STEREOCHEMICAL STUDIES OF NITROGEN BRIDGEHEAD COMPOUNDS BY SPECTRAL MEANS

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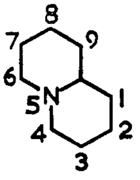
Contents

I. Introduction

A. SCOPE

Quinolizidine (**1**), indolizidine (**2**), and pyrrolizidine (**3**) form the nucleus of many compounds of biological and medicinal interest. For example, the quinolizidine moiety occurs in matrine (**4**), the yohimbine group of alkaloids (**5**), and the veratrum alkaloid cevine (**6**), while the indolizidine nucleus is found in the skeleton of the solanum alkaloid solanidine (**7**) and the veratrum alkaloid rubijervine. The necine alkaloids, *e.g.*, laburnine (**8**), are built around the pyrrolizidine ring. The stereochemistry of these classes of alkaloids will not be dealt with here since this has been reviewed elsewhere.[1-5]



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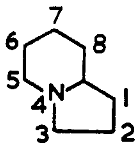

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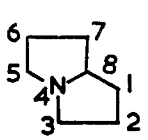

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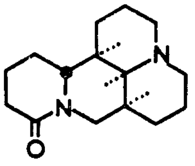

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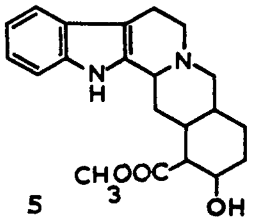

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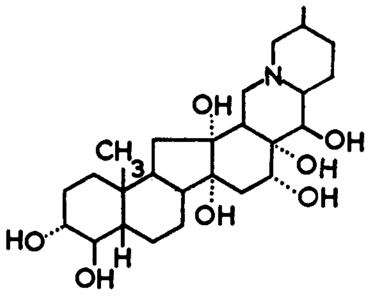

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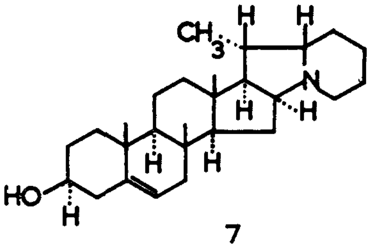

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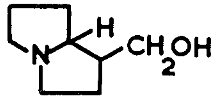

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Heterocyclic systems with bridgehead nitrogen atoms have been the subject of an extensive review,[6] but since this was published a considerable number of papers have appeared dealing with stereochemical studies of saturated heterocyclic systems, and it is this aspect of the subject which forms the basis of the present review. In particular, the stereochemistry of the simpler derivatives of **1**, **2**, and **3** together with related compounds possessing additional heteroatoms will be discussed with reference to spectroscopic methods of determining their configurations and preferred conformations. The bulk of the data will refer to the establishment of the cis or trans nature of the fusion between the two rings, but evidence for the configurations, *i.e.*, the cis or trans relationship of a substituent with respect to the bridgehead hydrogen, will also be presented. The extensive work on kinetic methods of determining stereochemistry has not been reviewed and will be mentioned only to provide the necessary background to a discussion of certain groups of compounds. Spectroscopic and stereochemical data relating to bridged systems such as quinuclidine are not included in this review.

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(1) G. A. Morrison, *Fortschr. Chem. Org. Naturst.*, **25**, 269 (1967).

(2) N. K. Kochetkov and A. M. Likhosherstor, *Advan. Heterocycl. Chem.*, **5**, 315 (1965).

(3) R. H. F. Manske and H. L. Holmes, "The Alkaloids," Academic Press, New York, N. Y., 1950.

(4) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965.

(5) L. B. Bull, C. C. J. Culvenor, and A. T. Dick, "The Pyrrolizidine Alkaloids," North-Holland Publishing Co., Amsterdam, 1969.

(6) W. L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms," Interscience, New York, N. Y., 1961.

B. QUINOLIZIDINE

The major difference between quinolizidine and its carbocyclic analog is the replacement of the axial C–H bond of the bridgehead carbon atom of the latter by the nitrogen lone pair of electrons in the former. The presence of the conformationally mobile nitrogen atom at the bridgehead permits ready interconversion between the trans-fused and cis-fused conformations (Figure 1). Barton and Cookson[7] predicted that the nitrogen lone pair would have a steric requirement approaching that of a methyl group, an idea supported by several experimental results.[8,9] Other workers, however, have interpreted these observations in terms of a small steric requirement for the nitrogen lone pair. Many of the papers relevant to this topic were mentioned in a recent review,[10] and the subject demands a separate treatment which falls outside the scope of the present work. The concensus of opinion now favors a negligible steric requirement for the nitrogen lone pair except under certain conditions, and, assuming this to be the case, Aaron[11] estimated that quinolizidine is more stable in the trans-fused ring conformation relative to the cis-fused ring conformation than is decalin by *ca.* 2.1 kcal/mol. This conclusion was arrived at by attributing the energy difference between the systems to the two nonbonded 1,3-diaxial hydrogen interactions (2 × 1.04 kcal/mol)[12] which destabilize *trans*-decalin relative to *cis*-decalin and which disappear when the bridgehead C–H is replaced by a tertiary nitrogen atom in quinolizidine. Thus *trans*-quinolizidine is estimated to be more stable than *cis*-quinolizidine by *ca.* 4.6 kcal/mol. Recently Aaron[13] has revised his estimate of $\Delta G°$ for the quinolizidine equilibrium and shown that it should be similar to the free energy difference between *cis*- and *trans*-decalin, since in the original paper only 1,3-diaxial hydrogen–hydrogen interactions were considered, the comparable 1,2-skew interactions being neglected. From a study of the kinetics of quaternization of monomethylquinolizidines using hexahydrojulolidines (**9**) as fixed models of the cis- and trans-fused ring conformations, Katritzky, Schofield, and coworkers[14] deduced that $\Delta G°$ for the cis ⇌ trans quinolizidine equilibrium was *ca.* −4.4 kcal/mol.

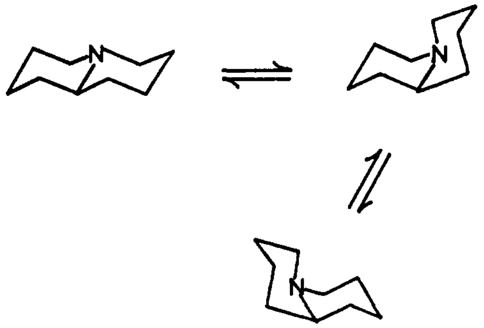
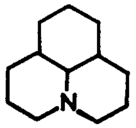


Figure 1. Equilibrium between *trans*- and *cis*-quinolizidine.



9

II. Spectroscopic Methods

A. INFRARED

Chemical methods of assigning stereochemistry are often tedious and several physical criteria have therefore been developed. The most widely used physical method has no doubt been infrared spectroscopy, and the stereochemistry and conformational preferences of a large number of quinolizidines and their derivatives have been assigned by this means.

The first correlation between the configuration about the ring fusion of a nitrogen bridgehead compound and the appearance of bands in the 2800–2700-cm^{-1} region of the infrared spectrum was made by Wenkert[15] in connection with studies on the stereochemistry of the yohimbines and related alkaloids. Comparison of the spectra of various pairs of C-3 epimers showed that all compounds possessing an α hydrogen at C-3 gave rise to two or more distinct peaks of medium intensity on the low wave number side of the symmetric C–H stretching band. Compounds possessing a 3β hydrogen showed only shoulders on the low wave number side of the main peak at 2860 cm^{-1}. During structural investigations of a large number of alkaloids containing the quinolizidine nucleus, Bohlmann[16] found that those in which the quinolizidine moiety was trans-fused exhibited a characteristic series of bands in the infrared spectrum between 2700 and 2800 cm^{-1}; these bands, which he termed "trans bands," were absent when the quinolizidine nucleus was cis-fused. In order to investigate this phenomenon further, a number of simple quinolizidines and deuterated quinolizidines were synthesized, and it was shown[17] that the appearance of the bands was due to the axial C–H bonds α to the nitrogen atom and trans to the nitrogen lone pair of electrons. Two such C–H bonds were found to be necessary for the bands to be observed; in cis-fused quinolizidines, only one such bond is present. Rosen[18] and Becket[19] have modified Wenkert's original infrared correlation, since only those alkaloids possessing in their preferred conformation(s) the C-3–H and at least one more C–H bond trans diaxial to the nitrogen lone pair will exhibit bands in the infrared spectrum between 2860 and 2700 cm^{-1}, while those alkaloids possessing in their preferred conformation(s) the C-3–H cis to the nitrogen lone pair will not. Wiewiorowski and Skolik[20] have undertaken a more quantitative study of the 2900–2500-cm^{-1} region of the

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(7) D. H. R. Barton and R. C. Cookson, *Quart. Rev., Chem. Soc.*, **10**, 44 (1956).

(8) M. J. Aroney and R. J. W. Le Fèvre, *J. Chem. Soc.*, 3002 (1958).

(9) M. J. Aroney, C. Y. Chen, R. J. W. Le Fèvre, and J. D. Saxby, *ibid.*, 4269 (1964).

(10) F. G. Riddell, *Quart. Rev., Chem. Soc.*, 364 (1967).

(11) H. S. Aaron, *Chem. Ind (London)*, 1338 (1965).

(12) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold, 1961, p 559.

(13) H. S. Aaron and C. P. Ferguson, *Tetrahedron Lett.*, 6191 (1968).

(14) C. D. Johnson, R. A. Y. Jones, A. R. Katritzky, C. R. Palmer, K. Schofield, and R. J. Wells, *J. Chem. Soc.*, 6797 (1965).

(15) E. Wenkert and D. Roychaudhuri, *J. Amer. Chem. Soc.*, **78**, 6417 (1956).

(16) F. Bohlmann, *Angew. Chem.*, **69**, 541 (1957); *Chem. Ber.*, **91**, 2157 (1958).

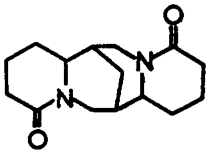
(17) F. Bohlmann, D. Schumann, and M. Schulz, *Tetrahedron Lett.*, 173 (1964).

(18) (a) W. E. Rosen, *ibid.*, 481 (1961); (b) W. E. Rosen and J. N. Shoolery, *J. Amer. Chem. Soc.*, **83**, 4816 (1961).

(19) W. F. Trager, C. M. Lee, and A. H. Becket, *Tetrahedron*, **23**, 365 (1967).

(20) M. Wiewiorowski and J. Skolik, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **10**, 1 (1962).

infrared spectra of the C-15 lupin alkaloids. Accordingly, the infrared spectra of 15 alkaloids of the sparteine series were examined under identical conditions and the following conclusions were drawn. The area within which "trans bands" (termed "T bands" by these authors) occur is from just below 2800–2700 cm^{-1} as suggested by Bohlmann. Of the compounds examined, dilactams of type **10** and the majority of neutral salts were the only compounds with no T bands, all the other compounds exhibiting a series of T bands from just below 2860 to 2500 cm^{-1}. The intensity of the T band was expressed in terms of the integrated area of the peak, and using this system it was found that the T-band area for a *cis*-quinolizidine system was normally only about 20% smaller than that for a *trans*-quinolizidine system. In *cis*-quinolizidines, however, the T bands were present as a stepwise descending set of maxima below the C–H stretching band at 2860 cm^{-1}, whereas in those compounds containing a trans-fused quinolizidine ring system, the main T bands were present as well-defined maxima at about 2800 and 2750 cm^{-1}. During a more recent study by the same authors[21] on a number of sparteine-type quinolizidine alkaloids and their selectively α-deuterated derivatives, the following points emerged. It was suggested that the lower frequency of the T bands compared with the normal C–H region was due to charge delocalization of the nitrogen lone pair of electrons to the α axial C–H bonds. In trans-fused quinolizidines all three α axial C–H bonds would take part in this delocalization. Since the axial C–H bonds on both C-4 and C-6 have the same symmetry and force constants, vibrational coupling can occur and two bands appear at 2800 and 2761 cm^{-1}, respectively. The first is due to the asymmetric and the second to the symmetric stretching vibration. In cis-fused quinolizidines both the chair–chair and the chair–boat conformations were considered. The chair–chair conformation has only one α axial C–H bond, and this gives rise to a single band between 2840 and 2600 cm^{-1}. In the chair–boat conformation three α axial C–H bonds are present and give rise to two main bands at *ca.* 2808 and 2761 cm^{-1}. In a further paper by Wiewiorowski, *et al.*,[22] the conditions necessary for the occurrence of Bohlmann bands were more precisely defined. It was found that in order for bands to occur, one hydrogen on a carbon atom alpha to a nitrogen atom situated trans and axial with respect to the nitrogen lone pair of electrons was necessary. The intensity and complexity of the absorption was found to be roughly proportional to the number of hydrogen atoms so situated. There have been several papers[23,24] dealing with the theoretical aspects of "Bohlmann bands," and it has been suggested that they are similar in origin to the characteristic *N*-methyl bands due to Fermi resonance which appear in the same region.



10

B. NUCLEAR MAGNETIC RESONANCE

Next to infrared spectroscopy, the most widely used physical method in conformational studies on bridgehead nitrogen systems has been nmr spectroscopy. In an investigation of the nmr spectrum of quinolizidine, Hamlow[24] identified the signals at τ 7.2–7.4 as due to the C-4 and C-6 equatorial protons, and a broad shoulder at τ 8.0 on the side of the main peak as due to the corresponding axial protons. The accurate chemical shifts of these protons were determined by spin decoupling, and it was found that the chemical shift difference between the C-4, C-6 axial and equatorial protons was 0.93 ppm. When the nmr spectrum of quinolizidine was run in trifluoroacetic acid, a protonating solvent, the equatorial protons absorbed at about τ 6.5 and the axial protons at τ 7.0, the chemical shift difference of 0.5 ppm being comparable to that observed for the axial and equatorial protons of cyclohexane. In order to explain the difference in chemical shift between the methylene protons adjacent to nitrogen in quinolizidines, it was suggested that partial participation of the nitrogen lone pair in a σ^* C–H$_{ax}$ orbital on the adjacent carbon atom occurs, and this leads to an increase in the electron density at the axial proton. The chemical shift difference should therefore be greatest when the nitrogen lone pair and the adjacent C–H bond have a trans-diaxial relationship with each other. The theory that the nitrogen lone pair of electrons is responsible for shielding the axial proton is supported by the decreased shielding of this proton in a protonating solvent. Hamlow[24] has suggested that it is the decrease in the bonding energy of the axial C–H bonds adjacent to the nitrogen atoms which is responsible for the appearance of bands in the 2800–2700-cm^{-1} region of the infrared spectra of quinolizidine. An explanation of the antiaxial shielding effect of a proton by a lone pair in terms of a dipole effect has also been offered.[25]

Bohlmann[17] showed that Hamlow's assignments for the C-4 protons in quinolizidine were correct by investigating the spectra of a range of deuterated and methyl-substituted quinolizidines. He found that the spectrum of quinolizidine exhibited a two-proton doublet at τ 7.2 and a two-proton multiplet at τ 7.8 to 8.2. Replacement of both the C-4 protons by deuterium reduced the intensity of each of these signals to one proton, and replacement of both the C-4 and C-6 protons by deuterium led to the complete disappearance of the signals. The nmr spectrum of *cis*-4,10-*H*-4-methylquinolizidine, which was assumed to exist predominantly in the trans-fused ring conformation, only showed a one-proton signal to low field at τ 6.85. When this 4-methyl compound was deuterated at the C-4 axial position, the nmr spectrum showed no change in the low-field signal.

Recently an alternative explanation for the large Δ value in quinolizidine has been put forward by Robinson,[26] who points out that previous workers[24] assumed that an equatorial methylene group on the nitrogen atom would have little effect on the chemical shift of protons on adjacent carbon atoms, whereas in fact the available unambiguous evidence[27–29] suggests that a vicinal axial hydrogen is shielded by an equatorial methyl or methylene group. The large chemical shift difference between

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[21] J. Skolik, P. J. Krueger, and M. Wiewiorowski, *Tetrahedron*, **24**, 5439 (1968).

[22] M. Wiewiorowski, O. E. Edwards, and M. D. Bratek-Wiewiorowska, *Can. J. Chem.*, **45**, 1447 (1967).

[23] T. Masamune and M. Takasugi, *Chem. Commun.*, 625 (1967).

[24] H. P. Hamlow, S. Okuda, and N. Nakagawa, *Tetrahedron Lett.*, 2553 (1964).

[25] R. F. Zürcher, "Progress in NMR Spectroscopy," Pergamon Press, London, 1967, Chapter 5.

[26] M. J. T. Robinson, *Tetrahedron Lett.*, 1153 (1968).

[27] J. B. Lambert, R. S. Keske, R. E. Carhart, and A. P. Jovanovich, *J. Amer. Chem. Soc.*, **89**, 3761 (1967).

[28] A. Segre and J. I. Musher, *ibid.*, **89**, 706 (1967).

[29] N. W. J. Pumphrey and M. J. T. Robinson, *Chem. Ind.* (*London*), 1903 (1963).

protons adjacent to the nitrogen atom in *trans*-quinolizidine can then be explained in terms of shielding of the axial proton by the methylene group on the nitrogen atom, rather than shielding caused by the trans nitrogen lone pair. The relative importance of the two shielding mechanisms has recently been discussed by Lambert.[30]

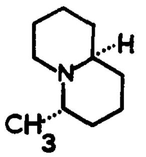
III. Stereochemical Determinations

A. FUSED 6/6 RING SYSTEMS WITH NO ADDITIONAL HETEROATOM

1. *Quinolizidines*

a. Methylquinolizidines

All the isomeric monomethylquinolizidines have been subjected to a thorough investigation[14,31,32] and are now known to exist predominantly in the trans-fused ring conformation. The configurations and preferred conformations were assigned to the compounds on the basis of chemical and spectroscopic evidence. All the compounds, with the exception of the *trans*-4,10-*H*-4-methyl derivative (**11**), showed a prominent band at 2760–2750 cm^{-1} together with other bands in the Bohlmann region of the infrared and were therefore assigned trans-fused conformations. The center of the methyl doublet and the apparent J_{CH-Me} was an excellent indication of the equatorial or axial orientation of the methyl group, it being found that the axial methyl group absorbed at lower field and showed a larger "*J*" than its corresponding epimer. This did not apply in the case of the 4-methyl compound mentioned above which was assigned a cis-ring fusion with an equatorial methyl group on the basis of the infrared and nmr evidence.



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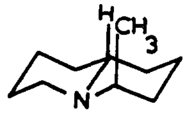

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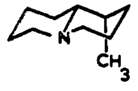
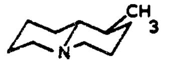
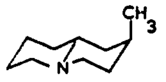
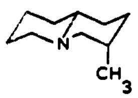
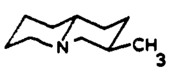
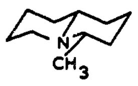
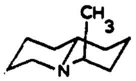
In a later paper,[14] in which the rates of quaternization of the monomethylquinolizidines and of the hexahydrojulolidines were measured and compared, it was shown that this latter assignment was incorrect and that, in fact, *trans*-4,10-*H*-4-methylquinolizidine exists in a predominantly trans-fused ring conformation (**12**) at room temperature. It should be mentioned that there is a strong band at 2805 cm^{-1} in the infrared spectrum of this compound which is in fact probably a trans band. It seems therefore that the Bohlmann criterion must be used with caution when dealing with 4-substituted quinolizidines.

The configurations of a 4,7-dimethyl and a 1,4,7-trimethyl quinolizidine have been assigned[33] and both compounds shown to exist in trans-fused ring conformations. The chemical shifts of the methyl groups are in accord with the observations on the monomethylquinolizidines (Table I).

Table I

Nmr and Ir Data on Monomethylquinolizidines[32]

	Nmr methyl doublet		
Compound	*Center of methyl doublet* (τ)	*Apparent J (Hz)*	*Ir Bohlmann region* (cm^{-1})
	9.05	5.8	2805 2755 2680 2610
	9.16	1.6	2805 2755 2685 2605
	9.09	2.7	2805 2760 2675 2605
	9.01	6.9	2800 2760 2675 2600
	8.92	6.6	2795 2755 2680 2615
	9.18	4.8	2805 2760 2685 2625
	9.00	5.1	2795 2760 2625
	9.07	4.6	2805

b. Hydroxyquinolizidines

This has been an attractive field to explore because of the potential biological activity of these compounds. Particular use has been made of infrared spectroscopy in assigning configurations which in many cases can be made on the basis of the presence or absence of intramolecular H-bonded OH frequencies.

Aaron[34] has studied the isomeric 1-, 2-, and 3-hydroxyquinolizidines (Table II), all of which showed Bohlmann bands and therefore exist in trans-fused ring conformations. The configurations of the 1- and 3-hydroxy compounds were deduced from the presence of a band at 3526 cm^{-1} in the infrared spectra of the axial-hydroxy epimers of the 1- and 3-hydroxy compounds indicative of intramolecular hydrogen bonding. Configurational assignments were made on the two 2-hydroxyquinolizidines by studying the C-2 proton signals in the nmr spectra. In all the six alcohols the carbinol CH proton in the equatorially substituted hydroxy compound absorbed at higher field and gave broader signals than that observed in the axial-hydroxy epimers.

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(30) J. B. Lambert and R. G. Keske, *Tetrahedron Lett.*, 2023 (1969).

(31) T. M. Moynehan and K. Schofield, *Proc. Chem. Soc. London*, 218 (1961).

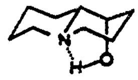
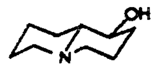
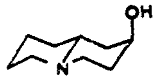
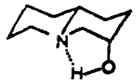
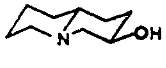
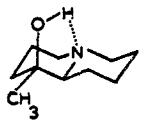
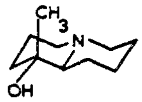
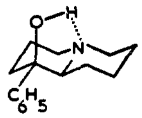
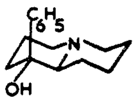
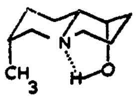
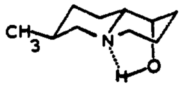
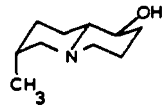
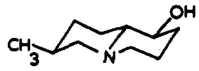
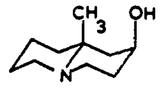
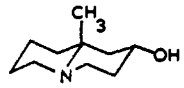
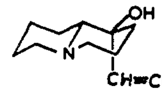
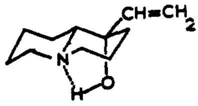
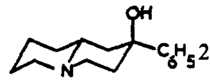
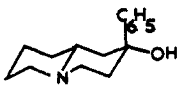
(32) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962).

(33) M. Kotake, I. Kawasaki, T. Okamoto, S. Matsurani, S. Kasumoto, and T. Kaneko, *Bull. Chem. Soc. Jap.*, **35**, 1337 (1962).

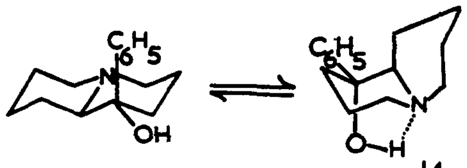
(34) H. S. Aaron, G. E. Wicks, Jr., and C. P. Rader, *J. Org. Chem.*, **29**, 2248 (1964).

Table II

Ir Data on Hydroxyquinolizidines

Compound	*Bohlmann region (cm⁻¹)*	*Free OH (cm⁻¹)*	*Intramolecularly bonded OH (cm⁻¹)*	*Ref*
	2800 2777	...	3526	34
	2795 2750	3618	...	34
	2802 2764	3625	...	34, 35
	2801 2762	3620	...	34, 35
	2797 2757	...	3527	34
	2800 2762	3609	...	34
	2800–2700	...	3480	36
	2800–2700	3620	...	36
	2820 2770	...	3480	37
	2810 2770	3620	...	37
	2800–2700	...	Intra	38
	2800–2700	...	Intra	38
	2800–2700	3620	...	38
	2800–2700	3620	...	38
	2800–2700	Free OH	...	35
	2800–2700	Free OH	...	35
	Prominent bands 2800–2600	3620	...	39
	Prominent bands 2800–2600	...	3520	39
	2800–2600	3605	None	40
	2800–2600	3605	3350	40

Other hydroxyquinolizidines (Table II) have been examined[35–40] by similar techniques and exist predominantly in the conformations shown. Recently the infrared spectra of *trans*-1,10-*H*-1-hydroxyquinolizidine has been studied[18] using long-path-length cells and 2% of the cis-fused conformation detected in the equilibrium mixture. Reexamination of 1-hydroxy-1-(phenyl *trans*-10-*H*)-quinolizidine shows it to exist as a conformational mixture of 60% trans-fused (**13**) and 40% cis-fused ring conformations (**14**).


13 14

In the two 1-hydroxy-1-methylquinolizidines[36] the equatorial methyl group in one isomer absorbed at τ 8.91 and the axial methyl in the epimer at τ 8.78 in agreement with the data presented in Table I.

Möhrle[38,41] has studied the 1-hydroxy-7-methyl- and the

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(35) F. Bohlmann, E. Winterfeldt, O. Schmidt, and W. Reusche, *Chem. Ber.*, **94**, 1767 (1961).

(36) D. Temple and J. Sam, *J. Heterocycl. Chem.*, **5**, 441 (1968).

(37) J. D. England and J. Sam, *ibid.*, **3**, 482 (1966).

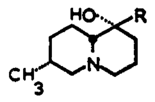
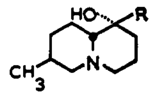
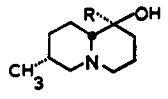
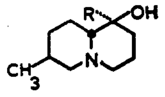
(38). H. Möhrle and C. Karl, *Arch. Pharm. (Weinheim)*, **301**, 530 (1968).

(39) R. van Hes, U. K. Pandit, and H. O. Huisman, *Recl. Trav. Chim. Pays-Bas*, **86**, 1255 (1967).

(40) J. Sam, J. D. England, and D. Temple, *J. Med. Chem.*, **12**, 144 (1969).

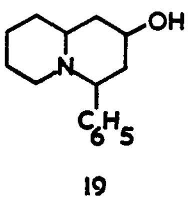
Table III

Nmr of 1-Hydroxy-7-methyl- and 1-Hydroxy-1,7-dimethylquinolizidines[38]

Compound	*No.*	*R = H*	*R = Me*
	**15**	7 Me (ax) τ 8.9 (J = 7 Hz)	7 Me (ax) τ 8.92 (J = 7.1 Hz) 1 Me (eq) τ 8.92
	**16**	7 Me (eq) τ 9.17 (J = 5.8 Hz)	7 Me (eq) τ 9.16 (J = 6 Hz) 1 Me (eq) τ 8.89
	**17**	7 Me (ax) τ 8.91 (J = 7 Hz)	7 Me (ax) τ 8.92 (J = 7 Hz) 1 Me (ax) τ 8.75
	**18**	7 Me (eq) τ 9.16 (J = 5.7 Hz)	7 Me (eq) τ 9.16 (J = 5.9 Hz) 1 Me (ax) τ 8.78

1-hydroxy-1,7-dimethylquinolizidines. All were assigned predominantly trans-fused ring conformations on the basis of the presence of Bohlmann bands in the infrared, and use was made of the results of hydrogen-bonding studies, methyl chemical shift data, and the values of "$J_{CH\text{-}Me}$" in assigning configurations (Table III). Isomers **17** and **18** showing intramolecular hydrogen bonding were assigned structures with the axial-hydroxy groups.

The four isomers of **19** have been obtained[42] and their con-



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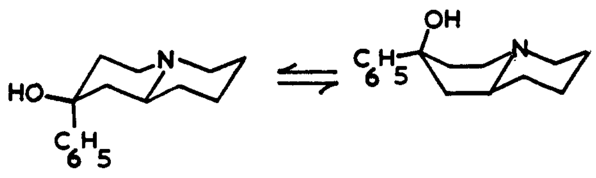
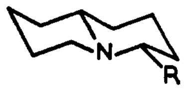
figurations and conformations assigned on the basis of the Bohlmann region of the infrared spectra and the chemical shifts and band widths of the carbinol protons. The epimeric 2-hydroxy-2-phenylquinolizidines have been synthesized[40] and configurations and conformations assigned on the basis of the chemical shifts of the methyl groups of the corresponding acetates. One of the isomers (**20**) shows intramolecular hydrogen bonding at low concentration and this is attributed to the boat form (**21**).



20 **21**

c. Arylquinolizidines

Bohlmann[43] has reported the nmr spectra of *cis*- and *trans*-4,10-*H*-4-phenylquinolizidines. The spectrum of *cis*-4,10-*H*-4-phenylquinolizidine (**22**, R = Ph) showed a two-proton



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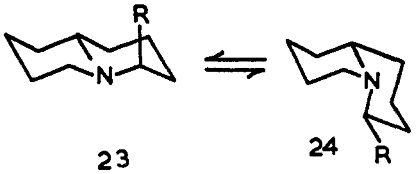
multiplet at τ 7.3 which was assigned to the equatorial C-6 proton and the axial C-4 proton since the latter should be deshielded by the phenyl group on C-4. The spectrum of *trans*-4,10-*H*-4-phenylquinolizidine, which had been assigned a cis-fused ring conformation on the basis of the lack of bands between 2800 and 2700 cm^{-1} in its infrared spectrum, showed a one-proton signal at τ 6.17 which was assigned to the C-4 proton, a signal at τ 7.00 which was assigned to the C-10 proton, and peaks at τ 7.37 and 7.61 assigned to the equatorial and axial C-6 protons, respectively. The correctness of these assignments was proved by deuteration experiments. From these figures it was deduced that *trans*-4,10-*H*-4-phenylquinolizidine exists in a predominantly cis-fused ring conformation (**24**, R = Ph). Thus the C-4 proton comes to low field

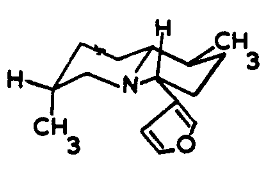


23 **24**

due to the 1,3-deshielding effects acting upon it across the ring fusion, and there is only a small chemical shift difference between the C-6 protons since in the cis-fused ring conformation the lone pair of the nitrogen atom bisects the C-6 methylene group. In addition the C-10 proton comes to low field since it is no longer trans and axial with respect to the nitrogen lone pair.

The isomers of 4-(α-furanyl)- and 4-(α-thiophenyl)quinolizidine have been prepared.[44] One furanyl isomer showed bands in the infrared at 2780 and 2740 cm^{-1}, and a thienyl isomer showed similar bands at 2795 and 2760 cm^{-1}. These compounds were therefore assigned the trans-fused ring conformation **22**. The two remaining isomers showed no Bohlmann bands and were therefore considered to have adopted the cis-fused ring conformation **24**.

Deoxynupharidine (**25**) has the stereochemistry shown[38]. It



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has [45-47] bands in the 2700–2800-cm^{-1} region of the infrared and τ values (benzene solution) for the axial 7-methyl of 8.90 and for the equatorial 1-methyl of 9.11. The 7-epi compound shows methyl peaks at τ 9.14 and 9.32 (equatorial methyl), and the 1-epi compound shows both axial methyls to absorb at τ 8.81 and 8.91.

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[41] H. Möhrle, C. Karl, and U. Scheideggar, *Tetrahedron*, 24, 6813 (1968).

[42] T. Matsunaga, I. Kawasaki, and T. Kaneko, *Tetrahedron Lett.*, 2471 (1967).

[43] F. Bohlmann, D. Schumann, and C. Arndt, *ibid.*, 2705 (1965).

[44] K. Kotera, Y. Hamada, and R. Mitsui, *Tetrahedron*, 24, 2463 (1968).

[45] Y. Arata, *Chem. Pharm. Bull. Jap.*, 13, 907 (1965).

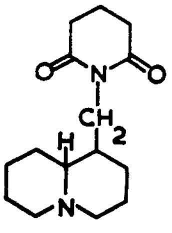
[46] Y. Arata, N. Hazama, and Y. Kojima, *Yakugaku Zasshi*, 82, 326 (1962).

[47] I. Kawasaki, S. Matsutani, and T. Kaneko, *Bull. Chem. Soc. Jap.*, 36, 1474 (1963).

A number of diphenyl- and phenylmethyl-substituted quinolizidines have been prepared[48] and assigned cis- and trans-fused ring conformations on the basis of Bohlmann bands.

d. Miscellaneous Quinolizidines

Both epimers of 4-hydroxymethylquinolizidine show Bohlmann bands in the infrared and are therefore assigned[49] the trans-ring fusion **22** (R = CH$_2$OH) (2750, 2780 cm^{-1}) and **23** (R = CH$_2$OH) (2790 and 2770 cm^{-1}), whereas only one of the 4-carbethoxyquinolizidines shows Bohlmann bands (2800, 2770 cm^{-1}); the second isomer must therefore adopt the cis-fused conformation **24** (R = COOEt). Lamprolobine (**26**)[50] and lusitanin (**27**)[51] both show trans bands.



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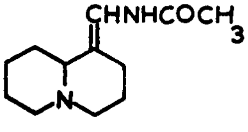

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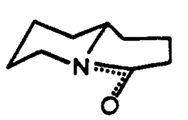
The diastereoisomers of 3-(4-chlorobenzyl)quinolizidine were[52] considered to possess trans-ring fusions because of the presence of Bohlmann bands in the infrared. The axial-equatorial nature of the substituent was confirmed by the position of the $^{+}$N–CH$_3$ signals in the nmr of the corresponding methiodides.

e. Oxoquinolizidines

Bohlmann bands are shown by 1-oxo- (2795, 2750, 2680 cm^{-1}), 2-oxo- (2785, 2740, 2680 cm^{-1}), and 3-oxo- (2780, 2735, 2645 cm^{-1}) quinolizidine, and circular dichroism measurements indicate that in isooctane solutions at room temperature the trans conformation represents 90% of the conformational equilibrium.[53,54]

The lactam **28** is considered[55] to exist in the conformation shown. The C-6 and C-10 protons all absorb at lower field than in quinolizidine and the C-6 equatorial proton lying in the amide plane is particularly deshielded by the amide carbonyl (τ 5.37 compared to τ 7.2 in quinolizidine). The spectra of two diastereoisomeric lactam carbinols **29**, degradation products of securinine, have been described.[56,57]



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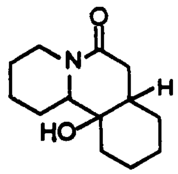

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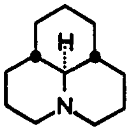
f. Cycloalkanoquinolizidines

Interest in matrine has stimulated research into the synthesis and stereochemistry of cycloalkanoquinolizidines. The most carefully studied systems have been the hexahydrojulolidines (**9**)[14,58,59] (three possible stereoisomers **30–32**), the corresponding cyclopentanoquinolizidines[60–62] (**30–32** with ring C five-membered), **33** and **34**, and the perhydronaphoquinolizidines (**35**).[63] The three diastereoisomeric hexahydrojulolidines have been shown to possess the stereochemistry shown by structures **36**, **37**, and **38**. *cis,trans*-Hexahydrojulolidine (**31**) was readily distinguished[58] from **30** and **32** since it showed only weak bands in the 2800–2700-cm^{-1} region of the infrared. The cis,cis isomer **36** possesses a nitrogen lone pair of electrons shielded from an attacking reagent by the C ring and accordingly was found[14] to react only slowly with methyl iodide. In fact, no reaction[59] occurred on refluxing **32** with methyl iodide in ether whereas the trans,trans isomer **30** reacted readily under the same conditions. By these techniques and by studying their rate of reaction[58] with mercuric acetate, the three isomers were characterized. The stereochemistry of the three isomeric



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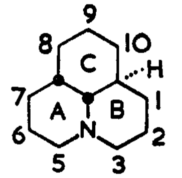

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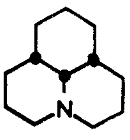

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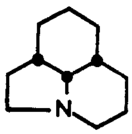

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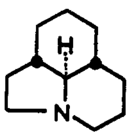

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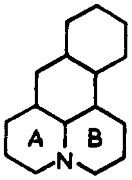

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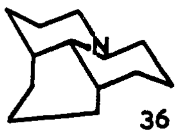

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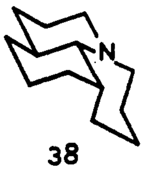

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(48) F. Bohlmann, E. Winterfeldt, G. Boroschewski, R. Mayer-Mader, and B. Gatscheff, *Chem. Ber.*, **96**, 1792 (1963).

(49) Y. Arata, Y. Asaoka, and M. Kassai, *Yakugaku Zasshi*, **82**, 1523 (1962).

(50) S. R. Johns, N. K. Hart, and J. A. Lamberton, *Aust. J. Chem.*, **21**, 1619 (1968).

(51) K. Wicky and E. Steinegger, *Pharm. Acta Helv.*, 40, 658 (1965).

(52) I. Matsuo, K. Sugimoto, and S. Ohki, *Chem. Pharm. Bull. Jap.*, **16**, 1680 (1966).

(53) S. F. Mason, K. Schofield, and R. J. Wells, *Proc. Chem. Soc. London*, 337 (1963).

(54) S. F. Mason, G. W. Vane, K. Schofield, R. J. Wells, and J. S. Whitehurst, *J. Chem. Soc. B*, 553 (1967).

(55) F. Bohlmann and D. Schumann, *Tetrahedron Lett.*, 2435 (1965).

(56) S. Saito, K. Kotera, N. Shigematsu, A. Ide, N. Sugumoto, Z. Horii, M. Hanaoka, Y. Yamawaki, and Y. Tamura, *Tetrahedron*, **19**, 2085 (1963).

(57) Z. Horii, Y. Yamawaki, M. Hanaoka, Y. Tamura, S. Saito, and H. Yoshikawa, *Chem. Pharm. Bull. Jap.*, **13**, 22 (1965).

(58) F. Bohlmann and C. Arndt, *Chem. Ber.*, **91**, 2167 (1958).

(59) K. Tsuda and S. Saeki, *Chem. Pharm. Bull. Jap.*, **6**, 391 (1958).

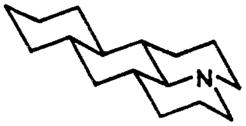
(60) K. Schofield and R. J. Wells, *J. Chem. Soc.*, 621 (1967).

(61) L. Mandell, J. U. Piper, and K. P. Singh, *J. Org. Chem.*, **28**, 3440 (1963).

(62) N. J. Leonard and W. J. Middleton, *J. Amer. Chem. Soc.*, **74**, 5114 (1952).

cylopentanoquinolizidines (**30**–**32**, ring C five-membered) has been established[60] by similar techniques, the trans,trans compound showing weaker Bohlmann bands than does *trans,trans*-hexahydrojulolidine. Both **33** and **34** (tentative assignment) show prominent Bohlmann bands.[61]

Four isomers of the perhydronaphthoquinolizidine **35** have been obtained and their stereochemistry deduced[63] as **39**–**42** on the basis of their rates of methylation, dehydrogenation, reaction with aluminum chloride, and from the appearance of Bohlmann bands in the ir spectra of all four isomers indicating a trans A:B ring fusion. **39** and **42** were readily methylated whereas reaction occurred only slowly with **40** and not at all with the isomer **41** in which the nitrogen lone pair is shielded from attack. **40** and **42** were converted to the more stable isomer **39** on treatment with aluminum chloride.



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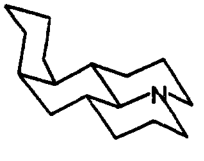

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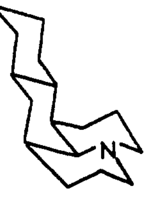

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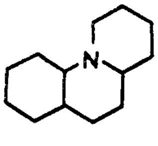
42

An 8-hydroxy derivative of **32** was characterized[64] by the appearance of an intramolecularly hydrogen-bonded OH frequency in the infrared. Pairs of various epimeric 3-substituted derivatives of **32** and **30** have been assigned[65] their structures from their manifestation of Bohlmann bands and from the chemical shifts of the protons on carbon atoms α to the nitrogen.

The three isomers of perhydrobenzo[*c*]quinolizine (**43**) have been assigned[66] the stereostructures **43a**–**c** on the basis of the presence or absence of Bohlmann bands in the infrared, their method of synthesis, and their rates of methylation (**c** > **b** > **a**).



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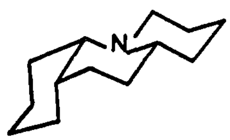
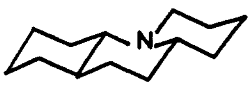
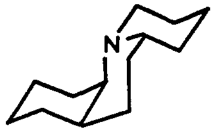


43a



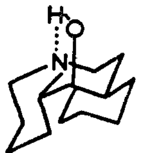
43b



43c

Infrared studies led to the assignment[67] of structures **44** and **45** to the hydroxy compounds related to securinine. **44** and **46** showed Bohlmann bands, and **45** and **46** showed absorption due to intramolecularly hydrogen-bonded hydroxy groups at 3505 and 3509 cm^{-1}, respectively. The free OH stretching frequency of **44** was at 3620 cm^{-1}. The cis-fused quinolizidine moiety has been shown[68] to be present in **47** by the absence of Bohlmann bands, and the presence of a hydrogen-bonded hydroxy group is shown by the absorption in the infrared at 3503 cm^{-1}.

44



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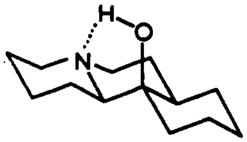

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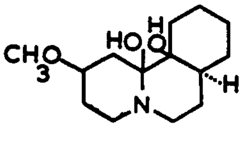
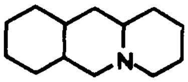


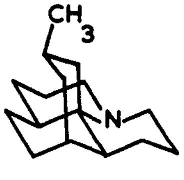
47

The stereochemistry of various hydroxylated derivatives of **48** and related compounds has been studied by Kupchan.[69–72]



48

The pair of compounds **49** and **50**[73] provide excellent examples of the use of Bohlmann's infrared criterion in making stereochemical assignments in compounds related to the Lycopodium alkaloids, **49** showing marked bands which are only hinted at in **50**.



49

50

g. Benzoquinolizidines

In conformational studies on benzoquinolizidines of type **51** (R = H, R′ = H), the chemical shift of the angular C-11b proton has been of considerable use. It was originally found that in methyl neoreserpate[18] (which adopts a conformation **53**

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(63) S. Saeki, *Chem. Pharm. Bull. Jap.*, **9**, 226 (1961).

(64) F. Bohlmann and O. Schmidt, *Chem. Ber.*, **97**, 1354 (1964).

(65) F. Bohlmann, D. Habeck, E. Poetsch, and D. Schumann, *ibid.*, **100**, 2742 (1967).

(66) S. Ohki, M. Akiba, H. Shimada, and K. Keenihiro, *Chem. Pharm. Bull. Jap.*, **16**, 1889 (1968).

(67) Z. Horii, M. Ikeda, Y. Yamawaki, Y. Tamura, S. Saito, and K. Kodera, *Tetrahedron*, **19**, 2101 (1963).

(68) J. Parello, *Bull. Soc. Chim. Fr.*, 1117 (1968).

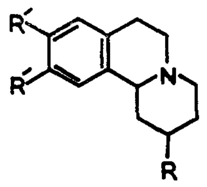
(69) S. M. Kupchan, G. F. Flouret, and C. A. Matuszak, *J. Org. Chem.*, **31**, 1707 (1966).

(70) S. M. Kupchan, A. D. J. Balon, and C. G. DeGrazin, *ibid.*, **31**, 1713 (1966).

(71) S. M. Kupchan and C. G. DeGrazin, *ibid.*, **31**, 1716 (1966).

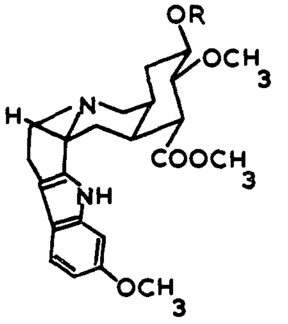
(72) S. M. Kupchan, J. H. Block, and A. C. Isenberg, *J. Amer. Chem. Soc.*, **89**, 1189 (1967).

(73) W. A. Ayer and G. G. Iverach, *Can. J. Chem.*, **42**, 2514 (1964).

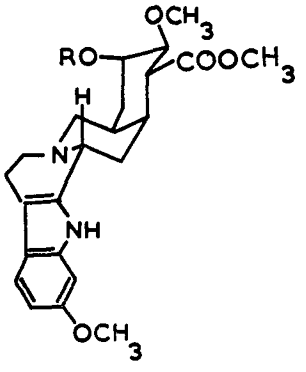


51

such that the angular proton and the nitrogen lone pair are trans diaxial) the angular proton absorbed at τ 6.8 whereas the angular proton in methyl reserpate (**52**) which is gauche to the lone pair absorbed at τ 6.2.

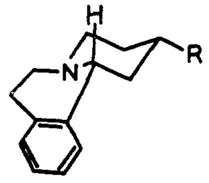


52

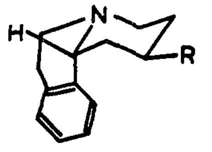


53

A similar difference in chemical shifts was observed[15] for ajmalicine and 3-isoajmalicine. Use has been made[74,75] of this variation in chemical shift of the angular proton with orientation with respect to the nitrogen lone pair in the conformational analysis of benzoquinolizidines (**51**). Thus the configurations and preferred conformations **54** and **55** (R = *p*-chlorophenyl) were assigned to the isomeric *cis*- and *trans*-2-(*p*-chlorophenyl)benzoquinolizidines since **54** exhibited Bohlmann bands in the infrared and the angular 11b proton absorbed at τ 6.2, whereas **55** showed no Bohlmann bands but its 11b proton appeared as a one-proton triplet (J_{ae} and J_{ee}) at τ 6.

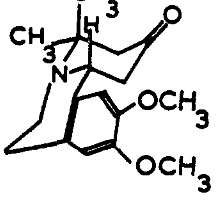


54



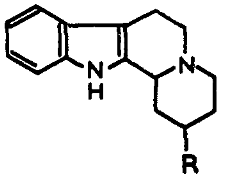
55

The alternative cis-fused conformation **56** was adopted by 2-keto-4,4′-dimethyl-9,10-dimethoxybenzoquinolizidine.



56

This compound showed no Bohlmann bands and its angular proton gave rise to a quartet (J_{aa} and J_{ee}) centered at τ 5.85. The stereochemistry of **51** (R′ = MeO; R = Ph, C_3H_7, *p*-tolyl, *p*-chlorophenyl) and **57** (R = CH_3, Ph)

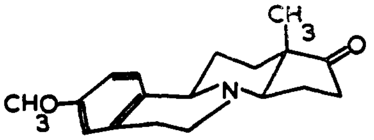


57

has been studied[76] using infrared data and rates of dehydrogenation. It would appear that the *cis*-2*H*,11b*H* compounds adopt the trans-fused ring conformation whereas some of the *trans*-2*H*,11b*H* compounds may exist as equilibrium mixtures of cis- and trans-fused ring conformations. The *trans*-2*H*,11b*H*-2-aryl compounds, however, undoubtedly adopt **55** as the preferred conformation. Bohlmann[65] has studied **51** (R′ = OMe, R = $COOCH_3$, CH_2OH, CH_2OAc) and found that the compounds exhibiting Bohlmann bands show a τ value for the angular 11b*H* proton of τ 6.55 whereas in the other isomers showing no Bohlmann bands this proton absorbs at τ 6.19–6.32.

Both epimers of the hydroxybenzoquinolizidine **51** (R′ = H, R = OH) have been shown[68] to exist in trans-fused ring conformations and the axial–equatorial orientation of the hydroxy group assigned from a study of the carbinol proton signals in the nmr. Derivatives of benzo[*c*]quinolizidines have been described by Kupchan.[70,71]

Three of the four possible isomers of 8-azaestrone have been obtained and assigned configurations and preferred conformations (**58**, **59**, and **60a**).[77] **58** and **59** showed Bohlmann bands whereas **60a** did not.



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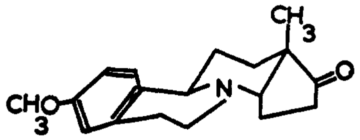
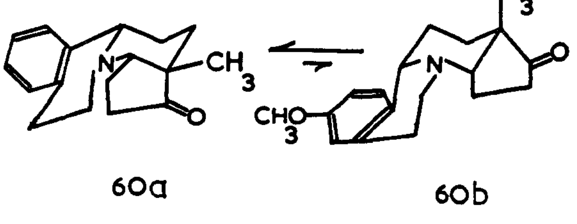


59

The chemical shift of the angular protons were in agreement with this assignment. Some 12-keto derivatives of this system have been described[78] together with 220-MHz spectral data.



60a **60b**

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(74) M. Uskokovic, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *J. Amer. Chem. Soc.*, **86**, 3364 (1964).

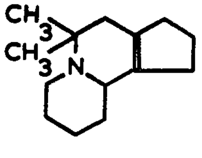
(75) H. Bruderer, M. Baumann, M. Uskokovic, and A. Brossi, *Helv. Chim. Acta*, 47, 1852 (1964).

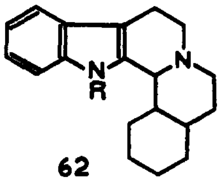
(76) J. Gootjer, A. M. de Roos, and W. Th. Nauta, *Recl. Trav. Chim. Pays-Bas*, **85**, 491 (1966).

(77) R. E. Brown, D. M. Lustgarten, R. J. Stanaback, and R. I. Meltzer, *J. Org. Chem.*, **31**, 1489 (1966).

(78) N. S. Bhacca, A. I. Meyers, and A. H. Reine, *Tetrahedron Lett.*, 229 (1968).

The cyclopentenoquinolizidine **61** has been assigned[79] a trans-fused ring conformation on the basis of infrared and nmr evidence.

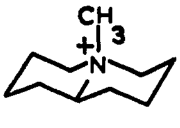

61


62

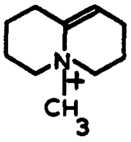
The four isomers of the inside yohimbanes (**62**) have had their stereochemistry assigned[80] on the basis of chemical and spectroscopic data.

h. Quinolizidine Methiodides

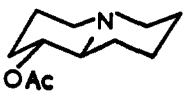
Quaternization of quinolizidine[81,82] gives the trans-fused methiodide **63** whereas treatment of 2-(4′-ethoxybutyl)-1-methylpiperidine with hydriodic acid affords the cis-fused methiodide **64**. This latter isomer was also obtained[81,82] by catalytic reduction of **65**. From an examination of the nmr spectra of these isomers and of the methiodides of the monomethylquinolizidines, it became apparent that the *N*-methyl group absorbs at lower field (τ 6.84–6.92) in the cis-fused salts than in the trans-fused analogs (τ 7.01–7.06).


63


64


65

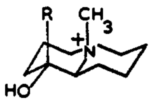
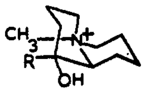
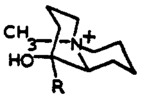
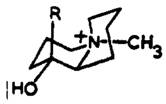
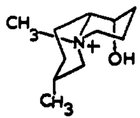
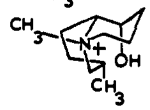
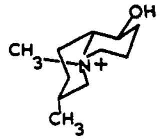
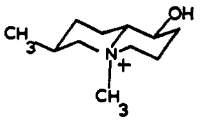
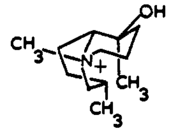
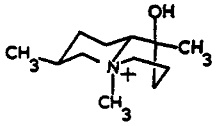
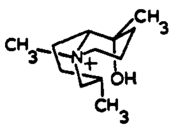
Methylation of **66** gave two salts, assigned[83] the trans- and cis-fused ring stereochemistry since their *N*-methyl resonances appeared at τ 6.90 and 6.65, respectively. The epimer of **66** gave only one methiodide (τ(*N*-methyl) 6.72), and this was tentatively assigned[83] the cis-ring fusion. Methylation studies on the epimeric 1-hydroxy-, 1-hydroxy-1-methyl-, and 1-hydroxy-1-phenylquinolizidines have been carried out[86] and stereochemical assignments made. These are as shown in Table IV.


66

The hydroxyquinolizidines shown in Table III have been quaternized and the structures shown in Table IV proposed[41] for the methiodides on the basis of the nmr data.

Table IV

Nmr Spectra of Quinolizidine Methiodides[86,41]

Compound		*Chemical shift N–Me* (τ)
	R = H	6.88
	R = Me	6.93
	R = Ph	6.42
	R = H	6.77
	R = Me	6.78
	R = Ph	5.99
	R = H	6.54
	R = Me	6.55
	R = Ph	5.99
		6.38
		6.38
		6.32
		6.54
		6.15
		6.51
		6.38

B. FUSED 6/6 RING SYSTEMS WITH ADDITIONAL HETEROATOMS

The introduction of a second heteroatom into the quinolizidine ring system might be expected to influence conformational preferences since in certain situations dipole–dipole interactions will be significant and there will also be differences in the types of nonbonded interactions and in bond lengths and angles.

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(79) A. I. Meyers and N. K. Ralhan, *J. Org. Chem.*, **28**, 2950 (1963).

(80) G. C. Morrison, W. A. Cetenko, and J. Shavel, *ibid.*, 32, 2768 (1967).

(81) K. Schofield and R. J. Wells, *Chem. Ind.* (*London*), 572 (1963).

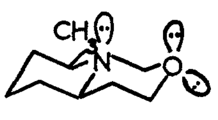
(82) K. Schofield and R. J. Wells, *Aust. J. Chem.*, **18**, 1423 (1965).

(83) J. D. England, D. Temple, and J. Sam, *J. Med. Chem.*, **11**, 353 (1968).

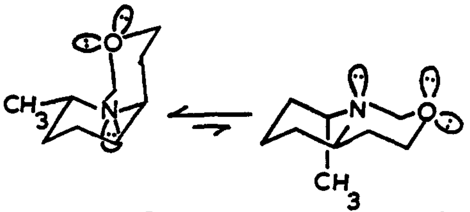
1. One Additional Oxygen Atom

Of particular importance in the conformational analysis of 1,3-hetero systems has been the value of the geminal coupling constant (J_{gem})[84,85] of the methylene protons situated between the heteroatoms. A molecular orbital theory[86] of geminal coupling constants shows that in such a system inductive removal of electrons from the symmetric bonding orbital of the CH_2 group and transfer of lone-pair electrons into the antisymmetric bonding orbital both result in a positive contribution to the value of J_{gem}. This latter process is dependent upon the dihedral angle between the heteroatom lone-pair orbitals and the adjacent C–H bonds: a parallel arrangement[87,88] of the lone-pair orbitals and a CH bond producing the most positive contribution to J_{gem} and an arrangement such that the lone pair bisects the CH_2 giving rise to no contribution from the lone pair.

Since the geminal coupling constants of the C-2 methylene protons of *cis*-10,6-*H*-10-methyl- and *trans*-10,6-*H*-10-methyl-3-oxa-1-azabicyclo[4.4.0]decane were[89] −8 and −10 Hz, respectively, they were assigned the preferred conformations shown (**67** and **68a**), the larger value of J_{gem} corresponding to the parallel arrangement of lone pair and CH bonds, and the more negative J_{gem} consistent with **68a** in which the nitrogen lone pair bisects the CH_2. The trans-fused ring compound **67** also showed Bohlmann bands which were absent in the *cis*-fused ring compound **68**. The *trans*-10,6-*H*-10-methyl-3-oxa-1-azabicyclo[4.4.0]decane adopts the cis-fused conformation **68a** rather than the alternative trans conformation **68b** not only to relieve nonbonded interactions involving the axial methyl group but also to alleviate the unfavorable interaction arising from the parallel arrangement of lone pairs of electrons on nitrogen and oxygen. The destabilizing effect of parallel lone pairs in 1,3-hetero systems has also been discussed by Eliel.[90] Both of the possible 4-methyl-3-oxa-1-azabicyclo-[4.4.0]decanes and the two 4-phenyl compounds have been shown[89] to adopt predominantly trans-fused ring conformations since they all show Bohlmann bands and a geminal coupling constant for the C-2 methylene protons of *ca.* −8 Hz. It has generally been assumed that Bohlmann's infrared criterion originally deduced for quinolizidines is applicable to other saturated systems with bridgehead nitrogen atoms, and all the available evidence supports this assumption.

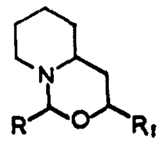


67

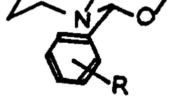


68a **68b**

Several other substituted 3-oxa-1-azabicyclo[4.4.0]decanes (**69**) have been prepared[89,91,92] and stereochemical studies carried out with them, in some cases, in order to determine the configurations of the alkaloids sedamin and sedridin. Condensation of the two racemic diastereoisomeric piperidylpropanols with aromatic aldehydes gave[91] one isomer in each case, and these were assigned the trans-fused ring conformations **70** and **71** with the bulky aryl group equatorial in both isomers. The axial–equatorial nature of the methyl group was deduced from the chemical shifts of the C-4 proton and from the values of the coupling constants with adjacent protons.



69



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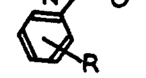
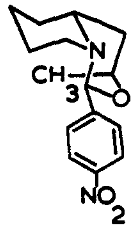


71

However, more recently two isomers have been reported[92] from the reaction of (−)-sedridine, a piperidylpropanol, with *p*-nitrobenzaldehyde. One of the isomers was assigned an axial 4-methyl group on the basis of nmr spectroscopy, and the cis-fused ring conformation **72** was considered in best agreement with the spectral evidence. The other isomer was assigned the trans-fused ring conformation **71** (R = *p*-nitro) with an equatorial methyl group. The cis-fused ring conformation **72** seems very unlikely for one of these isomers, particularly as models show that the axial 4-methyl group in this conformation points backwards under the other six-membered ring and introduces an extremely severe nonbonded interaction. The Bohlmann infrared criterion would also be expected to differentiate between the two conformations **71** and **72**, but it was stated that the infrared spectra of the two compounds were similar. A trans-fused ring conformation such as **71** with an axial *p*-nitrophenyl group would therefore appear to be a more probable structure for *trans*-2,*cis*-4,6-*H*-2-*p*-nitrophenyl-4-methyl-3-oxa-1-azabicyclo[4.4.0]decane.



72

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[84] R. C. Cookson, T. A. Crabb, J. J. Frankel, and J. Hudec, *Tetrahedron, Suppl.*, 7, 355 (1966).

[85] R. Cahill, R. C. Cookson, and T. A. Crabb, *Tetrahedron*, **25**, 4681 (1969).

[86] J. A. Pople and A. A. Bothner-By, *J. Chem. Phys.*, 42, 1339 (1965).

[87] M. Anteunis, *Bull. Soc. Chim. Belg.*, **75**, 413 (1966).

[88] R. C. Cookson and T. A. Crabb, *Tetrahedron*, **24**, 2385 (1968).

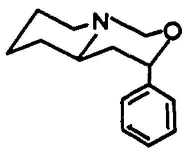
[89] T. A. Crabb and R. F. Newton, *ibid.*, **24**, 4423 (1968).

[90] E. L. Eliel, *Kem. Tidskr.*, **81**, 22 (1969).

[91] H. C. Beyerman, L. Maat, A. Van Veen, and A. Zweistra, *Recl. Trav. Chim. Pays-Bas*, **74**, 1568 (1955).

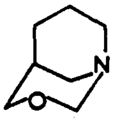
[92] G. A. Cooke and G. Fodor, *Can. J. Chem.*, **46**, 1105 (1968).

trans-4,6-*H*-4-Phenyl-3-oxa-1-azabicyclo[4.4.0]decane has been shown[89] to exist predominantly in a trans-fused ring conformation with an axial 4-phenyl group (**73**).



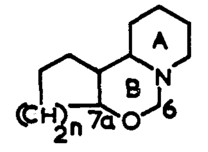
73

Riddell[93] reported the conformation of 3-oxa-1-azabicyclo-[3.3.1]nonane as being **74**. This compound had a J_{gem} for the C-2 methylene group of −10.5 Hz consistent with a conformation such that the nitrogen lone pair bisects the methylene group.



74

The four possible isomers of perhydrobenzo[*e*]pyrido-[1,2-*c*]-1,3-oxazine (**75**, *n* = 2) have been obtained[94] and assigned the stereostructures **76**–**79**. The trans A:B junction in **76**, **77**, and **78** was shown by Bohlmann bands and J_{gem} (C-6 methylene) of *ca.* −7.5 Hz and the cis A:B junction in **79** by a similar geminal coupling constant and the absence of Bohlmann bands. The nature of the B:C ring fusions was deduced from the chemical shift and couplings of the C-7a proton and the chemical shifts of the C-2 protons. Independent evidence for the assignments was obtained by studying the rates of methylation. The corresponding cyclopentano (**75**, *n* = 1) and cycloheptano (**75**, *n* = 3) compounds and some 5-methyl-substituted derivatives were also studied.



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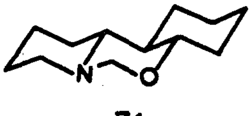

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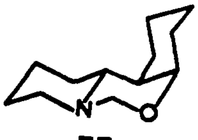

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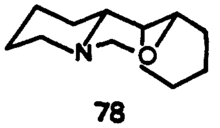

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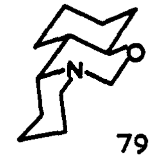
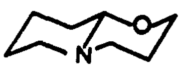


79

5-Oxa-1-azabicyclo[4.4.0]decane (**80**) showed two bands between 2800 and 2700 cm^{-1} in its infrared spectrum and was accordingly assigned[95] a trans-fused ring conformation. 6-Methyl-5-oxa-1-azabicyclo[4.4.0]decane (**81**), assigned a trans-fused ring conformation on the same basis, might be expected to exist as an equilibrium mixture containing significant amounts of the cis-fused ring conformation, but, as discussed above, infrared data in the CH stretching region are not able to demonstrate the presence of such conformations. The tricyclic 3-oxa-7-azatricyclo[7.3.1.0]tridecane was found by infrared to exist predominantly in the trans-fused ring conformation **82**.



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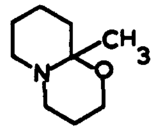

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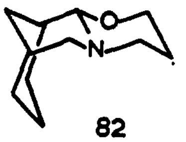
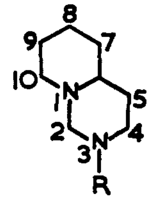


82

2. *One Additional Nitrogen Atom*

The configurations and preferred conformations of a series of substituted 1,3-diazabicyclo[4.4.0]decanes (**83**) have been deduced[96] from chemical and spectroscopic evidence. The 3-alkyl- and 3-aryl-1,3-diazabicyclo[4.4.0]decanes (**83**, R = CH_3, C_2H_5, $(CH_3)_3C$, C_6H_5) were all found to exist in predominantly trans-fused ring conformations with equatorial 3-nitrogen substituents (J_{gem} = −8.4 to −8.6 Hz and strong Bohlmann bands). The geminal coupling constant of −8.8 Hz for the C-2 methylene group showed that the *cis*-4,6-*H*-3,4-dimethyl and *cis*-4,6-*H*-3-methyl-4-ethyl epimers existed in the trans-fused ring conformation with an equatorial 3-methyl group (**84**), while the *trans*-4,6-*H*-3,4-dimethyl (J_{gem} = −10.8 Hz) and *trans*-4,6-*H*-3-methyl-4-ethyl compounds (J_{gem} = −11.4 Hz) existed predominantly in the trans-fused ring conformation with an axial 3-methyl group (**85**). This is a clear example of the importance of syn-axial lone-pair interactions in influencing the position of conformational equilibrium in such systems. Both of the possible 3,5-dimethyl-1,3-diazabicyclo[4.4.0]decanes were assigned trans-fused ring conformations with equatorial 3-methyl groups on the basis of their nmr spectra (J_{gem} = −8.4 and −8.7 Hz). The configurations of the 3,10-dimethyl- and 3-*tert*-butyl-10-methyl-1,3-diazabicyclo-[4.4.0]decanes were deduced from chemical evidence. The predominant conformation of 3-methyl- and 3-*tert*-butyl-*cis*-10,6-*H*-10-methyl-1,3-diazabicyclo[4.4.0]decane was found to be that with a trans-fused ring junction and an equatorial 3-



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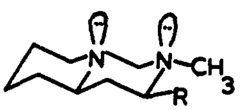

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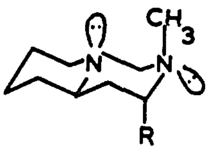

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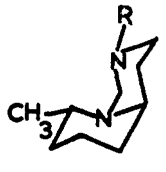
(93) F. G. Riddell and J. M. Lehn, *J. Chem. Soc. B*, 1224 (1968).

(94) T. A. Crabb and E. R. Jones, *Chem. Ind.* (*London*), 1695 (1968); *Tetrahedron*, 26, 1217 (1970).

(95) N. J. Leonard and W. K. Musker, *J. Amer. Chem. Soc.*, 82, 5148 (1960).

(96) T. A. Crabb and R. F. Newton, *Tetrahedron*, 26, 701 (1970).

alkyl group. The corresponding *trans*-10,6-H-10-methyl compounds existed as conformational mixtures containing appreciable amounts of the cis- and trans-fused ring conformations (**86** and **87**) as shown by values of $J_{\text{gem}} = -9.8$ and -9.9 Hz.



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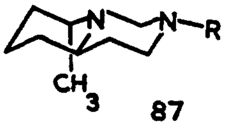
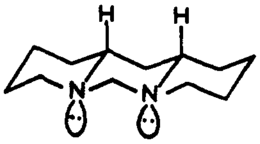


87

Both the syn (**88**) and anti (**89**) perhydrodipyrido[1,2-*c*:2′,1′-*f*]pyrimidines have been obtained[97] and the C-6 methylene protons in the syn compound show a J_{gem} of -8.5 Hz and a difference in chemical shift of 1.0 ppm, consistent with the structure shown with both lone pairs trans to C-6 H_{ax}. The unsubstituted anti compound (**89**) is in rapid conformational equilibrium as indicated. The syn compound **88** has Bohlmann bands of much greater area than the anti compound **89** since it possesses two trans-fused quinolizidine rings.



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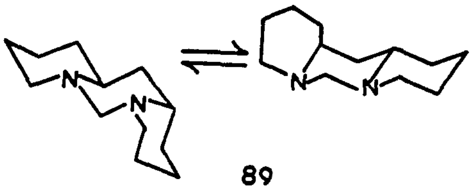
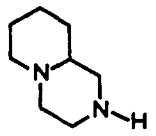


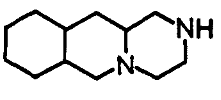
89

1,4-Diazabicyclo[4.4.0]decane (**90**) has been synthesized[98]



90

and assigned a trans-fused ring conformation on the basis of the infrared spectrum of its 4-phenylurea derivative which had bands at 2760 and 2785 cm^{-1}. The infrared spectra of 1,3-diaza-, 1,4-diaza-, and 1,5-diazabicyclo[4.4.0]decane all show Bohlmann bands, and these compounds were accordingly assigned[99] trans-fused ring conformations. The preferred conformations of **91** and **92** have been suggested from a study[100] of their infrared spectra. Two isomers of **93** have been obtained and their stereochemistry determined[101] from a study of the $C-CH_3$ chemical shifts and apparent coupling constants. Both isomers showed Bohlmann bands.



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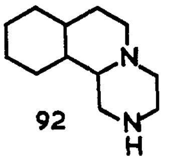

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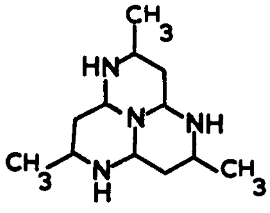
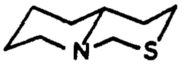


93

3. One Additional Sulfur Atom

3-Thia-1-azabicyclo[4.4.0]decane has been assigned[102] the trans-fused ring conformation on the basis of its infrared (strong Bohlmann bands) and nmr spectra ($J_{2\text{ax},2\text{eq}} = -12.0$ Hz) (Table V). *cis*-7,6-H-7-Methyl-3-thia-1-azabicyclo[4.4.0]-decane showed very weak Bohlmann bands in the infrared indicating the cis-fused conformation **95**. However, $J_{2\text{ax},2\text{eq}}$ was only slightly smaller (-12.8 Hz) than observed for **94**, and this has been explained in terms of deviation from chair geometry of the 1,3-hetero ring as a consequence of the long C–S bond.



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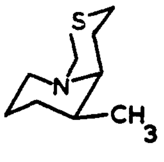
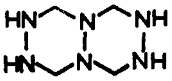


95

4. Two Nitrogen Atoms at a Ring Fusion

The nmr spectra and conformations of the compounds **96**[103] and **97**[104] have been discussed in detail.



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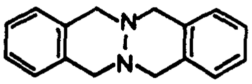

97

C. FUSED 6/5 RING SYSTEMS WITH NO ADDITIONAL HETEROATOM

1. Indolizidine

ΔG° for the cis $\rightleftharpoons$ trans indolizidine equilibrium has been determined[13] as -2.4 kcal/mol, a value very close to that for the quinolizidine equilibrium (-2.6 kcal/mol).[13] The free energy difference between the carbocyclic analogs *cis*- and *trans*-hydrindane and *cis*- and *trans*-decalin are 2.7 and 0.3 kcal/mol, respectively, and the small free energy difference between *cis*- and *trans*-hydrindane has been explained in terms of strain involving the ring fusion which raises the energy of

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(97) P. J. Chivers and T. A. Crabb, *Tetrahedron*, 26, 3369 (1970).

(98) M. E. Freed and A. R. Day, *J. Org. Chem.*, 25, 2108 (1960).

(99) R. L. Peck and A. R. Day, *J. Heterocycl. Chem.*, 6, 181 (1969).

(100) A. R. Day and H. B. Sullivan, *Diss. Abstr.*, 24, 1838 (1963).

(101) K. G. R. Pachler, *J. Chem. Soc B*, 7, 760 (1968).

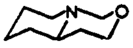
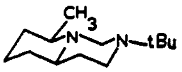
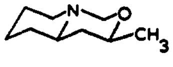
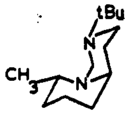
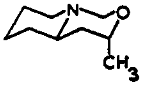
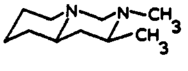
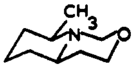
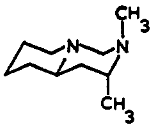
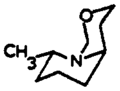
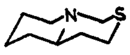
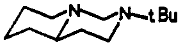
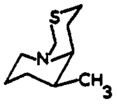
(102) T. A. Crabb and R. F. Newton, *Tetrahedron*, 26, 3941 (1970).

(103) J. P. Kintzinger, J. M. Lehn, and J. Wagner, *Chem. Commun.*, 5, 206 (1967).

(104) B. Junge and H. A. Staab, *Tetrahedron Lett.*, 8, 709 (1967).

Table V

Nmr and Ir Spectra of 3-Hetero-1-azabicyclo[4.4.0]decanes

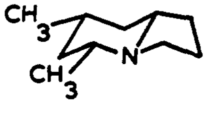
Compound	Nmr (C-2 protons) J_{gem} (Hz)	Nmr (C-2 protons) Δ^c (ppm)	Ir Bohlmann region cm^{-1} (ϵa)	Compound	Nmr (C-2 protons) J_{gem} (Hz)	Nmr (C-2 protons) Δ^c (ppm)	Ir Bohlmann region cm^{-1} (ϵa)
	−8.0[a]	0.66	2813 (50) 2776 (68) 2762 (84) 2739 (44) 2725 (50) 2682 (52)		−8.6[b]	2.00	2821 (51) 2790 (78) 2720 (43) 2680 (43) 2660 (40)
	−8.0[a]	0.61	2811 (58) 2764 (94) 2735 (54) 2723 (39) 2687 (36)		−9.8[b]	0.91	2821 (49) 2800 (55) 2760 (28) 2600 (26)
	−8.0 (benzene)	0[a]	2811 (60) 2759 (94) 2737 (64) 2714 (46) 2682 (54) 2656 (30)		−8.8[b]	0.96	2825 (71) 2795 (110) 2750 (60) 2732 (50) 2670 (45)
	−8.0[a]	1.31	2812 (46) 2774 (74) 2758 (62) 2725 (72) 2698 (50) 2683 (34)		−10.8 (benzene)	0[b]	2801 (50) 2775 (55) 2739 (35) 2670 (25)
	−10.0[a]	0.60	2760 (26) 2725 (23)		−12.0[a]	0.31	2782 (75) 2738 (32) 2720 (32)
	−8.5[b]	1.27	2822 (51) 2785 (70) 2740 (41) 2720 (41) 2677 (46)		−12.8	0.65	2790 (14) 2720 (12)

[a] 10% CCl_4 solution. [b] 10% $CDCl_3$ solution. [c] Difference in chemical shift between C-2 protons.

trans-hydrindane. In order to explain the difference in $\Delta G°$ values between the indolizidine and hydrindane systems, nmr evidence has been quoted[105] to suggest that the strain present in *trans*-hydrindane is relieved in *trans*-indolizidine by flattening of the bonds around the bridgehead nitrogen atom.

The Bohlmann regions of the infrared spectra of indolizidine (2), 3,3′-dideuterioindolizidine, and 9-deuterioindolizidine have been compared.[106] It was found that replacement of the C-9 axial hydrogen in indolizidine by deuterium reduced the intensity of the Bohlmann bands by 28%, whereas replacement of the pseudo axial C-3 hydrogen reduced the bands by 33%. This result was unexpected since the C-3 hydrogen atom is not strictly trans coplanar with the nitrogen atom lone pair of electrons.

The configurations and preferred conformations of the four 5,7-dimethylindolizidines have been assigned[107] on the basis of their nmr (*C*-methyl chemical shifts) and infrared spectra. **98** and **99** show prominent bands in the Bohlmann region but



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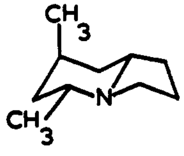

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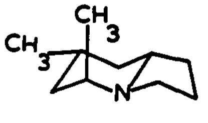
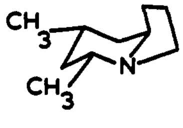


100



101

these are much reduced in **100**. The trans-fused conformation **100** has only two correctly orientated CH bonds necessary for strong Bohlmann bands compared with three in **98** and **99**, and so a drop in intensity would be expected for **100**. Isomer **101**

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(105) T. A. Crabb and R. F. Newton, *Tetrahedron Lett.*, 1551 (1970).

(106) A. E. Theobald and R. G. Lingard, *Spectrochim. Acta*, **24**, 1245 (1968).

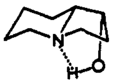
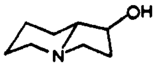
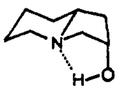
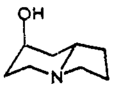
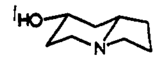
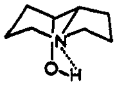
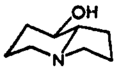
(107) B. Lüning and C. Lundin, *Acta Chem. Scand.*, **21**, 2136 (1967).

showed very little absorption in the 2800–2700-cm^{-1} region indicative of the cis-fused conformation shown.

The 1-, 2-, 7-, and 8-hydroxyindolizidines have been studied by Aaron.[108,109] All eight compounds (Table VI) show prominent Bohlmann bands indicating the trans-fused ring conformations **102–109**. **102**, **104**, and **108** show infrared absorptions characteristic of intramolecular hydrogen bonding and using long-path-length cells **109** has been shown[13] to exist in equilibrium with 3% of the cis-fused ring conformation with an axial intramolecularly hydrogen-bonded hydroxy group. The configurations of the remaining alcohols were assigned from the chemical shift and line width of the carbinol proton signals. In each case (with exception of **104** and **105**) the axial proton absorbed at higher field than the equatorial proton. However, in **104** and **105** the carbinol proton did not appear to be definitely pseudoaxial or pseudoequatorial.

Table VI

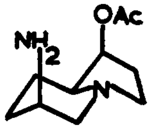
Nmr and Ir Spectra of Hydroxyindolizidines[108,109]

		Ir spectra (cm^{-1})		*Nmr spectra*	
Compound	*No.*	*OH*	*Bohlmann region*	τ	$W_h{}^a$ *(Hz)*
	**102**	3623, 3580	2790, 2750, 2725	6.10	11.5
	**103**	3632	2795, 2730	6.25	21
	**104**	3624, 3594	2785, 2720	5.90	17
	**105**	3626	2790, 2720	5.75	14
	**106**	3626	2800, 2745	5.98	7.4
	**107**	3624	2788, 2751, 2714	6.53	21
	**108**	3522	2789, 2736	6.32	6.5
	**109**	3627	2790, 2725	6.75	>20

^{a} Peak width at half-height.

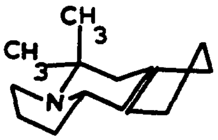
The 1-, 2-, 7-, and 8-ketoindolizidines also exist[109-111] in predominantly trans-fused ring conformations as shown by the presence of Bohlmann bands.

The carbinyl acetate proton of *N*-acetylslaframine absorbs at τ 4.76 (W_H = 13 Hz). Comparison with the chemical shifts of the corresponding protons in the acetates of **102** (τ 4.79, W_H = 13 Hz) and of **103** (τ, 5.24, W_H = 21 Hz) permitted[112] the assignment of configuration shown in **110**. The coupling constants in *N*-acetylslaframine hydrochloride (D_2O solution) were $J_{1,9}$ = 6.5 Hz, $J_{5ax,6}$ = 2.8 Hz, and $J_{5ax,5eq}$ = −13 Hz.

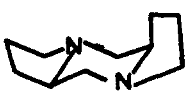


110

A dimethylcyclopentenoindolizidine was assigned the stereochemistry of **111** on the basis of the presence of Bohlmann bands and the chemical shift and coupling constant (10 Hz) of the angular proton. **112**[113] shows Bohlmann bands.



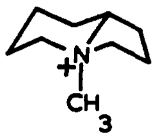
111



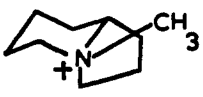
112

2. Indolizidine Methiodides

Methylation of indolizidine produced[114] a mixture of the cis- and trans-fused methiodides **113** and **114** showing *N*-methyl resonances at τ 6.88 and 7.18, respectively. The stereochemistry of the ring fusion was assigned from these τ values since very similar values had been observed for the corresponding quinolizidine methiodides.



113



114

The different τ values have been explained by Elvidge[115] in terms of the shielding effects of neighboring C–C and C–N bonds. The isomeric 5,7-dimethylindolizidines have been methylated[107] and whereas **98** and **99** each give two isomeric methiodides with *N*-methyl chemical shifts in the normal range, **100** and **101** give only one each. The methiodide of **101** must be cis-fused but shows an unusually high-field *N*-methyl resonance at τ 7.04; this may be due to the shielding influence of the adjacent equatorial methyl group.

D. FUSED 6/5 RING SYSTEMS WITH ADDITIONAL HETEROATOMS

The value of the J_{gem} for the $N–CH_2–X$ protons and the difference in chemical shift between these protons have been shown to be reliable criteria in determining the preferred conformations of **115** (X = O),[116] **115** (X = S),[117] **115** (X =

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(108) C. P. Rader, R. L. Young, and H. S. Aaron, *J. Org. Chem.*, **30**, 1536 (1965).

(109) H. S. Aaron, C. P. Rader, and G. E. Wicks, *ibid.*, **31**, 3502 (1966).

(110) S. Yamada and T. Kuneida, *Chem. Pharm. Bull. Jap.*, **15**, 490 (1967).

(111) R. Cahill and T. A. Crabb, unpublished work.

(112) R. A. Gardiner and K. L. Rinehart, *J. Amer. Chem. Soc.*, **90**, 5639 (1968).

(113) J. P. Li, *J. Heterocycl. Chem.*, **5**, 703 (1968).

(114) W. L. Meyer and N. Sapianchiay, *J. Amer. Chem. Soc.*, **86**, 3343 (1964).

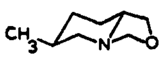
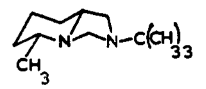
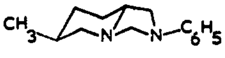
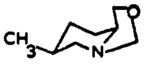
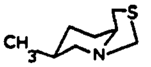
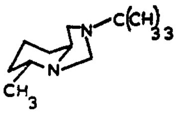
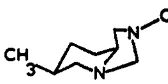
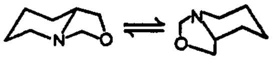
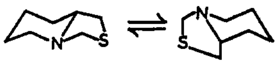
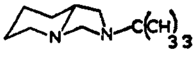
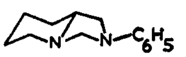
(115) J. A. Elvidge and I. M. Skvortsov, *J. Chem. Soc. B*, 1589 (1968).

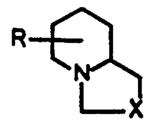
(116) T. A. Crabb and R. F. Newton, *Chem. Ind. (London)*, 339 (1966); *J. Heterocycl. Chem.*, **3**, 418 (1966); *Tetrahedron*, **24**, 1997 (1968).

(117) T. A. Crabb and R. F. Newton, *ibid.*, **24**, 2485 (1968).

Table VII

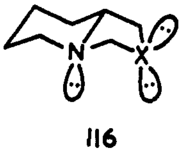
Nmr and Ir Spectra of 8-Hetero-1-azabicyclo[4.3.0]nonanes

Compound	*Nmr (C-9 protons)* J_{gem} *(Hz)*	$\Delta H_{99'}$ *(ppm)*	*Ir Bohlmann region* cm^{-1} *(εa)*
	−0.8	0.79	2808 (150) 2778 (146) 2762 (107) 2754 (96) 2727 (71) 2710 (46)
	−6.0	0.65	2785 (115) 2734 (30) 2715 (33) 2635 (21)
	−4.3	0.87	2796 (64) 2728 (43) 2600 (13)
	−3.6	0.77	2803 (81) 2777 (67) 2742 (77) 2708 (37)
	−5.0	0.19	2830 (57) 2777 (30)
	−8.5	0.22	2803 (60) 2722 (16)
	−5.7	0.18	2825 (60)
	−6.0	0.34	2803 (61) 2740 (45) 2710 (24)
	−2.4	0.58	2803 (97) 2776 (97) 2752 (62)
	−7.2	0.22	2785 (122) 2731 (19) 2718 (21) 2710 (21) 2634 (13)
	−4.1	0.72	2797 (82) 2770 (60) 2735 (51) 2670 (23)
	−3.8	0.72	2802 (84) 2774 (67) 2741 (74)

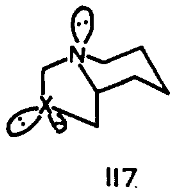


115

N-alkyl),[118] and **115** (X = *N*-phenyl).[119] Spectral data on these systems are summarized in Table VII. Trans-fused ring compounds (**116**) show a very positive value of J_{gem} and a large difference in chemical shift for the C-9 protons whereas cis-fused ring compounds (**117**) show a smaller chemical shift difference and a more negative J_{gem}. The very large value of $J_{99'}$ = −0.8 Hz for **116** (X = O) has been explained[116] in terms of flattening of the bonds involving the bridgehead nitrogen atom, thus increasing the overlap of the nitrogen lone-pair orbitals with the adjacent CH bonds.[105] The infrared spectra of trans-fused ring compounds exhibited strong absorptions in the Bohlmann region whereas the cis-fused ring compounds did not (Figure 2). The unsubstituted parent compounds (**115**, X = O and X = S) show intermediate values of J_{gem} and Δ(H9H9′) indicating an equilibrium between **116** and **117** at room temperature. Since indolizidine exists at room temperature almost entirely in the trans conformation, the existence of **115** (R = H; X = O and S) as equilibrium mixtures containing a large proportion of cis-fused conformations shows the destabilizing influence of the 1,3-heteroatom lone pairs in the trans-fused conformation **116**. **115** (X = N-R) exists at room temperature in a predominantly trans-fused ring conformation (**116**, X = N-R) contrary to an earlier report.[98]

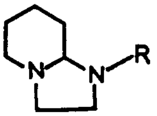


116

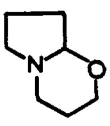


117

The 4-phenylurea derivative of 1,4-diazabicyclo[4.3.0]-nonane (**118**)[98] exhibited strong Bohlmann bands and was accordingly assigned a predominantly trans-fused ring conformation. Leonard[95] synthesized 7-oxa-1-azabicyclo[4.3.0]-nonane (**119**) and 5-oxa-1-azabicyclo[4.3.0]nonane (**120**) and assigned both predominantly trans-fused ring conformations on the basis of their infrared spectra.



118



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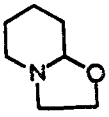
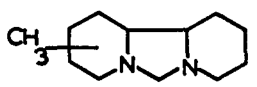


120

The configurations and preferred conformations of a series of monomethyl-substituted perhydrodipyrido[1,2-*c*:2′,1′-*e*]-imidazoles (**121**) have been assigned[120] from a study of their infrared and nmr spectra. With one exception, all the isomers obtained were assigned the trans,anti,trans (**122**) or the trans,



121

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(118) T. A. Crabb and R. F. Newton, *Tetrahedron*, 24, 6327 (1968).

(119) T. A. Crabb and R. F. Newton, *J. Heterocycl. Chem.*, **6**, 301 (1969).

(120) P. J. Chivers, T. A. Crabb, and R. O. Williams, *Tetrahedron*, **24**, 6625 (1968).

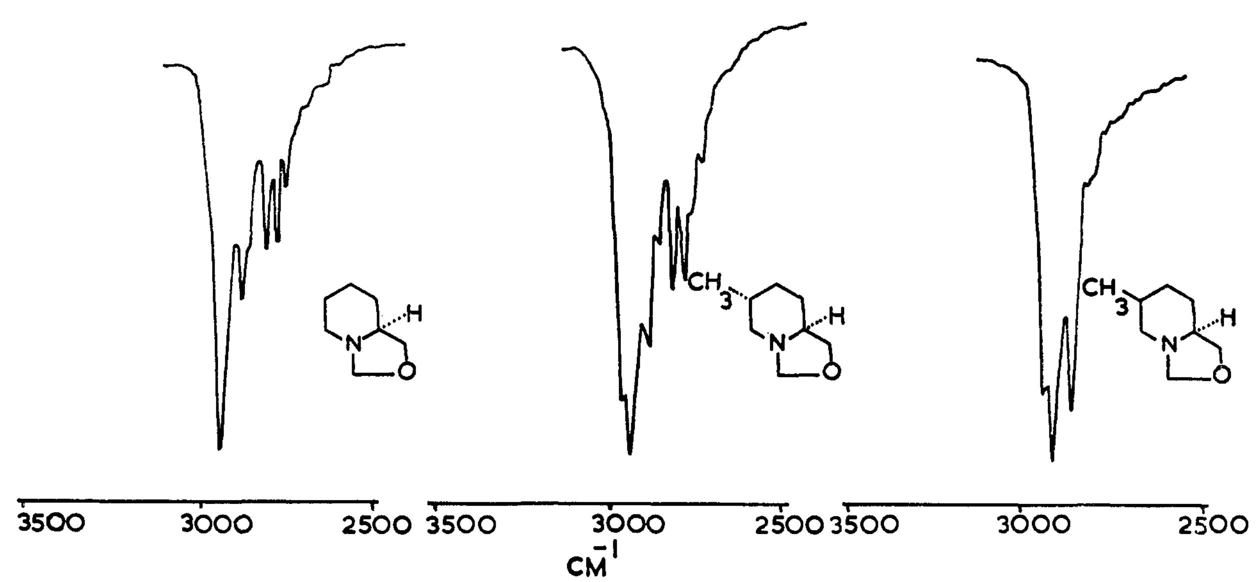
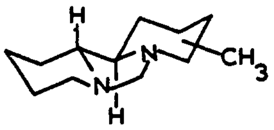
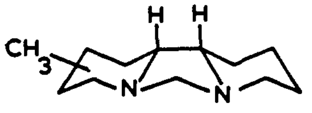


Figure 2. Infrared spectra (CH stretching region) of some 8-oxa-1-azabicylo[4.3.0]nonanes.

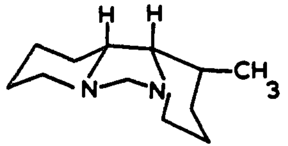
syn,trans (**123**) stereochemistry. These showed marked absorption in the Bohlmann region of the infrared, and compounds **122** showed either zero or very small chemical shift differences between the $N-CH_2-N$ protons whereas **123** showed chemical shift differences of *ca.* 0.4 ppm. $J_{H6H6'}$, for **122** and **123** varied between −3.4 and −4.5 Hz. *trans*-1*H*,11b*H*-1-Methyl-*syn*-perhydrodipyrido[1,2-*c*:2′,1′-*e*]imidazole was assigned the conformation **124** since it showed a marked reduction in the area of Bohlmann bands and a $J_{H6H6'}$ of −8.0 Hz. A similar study[121] of the perhydropyrido[1,2-*c*]pyrrolo-[2,1-*e*]imidazoles (**125**) permitted assignments of the structures **126** ($J_{H6H6'}$ = *ca.* −7 Hz, marked Bohlmann bands), **127** ($J_{H6H6'}$ *ca.* −4 Hz, marked Bohlmann bands), and **128** (J = *ca.* −6 Hz, weak Bohlmann bands) to the various isomers.



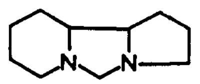
122



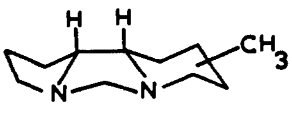
123



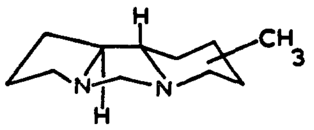
124



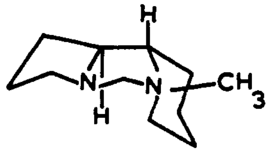
125



126



127

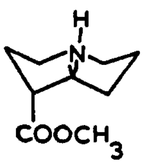


128

E. FUSED 5/5 RING SYSTEMS

A detailed discussion of the stereochemistry and nmr spectrum of pyrrolizidine (**3**) has been given by Skvortsov and Elvidge.[115] This compound exists mainly in the cis-fused ring conformation with pseudorotation occurring in each ring. The angular proton absorbs (CCl_4 solution) at τ 6.55 and the exo and endo protons adjacent to nitrogen absorb at τ 6.97 and 7.40, respectively; the geminal coupling constant for the $N-CH_2$ methylene protons is −9.75 Hz. The nmr spectrum of 3-*endo*-methylpyrrolizidine is temperature dependent, and at room temperature the compound must exist as a mixture of cis- and trans-fused ring conformations.

The 3-*exo*-methyl isomer exists in a cis-fused ring conformation at temperatures between −85 and +100°. The methyl resonances in the exo and endo compounds were at τ 8.84 and 8.88 (benzene solution), respectively. The *N*-methyl resonance in pyrrolizidine methiodide occurs at τ 6.86 (D_2O) (see also ref 114). The angular proton in 1-methoxycarbonypyrrolizidine (**129**)[122] absorbs at τ 6.2.



129

The 1- and 2-hydroxypyrrolizidines[109] exist in the cis-fused conformation. All four isomers show a free OH stretching vibration at 3625–3630 cm^{-1} and the *trans*-2,8-*H* compound

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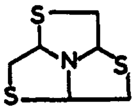
[121] P. J. Chivers, T. A. Crabb, and R. O. Williams, *Tetrahedron*, 25, 2921 (1969).

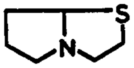
[122] B. Lüning and H. Trankner, *Acta Chem. Scand.*, 22, 2324 (1968).

shows in addition a band at 3590 cm^{-1} due to a weak intramolecular hydrogen bond.

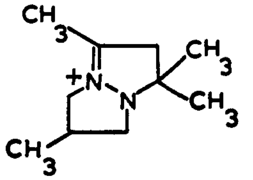
The stereochemistry of the pyrrolizidine alkaloids has been reviewed by Fodor,[123] and the nmr spectra of these alkaloids have been studied by Culvenor.[5] The nmr spectra of **130**,[124] derivatives of **131**,[125] and of **132**[126] have been reported. The temperature dependence of the nmr spectrum of **133** has been studied.[103] At −60° the ring methylenes appear as an AB quartet with $J = -9.6$ Hz, whereas at room temperature a singlet is observed. These changes may be attributed to the interconversion between the two cis-fused ring conformations by nitrogen inversion.



130



131



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133

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[123] G. Fodor, *Recent Develop. Chem. Nat. Carbon Compounds*, **1**, 15 (1965).

[124] R. C. Fort and W. L. Semon, *J. Org. Chem.*, **32**, 3685 (1967).

[125] R. G. Hiskey and S. J. Dominianni, *ibid.*, **30**, 1506 (1965).

[126] J. L. Aubagnac, J. Elguero, and R. Jacquier, *Bull. Soc. Chim. Fr.*, **9**, 3869 (1968).