RESEARCH ON 1-AZA TWO-RING SYSTEMS. 19.* PHYSICAL PROPERTIES, CHROMATOGRAPHIC BEHAVIOR, AND STEREOCHEMISTRY OF PYRROLIZIDINE HOMOLOGS

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The physical properties and chromatographic behavior of homologs of pyrrolizidine were investigated with the aid of squalane, polyethylene glycol 20,000, and triethanolamine as liquid stationary phases. It was found that the properties of pairs of unstrained isomers are subject to the conformational rule. The retention times of the trans isomers of unstrained 1-methyl- and 3-alkylpyrrolizidines are shorter on all three stationary phases than the retention times of the cis isomers. The less significant (than in the case of other epimers) difference in the physical properties of cis- and trans-3, 8-H-3-tert-butylpyrrolizidines and the peculiarity of their chromatographic behavior are explained by the distinct conformational heterogeneity of the ring fusion type of cis-3, 8-H-3-tert-buty1pyrrolizidine. With respect to all of the examined physical constants, strained cis-3,8-H-cis-5,8-H-3,5-dimethylpyrrolizidine and its epimer do not comply with the conformational rule. In the liquid phase at ambient temperature and at the boiling point and in solutions in squalane, polyethylene glycol 20,000, and triethanolamine at ~100°C, cis-3,8-H-cis-5,8-H-3,5-dimethylpyrrolizidine contains significant amounts of the trans-fused form, which affect the entire set of properties. An empirical dependence of the properties of the pyrrolizidines on their properties can be used in the conformational assignment of analogous compounds.

In the course of stereochemical studies of pyrrolizidine (I) and its homologs we obtained and separated isomeric 3-alkyl- (VIII-XV) and 3,5-dimethylpyrrolizidines (XVI-XVIII), while 1-methyl- (II, III) and 2-alkylpyrrolizidines (IV-VII) were prepared in the form of mixtures of epimers. The configurational assignment of bases II, III, and VIII-XVIII was described in [1-4].



I $R^1 = R^2 = R^3 = R^4 = H$; II. III $R^1 = CH_3$, $R^2 = R^3 = R^4 = H$; IV, V $R^1 = R^3 = R^4 = H$, $R^2 = CH_3$; VI, VII $R^1 = R^3 = R^4 = H$, $R^2 = C_2H_5$; VIII, IX $R^1 = R^2 = R^4 = H$, $R^3 = CH_3$; X, XI $R^1 = R^2 = R^4 = H$, $R^3 = i \cdot C_3H_7$; XII, XIII $R^1 = R^2 = R^4 = H$, $R^3 = i \cdot C_4H_9$; XIV, XV $R^1 = R^2 = R^4 = H$, $R_3 = t \cdot C_4H_9$; XVI, XVIII $R^1 = R^2 = R^4 = H$, $R^3 = R^4 = CH_3$

With this series of compounds at our disposal, it was interesting to compare the physical properties and chromatographic behavior of the bases with their stereochemistry. In the latter case we also examined the related (to pyrrolizidines) tertiary two-ring amines indolizidine (XIX) and quinolizidine (XX).

A comparison of the physical constants (Table 1) of pyrrolizidines VIII-XVIII makes it possible to evaluate the applicability of the known empirical correlations that link the constants of the epimers with their geometry for the solution of the problem of the configuration of 3-alkylpyrrolizidines and to arrive at the conclusion that the trans-fused form makes a significant contribution to the equilibrium mixture of the conformations of XVIII.

*See [1] for communication 18.

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TABLE 1. Physical Constants of the Homologs of Pyrrolizidine and Differences* in the Constants of the Epimers

Com-	bp, °C	Δ (bp)				1 11	MR _D		110	Literature
pound	(mm)	°C	d₄ ^{:0}	$\Delta d_{4^{20}}$	ⁿ D	Δn_D^2	found	calc.	J.SIKD	
11	155		-		1,4620		_			
III	(748) 168—170 (748)	13	-		1,4638	0.0018				[2]
VШ	77-78		0,8919		1,4608		38,51			
IX	85-86 (72)	8	0,9092	0,0173	1,4689	0,0081	38,34	38,68	-0,17	[18]
Х	94-96		0,8770		1,4628		48,11			
XI	(40) 102-103 (40)	7,5	0,8951	0,0181	1,4703	0,0075	47,81	47,92	-0,30	[1] and this research
XII	90-92		0,8759		1,4632		52,62			This re-
ХШ	(20) 103104 (20)	12,5	0,8911	0,0152	1,4708	0,0076	52,45	52,53	-0,17	search
XIV XV	122,8 (80) 123,6 (80)	0,8	0,8885 0,8982	0,0097	$1,4690 \\ 1,4726$	0,0036	52,44 52,21	52,53	-0,23	[3]
XVI	93.6†	66	0,8753	0.0204	1,4581	0.0088	43,43		-0.31	
XVII XVIII	$\begin{vmatrix} 100,2 & (86) \\ 89-89,4 \\ (86) \end{vmatrix}$	-11	0,8957 0,8658	-0,0299	1,4669 1,4600	- 0,0069	43,12 44,05	43,30	0,93	[4]
	1	1 .	1	1		•	1	1	1	4

*The constants of the trans isomers were subtracted from the constants of the cis isomers. The average temperature interval was used in the determination of the Δ (bp) values. +The boiling points of isomers XVI-XVIII described in [4] were redetermined at one pressure.

According to the conformational rule [5], the thermodynamically more stable isomer has a higher boiling point, density, and refractive index but a lower molecular refraction than its epimer [5, 6]. The limits of application of such empirical principles are not completely clear even in series of hydrocarbons, for which anomalous cases have been noted [6, 7]. In the case of compounds with polar groups the relationship between the constants and the geometry of the isomers becomes more complex in the general case [6]. Nevertheless, compliance with the conformational rule during comparison of the epimers is observed in some series of saturated heterocycles. For example, in the case of 1-, 2-, 3-, and 4-methylquinolizidines the thermodynamically less stable (more strained) isomer has a higher refractive index [8].

Among the pairs of epimers II and III, VIII and IX, X and XI, XII and XIII, XIV and XV, and XVI and XVII, cis epimers III, IX, XI, XIII, XV, and XVII have higher boiling points, densities, and refractive indexes but lower molecular refractions than the corresponding trans isomers II, VIII, X, XII, XIV, and XVI. Thus the relationship between the constants and the stereochemistry in the presented pairs of isomers is in agreement with the conformational rule, and the difference in the physical constants, at least for the epimeric 3-alkylpyrrolizidines, can be used for configurational assignment.

During a comparison of the differences in the constants of the epimeric 3-alkylpyrrolizidines one's attention is directed to the smallest difference in the physical properties of isomers XIV and XV. For the given pair the Δ (bp) value differs by an order of magnitude from the values of the remaining compounds. The first possible reason for drawing together of the boiling points of the epimers consists in the effect of branching at the α -carbon atom relative to the ring [6, 7]. Another factor that gives rise to a similar effect may be the relatively high percentage of the trans-fused XVB conformation in a dilute mixture with the cis-fused XVA conformations [3] (see scheme on following page).

If the above reasoning is valid, it can be seen that the presence of the XVB form in increased concentrations as compared with pyrrolizidines VIII-XIV, XVI, and XVII is responsible for the lower dipole moment of epimer XV than in the case of the other pyrrolizidines.



The latter is understandable from an examination of the dipole moments of various conformations of pyrrolizidine [9] calculated by a vector scheme [10] (Table 2). The dipole moments of the homologs of pyrrolizidine in analogous conformations will have the same values, since the group moment of alkyl radicals is zero [10]. All things being equal, the lower dipole moment of epimer XV determines the less significant contribution of orientation forces to the van der Waals interactions between its molecules and the lower boiling point than would be observed for the compound if it existed in the cis-fused XVA conformation. The transition from the XVA conformations to the XVB form is simultaneously accompanied by an increase in molecular exchange, which leads to weakening of the dispersion interactions and also lowers the boiling point of the isomer. Both of the examined factors — branching at the α carbon atom relative to the ring and weakening of the intermolecular interactions in base XV due to the significant weight of the XVB conformation — may act in the same direction.

Distinct noncompliance with the conformational rule with respect to all of the physical constants is observed for epimers XVII and XVIII, which differ with respect to the configuration at C(s). In this case cis isomer XVIII has a lower boiling point, density, and refractive index but a higher molecular refraction than trans isomer XVII. The similar properties of XVIII are a direct consequence of the fact that they exist primarily in the trans-fused XVIIIB form [4, 12] (see scheme on following page).

In the XVIIIB conformation the molecule occupies a greater volume and has a lower dipole moment than in the XVIIIA conformations, similar to the cis-fused conformations of the XVII

*Here and subsequently (XVIIIA), the entire set of cis-fused conformations is collectively depicted in similar form.

TABLE 2. Calculated Dipole Moments of Various Conformations of Pyrrolizidine*



*The projections of the unit bond vectors of the conformations of pyrrolizidine presented in the table were taken from [11].

FABLE 3	. Results of	Chromato-
graphic	Analysis of	I-IX and
XII-XX		

Com-	Retention times in columns with a stationary phase, min							
pound	squal-	polyethylene triethanol-						
	alle	glycol 20000 amine						
I	6,3	5,9	10,7					
11	9,2	7,2	11,8					
III	12,1	9,5	16,5					
IV V	9,3	7,2	10,8					
VI VII	17,7	13,0	19,1					
VIII	6,9	5,1	6,1					
IX	8,7	7,3	12,3					
XII	36,9	18,2	11,5					
XIII	50,1	27,1	25,4					
XIV XV	16,5	11,4*	2,0 3,2					
XVI	8,3	4,6	2,9					
XVII	11,8	7,5	8,6					
AVIII	7,5	3,4	1,0					
XIX	7,9	5,1	2,6					
XX	17,3	10,6	4,8					

*cis Isomer XV emerges from the column before trans isomer XIV.



isomer. In a geometrical respect, the XVII, XVIIIB pair is similar to the cis- and transbicyclo[3.3.0]octane pair, for which the conformational rule is not satisfied [6].

A study of the chromatographic behavior of a series of homologs of pyrrolizidine reveals empirical regularities that may be useful for the establishment of the configurations of epimers. In addition, a comparative analysis of the retention times of the compounds on liquid stationary phases of different types confirms the above reasoning with respect to the conformational peculiarities of bases XV and XVIII. The retention times of 1-aza two-ring systems on squalane (SQ), polyethylene glycol (PEG), and triethanolamine (TEA) are presented in Table 3.

Dispersion forces are the principal form of interaction between the sorbent and sorbate in the case of dissolving in SQ [13], and the order of emergence of the isomers from the column is determined by the compactness of the molecules [14]. trans Isomers II, VIII, XII, and XVI have large molecular volumes and interact weakly with the SQ molecules; they therefore emerge before the corresponding cis isomers III, IX, XIII, and XVII. Epimers XVII (the trans isomer) and XVIII (the cis isomer) constitute exceptions to this. The order of emergence of these compounds found in this study can be explained by the fact that isomer XVIII has a larger molecular volume than isomer XVII and consequently, as in other cases [4, 12], exists primarily in the trans-fused XVIIIB form.

The effect of branching of the hydrocarbon radical in the 3 position is manifested clearly in the case of isomers XII and XIII and XIV and XV — the latter emerge more rapidly than the first two compounds by a factor of greater than two and in a single peak. The retention times of the investigated pyrrolizidines on SQ change in the same direction as their boiling points.

Orientation forces play an important role in the dissolving of the pyrrolizidines in the polar PEG phase. As in the case of SQ, trans isomers II, VIII, XII, and XVI are retained more weakly on PEG than cis isomers III, IX, XIII, and XVII. In addition to the contribution of dispersion interactions, the steric factor, by hindering interaction of the base molecules on the side of the unshared electron pair of the nitrogen atom and the PEG molecules in the case of the trans isomers, plays a substantial role. Again one's attention is directed to the effect of the difference in the retention of epimers XII and XIII, on the one hand, and isomers XIV and XV, on the other. In contrast to the first pair of compounds, XIV and XV are poorly separated under the same conditions. Separate experiments with specially selected conditions showed that, in contrast to the epimeric pairs of 1-methyl- and 3alkylpyrrolizidines, cis isomer XV emerges before trans isomer XIV on PEG. This order of emergence of isomers XIV and XV can be explained by the fact that base XV exists to a considerable extent in the trans-fused XVB conformation, as a consequence of which the dipole moment is lower, and the orientation interactions with the molecules of the stationary phase are consequently weaker than in the case of isomer XIV. Weakening of the contribution of the dispersion interactions as the fraction of the XVB conformation increases also acts in the same direction. Similar factors determined the order of emergence of epimers XVII and XVIII. In this case the apparent anomaly is manifested particularly distinctly and is due to the greater contribution to the conformational equilibria of the trans-fused XVIIIB form of XVIII in solution in PEG.

When TEA is used as the stationary phase, specific sorbate—sorbent interactions caused by the formation of an intermolecular OH...N hydrogen bond, on the strength of which steric factors have a substantial effect [15], begin to play an important role. In the trans isomers the alkyl group oriented on the same side as the unshared electron pair of the nitrogen atom will shield it and prevent the formation of a hydrogen bond.

In 3-alkylpyrrolizidines the substituent is found at the α -carbon atom, and the difference in the shielding of the nitrogen atom of the epimers is therefore more pronounced and separation is better than in the case of 1-methylpyrrolizidines II and III. The paramount role of hydrogen bonding in the chromatography of epimeric 3-alkylpyrrolizidines is manifested in the considerably better separation of the isomers on TEA than on the other phases.

The short retention time of base XVIII as compared with the isomeric XVI and XVII and generally all other investigated pyrrolizidines can be explained by the fact that this compound exists to a significant degree in the XVIIIB conformation in solution in TEA at 96°C. In this conformation the unshared electron pair of the nitrogen atoms is sterically less accessible than in the cis-fused forms. In addition, in the XVIIIB conformation the unshared electron pair of the nitrogen atom, as is apparent from models, is antiparallel with respect to the C(s)-H bond, and it can therefore experience partial delocalization via a mechanism similar to that described for quinolizidine [16]. This circumstance possibly determines the reduced basicity (pK_a 10.28) of XVIII as compared with isomers XVI (pK_a 11.46) and XVII (pK_a 11.74) [17] and other pyrrolizidines [18]. It is understandable that in a case of this sort XVIII will form the weakest intermolecular hydrogen bond with TEA in the series of pyrrolizidines under examination.

The dominating effect of the basicities of the related tertiary amines on the specific interaction with TEA is displayed particularly distinctly when one compares the retention times of I (pK_a 11.68 ± 0.06) [18], XIX (pK_a 10.15 ± 0.05) [18], and XX (pK_a 10.19 ± 0.07) [19] on all three phases (Table 3).

We were unable to separate samples of the epimeric 2-alkylpyrrolizidines IV and V and VI and VII on any of the three selected liquid phases. The assumption that we are dealing in each case with one individual isomer rather than with a mixture of isomers is unlikely, since the compounds were obtained by hydrogenation of the corresponding 2-methyl- [20] and 2-ethyl-1,2-dihydropyrrolizine [21] on different catalysts and under different conditions [21]. The presence of both epimers IV and V (39 and 61%) in one of the samples was established from the 13 C NMR spectrum. From the results of the chromatographic studies it may be concluded that among the investigated compounds the properties of the isomers within the IV and V and VI and VII pairs differ to the greatest extent.

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EXPERIMENTAL

Chromatographic analysis was carried out with an LKhM-8M chromatograph with a thermalconductivity detector. The surface of Chromaton N-AW-HMDS (Chemapol) with grain size 0.20-0.25 mm was treated with 10% squalane (phase 1), 15% polyethylene glycol 20,000 (phase 2), or 15% triethanolamine (phase 3). Steel columns 2.9-m long with an inner diameter of 3 mm and thermostated at, respectively, 104, 93, and 96°C, were filled with phases 1-3. The carrier gas was hydrogen, the flow rates of which for columns containing phases 1-3 were, respectively, 91, 60, and 115 ml/min.

The boiling points of the isomers were determined in each case at one pressure, which was stabilized by means of a manostat.

Bases I-XX in the form of individual compounds (I, VIII, IX, XI, and XIV-XX) or mixtures of isomers (II and III, VI and VII, X and XI, and XII and XIII) were obtained by previously described methods [1, 3, 4, 18, 21-23].

<u>Mixture of trans- (IV) and cis-2,8-H-2-Methylpyrrolizidines (V).</u> A 610-ml autoclave was charged with 9 g of 2-methyl-1,2-dihydropyrrolizine [20], 50 ml of ethanol, and 2 g of Raney nickel. The initial hydrogen pressure was 114 atm. The hydrogenation was carried out at 100°C for 8 h, after which the catalyzate was removed by filtration and acidified to pH 3-4 with 15% hydrochloric acid. The ethanol was removed by distillation, and the residue was extracted with ether. The aqueous solution was saturated with solid KOH, the solvent was removed by distillation, and the residue was distilled at reduced pressure to give 6.4 g (68%) of a mixture of epimers IV and V with bp 73-74°C (40 mm). Found: C 77.2; H 12.2; N 11.2%. C₈H₁₅N. Calculated: C 76.7; H 12.1; N 11.2%.

<u>trans-3,8-H-3-Isopropylpyrrolizidine (X).</u> A 150-ml rotatory autoclave was charged with 2 g (13 mmole) of a mixture of isomers X (34%) and XI (66%), 15 ml of ethanol, and 1 g of a 5% Rh/Al₂O₃ catalyst. The hydrogen pressure was 120 atm. The autoclave was heated at 110-120°C for 20 h with periodic monitoring of the change in the isomeric composition by means of gas-liquid chromatography. At the end of the isomerization, HCl solution was added to the catalyzate until it was acidic, and the alcohol was removed by distillation at reduced

pressure. Base X was forced out of solution by the addition of solid KOH, and the mixture was extracted with ether. The extract was dried with KOH and distilled at reduced pressure to give 1.1 g (55%) of X. Found: C 78.5; H 12.6; N 8.9%. $C_{10}H_{19}N$. Calculated: C 78.4; H 12.5; N 9.1%.

trans-3,8-H-3-Isobutylpyrrolizidine (XII). Isomerization of 4.5 g (27 mmole) of a mixture of isomers XII (70%) and XIII (30%) by a method similar to that presented above gave 1.6 g (35%) of base XII. Found: C 79.4; H 13.2; N 8.6%. C11H21N. Calculated: C 79.0; H 12.7; N 8.4%.

<u>cis-3,8-H-3-Isobutylpyrrolizidine (XIII)</u>. A 3.8-g (23 mmole) sample of 60% perchloric acid was added to a solution of 3.8 g (23 mmole) of a mixture of isomers XII (12%) and XIII (88%) in 60 ml of ether, and the resulting oil crystallized after repeated washing with ether. Four recrystallizations of the mixture of salts of the isomers from decyl alcohol gave a perchlorate, which was dissolved in water and treated with alkali. The resulting base (XIII) was purified by the usual method to give 1.1 g (33%) of XIII with an isomeric purity of 98%.

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