 51.60.

3-Isopropylpyrrolizidines (II and VII). A 250-ml autoclave was charged with 9 g (0.06 mole) of XV, 1 g of 5% Rh/Al_2O_3 [5], and 20 ml of methanol. The initial hydrogen pressure was 80 atm. Hydrogenation was carried out at room temperature for 8 h, after which the catalyzate was acidified to pH 3-4 with 15% HCl solution, the alcohol was removed by distillation, and the unchanged 1,2-dihydropyrrolizine XV was extracted with ether. The aqueous solution was saturated with KOH, and the liberated oil was separated. The aqueous layer was extracted with ether, and the extract was combined with the oil and dried with KOH. Vacuum fractionation gave 6.2 g (67%) of a mixture of pyrrolizidines II (10%) and VII (90%) with bp 87-88°C (32 mm) and n_D^{20} 1.4685. Found: C 38.3; H 12.5; N 9.3%. $C_{10}H_{19}N$. Calculated: C 78.4; H 12.5; N 9.1%.

cis-3,8-H-3-Isopropyl-4-benzylpyrrolizidinium Chloride (XVII). A 4.6-g (36 mmole) sample of benzyl chloride (XII) was added to an ether solution of 5.6 g (37 mmole) of a mixture of isomers (10% II and 90% VII), and the mixture was refluxed on a water bath. The fractionation and analysis of the crystalline fractions were accomplished as in [6]. Workup gave 3.8 g (41% based on the cis isomer) of XVII with mp 210-212°C (from ethyl acetate). Found: C 72.8; H 9.6; N 5.1%. $C_{17}H_{26}ClN$. Calculated: C 72.9; H 9.4; N 5.1%.

cis-3,8-H-3-Isopropylpyrrolizidine (VII). A 250-ml rotating autoclave was charged with 3.6 g (13 mmole) of salt XVII, 20 ml of ethanol, and 1 g of urushivara nickel [9]. The initial hydrogen pressure was 50 atm. Hydrogenolysis was carried out at 60°C for 5 h, after which the catalyst was removed by filtration and worked up as in the synthesis of amine XIII to give 1.6 g (81%) of VII with bp 102-103°C (40 mm), d_4^{20} 0.8951, and n_D^{20} 1.4703. Found: C 78.6; H 12.8; N 9.4%; MR_D 47.79. $C_{10}H_{19}N$. Calculated: C 78.4; H 12.5; N 9.1%; MR_D 47.92.

3-Isobutyrylpyrrolizidines (III and VIII). A 610-ml autoclave was charged with 18 g (0.11 mole) of XVI, 2 g of 5% Rh/Al_2O_3, and 50 ml of ethanol. The initial hydrogen pressure was 130 atm. The reaction was carried out at 18-20°C for 16 h, after which the catalyzate was worked up as in the method described above for a mixture of II and VII to give 12.4 g (67%) of a mixture (16% III and 84% VIII) with bp 135-140°C (75 mm), and n_D^{20} 1.4672. Found: C 79.1; H 12.9; H 8.6%. $C_{11}H_{21}N$. Calculated: C 79.0; H 12.7; N 8.4%.

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