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(7) Since this synthesis was initially described,[4b] we, as well as others, have utilized this type of reaction sequence in problems of total synthesis. For examples, see (a) R. E. Damon and R. H. Schlessinger, *Tetrahedron Lett.*, 4551 (1975); (b) F. E. Ziegler and J. A. Schwartz, *ibid.*, 4643 (1975); (c) R. E. Damon and R. H. Schlessinger, *ibid.*, 1561 (1976); (d) R. E. Damon, R. H. Schlessinger, and J. F. Blount, *J. Org. Chem.*, **41**, 3772 (1976); (e) F. E. Ziegler and J. A. Schwartz, *ibid.*, **43**, 985 (1978).
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(12) M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.*, **93**, 4065 (1971).
(13) An interesting "methylene anion" of this type has recently been described by (a) J. P. Marino and D. M. Floyd, *J. Am. Chem. Soc.*, **96**, 7138 (1974); (b) J. P. Marino and D. M. Floyd, *Tetrahedron Lett.*, 3897 (1975); (c) J. P. Marino and J. S. Farina, *ibid.*, 3901 (1975).
(14) Shortly before this synthesis was published, B. M. Trost and T. N. Salzmann, *J. Am. Chem. Soc.*, **95**, 6843 (1973), published a similar type of elimination reaction leading to unsaturated carbonyl systems. We thank Professor Trost for a preprint of his work prior to its publication.
(15) This sulfoxide was used initially because we assumed that loss of the elements of MeSOH would require cis geometry between the MeSO and H residues. Clearly, with this reaction constraint, **27** can lose the elements of MeSOH only toward the methyl group.
(16) The authors thank Drs. F. Johnson, J. J. Ellis, and F. H. Stodola for their generous gifts of *l*-avenaciolide.
(17) Melting points were taken on a Fisher-Johns melting point block and are reported uncorrected. Analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Reactions were run in either insulated cryostats (for temperatures <0 °C) or thermostated silicone oil baths with a temperature accuracy of 1 °C. Solvents were evaporated to dryness using a rotary evaporator at steam-bath temperatures and reduced pressures. Anhydrous solvents were distilled immediately before use. Tetrahydrofuran, diethyl ether, and 1,2-dimethoxyethane were distilled from lithium aluminum hydride, *tert*-butyl alcohol was distilled from calcium hydride, and methanol was distilled from magnesium turnings. Other solvents were at least reagent grade and used as received. Reagents were distilled at least once prior to use. Amines were distilled from calcium hydride under a nitrogen atmosphere. Hydrogenations were carried out in a slanted manifold all-glass apparatus at 1 atm at 0 °C. The system was evacuated by a water aspirator and then filled with hydrogen while stirring (this was repeated four times). Thin layer chromatography was performed on microscope slides coated by dipping in a slurry of either silica gel G or silica gel HF-254 (Brinkman) suspended in chloroform. High pressure liquid phase chromatography was performed on a Water's Associates ALC-202 instrument equipped with both an ultraviolet and differential refractometer detectors. Vapor phase chromatography was performed on a Hewlett-Packard 5700A instrument with TC detector and HP-5702A temperature programmer. Infrared spectra were recorded on either a Perkin-Elmer 700 or a Perkin-Elmer 467 spectrophotometer. Nuclear magnetic resonance spectra were recorded on either a JEOLCO C-60 HL or a JEOLCO MH-100 spectrometer using deuteriochloroform as solvent and tetramethylsilane as internal reference and are expressed as δ values, with the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Ultraviolet spectra were recorded on a Perkin-Elmer Digital 602 spectrophotometer.
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Organic Structure Characterization by Natural-Abundance Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy. *Rauwolfia* Alkaloids and Model Compounds[1]

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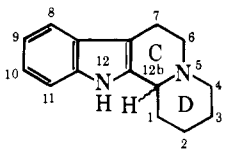
Abstract: ^{15}N chemical shifts of yohimbine, reserpine, and several structurally related alkaloids and model compounds as well as those of several trifluoroacetate salts have been obtained at the natural-abundance level. Both the nature of the quinolizidine ring fusion at N-5 and substituents in a γ-gauche conformation markedly affect ^{15}N resonance positions. The latter factor induces shieldings of magnitudes (7–12 ppm) comparable to those observed in ^{13}C NMR. Where γ effects are absent, a cis-fused quinolizidine nitrogen is shielded by 13–15 ppm compared with a trans-fused one. Protonation deshields nitrogens in both series, but the displacement is larger for the cis-fused case and serves to characterize this geometry. Hyperconjugation between the nitrogen lone pair and adjacent antibonding C–H orbitals is tentatively proposed to rationalize the shift difference between the cis and trans cases. The structure of sparteine is confirmed as existing in the all-trans configuration. Nitrogen resonance positions are solvent sensitive in a predictable manner.

Introduction

Nuclear magnetic resonance (NMR) spectroscopy has proven to be a highly effective tool in elucidating structures of natural products. Both ^{1}H[3] and ^{13}C[4] NMR have been employed extensively for this purpose; the latter has been especially useful in characterizing subtle differences in geometry. Neither technique, of course, can give explicit information about the nature of any constituent nitrogen atoms, which in many cases markedly determine the properties of these substances. With the demonstration that nitrogen-15 spectra of several classes of compounds can be obtained at the natural-abundance level within reasonable time periods,[5,6] natural-abundance ^{15}N NMR is expected to play an increasingly important role in structure elucidation despite the low isotopic natural abundance (0.365%) and sensitivity (0.1% relative to an equal number of protons). We have used this approach to characterize the nitrogen resonance positions of representatives of the *Rauwolfia* family of indole alkaloids, because these were expected to allow distinctions to be made between effects of substituents and effects of bridgehead nitrogen geometry in the indoloquinolizidine skeleton (**1**). We have found that nitrogen resonance positions at N-5 reflect both factors in a very



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sensitive manner; hence the method can serve as a means for characterizing the nature of the C/D ring fusion.

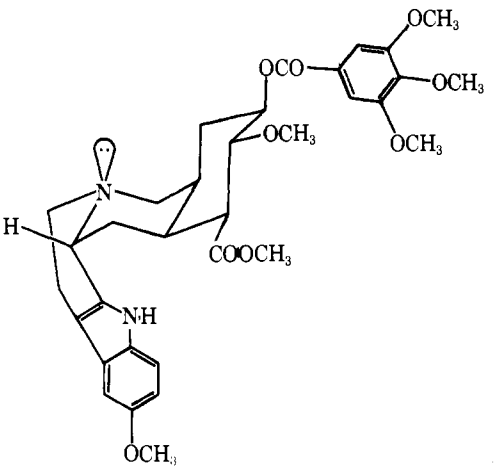
Experimental Section

With the exceptions noted below, alkaloids were obtained from commercial sources and were used without further purification. 3-Isoreserpine (**6**) was prepared from reserpine by literature methods.[7] The syntheses of indoloquinolizidines **3, 4,** and **12** have been reported.[8a,b] Trifluoroacetate salts were prepared by addition of 2–4 molar equiv of distilled trifluoroacetic acid to chloroform solutions of the amines.

Nitrogen-15 spectra were obtained in the Fourier-transform mode on a JEOL PS/PFT-100 spectrometer equipped with the JEOL EC-100 data system and operating at a resonance frequency of 10.09 MHz. ^{15}N spectra of **8, 9,** and the conjugate acids of yohimbine and reserpine were determined under similar conditions on a JEOL FX-100 spectrometer. Samples were run in 10-mm o.d. tubes in $CDCl_3$ or Me_2SO-d_6, which also served to provide the internal lock. Nitrogen chemical shifts, obtained with complete proton noise decoupling, were measured with respect to the resonance positions of a 2.9 M solution of ^{15}N-enriched ammonium chloride in 1 M HCl or of ^{15}N-enriched nitromethane contained in a 2-mm capillary held concentrically within the 10-mm tube. Values are reported with respect to anhydrous liquid ammonia,[9] which is shielded by −380.2 ppm from nitromethane and −23.6 ppm from the NH_4Cl used in this study. Normal operating conditions employed 15–30° pulse widths and 2–3 s repetition rates, with acquisition times corresponding to a 4 or 5 kHz range using 8K of memory for FID accumulation. Exponential filtering to improve sensitivity induced line broadening of 1.2 Hz.

Results

Spectra were determined for tetracyclic model compounds **2, 3, 4,** and **12,** as well as for yohimbine (**5**), reserpine (**6**), and isoreserpine (**7**). For comparison and to test the limits of applicability, chemical shifts of cevadine (**8**), corydaline (**9**), sparteine (**10**), and thermopsine (**13**) were also measured. Apparently because of its considerable insolubility, pseudoyohimbine (**11**) did not give rise to a nitrogen spectrum. The data are summarized in Table I, which also includes values for some small molecules useful as model compounds. Spectra were determined for the trifluoroacetate salts of **2, 4, 5, 6, 9,**



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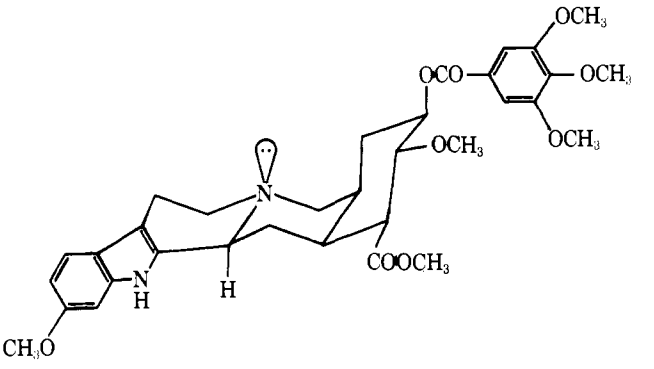

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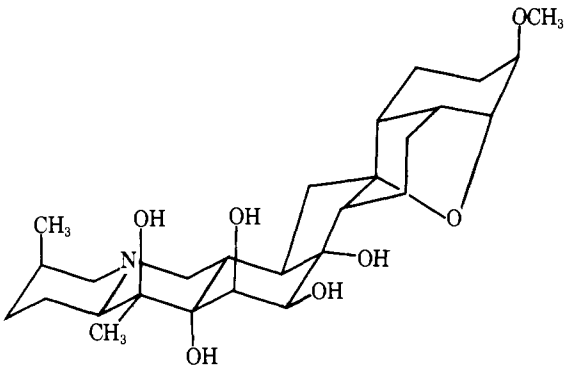

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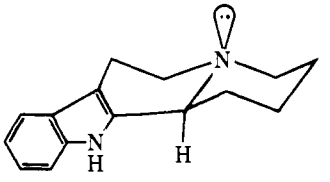

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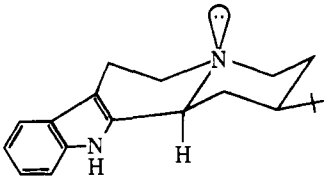

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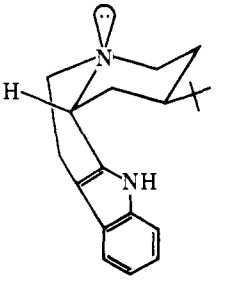

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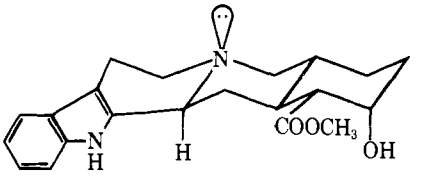

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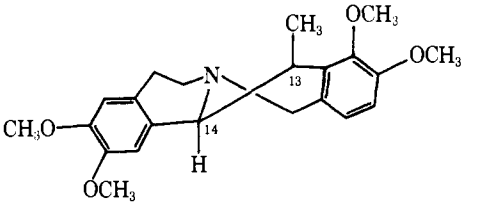

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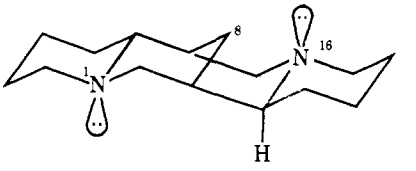

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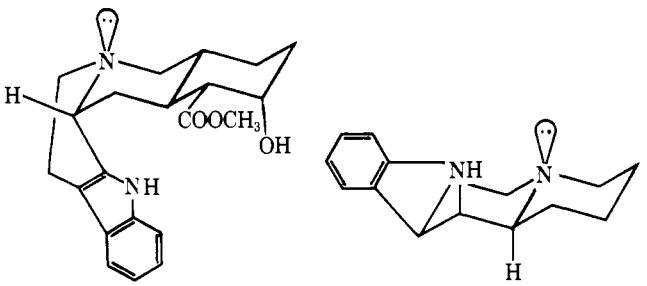
Table I. ^{15}N Chemical Shifts of Alkaloids and Model Compounds

compd	concn, M	solvent	δ, ppm[a] N-5	N-12
2	1.5	$CDCl_3$	57.9	118.2
		Me_2SO	56.2	124.6
3	0.7	$CDCl_3$	57.0	118.4
		Me_2SO	57.4	124.6
4	0.3	$CDCl_3$	43.8	119.6
5	1.0	Me_2SO	55.9	125.4
6	0.3	$CDCl_3$	31.9	117.9
7	0.4	$CDCl_3$	47.0	115.7
8	1.4	$CDCl_3$	41.3	
9	1.0	$CDCl_3$	38.7	
10		neat	48.6, 49.1	
12	1.5	$CDCl_3$	53.6	71.4
13	0.8	$CDCl_3$	52.8	178.0
3-(*e*)-methyl-*trans*-quinolizidine (**14**)	2.1	$CDCl_3$	63.2	
3-(*a*)-methyl-*trans*-quinolizidine (**15**)	0.3	$CDCl_3$	53.2	
indole	1.0	$CDCl_3$		124.8
	1.0	Me_2SO		131.2
indoline		neat		67.3
2-methylindoline		neat		84.6
piperidine		neat	38.1	
N-methylpiperidine		neat	39.4	
2-methylpiperidine		neat	55.3	
1,2,5,6-tetrahydropyridine		neat	28.0	

[a] Downfield from external anhydrous liquid ammonia. Experimental error ±0.2 ppm.



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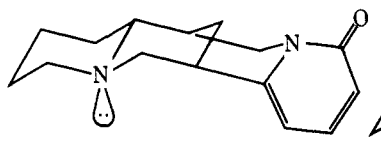

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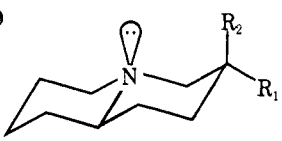


14, $R_1 = CH_3$; $R_2 = H$

15, $R_1 = H$; $R_2 = CH_3$

and several model compounds in order to evaluate the effect of removing the lone pair on the shifts of the parent compounds. A representative spectrum is given in Figure 1.

The phases of the resonances of **2–5** were the same as that of the ammonium resonance, which is known to undergo full nuclear Overhauser enhancement (NOE) and give rise to an inverted signal.[10a] Hence we assume that, consistent with the large molecular size and attendant longer molecular correlation times, the nitrogen nuclei in all the alkaloids display a NOE. In support of this, Levy recently reported ^{15}N T_1 values and NOEs of a series of nitrogen compounds, including **2**.[10b] Each nitrogen displayed the theoretical maximum NOE (−4), although T_1 values of the two nuclei differed. In accord with these results, intensities of N-5 were always less than those of N-12. It may be of interest that differences were smaller in the cis- than in the trans-fused compounds.

Small differences in chemical shift also arise as a function of solvent. Largely from studies on enriched compounds, nitrogen chemical shifts have been shown to be sensitive to solvent.[11] Resonance positions of saturated nitrogen atoms which are capable of hydrogen bonding either via the lone pair or via an attached proton undergo downfield shifts relative to their values in inert solvents.[12] For example, the ^{15}N nuclei of aniline in Me_2SO and of triethylamine in chloroform are deshielded by 7.7 and 4.4 ppm, respectively, from their corresponding values in cyclohexane.[12a] The same types of changes are displayed by several of the compounds discussed here. Thus, the nitrogen of indole, as well as N-12 of **2** and **3**, is deshielded, while the tertiary quinolizidine nitrogens N-5 are shielded, in changing from chloroform to Me_2SO. These results are consistent with enhanced and disrupted hydrogen bonding to N-12 and N-5, respectively, as a result of the solvent change. From the range of values spanned by **2–4** it is apparent that the substantially larger differences in the N-5 resonance positions among the various compounds cannot be attributed to solvent effects.

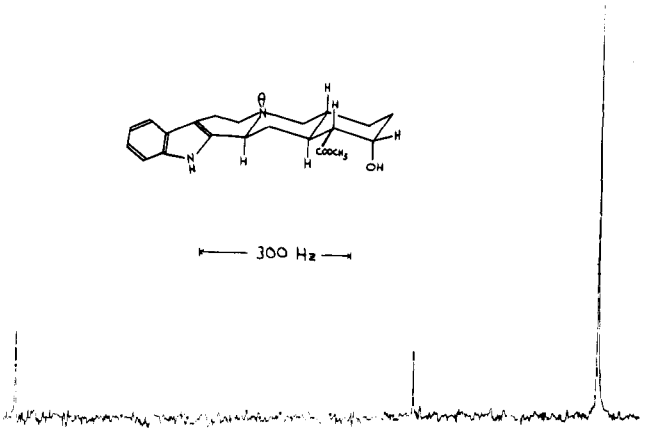


Figure 1. Natural-abundance ^{15}N spectrum of yohimbine, obtained after 25 100 transients, with a 30° pulse at a repetition rate of 2.5 s. The highest field signal is that of the ammonium ion reference.

Discussion

The chemical shift values exhibited by the N-12 nitrogens remain fairly unperturbed by remaining structural details, although they are expected to change on substitution in the aromatic system.[13] In general, N-12 is shielded compared with indole. This very likely reflects a balance between the deshielding influence of a β carbon (C-12b)[13] and the shielding influences of γ carbons (C-1 and C-7) and a γ nitrogen. However, it is important to note that these structural influences on the N-12 resonance position are *independent of* the cis–trans nature of the C/D ring fusion, whose largest consequence is to change the N-5 spatial orientation with respect to N-12.

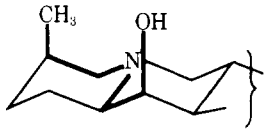
It is the saturated nitrogen N-5 which demands closer scrutiny. The chemical shifts of these nitrogens in **2, 3, 5,** and **13–15** lie in the range for similarly substituted piperidines,[6b-d] and hence can be considered characteristic of a normal *trans*-quinolizidine nitrogen. Flattening of the C ring because of the indole double bond appears to shield N-5 in **2** and **3** (5.3–6.2 ppm) compared to the resonance positions in **14.** This is apparent also in the ~10-ppm difference between piperidine and 1,2,5,6-tetrahydropyridine. A similar but substantially smaller difference is seen between the C-4 shift of cyclohexene (23.4 ppm) and that of cyclohexane (27.5 ppm). Part of the ^{15}N shielding may be attributable to the effect of N-12, owing to the known shielding effect of γ-oriented heteroatoms.[14] The shielding is larger (−9.6 ppm relative to **14**) when N-12 is gauche to N-5, as in **12.** In a similar manner, changing the γ-methyl orientation from equatorial in **14** to axial in **15** shields

Table II. ^{15}N Shifts of Trifluoroacetate Salts of Alkaloids and Model Compounds[a]

compd	concn, M solute	concn, M TFA	δ, ppm N-5	δ, ppm N-12	$\Delta\delta_{N\text{-}5}$[b]
2	1.5	3.0	59.1	118.3	1.2
4	1.0	2.0	50.8	116.3	7.0
5	1.0	2.0	59.1	119.1	3.2
6	1.0	2.0	43.9	117.4	12.0
9	1.5	3.0	48.9		10.2
12	1.0	2.0	60.6	54.0	7.0
indoline[c]	1.0	2.0		60.6	
2-methylindoline	1.0	2.0		71.9	

[a] In $CDCl_3$, reported with respect to anhydrous liquid ammonia. [b] Protonation shift, $\Delta\delta = \delta_{ion} - \delta_{amine}$. Positive value denotes that ion is deshielded. [c] In CH_2Cl_2.

the *trans*-quinolizidine nitrogen by −10 ppm. More strikingly, the highly shielded nitrogen of **8** may be associated with two axial substituents as shown in **16.**



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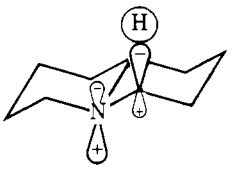
The behavior above follows trends displayed by ^{13}C resonances in similarly constituted compounds.[15] More recently, γ-methyl substitution on piperidine ^{15}N shifts was shown to have the same geometrical origins.[6d] Furthermore, the magnitude of the shielding induced by γ-methyl groups on acyclic aliphatic amine ^{15}N resonances was shown to decrease as the extent of substitution at the α and β carbons increases.[6c] This was attributed to the influence of such substitution on conformer populations, and hence on the contribution from each of these on the overall observed shift. Thus the actual magnitude of the γ effect very likely reflects a subtle balance of steric and electronic factors, and possibly the orientation of the lone-pair orbital.

From the data above, the range of values which the γ effect displays appears not to exceed ~10 ppm. Hence the 24-ppm difference which exists between the N-5 resonance positions of **5** and **6** must reflect structural factors in addition to that of the γ-gauche carbon of ring E in **6**. The obvious factor is the C/D ring fusion. The magnitude of this effect is evidenced in the difference between **3** and **4** (13.2 ppm) and between **6** and **7** (15.1 ppm); in each pair, other structural components are held constant. These differences are considerably larger than the corresponding value for *cis*- and *trans*-decalins (7.3 ppm),[16] part of which was attributed to a sterically induced bond deformation in the cis isomer. That spectroscopic properties can be influenced by a geometrical difference of this type has been known for almost 20 years, since Bohlmann[17] and Wenkert[18,19] noted absorption bands in the 2800–2700-cm^{-1} region of the infrared spectrum, which were characteristic of the presence of at least two axial hydrogens on carbons adjacent to nitrogen atoms of a quinolizidine system.[20] Quinolizidines with a cis ring fusion show weaker or no "Bohlmann bands" because this geometry allows only one axial C–H bond. To explain this apparent weakening of the C–H bond a hyperconjugative interaction between the nitrogen lone-pair orbital and antibonding orbitals of adjacent C–H bonds has been proposed.[20] Depicted qualitatively in **17,** this interaction has been shown by extended Hückel calculations to be favored when the two interacting orbitals are indeed antiperiplanar.[21] The consequent increased electron density at the α proton may rationalize the higher field position of H-4ax in quinolizidine itself relative to H-4eq. The difference between the two, 0.93 ppm,[22] is substantially larger than the 0.5-ppm difference normally exhibited by cyclohexane. The deshielded ^{13}C nuclei of C-12b in **2** and **3** (60.4 and 60.3 ppm, respectively) compared to that in **4** (54.3 ppm)[23] may be rationalized similarly. The associated increase in the C=N π-bond character in the trans isomer would thus be expected to result in a downfield shift for both carbon and nitrogen. This inference follows for nitrogen from the well-known fact that nitrogen is deshielded by delocalization of its lone-pair electrons into a π system.[24] For example, aniline is deshielded by ~14 ppm compared to cyclohexylamine.[14] This is presumed to arise from enhancement of the π bond order to the conjugated nitrogen, which increases the paramagnetic part of the chemical shift expression. To the extent that the hyperconjugative interaction described here is important, a similar downfield displacement would be expected in the trans C/D system. Hence shielding of the cis-fused nitrogen resonance may reflect inhibition of hyperconjugation because fewer antiperiplanar C–H orbitals are available.



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An alternative rationalization for the N-5 shift differences between the cis- and trans-fused compounds might appear to be the change in the orientation of the indole nitrogens N-12. However, N-12 of **12** is more nearly synclinal to N-5 than is N-12 of **4** or **6**, but the difference between the N-5 shifts of **12** and those of the trans-fused alkaloids is only 2–4 ppm. Furthermore, the differences in the N-5 shifts are reduced on protonation (see below), although the geometrical factors remain the same. Thus, while some contribution from the spatial disposition of N-12 to the shielding of N-5 cannot be excluded, this is unlikely to be a major factor.

Additional support for the argument above may be found by examining the effect of protonation on the nitrogen shifts (Table II). Protonation generally deshields an aliphatic amine nitrogen, although the magnitudes of the changes can be a function of solvent, concentration, and counterion.[25] Indeed, in recent studies by Duthaler et al.,[6b-d] protonation-induced changes on cyclic and acyclic aliphatic amine chemical shifts in methanol ranged from 0.4 ppm for 1-adamantylamine to 18.2 ppm for *N,N*-dimethyl-*tert*-amylamine. However, one of the factors expected to influence magnitudes of protonation shifts is extent of lone-pair interaction with adjacent orbitals, whether via conjugative or hyperconjugative mechanisms. In the former case, e.g., in anilines, nitrogen nuclei of ions are shielded relative to those of free bases, and the extent of shielding is roughly proportional to the extent of lone-pair delocalization.[26] Hence nitrogen nuclei whose lone-pair orbitals are hyperconjugatively delocalized would be expected to be deshielded less upon protonation than those whose lone pairs are localized. This is the situation which obtains in the alkaloid models: the trans compounds **2** and **5** are deshielded less ($\Delta\delta$ = 1.2 and 3.5 ppm, respectively) than are their cis analogues **4** and **6** ($\Delta\delta$ = 7.0 and 12.0 ppm, respectively). Similarly, protonation of 3-(e)- and 3-(a)-methylquinolizidine deshields the ^{15}N nuclei by only small amounts, even allowing for possible effects from differences in the solvents used.[6b-d] The generality of this behavior to other types of aliphatic nitrogens remains to be clarified.[6b,c]

In light of the above arguments, the protonation shift of N-5 in **12** seems unusually large. However, under the experimental conditions, N-12 is also protonated, and the effect of a positively charged center held synclinal to N-5 conceivably could deshield the nucleus further. Similarly, the nitrogen nucleus

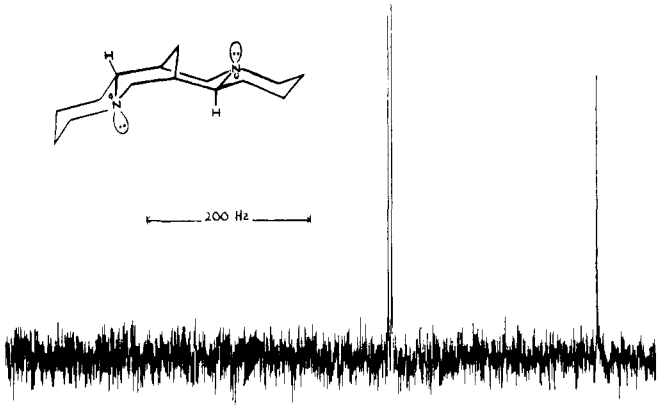

Figure 2. Natural-abundance ^{15}N spectrum of sparteine, obtained after 1900 transients, with a 30° pulse at a repetition rate of 10 s. The highest field signal is that of the ammonium ion reference. The separation between the sparteine resonances is 0.5 ppm.

of the protoberberine alkaloid **9**, which is thought to exist in the conformation indicated,[27a] is shielded to the same extent as a cis-fused alkaloid. A molecular model reveals that only the C(14)–H bond is antiperiplanar to the nitrogen lone pair; hence, hyperconjugative delocalization is not possible (see above). The shielding resulting from this adds to the shielding effect of the nearly gauche methyl group at C-13. The substantial (10.2 ppm) deshielding experienced on protonation is consistent with these suggestions.[28]

The observations described here may be applied to the ^{15}N spectrum of sparteine (Table I, Figure 2). The 0.5-ppm difference in resonance positions shows that the two nitrogens are in a similar environment typical of the *trans*-quinolizidine system and consistent with the generally accepted configuration **10**.[27b] Specific assignment of the resonances is difficult; however, the somewhat greater proximity of N-16 to C-8 (which, it should be noted, does not bear a precise γ-gauche relationship to N-16) suggests that the higher field value may be attributed to this nitrogen. More importantly, the chemical shift data exclude the suggestion[20] that the C/D rings are cis fused.

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References and Notes

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