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Advances in the Study of the Stereochemistry of Quinolizidines, Indolizidines, and Pyrrolizidines

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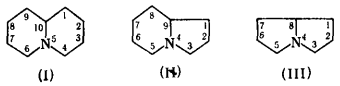
The results of studies on the stereochemistry of quinolizidines, indolizines, and pyrrolizidines are examined. Attention is concentrated on the application of non-spectroscopic methods in the determination of the configurations and preferred conformations. The possibilities and limitations of various physical and physicochemical methods in the study of the stereochemistry of the above 1-azabicyclic compounds are demonstrated.
The bibliography includes 193 references.

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I. INTRODUCTION

Quinolizidine (I), indolizidine (II), and pyrrolizidine (III) constitute the basis of many plant alkaloids and synthetic medicinal drugs. Interest in the stereochemistry of compounds (I)–(III) and their derivatives, whose specific features are due to the capacity of the bicyclic systems for reversible *cis*–*trans* transformations as a result of the inversion of the pyramidal nitrogen atom, is therefore quite justified.



(I) (II) (III)

Quinolizidines have now been investigated in greater detail as regards their stereochemistry, a comparatively few studies have been made on indolizidines, and the investigation of the conformational behaviour of compounds of the pyrrolizidine series is in essence only just beginning. We shall not consider the structures of quinolizidine, indolizidine, and pyrrolizidine alkaloids, with the exception of a few individual interesting examples, because since 1971 the appropriate compilations are being published annually[1-4]. A number of reviews have been devoted to the stereochemistry of pyrrolizidines.[5-8] In reviews[9,10] of stereochemical studies on compounds with a nodal nitrogen atom by spectroscopic methods quinolizidines,[9,10] indolizidines,[9] and (very briefly) pyrrolizidines [9] are considered among other heterocycles.

Analysis of research on the stereochemistry of compounds in Groups (I)–(III) shows that non-spectroscopic methods for the determination of steric structures have been used continuously. However, despite their evident importance, they have been frequently eclipsed by the effective achievements of infrared and NMR spectroscopy and have not been surveyed in the review literature.

Many similar stereochemical problems in the quinolizidine, indolizidine, and pyrrolizidine series have been solved by the same procedures, which shows that they have common features for the given series of compounds and makes it useful in the subsequent discussion to arrange the studies in groups based on the methods underlying the solution of particular problems.

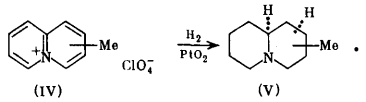
II. CONFIGURATIONAL ASSIGNMENT OF THE BASES

The problems of the configurational assignment and of the determination of the preferential conformations are sometimes closely related and are solved simultaneously. The systematic arrangement of data suggested in the present review is therefore sometimes somewhat conventional. The nomenclature adopted in the stereochemistry of 1-azabicyclic compounds is used in the description of the configurations[9].

1. The Employment of the Characteristic Features of the Stereochemistry of Catalytic Hydrogenation and of the Dependence of the Physical Properties of Isomers on Their Steric Structure

The configurational assignment of substituted quinolizidines, indolizidines, and pyrrolizidines, obtained by the catalytic hydrogenation of the corresponding quinolizidines, indolizines, and pyrrolizines, is based on the assumption of the preferential *cis*-addition of hydrogen by analogy with other aromatic systems[11].

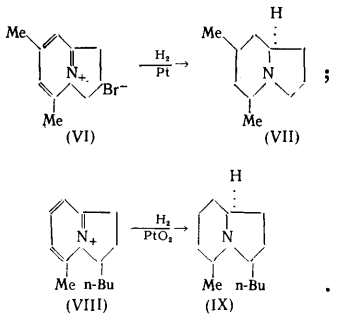
The hydrogenation of 1-, 2-, and 4-methyldehydroquinolizinium perchlorates (IV) [12] or 4-methyldehydroquinolizinium bromide[13] on PtO_2 resulted in the formation of isomers to which the *cis*-configuration (V) was attributed:



(IV) (V)

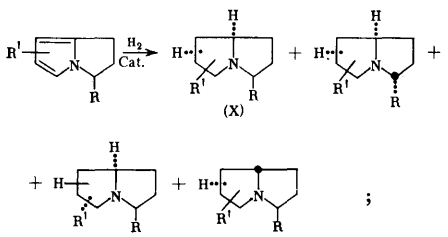
Dehydrogenation of the bromide (VI) in the indolizine series led to the isolation of *cis*-5,9-*H*-*cis*-7,9-*H*-5,7-dimethylindolizidine (VII) as the sole isomer[14] and the

reaction of the salt (VIII) gives *cis*-3,9-*H*-3-n-butyl-*cis*-5,9-*H*-5-methylindolizidine (IX) [15]:



The remaining three isomers of the last compound were obtained from the corresponding pyridine and pyrrole alcohols, the key process determining the configuration being the catalytic hydrogenation of these alcohols accompanied by the *cis*-addition of hydrogen [15].

As a result of hydrogenation, 5-methyl-,[16] 3,5-dimethyl-,[17] 5-hydroxymethyl-, 5-hydroxymethyl-3-methyl, [18,19] 5-(β-hydroxyethyl)-, 7-(β-hydroxyethyl)-,[20] and 7-ethoxycarbonyl-1,2-dihydropyrrolizine [21] and 7-ethoxycarbonyl-3*H*-pyrrolizine [22] give rise to mixtures of isomers in which compounds (X)†, with a relative *cis*-configuration at the carbon atom attached to the substituent R′, predominate [18]:

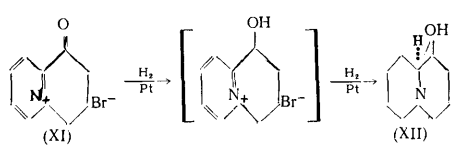


(R = H, Me; R′ = 5-Me, 5-CH_2OH, 5-$(CH_2)_2OH$, 7-$(CH_2)_2OH$, or 7-CO_2Et.

The hydrogenation of 1-methoxycarbonyl-7-oxo-6,7-dihydro-5*H*-pyrrolizine exhibits the same behaviour [23].

Examples of the stereoselective hydrogenation of aromatic systems with substituents in the "non-aromatic" half of the bicyclic system are formally similar but are nevertheless fundamentally different from the instances examined above. Here too isomers with the *cis*-configuration are formed preferentially, but the process selectivity is evidently ensured by the preferential adsorption of the compound hydrogenated from the sterically more accessible side [11].

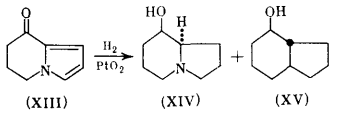
According to Swan's data [24], the hydrogenation of compound (XI) is completed by the formation of *cis*-1,10-H-1-hydroxyquinolizidine (XII):



Initially the carbonyl group is converted into a hydroxy-group, after which the ring is hydrogenated, hydrogen being attached to the angular $C_{(10)}$ atom from the side opposite to that of the hydroxy-group [24].

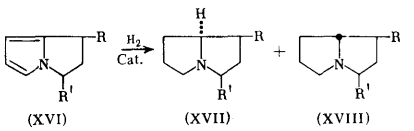
†Here and henceforth the symbol Cat. denotes a metallic catalyst.

The addition of hydrogen to 8-oxopyrrolo[1,2-*a*]piperidine (XIII) is less selective, the *trans*-isomer (XV) (24%) being formed together with the main product—the *cis*-isomer (XIV) (76%) [25]:



The *cis*-configuration at $C_{(3)}$ in the indolizine homologue (IX) is a consequence of the steric effect of the t-butyl group on the hydrogenation of compound (VIII). [15]

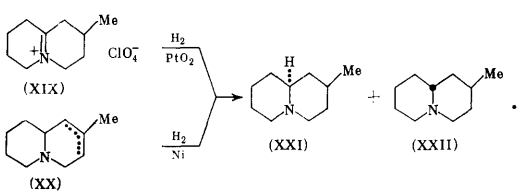
An analogous stereochemical effect is observed in the hydrogenation of 1,2-dihydropyrrolizidines and pyrrolizidines. 1,2-Dihydropyrrolizines (XVI) with alkyl groups in the 1- or 3-position are converted into mixtures of isomers (XVII) and (XVIII), among which compounds with the *cis*-configuration at $C_{(1)}$ or $C_{(3)}$ (XVII) predominate quantitatively [16,26-28]:



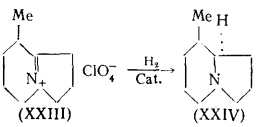
R = H, Me; R′ = H, Me, or t-Bu .

The hydrogenation of 1-methyl-3*H*-pyrrolizine in the presence of rhodium under mild conditions gives rise to *cis*-1,8-*H*-1-methylpyrrolizidine (*d,l*-heliotridane). [29] The stereochemistry of the hydrogenation of 1,2-dihydropyrrolizines with functional groups in the "non-aromatic half" of the bicyclic system [23,30,31] is also kinetically and not thermodynamically controlled, as was suggested by Adams et al. [32] The reaction leads to the formation of thermodynamically less stable isomers with the *cis*-configuration of the substituted atoms of the bicyclic system—the steric effects of the substituent has a decisive influence on the stereochemical result of the hydrogenation.

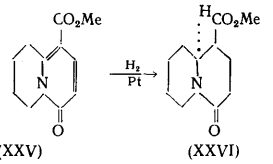
The preferential *cis*-addition of hydrogen in the hydrogenation of compounds with multiple bonds [11] and the adsorption of the substrate on the catalyst from the most accessible side were taken into account in the configurational assignment of quinolizidines, indolizidines, and pyrrolizidines obtained from the corresponding partly unsaturated derivatives. The catalytic addition of hydrogen to compounds (XIX) or (XX) yields mixtures of epimeric 2-methylquinolizidines (XXI) and (XXII). The *cis*-configuration was attributed to isomer (XXI), which is the dominant product in both cases [33]:



The hydrogenation of the perchlorate (XXIII) to *cis*-8,9-*H*-8-methylindolizidine (XXIV) takes place more selectively [34]:

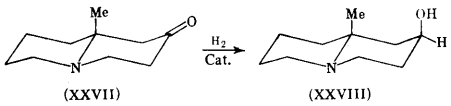


On platinum, hydrogen undergoes *cis*-addition to the $C_{(1)}$–$C_{(10)}$ bond in compound (**XXV**) and the quinolizidine derivative (**XXVI**) with the relative *cis*-configuration at $C_{(1)}$ is obtained[35]:



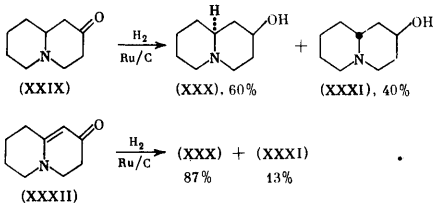
(XXV) (XXVI)

It has been shown that 10-methyl-2-oxoquinolizidine (**XXVII**) has a *trans*-junction between the two rings[36]. Bohlmann et al.[36] believe that the catalytic hydrogenation of the carbonyl group therefore leads to compound (**XXVIII**) with an axial hydroxyl owing to steric hindrance to adsorption generated by the methyl group:



(XXVII) (XXVIII)

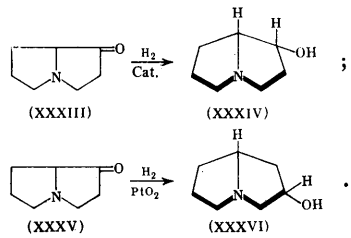
A conclusion has been reached[37,38] about the configurations of the epimeric 2-hydroxyquinolizidines by comparing the ratios of the isomers obtained on catalytic hydrogenation of 2-oxoquinolizidine (**XXIX**) and $\Delta^{1,10}$-2-oxoquinolizidine (**XXXII**) under identical conditions:



The authors attribute the *cis*-configuration (**XXX**) to the epimer whose fraction increases on transition from (**XXIX**) to (**XXXII**), assuming that the bulk of the hydrogen atoms add to molecules of compound (**XXXII**) from the same side in the course of a single adsorption step.

In the general case the hydrogenation of 1-oxoquinolizidine,[24,37] 2-and 3-oxoquinolizidines, and $\Delta^{1,10}$-2-oxoquinolizidine [37] under different conditions is not distinguished by high stereoselectivity and cannot serve as a basis for the configurational assignment of the 1-, 2-, and 3-hydroxyquinolizidines formed.

On the other hand, the catalytic addition of hydrogen to carbonyl-containing pyrrolizidines (**XXXIII**) and (**XXXV**) is characterised by its stereospecificity and, together with data derived from other methods, can serve as evidence in support of the configurations of the aminoalcohols (**XXXIV**) and (**XXXVI**) illustrated below[30]:



(XXXIII) (XXXIV)

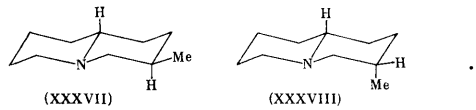
(XXXV) (XXXVI)

The different types of behaviour of carbonyl derivatives of quinolizidine and pyrrolizidine during catalytic reduction are probably due to geometrical factors.

In many other examples dehydropyrrolizidines containing a multiple bond in the ring combine catalytically with hydrogen from the sterically least hindered side of the molecule regardless of the position of the multiple bond, which leads to the *cis*-configuration of the new asymmetric centre in relation to $C_{(8)}$.[39-43] In the solution of the problems of the configurational assignment of isomers of more complex systems—deoxynupharidine,[44] perhydrobenzo[*c*]quinolizine,[45] 9-azasteroid cyclic systems[46], and 6-disubstituted perhydrobenzo[*c*]quinolizines,[47] whose synthesis involves a hydrogenation range—the concept of the catalytic *cis*-addition of hydrogen was taken into account.

Thus the characteristics of the stereochemistry of the catalytic hydrogenation can be used widely in the determination of the configurations of isomers. Caution must be exercised in reaching conclusions primarily in those cases where the hydrogenation is carried out under conditions permitting isomerisation, which is observed at high temperatures and when catalysts (for example, palladium) promoting the isomerisation process are used.

The examples described by Moynehan et al.[12] must be regarded as exceptions. The hydrogenation of 3-methyldehydroquinolinium perchlorate is distinguished by low stereoselectivity. Assuming the conformation with a *trans*-junction for quinolizidine and its methyl derivatives, Moynehan[12] attributed on the basis of the conformational rule[48] the structure (**XXXVII**) (*trans*-configuration) to the 3-methylquinolizidine with the lower refractive index and the *cis*-configuration (**XXXVIII**) to the more strained epimer with the higher refractive index:



(XXXVII) (XXXVIII)

The remaining three pairs of epimeric methylquinolizidines obey the conformational rule[12].

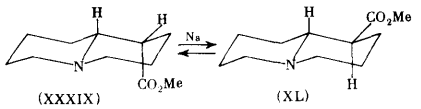
Among the epimeric pairs of 3-hydroxyquinolizidines,[38] 1-,[30] 2-,[30] and 8-hydroxyindolizidines,[25] and 3-hydroxymethylpyrrolizidines,[19] the isomers with an intramolecular hydrogen bond have lower boiling points.

2. Thermodynamic and Kinetic Methods

An *a priori* estimate of the relative thermodynamic stabilities of the isomers of substituted quinolizidines, indolizidines, and pyrrolizidines has served in a number of instances as the starting point for their configurational assignment. If the formation of both epimers is possible in thermodynamically controlled reactions, then the isomer with a larger store of free energy predominates quantitatively.

Assuming a *trans*-junction between the rings for simple monosubstituted quinolizidines, one may reach the conclusion, analogous to that of Leonard and Ryder[49], that the thermodynamically preferred isomer has the substituent in the equatorial position. Evidently among indolizidines this isomer has the equatorial substituent in the six-membered ring or the substituent is in a pseudoequatorial position in the five-membered ring. In the pyrrolizidine series, among the epimers differing in the position of the substituent at any one carbon atom, the isomers with the *trans*-configuration are thermodynamically more stable (see, for example, Refs. 30, 39, and 50) being more favoured by the non-bonding interactions. This rule is apparently valid for all monosubstituted pyrrolizidines.

The epimerisation of 1-substituted quinolizidines—lupinine [49,51-53] and the methyl ester of lupininic acid (XXXIX) [49,54]—under the influence of sodium or sodium methoxide has been described. According to Cookson's data[54], equilibrium is reached when 15% of the *cis*-isomer (XXXIX) and 85% of the *trans*-isomer (XL) is attained:

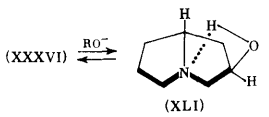


(XXXIX) (XL)

Other examples of the application of the isomerisation reaction in the configurational assignment of quinolizidines have been described[55-58].

In the pyrrolizidine series epimerisation was completed in most of the known instances by the formation of virtually only one compound and one can therefore attribute to the latter the *trans*-configuration quite reliably. The isomerisation of substituted pyrrolizidines under the influence of acids[50], bases[22,30,42,59], and metallic catalysts[17-20,28] has been investigated. The epimerisation can occur at the first[21,30,42,50,59], third[18-20,28], and third and fifth[18,19] carbon atoms with different substituents—alkyl[17,28] and hydroxyalkyl[18-20] groups as well as hydroxy-,[30] carboxy-,[50] and alkoxycarbonyl [22,42,59] groups.

Incomplete epimerisation of compound (XXXVI) led to a mixture of epimers (XXXVI) and (XLI) in proportions of 2 : 3:

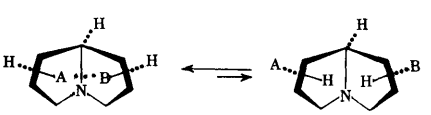


(XLI)

In this particular case the isomer (XLI) is thermodynamically preferred owing to the liberation of energy as a result of the formation of an intramolecular hydrogen bond on transition from (XXXVI) to (XLI) and is not caused by the difference between the non-bonding reactions in epimers (XXXVI) and (XLI).[30]

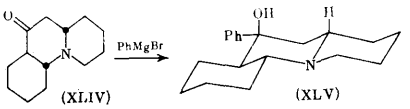
It has been shown[50] that only the asymmetric centre at $C_{(1)}$ is involved in the isomerisation of optically active pyrrolizidine-1-carboxylic acids and there is no racemisation.

The method described here can be extended to the pyrrolizidine systems in which the difference between the free energies of the epimers is determined mainly by the difference between their non-bonding interactions. The possibility of the existence of di- or poly-substituted pyrrolizidines, in which the attraction energy of the substituents, for example A and B, in isomer (XLII) is greater than their repulsion energy, can be postulated. Under equilibrium conditions, isomer (XLII) then predominates and not isomer (XLIII), as might have been expected on the basis of the formal analogy with the literature data.



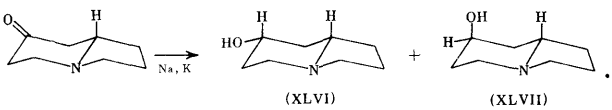
(XLII) (XLIII)

The hydride reduction of 1- and 2-oxoquinolizidines yields alcohols with an equatorial hydroxy-group (*trans*-junction between the rings) as the thermodynamically more stable isomers[24,36]. Similarly the configuration (XLV) with the phenyl group in an equatorial position has been attributed to the single isomer formed in the reaction of compound (XLIV) with phenylmagnesium bromide[47]:



(XLIV) (XLV)

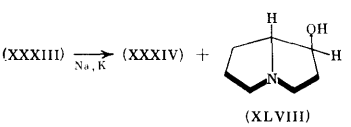
The configurations of 7-hydroxyindolizidines (XLVI) and (XLVII) have been determined from the reduction of 7-oxoindolizidine with sodium or potassium in alcohol:



(XLVI) (XLVII)

Isomer (XLVI) predominates quantitatively (96–98%) in a mixture with (XLVII) owing to its greater thermodynamic stability[25].

Similarly, on reduction with sodium or potassium, 1-oxopyrrolizidine (XXXIII) is converted into a mixture of epimers (XXXIV) (10–20%) and (XLVIII) (80–90%).[30] However, under the conditions of the reduction of compound (XXXIII) with sodium tetrahydroborate in water or with lithium tetrahydroaluminate, isomer (XXXIV) is formed as the main product (60%) [30]:



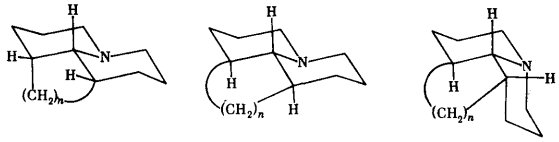
(XLVIII)

The greater reactivity of the substituent occupying the equatorial position compared with the axial position in the quinolizidine and indolizidine series or the greater reactivity of the substituent in the *exo*-position compared with the *endo*-position in pyrrolizidines may lead to the occurrence of side reactions, which alter the initial ratio of the isomers. The relevant findings have been obtained for substituted quinolizidines[60].

Kinetic methods are widely used in studies undertaken to determine the configurations of the 1-azabicyclic substances under discussion. The esters derived from the isomeric 2-hydroxyquinolizidines (XXX) and (XXXI) showed distinct differences in hydrolysis. The isomers with the sterically exposed equatorial functional group are hydrolysed faster than those with the more shielded axially oriented ester fragment[36]. In the acylation of isomeric 1-hydroxy-3-oxoindolizidines by benzoyl chloride the ester gives rise to only one of them[61]. This difference between the reactivities is explained by the fact that the hydroxy-group in the acylated isomer occupies a more accessible equatorial position and it occupies the axial position in the inactive isomer[61]. Comparison of the rate constants for the oxidative dehydrogenation of the three isomeric hexahydrojujolidines permitted a configurational assignment of the isomers[62].

In the solution of stereochemical problems comparison of the rate constants for the quaternisation of the isomers or a qualitative comparison of their reactivities in this reaction proved to be fruitful. The configurational assignment of cyclopenta[*ij*]quinolizidines (XLIX)–(LI) [63] was carried out; among these isomers, compounds (XLIX) and (L) behave in the reaction with methyl iodide similarly to compounds (LII) and (LIII). The configurations of the latter and of (LIV) were found by other methods[62] and are consistent with the rate constants for the reactions with

methyl iodide[64].

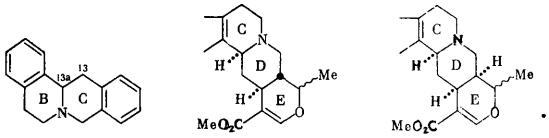


(XLIX), $n = 2$; (L), $n = 2$; (LI), $n = 2$;
(LII), $n = 3$ (LIII), $n = 3$ (LIV), $n = 3$

The molecules of the isomer (LI)‡ are chiral; the isomer was partly resolved into optical enantiomers and this fact served as an argument in support of the configuration shown[63].

Qualitative comparison of the rates of reaction of isomeric perhydrobenzo[*c*]quinolizines with methyl iodide led to stereochemical assignments in agreement with data obtained by other methods[45].

The rate of quaternisation of tetrahydroprotoberberines—derivatives of dibenzoquinolizidine (LV)—depends on the type of junction between the B and C rings, which is determined by the configuration at $C_{(13)}$.[65]



(LV) (LVI) (LVII)

Information about the junction between the D and E rings in heteroyohimbine alkaloids was obtained from kinetic measurements. Compounds of type (LVI) were methylated at a higher rate than those of type (LVII). The configuration with the *trans*-junction of the D and E rings, in which the nitrogen atom is more accessible than in compounds of group (LVII) having the *cis*-junction between the D and E rings, was attributed to the former compounds[66,67]. Similarly yohimbine reacts with methyl iodide 40 times faster than α-yohimbine.[65]

The configurations of 9-methoxy-3,12*b*-dimethyl-1,2,3,4,6,7,12,12*b*-octahydroindolo[2,3-*a*]quinolizidines[68] and biphenyl alkaloids with quinolizidine fragments—lythrine, vertine,[69] vertaline, and decaline[70]—were determined with the aid of data for the kinetics of reactions of these bases with methyl iodide.

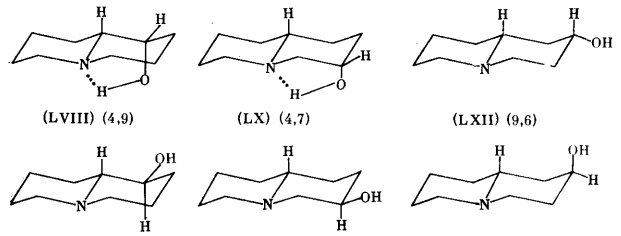
Various criteria for the determination of the stereochemistry of steroid indolizidines were examined by Kolb and Stefanovič[71], who found that the kinetic data for the quaternisation of isomeric compounds by methyl iodide constitute a more reliable basis for stereochemical assignments in the given group of compounds than spectroscopic methods. Qualitative observation of the course of competitive quaternisation of isomeric 3-substituted pyrrolizidines, first proposed for the determination of the configurations of epimeric 3-methyl pyrrolizidines,[72] can apparently be regarded as a general method for the determination of the steric structure of 3-substituted pyrrolizidines. It is based on the fact that isomers with the *trans*-configuration have a more shielded lone electron pair at the nitrogen atom and hence the rate of their reaction with alkyl halides is lower than that of the isomers having the *cis*-configuration. For correct conclusions, it is necessary that the quaternisation reaction should involve a decrease of the content of one of the epimers when its fraction in the mixture of isomers is 50% or less. The steric structure of isomeric 3,5-dimethylpyrrolizidines,[17] 3-hydroxymethylpyrrolizidines,[18,19] and 3-(β-hydroxyethyl)pyrrolizidines[20] were established with the aid of this method.

3. Chromatographic Methods

Bohlmann and coworkers[44,73] showed that the adsorbability of many compounds on alumina depends on the degree of shielding of the lone electron pair of the nitrogen atom. Comparison of the values of R_f or of the sequences in the elution of the isomers from the column[44,45,47,62,65,73-75] and examination of their models can therefore be a useful auxiliary method for the determination of the configuration. This same type of dependence has been found for perhydrobenzo[*c*]quinolizidines,[45] epimeric 6-methyl- and 6-ethylindolizidine-2-ones,[76] 3-methylpyrrolizidines,[72] and a number of saturated and unsaturated pyrrolizidine alcohols[77].

The application of gas–liquid chromatography (GLC) is particularly fruitful in the series of quinolizidines, indolizidine, and pyrrolizidine alcohols. The configurational assignments were most convincing for isomers one of which was capable of forming a relatively stable intramolecular hydrogen bond, while the other lacked this capacity by virtue of geometrical conditions.

In contrast to 2-hydroxyquinolizidines [compounds (LXII) and (LXIII)], the epimeric 1-hydroxyquinolizidines [compounds (LVIII) and (LIX)] and 3-hydroxyquinolizidines [compounds (LX) and (LXI)] have significantly different retention parameters§ on the polar phase Carbowax-20M.[38] Evidently epimers with stronger intramolecular hydrogen bonds should have shorter retention times than epimers with weaker hydrogen bonds or epimers which do not form such bonds at all. If the form with the *trans*-junction is adopted as the preferred conformation of the compounds considered on the basis of the adsorption observed in the range 2700–2800 cm^{-1}, then an intramolecular hydrogen bond can be formed only by compounds (LVIII) and (LX). The retention data for the isomers (LVIII)–(LXI) also indicate their configurational assignments, which have been confirmed by infrared spectroscopy[38].



(LVIII) (4,9) (LX) (4,7) (LXII) (9,6)

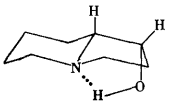
(LIX) (8,5) (LXI) (10,2) (LXIII) (8,6)

A distinct difference between the retention times has been observed for *cis*-3,10-*H*-3-hydroxymethylquinolizidine (LXIV) and *trans*-3,10-*H*-3-hydroxymethylquinolizidine (LXV)[60] and also for the stereoisomeric pairs of 3-hydroxymethyl-3-methylquinolizidines.[75] The configurational assignment of the epimeric 3-(4-chlorobenzyl)-quinolizidines has been made by analogy with compounds (LXIV) and (LXV), but the factors determining the retention of the isomers have not been discussed[60].

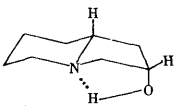
‡For simplicity, the formula of only one enantiomer is shown.

§Here and henceforth in this section the retention times in minutes are given in brackets.

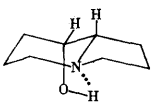
Similarly, comparison of the retention times in the GLC of 1-hydroxyindolizidines [compounds (LXVI) and (LXVII)], 2-hydroxyindolizidines [compounds (LXVIII) and (LXIX)], [30] and 8-hydroxyindolizidines [compounds (LXX) and (LXXI)] [25] permits conclusions about their configurations.



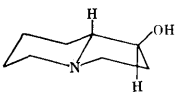
(LXVI) (3,7)



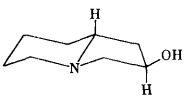
(LXVIII) (4,4)



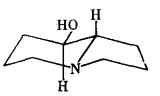
(LXX) (3,0)



(LXVII) (5,4)



(LXIX) (5,8)

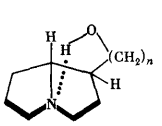


(LXXI) (5,7)

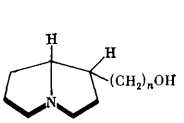
The epimeric 7-hydroxyindolizidines (LXVI) and (LXVII) do not form intramolecular hydrogen bonds and their retention times (6.4 and 7.1 min) [25] differ much less than for the preceding pairs of epimers.

Chalmers et al. [77] investigated the behaviour of pyrrolizidine alkaloids and certain saturated and unsaturated pyrrolizidine alcohols in GLC, thin-layer, and paper chromatography. Empirical correlations were found between the retention time on the siloxane polymer *SE*-30 and the orientation of the hydroxy-group in the 7-position: with the exception of retronecine and heliotridine, bases with a 7-*endo*-OH group (7β-OH). [77] The extremely weak intramolecular hydrogen bond in the isomer with a 7-OH *exo*-group evidently does not play a significant role in the retention of the compound on the stationary phase. The greater steric accessibility of the *exo*-hydroxyl is probably responsible for the greater energy of the interaction with the stationary phase than for the 7-*endo*-OH group. The same effect has been observed in the epimers (XLVIII) and (XXXIV) with the analogous difference between the positions of the hydroxy-group [30]. Even if a very weak intramolecular hydrogen bond is formed in compound (XLVIII), [30] it constitutes an unimportant factor in the interaction of the sorbate and the sorbent. Although weak, the intramolecular hydrogen bond, which is clearly present in the aminoalcohol (LIX), apparently weakens somewhat, compared with the epimer (XXXVI), the interaction with Carbowax-20M, which facilitates the separation of the isomers (XXXVI) and (XLI) by GLC. [30]

In GLC on both Apiezon L and on the polar stationary phase Reoplex-400, (±)-trachelanthamidine (LXXII), which has an intramolecular hydrogen bond, emerges from the column before its epimer (±)-isoretronecanol (LXXIII) [78] in which an intramolecular hydrogen bond cannot be formed for steric reasons.

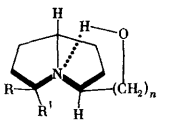


(LXXII), $n = 1$;
(LXXIV), $n = 2$ (32)

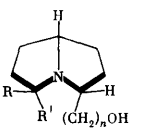


(LXXIII), $n = 1$;
(LXXV), $n = 2$ (42)

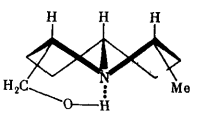
The stereochemistry of the diastereoisomeric 1-(β-hydroxyethyl)pyrrolizidines [compounds (LXXIV) and (LXXV)] [18,20], 3-hydroxymethylpyrrolizidines [compounds (LXXVI) and LXXVII)], [18,19] 3-(β-hydroxyethyl)pyrrolizidines [compounds (LXXVIII) and (LXXIX)], [18,20] 5-hydroxymethyl-2-methylpyrrolizidines, [19] and 5-hydroxymethyl-3-methylpyrrolizidines [compounds (LXXX)–(LXXXIII)]¶ [18,19] determines their different capacities for the formation of intramolecular hydrogen bonds and hence the energy of the interaction with the polar stationary phase.



(LXXVI), $n = 1$, R = R' = H (14);
(LXXVIII), $n = 2$, R = R' = H (16);
(LXXX), $n = 1$, R = Me, R' = H (32);
(LXXXII), $n = 1$, R = H, R' = Me (45).



(LXXVII), $n = 1$, R = R' = H (22);
(LXXIX), $n = 2$, R = R' = H (24);
(LXXXI), $n = 1$, R = Me, R' = H (70)

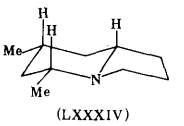


(LXXXIII)

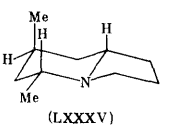
Analysis of the geometries of the isomers and data for the retention on Carbowax-20M were used in the configurational assignment of compounds (LXXIV)–(LXXXIII). [18,20]

The steric structures of the four isomeric 1,7-dimethylquinolizidines were determined [44] on the basis of chromatographic retention times of quinolizidine and 1-methyl-, 3-methyl-, and 1,7-dimethyl-quinolizidines. The shielding of the lone electron pair of the nitrogen in the isomeric perhydrobenzo[*c*]quinolizidines is regarded as a factor determining the difference between their retention times in GLC. [45] In the four isomeric 1-hydroxy-7-methylquinolizidines the orientations of the hydroxy- and methyl-groups are determined from the relative retentions obtained when the compounds are passed over a polar stationary phase [80], the positions of the methyl groups being established from the results of the GLC of methylquinolizidines [81]. An analogous method was used in the more complex case of the isomeric 1-hydroxy-1,7-dimethylquinolizidines. [82]

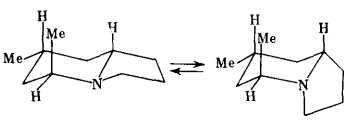
On the basis of the foregoing considerations, the relative retention times of cyclopenta[*ij*]quinolizidines (LXIX)–(LI), quoted by Schofield and Wells [63] without comment, may be regarded as independent confirmation of their structure, established by other methods. Quoting the results of the GLC of 5,7-dimethylindolizidines on the *SE*-52 stationary phase, Lüning and Lundin [14] do not relate the elution sequence of the isomers (LXXXIV), (LXXXV), (LXXXVI), and (LXXXVII) to their steric structure.



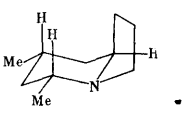
(LXXXIV)



(LXXXV)



(LXXXVIa) (LXXXVIб)



(LXXXVII)

However, if account is taken of the set of data concerning the relation between the retention times and the structure of 1-azabicyclic compounds examined above, one may note that the interaction with the stationary phase is as a rule stronger for the less shielded lone electron pair of the

¶ Isomer (LXXXIII) is represented in the formulae as having a conformation with the *trans*-junction, which may be regarded as preferred according to the data of Skvortsov et al. [18] and by analogy with *cis*-3,8-H-*cis*-5,8-*H*-3,5-dimethylpyrrolizidine. [17,19]

nitrogen. The sequence in which the isomers are eluted from the column (stationary phase Carbowax-20M) is as follows: (LXXXIV)–(LXXXVII), 6-methyl-2-oxoindolizidine, and 6-ethyl-2-oxoindolizidine.[76]

Despite the evidently fruitful nature of the configurational assignment based on chromatographic data, one should note that in specific instances when there are difficulties in choosing the preferred conformation of the sorbate molecules at the instant of interaction with the sorbent, the stereochemical assignment becomes doubtful. A general deficiency of chromatographic methods for the solution of stereochemical problems involves the necessity to have at one's disposal at least two isomers at the same time in order to compare their chromatographic properties.

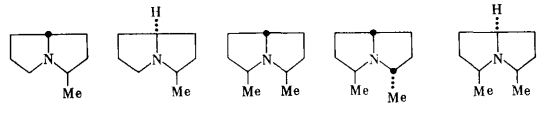
4. Basicities

The measurement of the pK_a values for the epimers of a series of quinolizidine and indolizidine alcohols in many cases permits conclusions about their configuration. Distinct differences between the pK_a values are shown by the epimeric pairs of 1-hydroxyquinolizidines [compounds (LVIII) and (LIX)] ($\Delta pK_a = 1.47$), 3-hydroxyquinolizidines [compounds (LX) and (LXI)], ($\Delta pK_a = 1.27$),[38] 1-hydroxyindolizidines [compounds (LXVI) and LXVII)] ($\Delta pK_a = 1.11$), 2-hydroxyindolizidines [compounds (LXVII) and (LXIX)] ($\Delta pK_a = 0.33$),[30] 8-hydroxyindolizidines [compounds (LXX) and (LXXI)] ($\Delta pK_a = 1.47$),[25] 1-hydroxy-1-methylquinolizidines ($\Delta pK_a = 1.1$), and 1-hydroxy-1-phenylquinolizidine ($\Delta pK_a = 0.9$).[83] Assuming the *trans*-junction of the rings in the above compounds, it can be clearly seen that the intramolecular hydrogen bond can be formed by isomers with axial or pseudoaxial hydroxy-groups, so that within each pair the epimer with the higher pK_a has the *cis*-configuration.

On average, smaller differences between the basicities are observed for the isomeric 2-hydroxyquinolizidines [compounds (XXX) and (XXXI)] ($\Delta pK_a = 0.33$),[38] 2-hydroxy-2-phenylquinolizidines ($\Delta pK_a = 0.20$),[84] 7-hydroxyindolizidines [compounds (XLVI) and (XLVII)] ($\Delta pK_a = 0.57$),[25] and 7-hydroxy-7-phenylindolizidines ($\Delta pK_a = 0.09$),[84] none of which forms an intramolecular hydrogen bond for steric reasons. In this case compounds with an axial hydroxy-group are stronger bases than the epimers with an equatorial hydroxy-group. In the series of heteroyohimbine alkaloids the pK_a reflects the degree of shielding of the nitrogen and is determined by the configuration of the compound[66,67].

The epimeric 1-hydroxypyrrolizidines (XXXIV) and (XLVIII) have similar pK_a values (10.35 and 10.25 respectively)[30]. A more distinct difference between the basicities is observed for 2-hydroxypyrrolizidines [compounds (XXXVI) and (XLI)] ($pK_a = 10.25$ and 10.42). The weak intramolecular hydrogen bond in the isomer (XLI) [30] is probably responsible for its high basicity[85].

Pyrrolizidine (III) and its homologues (LXXXVIII)–(XCII) have respectively $pK_a = 11.68$, 11.62, 11.94,[86] 11.46, 11.74, and 10.28.[87]



(LXXXVIII) (LXXXIX) (XC) (XCI) (XCII)

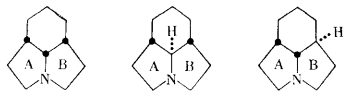
The lone pair of electrons on the nitrogen atom in compound (LXXXVIII) is more shielded by the methyl group than in its epimer (LXXXIX), which gives rise to steric hindrance to hydration and explains the weaker basicity of the former compound. The causes of the different basicities of the epimers (XC) and (XCI) are similar. The relatively low pK_a value of the isomer (XCII) is regarded as a direct consequence of its preferential state, in which there is a *trans*-junction[87].

5. Infrared Spectroscopy

The results of the application of infrared spectroscopy to the configurational assignment of numerous alcohols of the quinolizidine and indolizidine series as well as 1- and 2-hydroxypyrrolizidines have been summarised in a review[9].

The configuration of 2-hydroxyquinolizidines (XXX) and (XXXI), established by Bohlmann et al.[36], has been confirmed by a study of the frequencies and shapes of the absorption bands in the spectra of these epimers[38]. Dilute solutions of platynecine and retronecine [88] have 3467 and 3515 cm^{-1} absorption bands, which are characteristic of intramolecular hydrogen bonds, confirming the structure of these aminoalcohols[88]. The strong absorption by the hydroxy-groups involved in the intramolecular hydrogen bond is consistent with the structure of compounds (LXXVI) and (LXXX). The intramolecular hydrogen bond energies are approximately the same in the two compounds [$\Delta\nu$(OH) = 177 and 178 cm^{-1}].[19] A stronger intramolecular hydrogen bond [$\Delta\nu$(OH) = 380 cm^{-1}] is formed in the pyrrolizidine alcohol (LXXVIII) as a result of the more favourable geometry of the hydrogen bridge[20].

One of the three possible diastereoisomers of 1-azatricyclo[6,2,1,$0^{4,11}$]undecane, which absorbs in the range 2700–2800 cm^{-1}, has been isolated[89]. In choosing from the three possible configurations (XCIII)–(XCV), the last one was rejected, because, according to the authors[89], Bohlmann absorption can be manifested only by compounds with the configurations (XCIII) and (XCIV) (evidently with the *trans*-junction of the A and B rings). The structure (XCIII) was adopted tentatively[89].



(XCIII) (XCIV) (XCV)

The construction of models of isomers (XCIII) and (XCV) shows that in both cases the *cis*-junction of the A and B rings is free from strain and is therefore preferred to the *trans*-junction. The skeleton of the tricyclic compound (XCIV) is highly strained for both types of junction between the five-membered rings. We suggest that structure (XCIV) is therefore apparently more probable rather than structure (XCIII), since there should be no Bohlmann bands for the preferential *cis*-junction between the A and B rings in (XCIII). On the other hand, the existence of comparable amounts of conformations of isomer (XCIV) with the *cis*- and *trans*-junctions, the latter of which should be active in the range 2700–2800 cm^{-1}, may be expected.

6. NMR Spectroscopy

The successful application of ^1H NMR spectroscopy in the solution of stereochemical problems involving the series of quinolizidine and indolizidine derivatives is successfully dealt with in a review[9] and is based on the

analysis of the chemical shifts of the ring and methyl protons as well as the spin–spin coupling constants and the nature of the splitting of the signals. In studies which have not been included in the above review[9] it is possible to encounter new examples of the analogous use of the given method for the determination of the configurations of quinolizidine[75,90-92], indolizidine,[76,93] and pyrrolizidine[17,28,42,59,94-99] series.

The steric orientation of the methyl groups in the quinolizidine alkaloids of the yellow lily has been found with the aid of the benzene-induced shift of the NMR signal due to these groups[100,101]. The dependence of the shift of the signal of the methyl group induced by an aromatic solvent on the latter's position in the bicyclic system was studied recently[102] for nine monomethylquinolizidines. The conclusions reached in the above studies[100,101] are consistent with the observed empirical correlation[102] and the latter can evidently be useful for the determination of the orientations of the methyl or methylene groups in other quinolizidine derivatives.

New possibilities for the investigation of the stereochemistry of 1-azabicyclic systems arose owing to the introduction of ^{13}C NMR spectroscopy. The ^{13}C chemical shifts in quinolizidine (I),[103-105] indolizidine (II),[104] and pyrrolizidine (III)[106] were determined, which constitutes the essential starting point in the investigation of derivatives of compounds (I)–(III) by ^{13}C NMR.

On the basis of spectroscopic data for quinolizidine (I) and methyldecalins with the *trans*-junction, LaLonde and coworkers interpreted the ^{13}C NMR spectra of eight monomethylquinolizidines[105] and isomeric 3-methyl-3-methylthiomethylquinolizidines.[107] The results were used in the analysis of the ^{13}C NMR spectra of nine *Nuphar* alkaloids[107]. The determination of the chemical shifts in (I), the epimeric 1-hydroxymethylquinolizidines, and their benzoates assisted in the interpretation of the ^{13}C NMR spectra and the determination of the steric structures of 1,9-disubstituted quinolizidines[92].

The consideration of the ^{13}C NMR spectra of lactams of the sparteine series was preceded by a study of the spectra of 3-oxo- and 1-methyl-3-oxoquinolizidines.[108] The signals of the ^{13}C nuclei in 9-hydroxymethyl-3-methyl- and 7-hydroxymethyl-1-methyl-*cis*-2,10-*H*-2-hydroxyquinolizidines and azabenzenecarboxylate esters of 3-hydroxyquinolizidines were assigned in the same investigation[108].

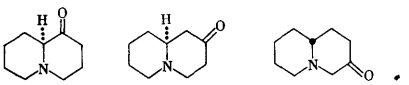
The results obtained can serve as a basis for the study of the steric structures of new and more complex compounds, particularly natural products. The relevant examples have been described in a number of communications[92,107-109].

7. X-Ray Diffraction Analysis

In connection with the automation of X-ray diffraction analysis[110], on the one hand, and the possibility of preparing crystalline salts of quinolizidine, indolizidine, and pyrrolizidine bases, on the other, this method is one of the most promising for the determination of the steric structures and, particularly, the absolute configurations of the derivatives of the 1-azabicyclic compounds under consideration. Studies on the application of X-ray diffraction analysis in the determination of the configurations of salt-like quinolizidines, indolizidines, and pyrrolizidines are reviewed in Section IV.

8. Other Methods

The study of the circular dichroism of optically active (–)-1-oxoquinolizidine (XCVI), (+)-2-oxoquinolizidine (XCVII), and (–)-3-oxoquinolizidine (XCVIII) made it possible to determine the absolute configurations of these aminoketones[111].



(XCVI) (XCVII) (XCVIII)

The identity of the configurations at the $C_{(4)}$ atom in the quinolizidine alkaloids vertaline and decaline follows from a comparison of their optical rotatory dispersion and circular dichroism curves[70]. The circular dichroism data have been used in the determination of the structures of 6-hydroxythiobinupharidine, 6-hydroxythionuphlutine,[112] and the quinolizidine mono-*gem*-aminals from *Nuphar luteum*.[113]

Culvenor and coworkers studied the circular dichroism of a series of simple pyrrolizidine bases and certain pyrrolizidine alkaloids. The sign and magnitude of the Cotton effect for both the simplest bases and open-chain ester alkaloids depend on the configuration at $C_{(8)}$, on the positions of the substituents, and on the degree of saturation of the bicyclic system[114]. Saturated pyrrolizidines with one substituent in the 1-position, namely heliotridane, the enantiomer of isoretronecanol, 1β,2β-epoxy-1α-hydroxymethyl-8α-pyrrolizidine, and 1α,2α-epoxy-1β-hydroxymethyl-8α-pyrrolizidine exhibit a negative Cotton effect. Retronecanol, which has a 7β-hydroxy-group, in contrast to the previous compounds, and the unsaturated bases supinidine, deoxyretronecine, retronecine, and heliotridine exhibit a positive Cotton effect. The magnitude of the effect for the last two compounds apparently depends on the configuration at $C_{(7)}$.[114]

The applicability of the octant rule to the determination of the absolute configurations of α-aminoketones of the quinolizidine, indolizidine, and pyrrolizidine series has been examined[115].

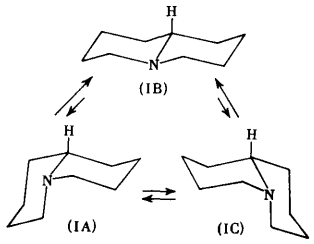
Slight differences have been observed between the mass spectra of lupinine and epilupinine[116] and between those of the four isomeric 4-phenyl-1-quinolizidinols.[117] A mass-spectrometric study of 6-hydroxythiobinupharidine, 6-hydroxythionuphlutine *B*, and 6'-hydroxythionuphlutine *L* assisted in the determination of the configuration at $C_{(6)}$ in these compounds[112]. The mass spectra of the isomeric 7-hydroxy-1-hydroxymethylpyrrolizidines (platynecine, dihydroxyheliotridane, hastanecine, and turneforcidine) are similar, but differ from the spectra of 2-hydroxy-1-hydroxymethylpyrrolizidines[59]. Using mass spectra, it is difficult to reach a conclusion about the orientation of the hydroxymethyl group in the isomeric 1-hydroxymethylpyrrolizidines (trachelanthamidine and lindelofidine).[118] However, it has been suggested[118] that, in a mass spectrometric study of pyrrolizidines with bulky substituents, it might be possible to determine their steric positions.

The dipole moment method has not so far been used widely in the determination of the configurations of quinolizidines, indolizidines and pyrrolizidines. Satisfactory results have been obtained by this method in the stereochemical study of 1- and 3-hydroxymethylquinolizidines[60,119] and also 3-(4-chlorobenzyl)quinolizidines.[60] The isomers were assigned by a qualitative interpretation of the vector scheme for each pair of epimers, which makes it possible

to predict higher dipole moments for compounds with the *cis*-configurations. The equatorial location has been attributed to the hydroxyethyl group of 6-hydroxyethyl-3,9-dimethylquinolizidine on the basis of its dipole moment[120].

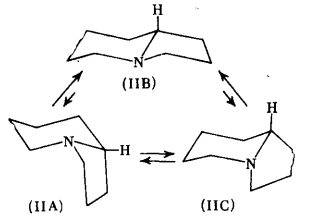
III. CONFORMATIONAL ANALYSIS OF THE BASES

The central problem of the conformational analysis of quinolizidines is the ratio of forms having *cis*- and *trans*-junctions, which can undergo interconversions by virtue of the inversion of the nitrogen atom. For quinolizidine itself, these ratios are reflected in the following scheme:



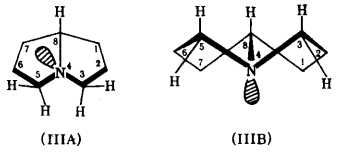
The flexible forms (IA) and (IC) with the *cis*-junction are interconvertible enantiomers and henceforth will be treated as a single conformation (IA). The conformations with one or two rings in the boat form are not discussed because they are known to be unfavourable owing to non-bonding interactions. However, among certain quinolizidine derivatives compounds are encountered where the boat conformation of one of the rings is possible.

Indolizidine (II) also has two conformations (IIA) and (IIC) with a *cis*-junction and a conformation (IIB) with a *trans*-junction:



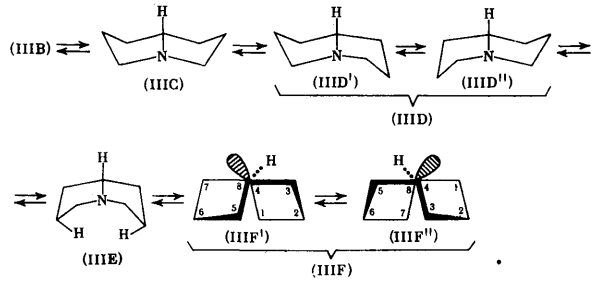
It is readily seen that, in contrast to the quinolizidine conformers (IA) and (IC), the *cis*-conformers (IIA) and (IIC) are energetically non-equivalent.

Of the two forms of pyrrolizidine (IIIA) and (IIIB), the (IIIA) form with a *cis*-junction was chosen because, in contrast to (IIIB), it is free from appreciable strain[121].



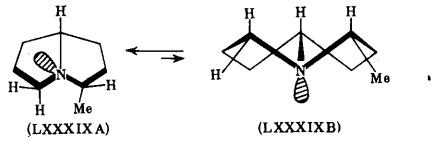
Subsequently the idea of a *cis*-junction between the rings in pyrrolizidines was adopted in many investigations[30,72,122-124]. However, it was shown[125] that in certain intramolecular quaternisation reactions there is a possibility of the formation of quaternary salts with a fixed pyrrolizidine skeleton having a *trans*-junction.

trans-Fused (IIIB), open (IIIC), half-folded (IIID)†, and folded (IIIE) conformations have been postulated[126] for pyrrolizidine (III):



As a result of unfavourable non-bonding interactions, the conformation (IIIE) resembles the cyclohexane boat form and, by analogy with cyclohexane and derivatives of *cis*-bicyclo[3,3,0]octane,[127] it can be assumed that, in an "endeavour" to weaken non-bonding *trans*-2-*H*...*trans*-6-*H* interactions, the (IIIE) conformation undergoes a twisting deformation. This results in two enantiomeric twisted conformations (IIIF′) and (IIIF″) (the five-membered ring exists in the half-chair form) and these acquire some angular strain, which relates them to the twist-form of cyclohexane. The (IIIC) and (IIID) conformations are free from strong non-bonding interactions and angular strain and their enthalpies are apparently similar, which is a feature resembling the insignificant difference between the energies ($\Delta H \simeq 0.1$ kcal mole^{-1}) of the C_{2v} (open) and C_s (half-folded) conformations of *cis*-bicyclo[3,3,0]-octane.[128]

The change in the conformational equilibrium between the (LXXXIXA) and (LXXXIXB) forms of the free pyrrolizidine base with *cis*-‡ and *trans*-junctions under the influence of a change in temperature has been observed[126] by NMR in relation to (LXXXIX):

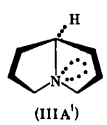


Analogous conformational effects may be expected also in those cases where a hydroxymethyl[18,19] or a β-hydroxyethyl group is introduced instead of the methyl group[20].

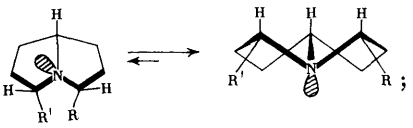
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†Each pair of enantiomeric conformations (IIID′), (IIID″), and (IIIF′), (IIIF″), will be treated for simplicity as (IIID) and (IIIF) forms.

‡In those cases where the *cis*-fused conformations are not distinguished, their families are nevertheless designated by schematic diagrams of type (IIIA) or (IIIA′):



Evidently the fraction of the *trans*-fused form can be significantly increased by intensifying the non-bonding interactions in the *cis*-fused conformations of pyrrolizidines. This was achieved in two ways: by introducing a t-butyl group instead of the *trans*-3-*H* atom and by introducing two methyl groups instead of the *trans*-3-*H* and *trans*-5-*H* atoms in the pyrrolizidine molecule. The non-bonding interactions in the *cis*-fused conformations (XCIXA) and (XCIIA) of pyrrolizidines (XCIX) [28] and (XCII) [17] are so intense that the compounds exist mainly in the *trans*-fused forms (XCIXB) and (XCIIB) despite the marked angular strain in them [17,28,79]:



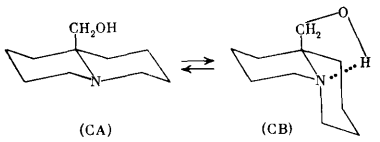
(XCIXA), R = t-Bu, R'=H; (XCIXB), R = t-Bu, -Bu, R'=H;
(XCIIA), R = R' = Me; (XCII), R = R' = Me.

The idea of an appreciable contribution by the *trans*-fused form to the equilibrium mixture of the conformations of compound (XCV) has been confirmed by experiments on its oxidative dehydrogenation by mercury acetate [129].

1. Determination of the Preferred Conformations. A Qualitative Approach

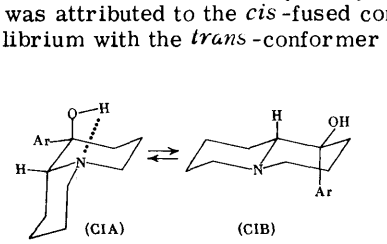
(a). Vibrational spectroscopy. The application of infrared spectroscopy in the conformational analysis of quinolizidines and indolizidines has been described in detail in a review [9]. In the range 2700–2800 cm^{-1} (in the region of the stretching vibration frequencies of the hydroxy-group) "spectroscopy" proved to be particularly valuable in the determination of the preferred conformations of alcohols of the quinolizidines [9,56,74,84,100,117] and indolizidine [9,83,84] series.

In contrast to other simplest quinolizidine alcohols [9], 10-hydroxymethylquinolizidine (C) in a dilute solution exhibits absorption bands due to both free and bound hydroxy-groups, which indicates the existence of an equilibrium between conformations (CA) and (CB) with *trans*- and *cis*-junctions respectively [130]:



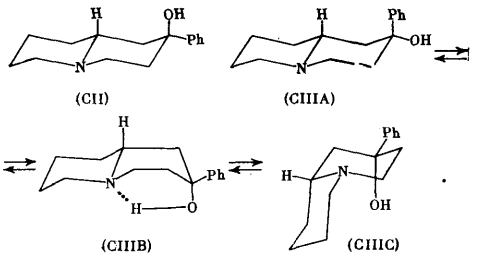
(CA) (CB)

The appreciable absorption typical of intramolecular hydrogen bonds in the spectra of 1-aryl-1-hydroxyquinolizidines (CI) was attributed to the *cis*-fused conformation (CIA) in equilibrium with the *trans*-conformer (CIB) [56];



(CIA) (CIB)

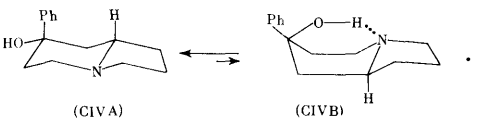
The structures of 2-hydroxy-2-phenylquinolizidines (CII) and (CIII) [84,131] were examined almost simultaneously and independently:



(CII) (CIIIA) (CIIIB) (CIIIC)

The spectrum of isomer (CII) in dilute solutions has only one peak corresponding to the free hydroxyl, while the spectrum of its epimer (CIII) has a weak absorption band characteristic of the vibrations of an intramolecular hydrogen bond. This observation enabled the authors [84,131] to conclude that the equilibrium mixture contains, together with form (CIIIA), also the conformation (CIIIB), in which the six-membered ring with substituents is in the boat form. The (CIIIC) conformation was not discussed [84,131], although it can apparently make a contribution, by analogy with (CIA).

Similarly the spectrum of 7-hydroxy-7-phenylindolizidine (CIV) in dilute solutions has absorption bands due to free [(CIVA) conformation] and bound hydroxyls [(CIVB) conformation with the six-membered ring in the boat form] [84]:



(CIVA) (CIVB)

Vibrational spectroscopy is in essence only just beginning to be applied in the study of the conformations of pyrrolizidines. Comparison of the infrared and Raman spectra of pyrrolizidine and *cis*-bicyclo[3,3,0]octane and also the results of the calculation of the frequencies and modes of the normal vibrations of these compounds show that, under the usual conditions, pyrrolizidine is a mixture of mainly two conformations—the open conformation (IIIC) and the half-folded conformation (IIID). [132,133]

In the region of the skeletal-deformation vibrations the Raman spectra of the strained pyrrolizidines (XCII) and (XCIX) have a smaller number of frequencies than the spectra of the corresponding isomers with a *cis*-junction between the rings, which is interpreted as a consequence of the preferential *trans*-junction in the (XCIIB) and (XCIXB) states [28,133,134]. From the standpoint of the study of the region of applicability of the Bohlmann correlation, discussed in a review [9], it is of interest to observe the absorption in the range 2700–2800 cm^{-1} characteristic of the strained preferentially *trans*-fused pyrrolizidines (XCII) and (XCIX). [79,134] The contribution of the $C_{(8)}$–H bond to the effect was demonstrated by introducing deuterium instead of hydrogen in the 8-position [79].

(b) NMR spectroscopy. The chemical shifts of the protons attached to the α-carbon atoms and the gemina (α-methylene group) and vicinal spin–spin coupling constants for protons are used as criteria for the determination of the preferential type of junction between the rings in quinolizidines, indolizidines, and pyrrolizidines.

The spectra of *trans*-fused 1-azabicyclic compounds contain the signal due to the angular proton at a higher field than the corresponding *cis*-fused bases[9,126,135]. Measurement of the chemical shifts of the signals due to the protons attached to the bridgehead carbon atoms serves as a fairly general procedure for the investigation of the conformations of 1-azabicyclic compounds[57,136,138]. Under these conditions, a comparison of the chemical shifts obtained for the test base and its isomer or another compound used as a standard (with a definite type of junction between the rings) is as a rule required. In certain instances[17,28,92,139] difficulties are encountered owing to the localisation of the angular proton multiplet in the ^{1}H NMR spectra.

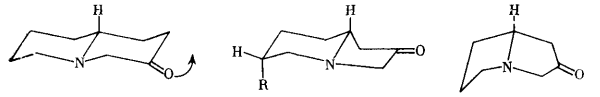
The virtual invariance of the pyrrolizidine spectrum in the temperature range from −17° to +190° leads to the conclusion that the compound is largely if not entirely in the *cis*-fused conformation (IIIA).[126] The ^{1}H NMR spectrum of compound (LXXXIX) exhibits, in contrast to the spectra of its epimer (LXXXVIII) and pyrrolizidine (III), a distinct dependence of the chemical shifts of a number of signals, which reflects a change in the equilibrium between the *cis*-fused and *trans*-fused forms [(LXXXIXA) and (LXXXIXB)] respectively. The upfield displacement of the 8-H proton signal with increase of temperature serves as a criterion indicating an increase of the content of the *trans*-fused conformation (LXXXIXB).[126] The similarity of the chemical shifts of the 8-H protons in pyrrolizidine (3.33 p.p.m.) and in the epimers (LXXXVIII) (3.45 p.p.m.) and (LXXXIX) (3.31 p.p.m.) as well as the results of measurements of the temperature variation show that the *cis*-fused conformations of compound (LXXXIX) predominate[126].

When the methyl group in (LXXXIX) is replaced by the t-butyl group as in (XCIX), a significant diamagnetic shift of the 8-H proton signal is observed ($\delta \leqslant 2.95$ p.p.m.).[28] The H-8 proton resonates at a higher field also in compound (XCII) ($\delta < 3$ p.p.m.).[17] The preferentially *trans*-fused conformations (XCIXB) and (XCIIB) have been attributed to these pyrrolizidine homologues[17,28].

The position of the signal due to the 4-H proton in 4-arylquinolizidines serves as a diagnostic characteristic of the *cis*- or *trans*-fused conformation—in the former the signal is at a lower field than in the latter[58,69,70,135,140,141]. Comparison of the ranges of the chemical shifts for *cis*- or *trans*-fused 4-arylquinolizidines[69] shows that they can overlap for different groups of compounds, but, according to the literature, the determination of the preferential conformations of epimers is fairly reliable.

The preferential *trans*-junction between the rings in lupinine is evident from the chemical shifts of the axial and equatorial protons at $C_{(4)}$ and $C_{(6)}$.[142]

The amount of information about the geminal spin–spin coupling constants in the quinolizidine, indolizidine, and pyrrolizidine series is still relatively limited[143,144] and the influence of different types of junction between the rings on J_{gem} is apparently small[145] as long as the CH_2 group is not located between nitrogen and another heteroatom[9] or a carbonyl group[76]. The contribution of π electrons ($\Delta J = -3.2$ Hz) to $^2J_4$-CH_2 was determined by comparing the geminal constants for the 4-CH_2 group in 3-oxoquinolizidine (CV) and [3D$_2$]quinolizidine, whence it was found that the ring with the carbonyl group is deformed; the carbonyl group is slightly rotated towards the 10-H atom owing to the dipole repulsion interaction between it and the nitrogen atom[76]:



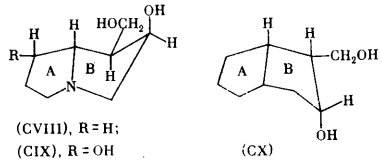
(CV) (CVI), R = Me; (CVII), R = Et (XXXVA)

Having investigated the geminal constants for the 3-CH_2 group and in certain cases the 5-CH_2 group in 3-, 5-, 6-, 7-, and 8-alkyl-2-oxoindolizidines, Cahill and Crabb[76] concluded that they exist in *cis*-fused conformations. The problem of the contribution of the *cis*-fused forms was studied specially in relation to compounds (CVI) and (CVII). The conformational homogeneity of compounds (CVI) and (CVII) was inferred on the basis of the constant $^2J_5$-CH_2 = −11.0 Hz. The contributions of the lone electron pair of the nitrogen atom and the π electrons of the carbonyl group to the constant $^2J_3$-CH_2 for 3-, 5-, 6-, 7-, and 8-alkyl-2-oxoindolizidines were separated. According to the last contribution (−6.7 Hz), the $C_{(1)}$, $C_{(2)}$, $C_{(3)}$, and N atoms are located in the same plane[76].

The very low geminal constant J_3-CH_2 = −18.5 Hz in compound (XXXV) was attributed to the bisector location of the carbonyl group in relation to the 3-CH_2 group and the conformation with an *endo*-puckered N, $C_{(5)}$, $C_{(6)}$, $C_{(7)}$, $C_{(8)}$ ring (XXXVA).[76]

The splitting of the signal due to the angular proton in benzo[*a*]quinolizidine, indolo[*a*]quinolizidine,[137] and dibenzo[*a*,*g*]quinolizidines[136,138] was used to choose one of the possible conformations with a *cis*-junction between the rings.

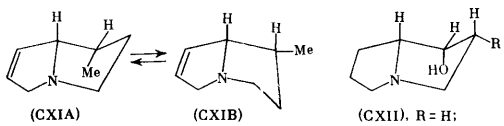
In the study of *cis*-fused conformations of pyrrolizidines considerable progress has been achieved as a result of the investigation of substituted and partly unsaturated bases, from the ^{1}H NMR spectra of which the spin–spin coupling constants for the vicinal protons were determined and their dependence on the geometry was employed. Thus it was found from the values of $J_{H,H}$ for the B rings in compounds (CVIII)–(CX) that the first two compounds[59,98] have conformations with an *exo*-puckered B ring, while the last compound[59] has a conformation with an *endo*-puckered ring.



(CVIII), R = H; (CIX), R = OH (CX)

In all three cases the conformation of the B ring is apparently dictated by the preferential pseudoequatorial orientation of the hydroxymethyl group in the 1-position; the conformation of the A ring has not been discussed.

Detailed analysis of the ^{1}H NMR spectrum of heliotridene (CXI) showed that the free base in solution in $CDCl_3$ consists of an equilibrium mixture of two conformations, (CXIA) and (CXIB), in proportions of approximately 1 : 1[97]:

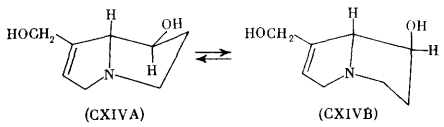


(CXIA) (CXIB) (CXII), R = H; (CXIII), R = OH

The angle of pucker§ of the saturated ring in conformations (CXIA) and (CXIB) is 45°.

The retronecine molecules have the (CXII) conformation with an *exo*-pucker of the saturated ring (angle of deflection 40°) and a pseudoaxial 7-OH hydroxyl; furthermore, they undergo additional twisting of the bicyclic system about the axis passing through the $C_{(2)}$ and $C_{(6)}$ atoms in a direction such that the 3β-H atom tends to occupy a pseudoequatorial position and the saturated ring approaches the half-chair form[96]. Crotanecine has a similar form (CXIII) in aqueous solution[99].

Agreement between the experimental and calculated vicinal spin–spin coupling constants for heliotridine (CXIV) is achieved if it is assumed that the compound is an equilibrium mixture of the (CXIVA) and (CXIVB) conformations with angles of pucker of the saturated ring equal to 40° [96]:



(CXIVA) (CXIVB)

The application of modified Karplus equations, taking into account the influence of nitrogen and oxygen atoms in (CXIV), made it possible to obtain a very satisfactory agreement between the calculated and experimental values of $^3J_{H,H}$ for the (CXIVA) : (CXIVB) = 35 : 65 mixture[97].

On the basis of the results of the calculation of the geometries of the molecules with the aid of a mechanical model and analysis of the geminal, vicinal, and allyl spin–spin coupling constants, Van Binst et al.[146] concluded that the geometry of the bicyclic system in compounds (CXV)–(CXVII) is virtually the same—the nitrogen is in the sp^2-hybridised state and the bicyclic system has a rigid highly strained (17.2 kcal mole^{-1}) skeleton.

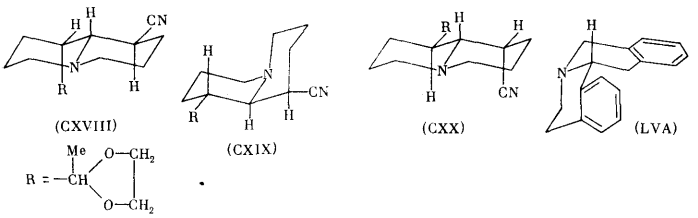


(CXV), X=Y=O;
(CXVI), X=Y=CHCN;
(CXVII), X=O, Y=$CHCO_2Et$.

Whereas the identification of the signals in the ^1H NMR spectra which cannot be interpreted initially sometimes constitutes a very complex problem[92,139], ^{13}C NMR spectra are frequently fairly simple. In the determination of the type of junction between the rings in quinolizidine, lupinine, epilupinine, their benzoate esters, and the isomeric compounds (CXVIII)–(CXX) the positions of the signals due to $C_{(4)}$, $C_{(6)}$, and $C_{(10)}$ are instructive. The shift of the signal due to the $C_{(4)}$ and $C_{(6)}$ nuclei in the *trans*-fused isomers (CXVIII) and (CXX) is approximately constant (57 p.p.m.). On the other hand, in the *cis*-fused compound (CXIX) the signals due to the $C_{(4)}$ and $C_{(6)}$ nuclei are significantly displaced in the upfield direction. According to Wenkert et al.[92], the location of the $C_{(4)}$ signal of this isomer at an anomously high field (47.1 p.p.m.) is a consequence of two γ-effects generated by the carbon atoms of a neighbouring ring, i.e. caused by 1.3-diaxial non-bonding interactions of one of the 4-H atoms with the hydrogen atoms of the neighbouring ring.

The chemical shift of the $C_{(10)}$ nucleus in compound (CXIX) is approximately 6 p.p.m. higher than in the *trans*-fused bases (CXVIII) and (CXX).[92,104] This finding can be given an explanation analogous to that quoted above for the $C_{(4)}$ and $C_{(6)}$ nuclei.

The stereochemistry of tetrahydroprotoberberines, which are derivatives of dibenzo[*a*,*g*]quinolizidine (LV), can be readily inferred from the chemical shifts of the $C_{(6)}$ nuclei: compounds with a *cis*-junction between the B and C rings have chemical shifts of 48.3 p.p.m. or less, while compounds with a *trans*-junction give rise to signals at lower a field (51.4 ± 0.1 p.p.m.). The position of the signal due to the angular $C_{(13a)}$ atom depends just as clearly on the nature of the junction between the rings[136,147]. Tetrahydroprotoberberines with a methoxy-group at $C_{(1)}$ assume preferentially the *cis*-fused conformation of type (LVA) in which non-bonding interactions between the methoxy-group and 13-H, which occur in the *trans*-fused and the second *cis*-fused conformations[136,147], are eliminated[136,147]:



(CXVIII) (CXIX) (CXX) (LVA)

The chemical shift of the $C_{(6)}$ atom in capaurimine is 49.3 p.p.m. and the compound consists of a mixture of *cis*- and *trans*-fused conformations[36].

The symmetry and stereochemistry of the isomeric perhydropyrido[2,1,6-*de*]quinolizidines have been inferred from the number of signals in their ^{13}C NMR spectra[109].

The similarity of the conformations of the strained pyrrolizidines (XCII) and (XCIX) is clearly seen from their ^{13}C NMR spectra. The signals due to the $C_{(8)}$ nuclei in these compounds are in the range 70.1–72.7 p.p.m., while other unstrained *cis*-fused pyrrolizidines are characterised by shifts of the $C_{(8)}$ signals in the range 64–66.6 p.p.m.[106]

Other methods. The rate of methylation of alkaloids of the yohimbine and heteroyohimbine series is satisfactorily correlated with their stereochemistry[66,67]. Yohimbine reacts with methyl iodide more slowly approximately by two orders of magnitude than does pseudoyohimbine, which, in contrast to the former compound, has a *cis*-fused quinolizidine fragment and a sterically more accessible nitrogen atom[65].

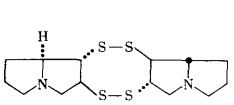
The 1-H and 13-H atoms, which are in the *cis*-positions relative to 13a-H, are closer together in dibenzoquinolizidine (LV). The introduction of a more bulky substituent in place of one of these atoms gives rise to intense non-bonding interactions, which forces the molecule to assume the conformation with a *cis*-junction between the B and C rings. Study of the kinetics of the quaternisation of dibenzoquinolizidine derivatives (tetrahydroprotoberberines) served as a means for determining the conformations of these compounds in solution. It has been shown in this way that capaurine and capaurimine exist in solution in conformations with a *cis*-junction between the B and C rings[65]. Vertine and vertaline, which have a *cis*-fused quinolizidine fragment, react with methyl iodide much faster than their epimers lythrine and decaline, in which the quinolizidine rings are *trans*-fused[69,70]. The relative inertness of compound (XCII) compared with its isomers (XC) and (XCI) in the reaction with n-propyl iodide can be

§The angle between the planes passing through the $C_{(1)}$, $C_{(3)}$, N, and $C_{(8)}$ atoms, on the one hand, and through the $C_{(1)}$, $C_{(2)}$, and $C_{(3)}$ atoms, on the other[97].

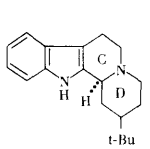
accounted for by the considerable contribution of the *trans*-fused form (XCIIB) (see the beginning of this section) to the equilibrium mixture of its conformations[17].

According to X-ray diffraction data, the free base of capaurimine *p*-bromobenzoate has a *cis*-junction between the B and C rings in the crystalline state[148]. In crystalline cassipourine (CXXI) the pyrrolizidine rings have a half-folded conformation of type (IIID), the angle between the planes passing through the $C_{(1)}$, $C_{(3)}$, N, and $C_{(8)}$ atoms, on the one hand, and the $C_{(5)}$, $C_{(7)}$, $C_{(8)}$, and N atoms, on the other, is 123°.[149]

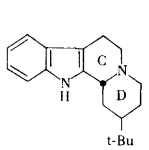
A difference has been observed between the mass spectra of compounds (CXXII) and (CXXIII). On electron impact, the epimer (CXXII) loses the oxygen at $C_{(12)}$ much more readily than the epimer (CXXIII), since the 12-H atom and the lone electron pair of the nitrogen atom are in the *trans*-diaxial positions and there is a *trans*-junction between the C and D rings only in the former epimer[150]:



(CXXI)



(CXXII)



(CXXIII)

The dependence of the mass spectra of the stereoisomeric alkaloids matrine, allomatrine, isosophoridine, and sophoridine on the steric structure has been demonstrated and studies on the mass spectrometry of these and other quinolizidine alkaloids have been reviewed[151].

By studying the ultraviolet spectra of compounds (XCVI)–(XCVIII), Mason et al.[111] found that the carbonyl group in compounds (XCVI) and (XCVIII) absorbs more intensely than that in (XVII) and other carbocyclic ketones owing to the interaction of the carbonyl π orbitals and the lone pair of electrons of the nitrogen. Such interaction can occur only in *trans*-fused forms of compounds (XCVI) and (XCVIII), whence it is concluded that this conformation is preferred[111].

The type of junction between the rings in pyrrolizidines has a fairly marked influence on their basicity. While the *cis*-fused compounds (I), (LXXXVIII), (LXXXIX), heliotridane (pK_a = 11.48),[152] (XC), and (XCI) are some of the strongest saturated bases with a tertiary nitrogen atom (for the values of pK_a see Section II, subsection 4), the predominantly *trans*-fused (XCII) has a relatively low pK_a = 10.28,[87] close to the pK_a values of related typically *trans*-fused 1-azabicyclic compounds, such as quinolizidine (10.19)[64] and indolizidine (10.15).[86]

The comparatively high basicity of *cis*-fused pyrrolizidines[86,123,152,153] can be explained by their stereochemical characteristic feature consisting in the steric accessibility of the nitrogen[123,153] and a geometry which is unfavourable for the delocalisation of the lone electron pair of the nitrogen[86]. This property of the pyrrolizidine *cis*-fused bicyclic system can be readily discovered by comparing the basicities of quinolizidine, indolizidine, and pyrrolizidine alcohols with the hydroxy-group in the 2-position relative to the nitrogen, which do not form intramolecular hydrogen bonds (Table 1). Thus one may reach a conclusion about the sequence of increasing basicities of unsubstituted bicyclic systems. Quinolizidine and indolizidine are virtually equivalent as bases, whereas pyrrolizidine is significantly stronger. This conclusion is confirmed by recent direct observations for the free bases (I)–(III),[86] whose pK_a values are 10.19,[64] 10.15, and 11.68[86] respectively. In aqueous solution base (III) differs in strength from compounds (I) and (II) by more than an order of magnitude.

Table 1. The basicities of certain quinolizidine, indolizidine, and pyrrolizidine alcohols.

Compound	pK_a	Refs	Compound	pK_a	Refs
(LIX)	8.73	38	(LXXI)	8.33	25
(LXI)	8.60	38	(XXXIV)	10.35	30
(LXVII)	8.59	30	(XLVIII)	10.25	30
(LXIX)	8.82	30	(XXXVI)	10.25	30

2. Quantitative Results

Certain results of the quantitative study of the *cis–trans* interconversion of quinolizidine and indolizidine have been published[9]. We arranged systematically and compiled in Table 2 data for the conformational equilibria involving both the bases (I)–(III) themselves and their derivatives.

The conflicting results obtained in the determination of the thermodynamic parameters of the *cis–trans* interconversion in quinolizidine led us to calculate the enthalpy of this process in two independent ways[159]. The calculation was based on the enthalpy of the *cis–trans* isomerisation of decalines. Ultimately, as a result of this treatment[159], the energy of the additional stabilisation of the *trans*-fused form of quinolizidine relative to *trans*-decaline was obtained from data for piperidine and calculated from the results of the determination of the energies of hydrogen bonds in the quinolizidine–phenol and quinuclidine–phenol systems[159]. It was shown[158,162] that at least in the gas phase the values of ΔG°_{25} for the *cis–trans* interconversions in quinolizidine and indolizidine differ more significantly than is believed in the literature[157,163].

At the present time there have been no rigorous determinations of the thermodynamic parameters of the *cis–trans* interconversion in pyrrolizidines. It has been suggested[126] that there is a difference between the heat contents of the *cis*- and *trans*-fused pyrrolizidines, which is close to that described for the isomeric *cis*- and *trans*-bicyclo[3,3,0]octanes (6.0 kcal mole^{-1}).[164]

Assuming that an increase of the content of the *trans*-fused form of pyrrolizidine to 5% on heating its vapour from 20° to 300°C would be observed from the appearance of Bohlmann bands in the range 2700–2800 cm^{-1} and having failed to observe this effect with increase of temperature, Skvortsov et al.[158] calculated $\Delta H < -3.4$ kcal mole^{-1} for the *trans–cis* conversion in pyrrolizidine.[158]

IV. THE CONFIGURATIONS AND CONFORMATIONS OF THE BASES AND QUATERNARY SALTS PROTONATED AT THE NITROGEN ATOM

The quinolizidinium cation in trifluoroacetic acid has a *trans*-junction between the rings; its ^1H[165] and ^{13}C[103] NMR spectra have been described. A *trans*-junction

Table 2. Quantitative data for the conformational equilibria in quinolizidines, indolizidines, and pyrrolizidines.

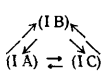
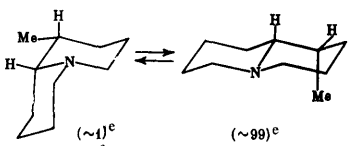
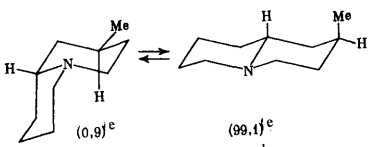
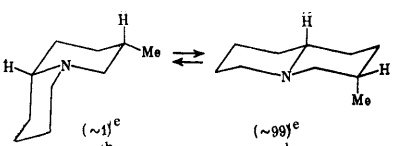
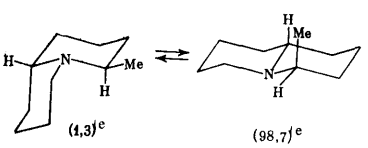
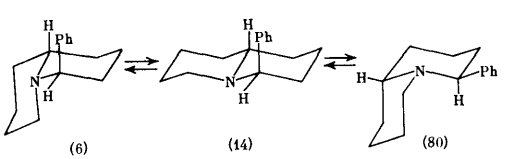
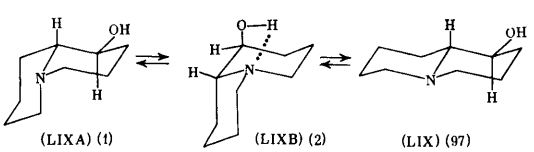
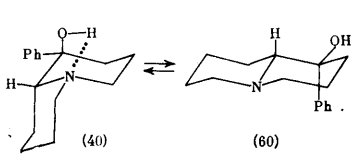
Equilibrium conformation[a] (content in % at 20–33°)	Method[m]	$-\Delta H^\circ$, kcal mole^{-1}	$-\Delta G^\circ_{20-33^\circ}$, kcal mole^{-1}	References
1	2	3	4	5
 (IA) ⇄ (IC)	*A*	1.9	—	154
	A	—	4.6	155
	—	2.6		156
	B	—	4.4	64
	C	—	2.6	157
	C	>3.4	—	158
	A, C	—	2.0±0.35[b]	117
	A	3.3[c]	—	
		3.7; 4.3[d]	—	159
 (~1)[e] (4)[f] (~99)[e] (96)[f]	*B*	—	—	64
 (0,9)[e] (1)[b] (99,1)[e] (99)[b]	B	—	—	64
 (~1)[e] (7)[b] (~99)[e] (93)[b]	*B*	—	—	64
 (1,3)[e] (98,7)[e]	*B*	—	—	64
 (6) (14) (80)	*A, C*	—	—	117
 (LIXA) (1) (LIXB) (2) (LIX) (97)	*C*	—	2.1[g]	157
 (40) (60)	*C*	—	—	157

Table 2 (cont'd.).

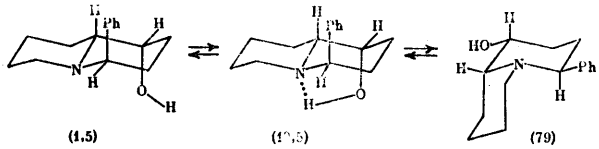
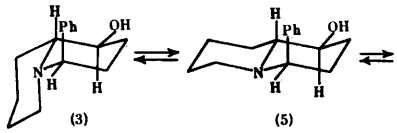
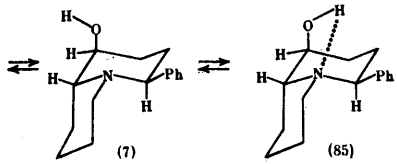
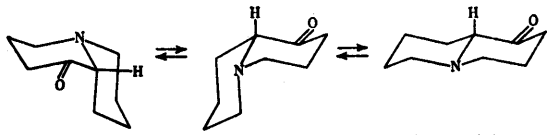
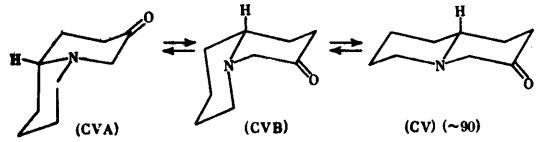
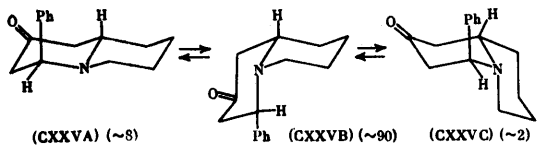
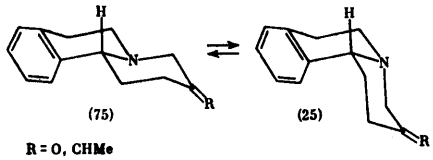
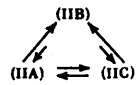
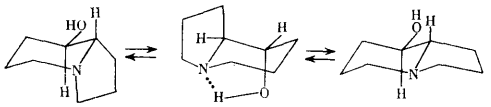
Equilibrium conformation[a] (content in % at 20–33°)	Method[m]	$-\Delta H°$, kcal mole^{-1}	$-\Delta G°_{20-33°}$, kcal mole^{-1}	References
1	2	3	4	5
 (1,5) (1?,5) (79)	*C*	—	—	117
 (3) (5)	*C*	—	—	117
 (7) (85)				
 (CXXIVA) (3) (CXXIVB) (~7) (CXXIVC) (~90)	*D*	1.95[h]	—	111
 (CVA) (CVB) (CV) (~90)	*D*	2[i]	—	111
 (CXXVA) (~8) Ph (CXXVB) (~90) (CXXVC) (~2)	*A*	—	1.5[j] 2.3[k]	140
 (75) (25) R = O, CHMe	*E*	—	—	160
 (IIB) (IIA) (IIC)	*A* *B* *C*	0.3 0.9 —	— — 2.4	154 161 157

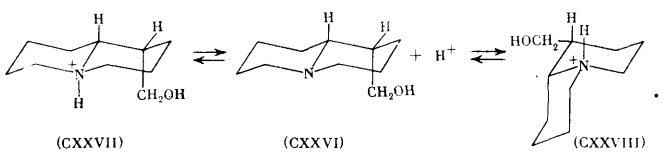
Table 2 (cont'd.).

Equilibrium conformation[a] (content in % at 22-33°)	Method[m]	$-\Delta H^{\circ}$, kcal mole^{-1}	$-\Delta G^{\circ}_{20-33^{\circ}}$, kcal mole^{-1}	References
1	2	3	4	5
 (LXXIA) (1) (LXXIB) (3) (LXXI) (96)	*C*	—	1.9[l]	157
(III B) ⇄ (III A)	*C* *A*	≥3.4 <6	— —	158 126

[a]Conformations whose content is close to zero are not taken into consideration.
[b]The value is applicable only to calculations for the series of derivatives of *trans*-4,10-*H*-4-phenylquinolizidine.[117]
[c]For the liquid phase.
[d]For the gas phase.
[e]In solution in MeCN.
[f]In solution in MeOH.
[g]For the equilibrium(LIXA) + (LIXB) ⇌ (LIX).
[h]For the equilibrium (CXXIVA) + (CXXIVB) ⇌ (CXXIVC).
[i]For the equilibrium (CVA) + (CVB) ⇌ (CV).
[j]For the equilibrium (CXXVA) ⇌ (CXXVB).
[k]For the equilibrium (CXXVC) ⇌ (CXXVB).
[l]For the equilibrium (LXXIA) + (LXXIB) ⇌ (LXXI).
[m]*A* = conformational analysis, *B* = kinetic analysis, *C* = infrared spectroscopy, *D* = chiro-optical analysis, and *E* = NMR spectroscopy.

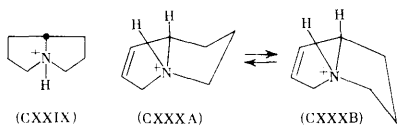
between the rings has been attributed to protonated quinolizidine, *trans*-1,10-*H*-1-methylquinolizidine, 2-methylquinolizidine, 3-methylquinolizidine, and *cis*-4,10-*H*-4-methylquinolizidine in aqueous solution[12], i.e. the cations have the same configuration as the conformations of the corresponding free bases. Two doublets due to the methyl group were observed for *cis*-1,10-*H*-1-methylquinolizidine. This was explained by the tautomeric equilibrium between approximately equal amounts of the *trans*- and *cis*-fused forms of the cation[12]. According to the authors[12], the *trans*-4,10-*H*-4-methylquinolizidinium cation has a *cis*-junction between the rings.

Whereas according to NMR spectra protonated epilupinine exists in the *trans*-fused form[166], the protonation of lupinine (CXXVI) gives rise to cations with a *cis*-junction [compound (CXXVII)] and a *trans*-junction [compound (CXXVIII)] junction between the rings, which can undergo interconversions in solution; the equilibrium position depends on the concentration, the pH, and temperature[166]:


(CXXVII) (CXXVI) (CXXVIII)

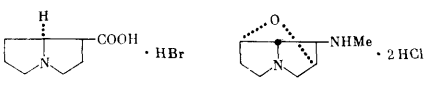
Protonated 1-hydroxy-7-methyl- and 1-hydroxy-1,7-dimethyl-quinolizidines in trifluoroacetic acid retain the *trans*-fused form of the free bases according to ^{1}H NMR spectra[167]. Protonation of 5,7-dimethylindolizidines (LXXXIV)–(LXXXVII) leads to salts whose configurations are claimed[14] to consist of the fixed preferred conformation of the bases, compound (LXXXVI) giving rise to a mixture of the *cis*- and *trans*-fused forms[14].

The ^{1}H NMR spectrum of protonated pyrrolizidine agrees with the hypothesis of a *cis*-junction between the rings in the cation of compound (CXXIX).[126] Protonation of the nitrogen atom in heliotridene leads to an increase, relative to the free base, of the fraction of the conformation with an *endo*-puckered saturated ring; (CXXXA):(CXXXB) = 1 : 3.[97]


(CXXIX) (CXXXA) (CXXXB)

The structures of the quinolizidine alkaloids neothiobinupharidine,[168,169] thiobinupharidine[170] (hydrated dihydrobromides), poranthericine,[171] porantherine,[172] and vertaline[173] (hydrobromides) were elucidated by X-ray diffraction. It has been shown that the quinolizidine rings in capaurine hydrobromide[138] and isocapaurimine hydrobromine monohydrate[174] have a *cis*-junction between the rings[138,174].

Analogous studies have been made on compounds of the pyrrolizidine series. The absolute configuration was found and the bond lengths and valence angles were determined in the hydrobromide of *cis*-1,8-*E*-1-carboxypyrrolizidine (CXXXI).[175] Application of the method of anomalous dispersion made it possible to establish the absolute configuration of the dihydrochloride (CXXXII).[176]


(CXXXI) (CXXXII)

The structure of nitropolyzonamine, in the form of its perchlorate, has been elucidated. The pyrrolizidine rings in this compound have the envelope conformation (C_s).[177]

It has been shown[178] that the 1,2-dehydropyrrolizidine skeleton in jacobine hydrobromide exhibits has an *exo*-puckered and twisted saturated ring.

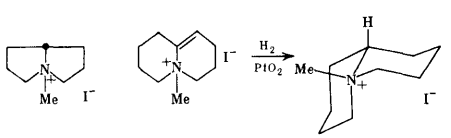
The conversion of the tertiary nitrogen in quinolizidines, indolizidines, and pyrrolizidines into a quaternary form leads to the fixation of the *cis*- or *trans*-junction between the rings[9]. A convenient criterion for the determination of the configurations of *N*-methylquinolizidinium and *N*-methylindolizidinium ions is the chemical shift of the protons in the methyl group attached to the nitrogen [9,12,179]. The reliability of this criterion demonstrated the agreement between NMR and X-ray diffraction data[180-182]. However, this method is applicable only to methiodides without a substituent in the angular position. If different substituents (except CN) are located in the 10-position in quinolizidinium salts, the signal of the $\geq^{+}$N–Me group in the *cis*-fused salts occurs at a higher field than for the *trans*-fused compound[183]. At the same time the configurational assignment of quaternary quinolizidinium salts can be achieved on the basis of the measurements of the half-widths of the signals of the $\geq^{+}$N–Me group. Thus *trans*-fused *N*-methylquinolizidinium has a half-width of the methyl singlet of 1.53 Hz, while the *cis*-fused salt has a corresponding width of 0.96 Hz.[184] It has been suggested that this criterion is applicable to other *N*-methylated heterocycles of a similar type[184].

The stereochemistry of quinolizidine methiodides with a single substituent in the 10-position can be readily inferred from the number of signals in their ^{13}C NMR spectra—the *trans*-fused salts have a plane of symmetry which gives rise to four signals due to the ring nuclei.[183]

One must note that the type of junction between the rings in the quaternary salt and in the free base may be the same[69,70], but in the general case this is not necessarily so[179]. Instances are known where the base has a preferentially *trans*-fused conformation, but gives rise either to a *cis*-fused salt [166,185,186] or to a mixture of epimers[12,64,186].

With the exception of the case of intramolecular quaternisation, which is possible only for a *trans*-junction between the rings[125], it is believed that pyrrolizidines usually form unstrained *cis*-fused salts[7]. On reaction with methyl iodide, pyrrolizidine gives a single *cis*-fused quaternary salt (CXXXIII), which has been confirmed by its ^{1}H NMR spectrum[126].

The *cis*-junction between the rings in the quaternary salt (CXXXV) is regarded as a consequence of the catalytic hydrogenation of the unsaturated compound (CXXXIV) from the sterically least hindered side of the molecule[81,187].



(CXXXIII) (CXXXIV) (CXXXV)

By comparing the optical rotations of (+)-epilupinine and (–)-lupinine and the methiodides obtained from the bases, it has been shown that the quaternary salts have respectively *trans*- and *cis*-junctions between the rings. The configurations (*cis*- and *trans*-) of the methiodides prepared from optically active 1-methylquinolizidines have been demonstrated similarly[81].

Crystalline quaternary salts have been investigated by X-ray diffraction. In the quinolizidine series an example of this type of investigation is provided by the determination of the nature of the junction between the rings in α- and β-methiodides of hunterburnine.[180,181] The study of the steric structures of the methiodides of alkaloids with an indolizidine fragment–kopsanone [189] and tylophorinidine [190]—yielded data for the absolute configurations of these alkaloids. In the pyrrolizidine-based thelepogine methiodide *exo*-puckering of the saturated five-membered ring is observed (angle of deflection 55°),[191] while in the cation of the diester of 8-hydroxymethylretronecine the unsaturated ring exhibits *endo*-puckering and is somewhat twisted[192].

The arsenal of available physical and physicochemical methods makes it possible to determine the configurations and preferred conformations of both the simplest bases and complex natural products of the quinolizidine, indolizidine, and pyrrolizidine series. In many of the studies quoted, a combined application of various methods was achieved in the course of stereochemical investigations, which yields the most reliable results.

A quantitative description of the conformational equilibria of 1-azabicyclic systems in liquid and gaseous phases has remained difficult hitherto. In the immediate future the situation is most likely to change in connection with the introduction of the interesting method of the kinetically controlled protonation of amines,[193] which has been studied in detail and which makes it possible to detect invertomers in the form of the corresponding cations. The ratio of the latter is determined by NMR.[193]

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