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cis-trans-CONVERSION OF THE BICYCLE IN PYRROLIZIDINES: THE EFFECT OF THE PREFERRED CONFORMATIONS ON THE PROPERTIES OF THE BASES AND THE THERMODYNAMICS OF CONFORMATIONAL TRANSFORMATION OF THE RING FUSION TYPE. (REVIEW)

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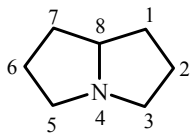
The cis-trans conversion in pyrrolizidines and the deciding effect of steric factors on their conformational equilibrium are discussed. Work on the synthesis and characteristics of sterically strained pyrrolizidines is analyzed and discussed. It is shown that such compounds (predominantly trans-fused) have a series of features in their properties that greatly distinguish them from unstrained pyrrolizidines. The first results from study of the thermodynamics of cis-trans conversion of the pyrrolizidine bicycle are summarized.

Keywords: conformers, pyrrolizidines, *trans*-fused pyrrolizidines, *cis-trans* conversion, thermodynamics.

An important aspect of the conformational analysis of pyrrolizidines is their heterogeneity resulting from the possibility of different types of ring fusion.

During discussion of the probable conformations of pyrrolizidine (**1**),* i.e., its *trans*-fused (**1A**) and *cis*-fused (**1B**) forms, the choice was made in favor of the latter since, unlike the conformation **1A**, it is free from strong angular strains [1].



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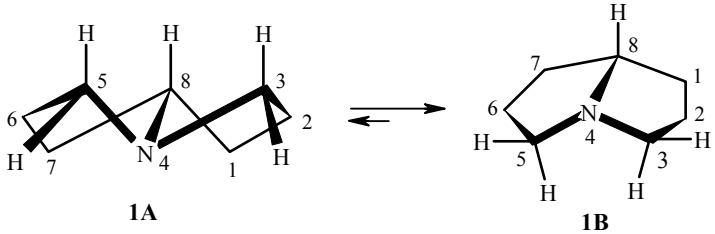

1A **1B**

* The formulas of the specific compounds are numbered systematically irrespective of the form in which they are presented. The letter **A** indicates the *trans*-fused form of the pyrrolizidine [2, 3] or its derivative. The letter **B** indicates the whole family of *cis*-fused conformations of such compounds.

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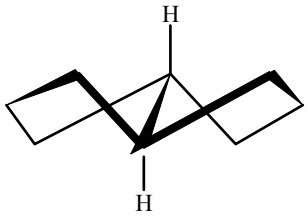
The idea that the **1B** conformer predominates in the equilibrium state received serious support during comparison of the enthalpies of formation of the hydrocarbon analogs of *trans*- and *cis*-bicyclo[3.3.0]octane **2** and **3**, geometrically similar to conformers **1A** and **1B**.



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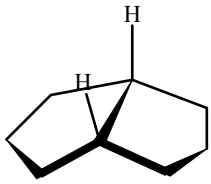


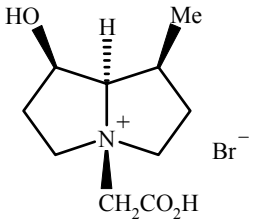
3

The difference between the enthalpies of formation of compounds **3** and **2** amounts to -26.8 and -27.2 kJ/mol for the gas and liquid phases respectively [4].*

The assumption made in [1] about the preference for the *cis*-fused form **B** of pyrrolizidine **1** seems Justified in the light of the data presented in [4].

Subsequently the concept of *cis*-fusion of the rings, both in the parent base **1** and in its numerous derivatives, received general recognition, and it was used in many papers [5-9] and textbooks (e.g., see [10]).

A *trans*-fused system of two saturated condensed five-membered rings with one bridgehead (although quaternary) nitrogen atom (with fixed configuration) was first realized in the salt **4** [11].



4

From the standpoint of the basic principles of conformational analysis [12, 13] it is easy to see that for the pyrrolizidine derivatives the fraction of the *trans*-fused form **A** in the **A** $\rightleftharpoons$ **B** equilibrium must be greater in the case of compounds where there are strong nonbonding interactions together with an inversion center at the nitrogen atom, i.e., at positions 3 and 5, in all the *cis*-fused conformations **B**. In form **A** these interactions are weaker, but a strong angular strain appears. Thus, the state of the specific conformational equilibrium is determined by the difference between the energies of the nonbonding interactions in the *cis*-fused conformations **B** and the energy of the angular strain in the *trans*-fused conformation **A** of the pyrrolizidine framework.

The pyrrolizidines were subdivided provisionally into unstrained and weakly and highly strained bases, according on the strength of the nonbonding interactions in the *cis*-fused forms **B** [14, 15]. It should be understood that we are not discussing compounds in which the strain originates from interaction between sterically close substituents at the $C_{(1)}$ and $C_{(7)}$ atoms.

Unstrained pyrrolizidines are, for example, pyrrolizidine **1** itself and its homologs in which the **B** forms are free from substantial nonbonding interactions. In such compounds the conformational equilibrium is shifted very strongly toward these forms, and it is quite difficult to detect the extremely small amounts of the *trans*-fused **A** forms experimentally.

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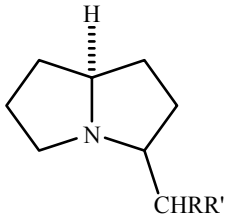
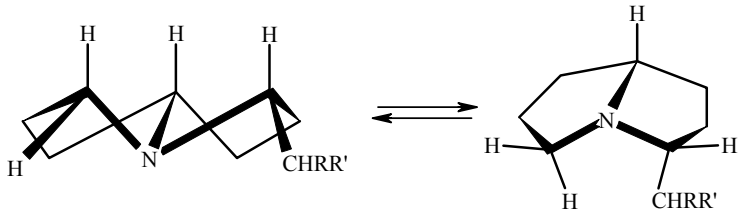
* In the cited papers the enthalpies and free energies are given either in kJ/mol or in kcal/mol. Throughout the review the thermodynamic parameters are given in kJ/mol for convenience of comparison.

Compounds of type **5** containing a substituent attached to the bicycle by a secondary or tertiary carbon atom instead of the *trans*-H-3 atom are consider weakly strained pyrrolizidines.



R, R' = H, Alk, Ar, functionally substituted Alk, Ar

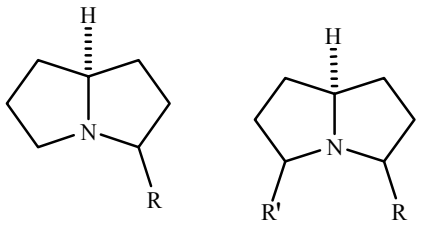
Here, nonbonding interactions occur in any of the *cis*-fused conformations **5B**, while the *trans*-fused form **5A** has strong angular strain.



5A **5B**

It is clear that the nonbonding interactions in the *cis*-fused forms **B** of compound **5** are increased on account of the presence of the more bulky substituent (compared with the base **1**) at position 3. This increases their strain and reduces the absolute value of the difference in free energies between forms **5B** and **5A**. Experiment shows that it becomes possible to observe a change in the conformational equilibrium **5A** $\rightleftharpoons$ **5B** with variation of temperature [16] and to determine the content of the individual conformers [17, 18] even in the case of the smallest substituent Me.

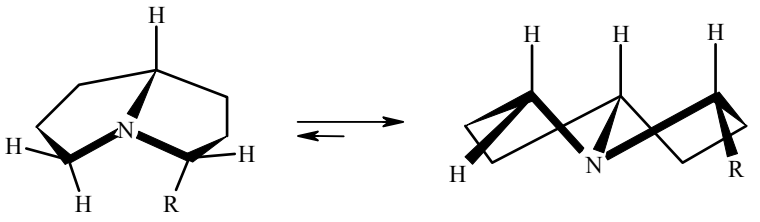
The highly strained pyrrolizidines include 3-substituted and 3,5-disubstituted bases of types **6** and **7** respectively.



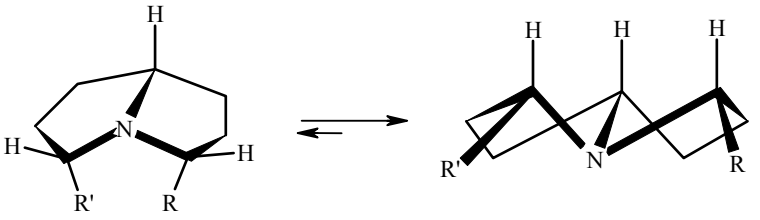
6 **7**

6 R = *t*-Alk; **7** R, R' = Alk, Ar, alkenyl, functionally substituted Alk, Ar

In such compounds in all the *cis*-fused conformations **6B** or **7B** there are very substantial steric interactions that significantly raise the level of their free energy. These nonbonding interactions are removed during the transition of the molecules to the *trans*-fused form **6A** or **7A**.



6B **6A**



7B **7A**

However, there are strong angular strains in forms **A** [2, 14, 15, 17]. In spite of this many pyrrolizidine derivatives of types **6** and **7** exist preferentially in the *trans*-fused conformations **A** [14, 17-23], demonstrating the considerable supremacy of the *cis*-fused forms **B** with respect to strain that determines the preference for the **A** forms.

In each specific case the position of the conformational equilibrium can clearly be affected also by intramolecular interactions (e.g., hydrogen bonds) and by the nature of the medium in which the base is situated.

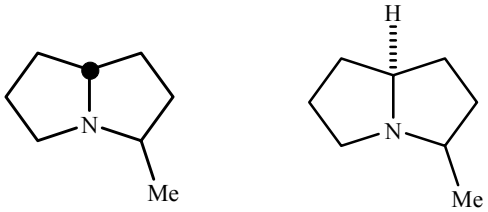
The number of described cases of highly strained pyrrolizidines is still small. These compounds can be considered unique in so far as, having an sp^3-hybridized nitrogen atom and existing predominantly in the *trans*-fused form **A**, they do not change into the *cis*-fused form **B** that is usual for the majority of known pyrrolizidines. (This form is even more thermodynamically unstable for them on account of the unfavorable nonbonding interactions.)

The particular geometry and the strain in the *trans*-fused framework of the two five-membered rings with a bridgehead nitrogen atom in pyrrolizidines give rise to a series of unusual physical, physicochemical, and chemical properties in these compounds in comparison with their *cis*-fused analogs, and this is of general theoretical interest. The obtained comparatively low absolute value of ΔH for the *trans*-*cis*-conversion of forms **1A** and **1B** [24] compared with the heats of formation of their carbocyclic analogs **2** and **3** raises the question of the nature of the stabilization of the *trans*-fused conformation of pyrrolizidines.

In connection with the foregoing it is of interest to analyze and classify data on investigation of the conformational heterogeneity of pyrrolizidines and also on the synthesis and properties of the highly strained predominantly *trans*-fused forms of these compounds.

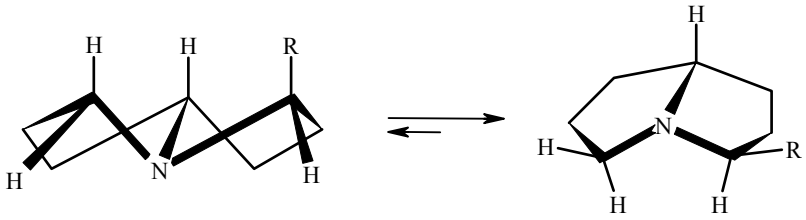
1. DETECTION OF CONFORMATIONAL HETEROGENEITY IN PYRROLIZIDINES ACCORDING TO THE TYPE OF RING FUSION

The first attempt at the experimental detection of conformational heterogeneity in pyrrolizidines involved observation of the temperature dependence of the ^{1}H NMR spectra of unsubstituted pyrrolizidine **1** and also of 3-methylpyrrolizidines **8** and **9** [16]. The spectra of compound **1** and of *trans*-3,8-H-3-methylpyrrolizidine **8** hardly changed at all with variation of the temperature in the ranges between -70 and +190 and between -80 and +100°C respectively.



8 **9**

According to the reasoning in [25], the obtained results indicate an initially strong shift of the equilibria **1A** ⇌ **1B** and **8A** ⇌ **8B** toward forms **1B** and **8B** respectively.

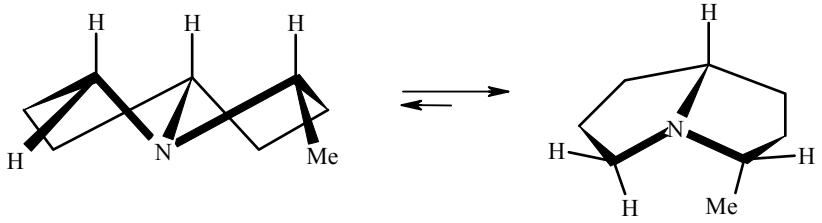


1A, **8A** **1B**, **8B**

1 A, **B** R = H; **8 A**, **B** R = Me

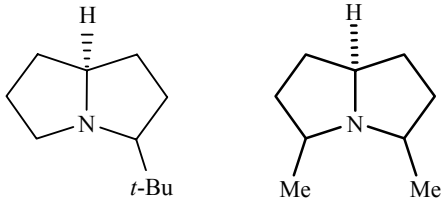
On the contrary, a clear temperature dependence was observed for the ^{1}H NMR spectrum of *cis*-3,8-H-3-methylpyrrolizidine **9** in a close temperature range (between -85 and +171°C) [16].

From analysis of the temperature variations in the chemical shift of the H-8 proton of the isomer **9** (the upfield shift of the signal of this proton with increase in temperature) and the effects of its screening in conformations **9A** and **9B** it was concluded that the conformational equilibrium is shifted toward form **9B** and that the fraction of the conformer **9A** increases in the transition from low to higher temperatures [16].



9A **9B**

The validity of this suggestion was later confirmed by data from the ^{1}H NMR spectra of the highly strained predominantly *trans*-fused *cis*-3,8-H-3-*tert*-butylpyrrolizidine (**10**) and *cis*-3,8-H-*cis*-5,8-H-3,5-dimethylpyrrolizidine (**11**) [17].

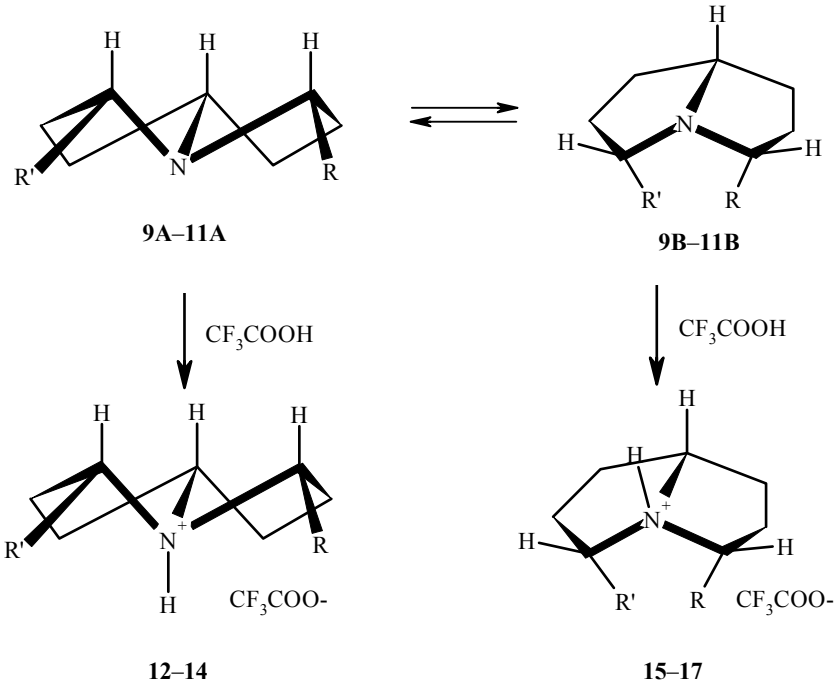


10 **11**

The signal of the H-8 proton of these bases in the spectra lies at 2.51 and 2.43 ppm respectively and is shifted by approximately 0.9-1.1 ppm upfield compared with the analogous signal of the unstrained pyrrolizidines **1** and **8** [17].

What was said above about the conformational state of the base **9** was confirmed by observation of the temperature dependence of its ^{13}C NMR spectrum. With increase in temperature the signal of the bridgehead $C_{(8)}$ atom is shifted downfield to the region where the signals of the $C_{(8)}$ atoms of the highly strained predominantly *trans*-fused compounds **10** (70.1 or 71.0 ppm) and **11** (72.7 ppm) lie [14, 19].

Other evidence for the conformational heterogeneity (of the ring-fusion type) in compounds **9-11** was obtained during comparison of the ^{13}C NMR spectra of their protonated forms **12-14** and **15-17**, formed as a result of reaction of the bases **9-11** with trifluoroacetic acid [18].



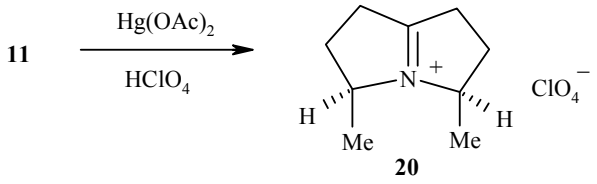
12–14 **15–17**

9A, **9B, 12**, **15** R = Me**,** R' = H; **10A**, **10B**, **13**, **16** R = *t*-Bu, R' = H;
11A, **11B**, **14**, **17** R = R' = Me

Unlike pyrrolizidine **1** [9] and *cis*-3,8-H-*trans*-5,8-H- and *trans*-3,8-H-*trans*-5,8-H-3,5-dimethylpyrrolizidines **18** and **19**, their isomer **11** enters readily into oxidative dehydrogenation with mercuric acetate and forms *cis*-3,5-dimethyl-$\Delta^{4(8)}$-dehydropyrrolizidinium perchlorate (**20**) [26].

18 **19**

In this paper the above-mentioned fact is regarded as evidence for the relatively large content of form **11A** in the equilibrium mixture of conformations **11A** and **11B**.

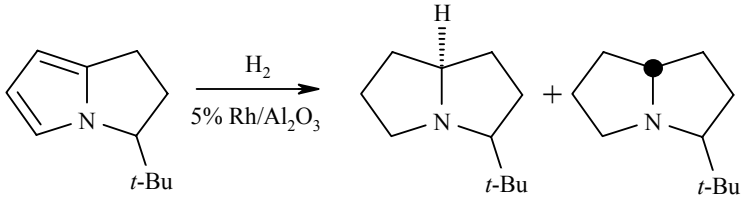


20

This conclusion follows from the previously established fact that saturated bicyclic bases with a bridgehead nitrogen atom enter readily into such a transformation on the condition that the unshared electron pair of the nitrogen atom and the C–H bond at the bridgehead carbon atom common to both rings have an anticoplanar arrangement [27], i.e., with *trans*-fusion of the rings.

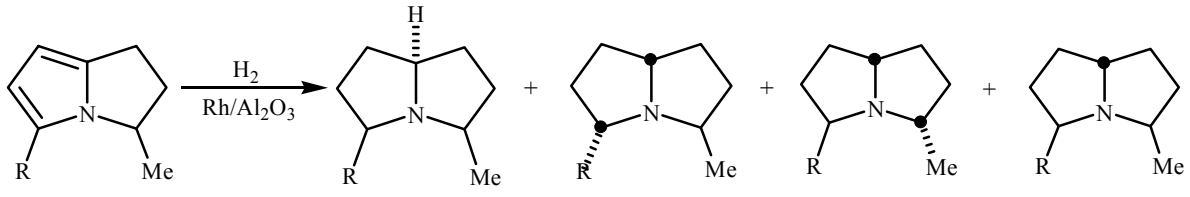
2. THE PRODUCTION OF HIGHLY STRAINED PYRROLIZIDINES

At the present time comparatively few cases of the production of pyrrolizidine bases with preferred *trans*-fusion of the rings have been described. Among the employed methods of synthesis none are stereospecific. Mixtures of isomers, of which one is highly strained, are usually formed. This isomer is isolated from the mixture by using the difference between its physical or chemical properties and the properties of the other isomers. Thus, a mixture of *cis*-3,8-H-3-*tert*-butylpyrrolizidine (**10**) and its isomer **22** is obtained during the catalytic hydrogenation of 3-*tert*-butyl-1,2-dihydropyrrolizidine (**21**) [28].



21 **10** (9)* **22** (1)

During the hydrogenation of various 3,5-disubstituted 1,2-dihydropyrrolizidines **23-25** the highly strained pyrrolizidines **11**, *cis*-3,8-H-3-methyl-*cis*-5,8-5-H-hydroxymethylpyrrolizidine (**26**), and *cis*-3,8-H-3-methyl-*cis*-5,8-H-5-(3'-hydroxypropyl)pyrrolizidine (**27**) are formed, each in a mixture with their isomers: **18** and **19**; **28**, **30**, and **32**; **29**, **31**, and **33** respectively [29-32].

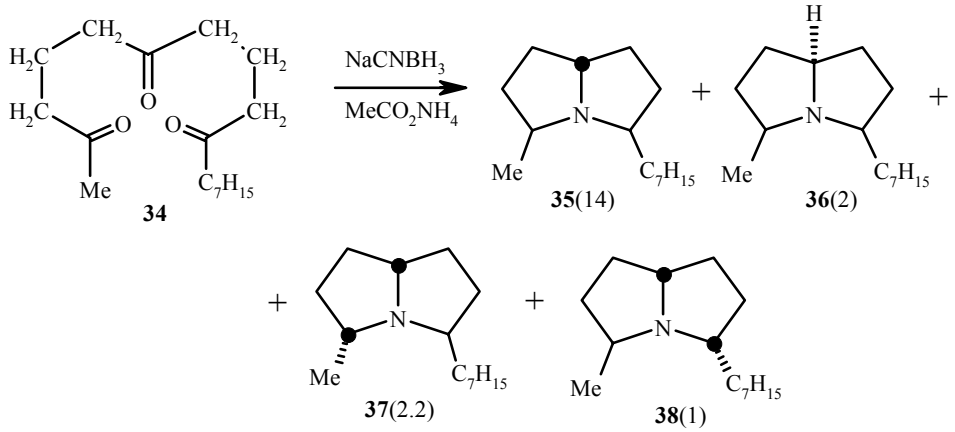


23-25 **11**, **26**, **27** **18**, **28**, **29** **18**, **30**, **31** **19**, **32**, **33**

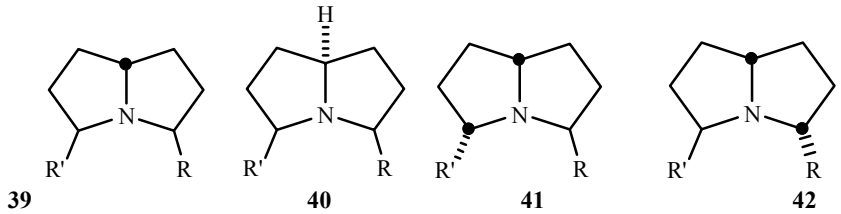
11, **18**, **19**, **23** R = Me; **24**, **26**, **28**, **30**, **32** R = CH_2OH; **25**, **27**, **29**, **31**, **33** R = $(CH_2)_3OH$

* Here and subsequently the relative weight fractions of the formed isomers are given in parentheses after the compound number. In a number of cases they were calculated by ourselves from the percentage contents of their mixtures and data on the yields of the isomers.

The reductive amination of heptadeca-2,6,10-trione (**34**) with a mixture of sodium cyanoborohydride and ammonium acetate was used for the synthesis of the pheromone **35** of ants of the *Solenopsis sp.* species. All four possible isomers of 3-heptyl-5-methylpyrrolizidine **35-38** were formed here, and among them the base **36** must be regarded as highly strained. Its proportion in the mixture was comparatively small [20].



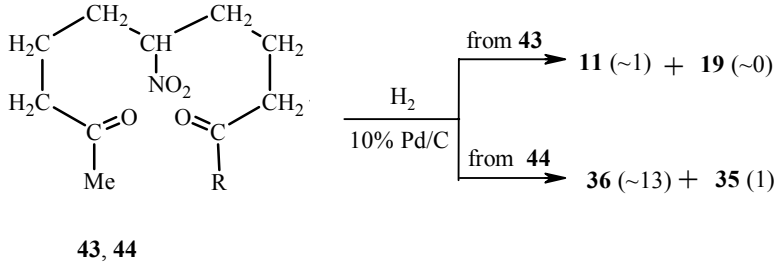
In [21] a mixture of the isomeric bases **39-42** was obtained by a series of transformations differing little from those described in [20].



39-42 R = $(CH_2)_7CH{=}CH_2$, R' = CH=CH–Me

According to the classification of the degree of strain of pyrrolizidines in relation to structure given in the introduction, compound **40** in the series above is highly strained.

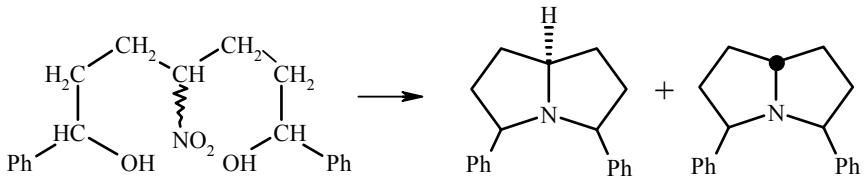
The catalytic hydrogenation of 6-nitroundecane-2,10-dione (**43**) and 6-nitroheptadecane-2,10-dione (**44**) at 10% Pd/C catalyst gave the respective isomeric pyrrolizidines **11** and **19** (traces) and also 3,8-H-3-heptyl-*cis*-5,8-H-5-pyrrolizidine (**36**) with a relatively small amount of its isomer **35** [22].



43, **44**

43 R = Me; **44** R = C_7H_{15}

A mixture of the isomeric 3,5-diphenylpyrrolizidines **46** and **47** (1:1) was formed with a yield of 18% as a result of the reductive cyclization of 4-nitro-1,7-diphenylheptane-1,7-dione (**45**) [23].



45 **46** **47**

The mixture could not be separated, and the stereochemical assignments were made on the basis of data from the ^{1}H and ^{13}C NMR spectra, indicating the isomer **46** has *trans*-fusion of the rings [23] and must therefore be assigned to the group of highly strained pyrrolizidines.

3. FEATURES OF THE PHYSICAL, PHYSICOCHEMICAL, AND CHEMICAL CHARACTERISTICS OF HIGHLY STRAINED PYRROLIZIDINES IN COMPARISON WITH THE ANALOGOUS CHARACTERISTICS OF UNSTRAINED AND WEAKLY STRAINED PYRROLIZIDINES

Comprehensive study of the pyrrolizidine bases revealed extremely remarkable differences in many of the characteristics of the highly strained pyrrolizidines and the corresponding characteristics of their unstrained and weakly strained isomers.

Comparison of the main physical characteristics of the pairs of isomers **11** and **18**, **11** and **19**, **10** and **22**, **26** and **32**, **27** and **33**, **36** and **35**, and **46** and **47**, in which the first in each pair is a highly strained pyrrolizidine, reveals the remarkable relationships discussed below.

3.1. Physical Constants and Gas-Liquid Chromatography

Comparison of the physical characteristics of the epimers **11** and **18** [33] shows that they do not conform to the conformational rule in all the main physical characteristics; the first has lower boiling point, density, and refractive index than the second. The analogous characteristics of the base **11** agree with the idea that *trans*-fusion is preferred for this compound in the liquid phase. Its molecule in conformation **A** occupies a larger volume and has a smaller dipole moment [33] than in the *cis*-fused form **B**. In geometric respects the investigated pair of isomers is similar in the form of the bicycle to the pair of their carbocyclic analogs **2** and **3**, for which the conformational rule is not obeyed [13].

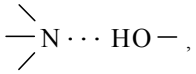
3-*tert*-Butylpyrrolizidines **10** and **22** are distinguished among the 3-alkyl-substituted compounds isomeric with them by the smallest difference in most of the physical constants. In particular, the difference in their boiling points is an order of magnitude lower than for the other pairs of isomers [17, 33].

Comparison of the physical characteristics in the pairs of isomers **11** and **19**, **26** and **32**, and **27** and **33** shows that, as in the cases examined above, the predominantly *trans*-fused bases also have lower boiling points, densities, and refractive indices than their isomers with predominantly *cis*-fused rings [30, 32, 33].

Features of the chromatographic behavior of the isomeric unstrained and weakly strained pyrrolizidines, on the one hand, and the highly strained compounds on the other, are due to some degree to the observed differences in the main physical characteristics. The separation of such bases on stationary liquid phases of various types (squalane, polyethyleneglycol, and triethanolamine) was studied in [33]. During GLC analysis of groups of isomeric bases such as 3,5-dimethylpyrrolizidines **11**, **18**, and **19** [33] and their 3-heptyl-5-methyl-substituted homologs **35-38** [20], pyrrolizidines with unsaturated substituents **39-42** [21], and also 5-hydroxymethyl-3-methyl-substituted compounds **26**, **28**, **30**, and **32** and 5-(3'-hydroxypropyl)-3-methyl-substituted pyrrolizidines **27**, **29**, **31**, and **33** on polar stationary liquid phases (polyethyleneglycol,

triethanolamine, and SP-1000) in all cases the highly strained bases **11**, **36**, **40**, **26**, and **27** were eluted from the column earlier than their unstrained or weakly strained isomers. In [17, 33] it was noticed that the *trans*-fused pyrrolizidines have a larger molecular volume and a smaller dipole moment than the other isomers mentioned above. In the interaction of the former with squalane weaker dispersion interactions occur, and they are therefore eluted more readily than the bases isomeric with them. On the polar phases a significant role is played by orientational forces, as a result of which the highly strained pyrrolizidines interact with them more weakly and have shorter retention times than the unstrained or weakly strained bases isomeric with them. In addition, in the highly strained alcohols **26** and **27** with preferred *trans*-fusion of the rings there are favorable steric conditions for the formation of a strong intramolecular hydrogen bond. This weakens the interaction between the hydroxyl group and the polar stationary liquid phase and also promotes decrease in the retention time compared with the other isomers [15, 31].

It was shown that during GLC of the isomeric 3,5-dimethylpyrrolizidines **11**, **18**, and **19** with triethanolamine, which is capable of forming hydrogen bonds of the type



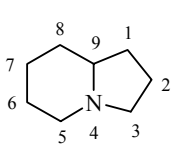
between the molecules of the sorbate and sorbent, as liquid stationary phase the shortest retention time is observed for the highly strained isomer **11** [33]. As known [34], the latter has the lowest basicity, and the energy of interaction between its molecules and the stationary phase will consequently be smaller than in the case of the isomers **18** and **19**. According to data in [17, 33], the differences in the dispersion and orientational interactions and also in the energy of formation of the hydrogen bond between the sorbate and sorbent molecules act in one direction during the chromatography of the investigated compounds **11**, **18**, and **19** on triethanolamine, leading to more rapid passage of the highly strained pyrrolizidine **11** through the column.

The isomeric 3-*tert*-butylpyrrolizidines **10** and **22**, of which the former belongs to the highly strained bases, fit less well into the above-mentioned relationships according to their properties on account, probably, of the presence of the bulky substituent at the α-carbon atom with an inversion center at the nitrogen atom.

3.2. Infrared and ^{1}H and ^{13}C NMR Spectra

According to an empirical Boltzmann correlation, the *trans*-fused conformations of 1-azabicycles are characterized by absorption in the region of 2700-2800 cm^{-1},* which is not observed in compounds with preferred *cis*-fusion of the rings [35]. However, it was not known whether the correlation applied to the strained system of *trans*-fused five-membered rings with a bridgehead nitrogen atom, i.e., to the pyrrolizidines discussed in the present review.

While analyzing the possible application of the Boltzmann test to the series of predominantly *trans*-fused pyrrolizidines, the authors of [17] started from the considerations presented below. As known, the indolizidine **48** has characteristic absorption in the region of 2700-2800 cm^{-1} [36].



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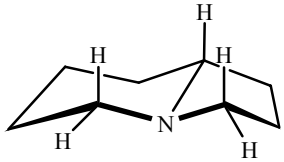


48A

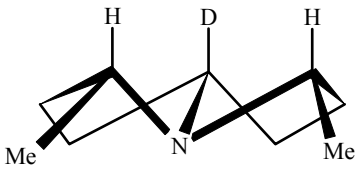
* Some authors consider the low-frequency limit to be 2650 [23] or even 2649 cm^{-1} [20].

In its *trans*-fused conformation compound **48A** shows departures from the geometric requirements of antiparallelism in the axis of the unshared electron pair of the nitrogen atom in both the axial and the pseudoaxial C–H bonds at the α-atoms $C_{(5)}$, $C_{(9)}$, and $C_{(3)}$. By measurements on molecular models it was possible to estimate approximately the degree of these departures not leading to loss of the effect. Thus, in the *trans*-fused conformation **48A** the dihedral angles in the H–$C_{(3)}$–N, H–$C_{(5)}$–N, and H–$C_{(9)}$–N fragments are 156, 178, and 170° respectively [17]. Consequently, the simultaneous departure of even two C–H bonds from the postulated value of 180° [35] by ~10-20° does not prevent retention of the effect [17].

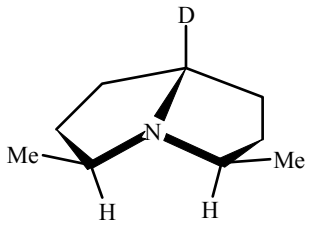
In this connection it was suggested that the *trans*-fused pyrrolizidines would absorb in the Boltzmann region of the IR spectrum, since the departures determined on models of the *trans*-fused pyrrolizidine **1A** for the $C_{(3)}$–H and $C_{(5)}$–H bonds amount to ~10°, while the $C_{(8)}$–H bond is strictly antiparallel to the axis of the unshared electron pair of the nitrogen atom [17].

This suggestion was confirmed by experiment. Thus, in the IR spectra of the highly strained pyrrolizidines **10** and **11** [37-39], **26** [17], **27** [32], **36** [20, 22], and **46** [23] in the region of 2650-2800 cm^{-1} there are 3-5 so-called Boltzmann bands of weak and medium intensity typical of *trans*-fused azabicycles with a bridgehead nitrogen atom [35].

The role of the H-8 carbon atom in the appearance of the Boltzmann absorption was demonstrated in the case of compound **11** (which exists, as stated above, predominantly in form **A**) by isotopic substitution with the introduction of a deuterium label at position 8 and investigation of the IR spectrum of the 8-deutero derivative **49**, for which the *trans*-fused form **49A** predominates [37-39]. The *cis*-fused compound **50B** with the deuterium label also at position 8 was prepared in order to reveal the effect of *trans*-fusion of the rings on the ν_{C-D} vibrations [37, 38].



49A



50B

The strongest ν_{C-D} bands of the conformers **49A** and **50B** at 1992 and 2125 cm^{-1} respectively differ in frequency by 133 cm^{-1}. The high-frequency shift of ν_{C-D} in the transition from the **49A** form to the family of *cis*-fused conformations, denoted as **50B**, is due to substitution of the transoid fragment (the unshared electron pair of the nitrogen atom – the C–D bond) by the analogous cisoid fragment [40]. The presented dependence of ν_{C-D} on the preferred conformations of the isomeric compounds represents an extremely graphic example.

Absorption in the region of 2700-2800 cm^{-1}, characteristic of 1-azabicycles with *trans*-fused rings, has been observed in a large number of compounds [35] in which at least one ring is six-membered.

In [17, 20, 22, 23, 32, 37-39] it was shown that Boltzmann absorption also appears in the case of strained *trans*-fusion of two saturated five-membered rings with a bridgehead nitrogen atom. The region of application of the correlation has thus been extended.

The difference between the unstrained and weakly strained pyrrolizidines was detected most simply and distinctly during comparison of the chemical shifts of the H-8 protons at the bridgehead carbon atom in the ^{1}H NMR spectra and the signals of the bridgehead $C_{(8)}$ atoms in the ^{13}C NMR spectra.

The ^{1}H NMR spectra of the highly strained pyrrolizidines **10** and **11**, obtained on instruments working at 60 and 90 MHz, differ greatly in form from the spectra of the corresponding unstrained isomers **22** and **19**, recorded on the same instruments under analogous conditions [28, 29, 34]. Identification of the signals for the protons at the α-C atoms in such spectra was difficult, but it was clear that their lower limit, where the signal of

the H-8 proton in *cis*-fused pyrrolizidines is usually located, is shifted upfield [34]. This fact was interpreted as reflecting the displacement of the conformational equilibrium toward the *trans*-fused forms **10A** and **11A** [34]. The spectra recorded on instruments working at 250 MHz and above make it possible to interpret them more fully and to determine the position of the signal for the H-8 proton. In all known cases it lies in the range of 2.43-2.72 ppm [17, 20-23], whereas this signal in the spectra of the unstrained and weakly strained pyrrolizidines lies in the region of 3.30-3.69 ppm [17, 20, 22].

An analogous substantial difference is observed for the position of the resonance signal of the $C_{(8)}$ atom in the ^{13}C NMR spectra of highly strained and unstrained or weakly strained pyrrolizidines; in the spectra of the former this signal lies in a significantly more downfield region (70.1-72.7 ppm) than in the spectra of the other bases [17, 19, 20, 22, 23, 32]. We note that the position is as a rule unusually low in comparison with the position of the signals for the bridgehead carbon atoms in the spectra of quinolizidine and indolizidine (62.9-64.1 ppm), which also have *trans*-fusion of the rings [41-43]. It was suggested that the anomalously low position of the signal for the $C_{(8)}$ carbon atom in the spectra of the predominantly *trans*-fused pyrrolizidines is due to the action of electronic effects caused by the strong angular strain and also to screening factors caused by the geometry of the molecules [19].

3.3. Basicity

In aqueous solution the unstrained and weakly strained pyrrolizidines **1**, **8**, **9**, **18**, **19**, and **22** have comparatively high basicity (pK_a 10.88-11.94) [32, 34, 44-46] and are apparently the strongest bases among saturated amines with tertiary nitrogen atoms [17, 46]. This feature is due to the geometry of the *cis*-fused pyrrolizidines, which have the unshared electron pair of the nitrogen atom sterically accessible for hydration [7, 17, 45, 46]. As far as the basicity of the highly strained pyrrolizidines with preferred *trans*-fusion of the rings is concerned, it has only been measured for compounds **10** and **11** (in aqueous acetonitrile for the first and in water and aqueous acetonitrile for the second) [34]. In both solvents the latter is almost 1.5 times weaker as a base than its isomer **18** [34]. Like the unstrained *cis*-fused pyrrolizidines, the base **11** in the **11A** conformation no longer has such an accessible unshared electron pair of the nitrogen, which can moreover undergo partial delocalization according to the familiar mechanism [47-50]. Taken all together this makes the similar values of the basicity of compound **11** (pK_a 10.28 ± 0.10), indolizidine (pK_a ± 0.05) [46], and quinolizidine (pK_a 10.19 ± 0.07) [51] understandable.

In [34] the pK_a value for the *trans*-fused conformation **A** of pyrrolizidine **1** was calculated. The authors here started from the additivity of the contributions from the substituents to the basicity of the amines [52]. With allowance for the fact that compound **11** exists almost entirely in the *trans*-fused form **A** [17, 18, 24] $pK_a \leq 9.9$ was obtained.

According to the spectroscopic data examined above, the base **10** is predominantly *trans*-fused. However, comparison of the pK_a values of the isomers **10** and **22** in aqueous acetonitrile shows an unexpectedly small difference (ΔpK_a = -0.30), i.e., approximately the same as in the case of the pairs of isomeric weakly strained and unstrained pyrrolizidines. A satisfactory explanation for this fact was not given in [34].

3.4. Protonation of Pyrrolizidines

The reduced basicity of the highly strained pyrrolizidines **11**, **26**, and **27** was used to isolate these compounds preparatively from mixtures with the other isomers. Thus, when the mixtures of isomeric compounds indicated in brackets (**11**, **18**, **19**), (**26**, **28**, **30**, **32**), and (**27**, **29**, **31**, **33**) were gradually neutralized

with acid while their composition was constantly monitored by chromatography, salts of the unstrained and weakly strained pyrrolizidines were formed in the first place. With incomplete neutralization the bases **11**, **26**, and **27** remained in solution and were extracted with solvents immiscible with water, such as ether [17, 24, 32].

3.5. Oxidation of Pyrrolizidines with Mercury Acetate

As known [9, 53], pyrrolizidine does not undergo oxidative dehydrogenation with mercury acetate – a reaction into which 1-azabicycles with *trans*-fusion of the rings enter readily [27, 54, 55]. The isomeric 3-methylpyrrolizidines **8** and **9** were also inactive in this transformation [17, 26].

It was shown that only the highly strained predominantly *trans*-fused isomer **11** was readily dehydrogenated during the concurrent oxidative dehydrogenation of a mixture of the isomers **11**, **18**, and **19**. With an individual sample of **11** the reaction took place smoothly, and the perchlorate **26** was formed [26] (see also section 1).

The obtained results were explained by the fact that the base **11** reacts with its predominantly *trans*-fused form **11A** [17, 26], which has three anticoplanar fragments: $\gtrless C-H$ and the unshared electron pair of the nitrogen atom.

In [22] the stage-by-stage isomerization of the strained dialkylpyrrolizidine **36** to compound **35** was described. The initial stage of the transformation involved oxidation of the former by mercury acetate. The obtained intermediate product (probably, an analog of compound **20**) was reduced to the isomer **35** without isolation.

4. THERMODYNAMICS OF THE *cis-trans* CONVERSION OF PYRROLIZIDINE AND QUANTITATIVE DATA ON THE CONFORMATIONAL EQUILIBRIA OF ITS HOMOLOGS

The most important thermodynamic parameters in the conformational analysis of pyrrolizidines are the enthalpy (ΔH_i^0) and free energy (ΔG_i^0) of *trans-cis* conversion **1A** $\rightleftharpoons$ **1B** of the parent base.

The ΔH_i^0 value was first determined by investigation of the temperature dependence of the IR spectrum of the vapor of the pyrrolizidine **1**. It was assumed that this compound exists almost entirely in form **B** at room temperature and that increase in the content of the *trans*-fused form **A** to 5% during heating of its vapor from 20 to 300°C would be detected from the appearance of characteristic absorption bands in the region of 2700-2800 cm^{-1}. Increase of the absorption in this region of frequencies was not observed experimentally. By disregarding the change of entropy and assuming that the content of the conformation **1A** was less than 5% even at 300°C, we found the first limit of ΔH_i^0 [17, 56]. The second limit of ΔH_i^0 was adopted on the basis of the formal geometric similarity of the *trans* (**A**) and *cis* (**B**) forms of the base **1** to the carbocyclic analogs **2** and **3**. The difference in enthalpies for the last two isomers was determined in [4].

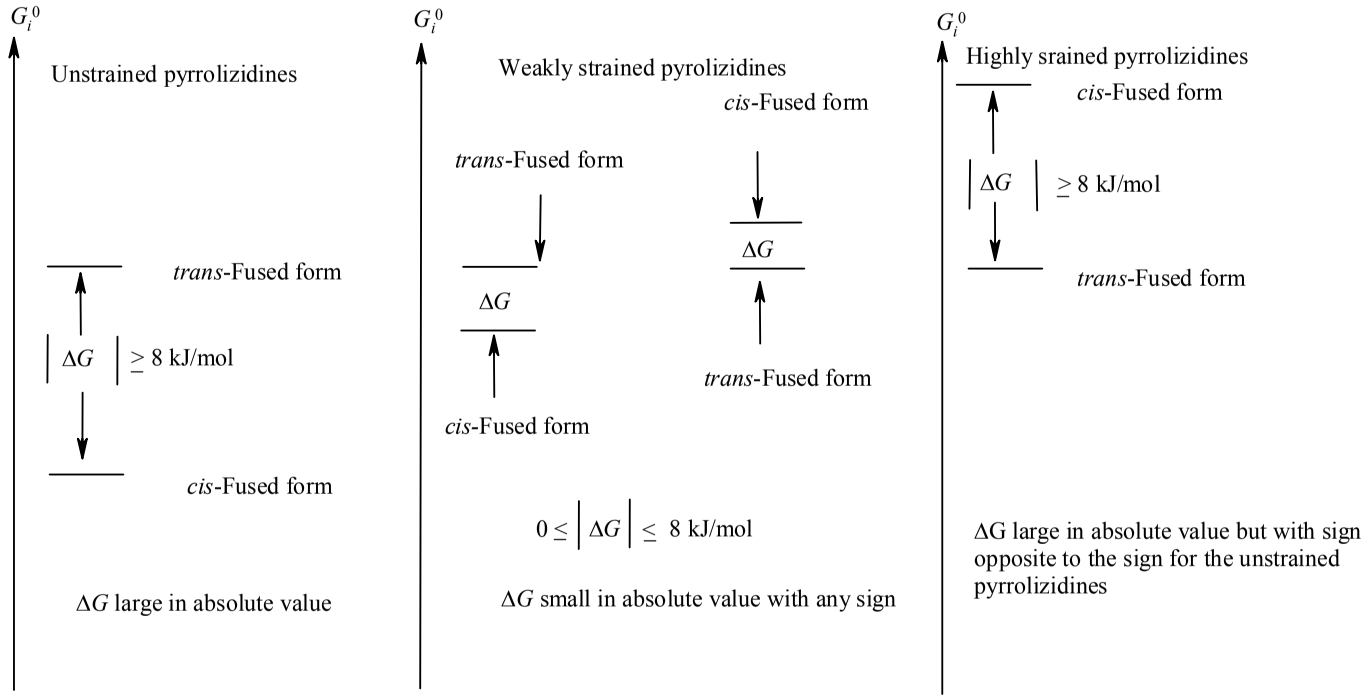
In comparison with compound **3** the base **1** in conformation **B** is destabilized on account of the stronger nonbonding interactions of the *endo*-oriented hydrogen atoms at $C_{(3)}$ and $C_{(5)}$ [16, 17], since the C–N bonds are shorter than the C–C bonds. On the other hand, in the *trans*-fused conformation **A** it experiences further stabilization in connection with the delocalization of the unshared electron pair of the nitrogen atom according to the above-mentioned mechanism [47-50]. From this it had to be expected that ΔH_i^0 of the *trans-cis* conversion of pyrrolizidine **1** is smaller in absolute value than the difference between the enthalpies of compounds **3** and **2** [4]. On the basis of the considerations above the range of ΔH_i^0 values for the equilibrium **1A** $\rightleftharpoons$ **1B** in the gas phase, the equilibrium constant *K*, and the fractions of each invertomer expressed as percentages were obtained [17, 56] (see Table 1).

TABLE 1. The ΔH_i^0 and ΔG_i^0 Values (25°C), the Constants of the Conformational Equilibrium (K), and the Percentages of the Invertomers in the Equilibrium State for the Pyrrolizidines **1**, **9**, and **11** in the Gas (g) and Liquid (l) Phases

Conformational equilibrium	Method for determination of parameters of conformational equilibrium	Phase	$-\Delta H_i^0$, kJ·mol^{-1}	$-\Delta G_i^0$, kJ·mol^{-1}	K	Content of invertomers in mixture, %		References
						cis-	*trans*-	
1A ⇌ **1B**	IR spectroscopy	g	>14.2 <26.8		>19* <275*	>95 <99.6	<5 >0.4	[17, 56]
	Thermochemical	g	8.4 11.9	11.1 14.6	88 363	98.9 99.7	1.1 0.3	[17, 24]
		l	7.5±3.8 10.9±3.8	10.2 13.6	61 242	98.4 99.6	1.6 0.4	[17, 24]
	Calculation by molecular mechanics		10.9 11.3		81* 96*	98.8 99.0	1.2 1.0	[3] [57]
9A ⇌ **9B**	Kinetically controlled protonation and ^{13}C NMR spectroscopy	g		4.6	6.4	86.5±2.4	13.5±2.4	[17, 18],
		l		6.4	13.3	93.0	7	The present work
11B ⇌ **11A**	Kinetically controlled protonation and ^{13}C NMR spectroscopy	g		>7.66	34.0±14.4	<4.2	>95.8	[17, 18]

* Calculated from ΔH_i^0 data on the assumption that $\Delta S = 0$.

Scheme 1. Free energy levels of the *cis* and *trans* forms of unstrained and weakly and highly strained pyrrolizidines



A more accurate value for ΔH_i^0 was obtained by the thermochemical method using the experimentally determined heats of combustion and formation for the liquid (l) and gas (g) states of the base **1** [24]. The pyrrolizidine **1** and its homolog **11** were chosen as models with *cis*- and *trans*-fusion of the rings. In each case the insignificant contribution from conformations with the opposite type of ring fusion were disregarded [24]. Authentic data on the heats of formation of the methylene group at the carbon atoms adjacent to the nitrogen atom were used during calculation of ΔH_i^0 for pyrrolizidine **1** by the additive method [58, 59]. The change of entropy in the transition from **1A** to **1B** was taken as approximately *R*ln3, i.e., 9.1 J/deg [17, 24]. This assumption was made on the basis of the number of *cis*-fused conformations with similar entropy values [2, 3].

By calculation using molecular mechanics [57] it was possible to determine the difference between the energies of the *trans*-fused (**A**) and *cis*-fused (**B**) forms of the **1**. In [3] its conformational dynamics were also investigated by molecular mechanics (the version based on the MM3 force field). The results were checked by *ab initio* quantum-mechanical calculations. In respect of one of the series of *cis*-fused conformations (*syn-anti-bis-twist*)* the energy of the *trans*-fused conformation **A** (*trans-syn-bis-twist* according to the terminology used by the authors of [3]) was determined. Sufficiently close results were obtained in the papers cited above.

As seen from Table 1, the calculated data on the difference in the enthalpies of conformations **A** and **B** of compound **1**, presented in [3, 57], agree well with the experimental values of ΔH_i^0 (g) for its *trans-cis* conversion in the gas phase [24].

From the collection of published data [17, 18] it was possible to determine the parameters of the conformational equilibrium **9A** $\rightleftharpoons$ **9B**, calculated by two different methods. The first started from data on the integral intensities of the signals for the $C_{(3)}$, $C_{(5)}$, $C_{(6)}$, $C_{(8)}$, and C(Me) atoms in the ^{13}C NMR spectra of the salts **12** and **15**, obtained during kinetically controlled protonation [60] of the base **9** by the absorption of its vapor with concentrated sulfuric acid at 25°C [18]. The contents of the respective conformations **9A** and **9B** were determined from the intensity ratios of the signals for the above-mentioned atoms in compounds **12** and **15**, and the conformational equilibrium constant *K* and the free energy ΔG_i^0 were then determined in the usual way.

The calculation by the first method was done by means of the equation

$$\delta_H = N_{cis} \cdot \delta_{cis} + N_{trans} \cdot \delta_{trans},$$

(similar to the equation widely used in the conformational analysis of cyclohexane derivatives [61]), where δ_H is the chemical shift of the H-8 proton in the ^1H NMR spectrum of the investigated pyrrolizidine base, δ_{cis} is the chemical shift of the H-8 proton in the pyrrolizidine **1** (used as model compound with *cis*-fusion of the rings), δ_{trans} is the chemical shift of the H-8 proton in the base **11** (used as standard pyrrolizidine base with *trans*-fusion of the rings), and N_{cis} and N_{trans} are the mole fractions of conformations **1A** and **1B**. It was assumed on the basis of published data [17] that the presence of the methyl groups at positions 3 and 5 does not have a substantial effect on the chemical shift of the H-8 proton. On this basis the chemical shift of the H-8 proton in the spectrum of each of the standard compounds **1** and **11** was attributed to the H-8 proton of compound **9** in conformations **B** and **A** respectively. Similar assumptions were made for the ^{13}C NMR spectra. As seen from Table 1, the two methods examined above for calculation of the parameters of the conformational equilibrium **9A** $\rightleftharpoons$ **9B** lead to results that agree satisfactorily.

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* The three stable *cis* conformers *syn-anti-bis-twist*, *cis-syn*-3,7-double *envelope*, and skew *syn-anti*-3,7-double *envelope* [3] clearly correspond to the twisted, open, and half-folded conformations [2]. Their energies differ over a range of 1.7 kJ/mol.

The equilibrium was investigated quantitatively by kinetically controlled protonation [60] of the base **11** followed by determination of the ratio of the formed salts **14** and **17** by ^{13}C NMR spectroscopy [17, 18]. One of the parameters characterizing the conformational equilibrium **11B** $\rightleftharpoons$ **11A** was obtained by this method.

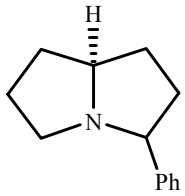
Compound **11** can be regarded to a first approximation as a standard *trans*-fused pyrrolizidine base since it is present to the extent of not less than 95.8% in conformation **A** [17, 18]. In this connection it is interesting to note that its strength (E_s), defined as the difference between the experimental value of the enthalpy of formation and the value calculated by an additive method, amounts to 63.7 kJ/mol [62]. In the same paper the value E_s = 53.8 kJ/mol is given for the unstrained pyrrolizidine **1**.

On the basis of the ΔH_i^0 and ΔG_i^0 data, the constants of the conformational equilibrium of the pyrrolizidine bases, and the content of the invertomers in the equilibrium mixture, summarized in Table 1, and returning to the classification of the pyrrolizidines according to the degree of strain given in the introduction, it is possible to represent the ratio of the strains of the three types of bases qualitatively by means of the scheme presented after the table.

It should be noted that the free energy levels of the *cis*- and *trans*-fused forms in each type of base should not be taken as completely fixed; their values are only given as a guide. The aim here was merely to demonstrate the similarity in the values of the free energy of the *trans*-fused forms. The high energy of the latter is due in all cases to the strong angular strain of the *trans*-fused bicyclic system, which is approximately the same in all the compounds. In contrast, the values for the free energy of the *cis*-fused forms differ significantly. For the pyrrolizidine **1** and its homologs they depend on the nonbonding interactions in the *cis*-fused conformations.

The stereochemistry of 3-phenylpyrrolizidine, produced by the hydrogenation of 3-phenyl-Δ^2-dehydropyrrolizidine at atmospheric pressure (catalyst Pd/C), requires special comment [63].

The question of the stereoselectivity of the addition of hydrogen is not discussed in the indicated paper. As known, *cis*-addition mostly occurs during the catalytic hydrogenation of dehydropyrrolizidines, at least under mild conditions [64]. If the foregoing is taken into account, the production of a mixture of isomers, i.e., *cis*-3,8-H-3-phenylpyrrolizidine **51** and *trans*-3,8-H-3-phenylpyrrolizidine **52** with a preference for the latter, should be expected in the reaction presented above.



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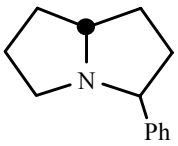

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Later on [65] an attempt to explain the stereochemistry of the 3-phenyl-substituted base obtained in [63] was described. However, it was not possible to solve the problem by NMR, and the authors of [65] calculated, contrary to the familiar laws of stereochemistry mentioned above and without quoting any specific experimental data, that the compound probably has the *trans* configuration. As a result the isomeric composition of 3-phenylpyrrolizidine (probably a mixture of the bases **51** and **52**) and their structure remained open.

Compound **51** is extremely interesting in the light of the questions discussed in the present review. Comparison of the conformational energies ($-\Delta G^0$) of phenyl- and *tert*-butyl-substituted cyclohexanes (amounting to 12.6 and >15.1 kJ/mol respectively [66]) shows that there are significant nonbonding interactions in the former, although they are weaker than in the latter. By transferring these differences somewhat arbitrarily to the pyrrolizidines, it can be supposed that the base **51** will approach the highly strained compounds in its characteristics.

CONCLUSION

In the present work the as yet small amount of data on the synthesis of weakly and highly strained pyrrolizidines has been analyzed. The bases represent are like two poles in a multitude of pyrrolizidine systems, differing radically in the preferred type of ring fusion and in a number of their characteristics. At the same time they are examples of strong displacement of the conformational equilibrium to one side, for which it is at times difficult to make a quantitative assessment. On the other hand, in view of the small absolute values of ΔG_i^0 the weakly strained pyrrolizidines present a suitable subject for quantitative conformational analysis.

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