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Studies on Carbon-13 Magnetic Resonance Spectroscopy. VIII.[1] Stereochemistry of Quinolizidines (1)

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The C-13 magnetic resonance chemical shifts of quinolizidine and *cis*- and *trans*-4-methylquinolizidine were examined. The correlations between the stereochemistry of these compounds and results on their C-13 chemical shifts and protonation and quaternization effects were examined.

trans-4-Methylquinolizidine was concluded to have a *trans*-fused ring and an axial methyl proup.

The C–H coupling constants of those compounds were also examined.

Introduction

The quinolizidine skeleton is well known, because it forms the nucleus of a number of alkaloids, and the stereochemistry of quinolizidine and methylquinolizidines have been studied by infrared, proton magnetic resonance spectroscopy[3] and measurement of their rate of quaternization.[4] The C-13 magnetic resonance spectra of these compounds have also been examined by comparison with substituted decalines.[5] Moreover the N^+-methyl chemical shifts of the C-13 magnetic resonance spectra of 10-substituted quinolizidine methiodides have been examined to confirm the configurations of these compounds.[6]

The purpose of our work is to examine the stereochemistry of the quinolizidine derivatives, which is important in determining the conformations of berberine type alkaloids. In this study, the C-13 chemical shifts of quinolizidine derivatives were examined. The correlations between the stereochemistry of these compounds and results on their C-13 chemical shifts and protonation and quaternization effects were examined.

Experimental

Materials——Quinolizidine was prepared by the method of Katritzky, *et al.*[3] *cis*- and *trans*-4-methylquinolizidine were prepared by cyclization of *cis*- and *trans*-2-4′-ethoxybutyl-6-methylpiperidine, respectively, which were separated by column chromatography on silica gel (MeOH 1: $CHCl_3$ 2) from the mixture of *cis*- and *trans*-derivatives.[3]

The methiodides were prepared by heating under reflex with an excess CH_3I in EtOH according to conventional methods.[3]

Measurements of C-13 NMR Spectra——C-13 FT nuclear magnetic resonance (NMR) spectra were measured with a NEVA NV-21 spectrometer at 22.6 MHz in 8 mm tubes at ordinary probe temperature. The samples of free bases were dissolved in $CDCl_3$ containing tetramethyl silane (TMS) as an internal reference (δ_C 0); concentrations were *ca.* 1.5—2 mole/liter and then added trifluoro acetic acid (TFA) to excess to observe protonation shifts. The samples of methiodides were dissolved in CD_3OD; concentrations were *ca.* 0.5—1 mole/liter.

1) Part VII: Y. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **21**, 1901 (1973).
2) Location: *a) Motoyama-Kitamachi, Higashinada, Kobe; b) Yamadakami 133–1, Suita, Osaka.*
3) T.M. Moynehan, K. Schofield, R.A. Jones, and A.R. Katritzky, *J. Chem. Soc.*, **1962**, 3637.
4) C.D. John, R.A.Y. Jones, A.R. Katritzky, C.R. Palmer, K. Schofield, and R.J. Wells, *J. Chem. Soc.*, **1965**, 6797.
5) R.T. LaLonde and T.N. Dovito, *Can. J. Chem.*, **52**, 3788 (1974).
6) Y. Arata, T. Aoki, M. Hanaoka, and M. Kamei, *Chem. Pharm. Bull.* (Tokyo), **23**, 333 (1975).

FT NMR measurement conditions were almost the same for all compounds; spectral width: 2500 Hz, pulse width: 25 μsec (flipping angles of about 45°), aquisition time: 0.8 sec, number of data point: 4096, and number of transients: 1K—4K.

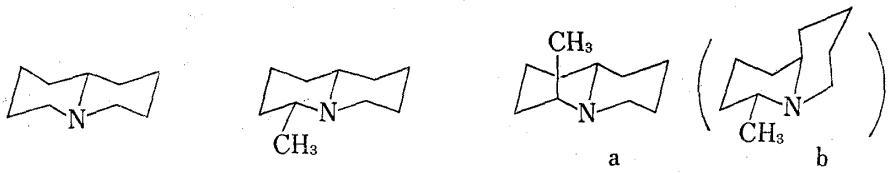
To observe C–H coupling constants, alternative decoupling method was used.

Results and Discussion

1) C-13 Chemical Shifts of Free Bases

The C-13 chemical shifts in deuterochloroform of quinolizidine (I), *cis*-4-methylquinolizidine (II) and *trans*-4-methylquinolizidine (III) are shown in Table I. The data on I and II are in accord with reported values.[5] The assignments for III were made by off-resonance decoupling and comparison with results on other compounds.

In Table I, δ_{cis} and δ_{trans} represent the differences between the chemical shifts of II and III and I, respectively, and $\delta_{trans-cis}$ represent the differences between III and II.



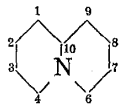
I II III

Table I. C-13 Chemical Shift[a] of Quinolizidine (I), *cis*-(II) and *trans*-4-Methylquinolizidine (III)

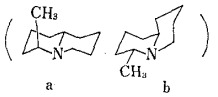
Carbon[b]	I	II	δ_{cis}[c]	III	δ_{trans}[d]	$\delta^{obs.}_{trans-cis}$[e]	$\delta^{calc.}_{trans-cis}$[f] "a"	$\delta^{calc.}_{trans-cis}$[f] "b"
10	63.14	63.23	0.09	54.29	−8.85	−8.94	−9.0	−4.5
4	56.81	59.12	2.31	53.58	−3.23	−5.54	−4.5	−9.0
6	56.81	51.95	−4.86	52.65	−4.16	0.70		
3	26.06	35.53	9.47	32.74	6.68	−2.79	−2.4	0
1	33.63	34.25	0.62	34.20	0.57	−0.05		
9	33.63	34.03	0.40	34.20	0.57	0.17		
7	26.06	26.46	0.40	26.24	0.18	−0.22		
2	24.78	24.83	0.04	18.89	−5.89	−5.93	−5.9	−5.9
8	24.78	24.69	−0.09	24.91	0.13	0.22		
C–CH_3		20.80		9.73		−11.07		

a) relative to TMS in ppm
The minus sign means a high field shift.

b) Carbons are numbered as follows:



c) δ_{cis}: difference between chemical shifts of II and I
d) δ_{trans}: difference between chemical shifts of III and I
e) $\delta^{obs.}_{trans-cis}$: difference between chemical shifts of III and II
f) $\delta^{calc.}_{trans-cis}$: calculated *trans-cis* for conformations "a" and "b"



Large values were observed for δ_{cis} with C-4, C-6 and C-3, for δ_{trans} with C-10, C-4, C-6, C-3 and C-2 and for $\delta_{trans-cis}$ with C-10, C-3, C-2 and the C-methyl group; these seem to be mainly due to substituent effects of methyl groups on the C-4 position. Thus, δ_{cis} values are ascribed to the substituent effects of equatorial methyl groups on C-4 for each carbon.

The two conformations are possible for III; *trans*/axial (form "a")[4] and *cis*/equatorial (form "b").[3] For "a" (*trans*/ax.), δ_{trans} should correspond to the effect of the axial methyl

group at the C-4 position, and $\delta_{trans-cis}$ to configurational variations of the C-4 methyl group from axial to equatorial. In contrast, for "b", δ_{trans} would correspond to the sum of the effects of the equatorial C-4 methyl group of the configurational variation of the C-10 bond from equatorial to axial for ring A, and $\delta_{trans-cis}$ to the effect of configurational variation of the C-10 bond from equatorial to axial for ring A. Table I also shows values of $\delta_{trans-cis}$ for the C-10, C-4, C-3 and C-2 positions in ring A estimated from the methyl substituent parameter,[7] for the "a" and "b" forms. As seen from Table I, the observed values were much closer to the calculated values for form "a" than to those for form "b". This suggests that III has the *trans*/ax. conformation (form "a").

The $\delta_{trans-cis}$ value for the C-methyl group showed an unusual shift of −11.07 ppm. If the methyl group of III is equatroial (form "b"), it should show a similar chemical shift to that of (II). Thus, the high field shift of the C-methyl group of (III) also suggests the *trans*/ax. conformation. Hawever the shift difference, −11.07 ppm, may be larger than the expected difference between axial and equatorial methyl substituents. LaLonde and Dovito[5] reported that the chemical shift differences between axial and equatorial methyl substituents of 1-, 2- and 3-methylquinolizidine are 4.98, 4.36 and 1.51 ppm, respectively, and that the chemical shifts of their axial methyl groups are 13.75, 17.81 and 18.26 ppm, respectively. Compared with these values, the chemical shift of the axial methyl group in (III) has a very high field shift. This very high value is probably because the axial C-methyl group is in the α-position to the nitrogen and oriented *trans* to the nitrogen lone-pair. This is consistent with the fact that the chemical shift of the methyl group of 10-methylquinolizidine, which is also situated in the α-position to the nitrogen and oriented *trans* to the lone-pair, also shows a high field shift, 10.7 ppm.[5]

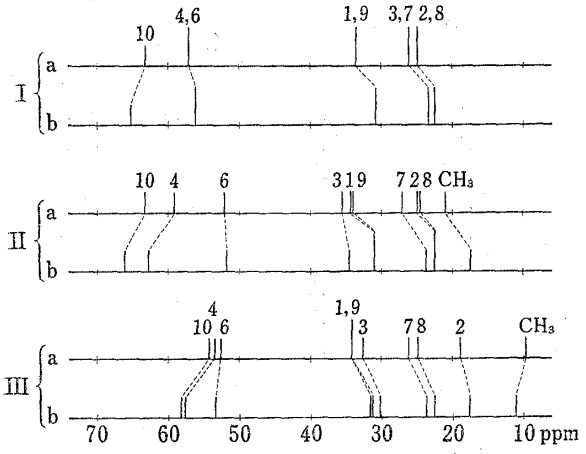


Fig. 1. Stick Diagram of C-13 NMR of Quinolizidine (I), *cis*-(II) and *trans*-4-Methylquinolizidine (III)

a) in $CDCl_3$, b) in $CDCl_3$+excess TFA

The above considerations show that III has a *trans*/ax. conformation (form "a"). This conclusion is consistent with the results of rate studies on quaternization.[4]

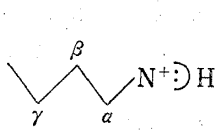
2) Protonation Shifts

Fig. 1 is a stick diagram of the C-13 magnetic resonance spectra of I, II and (III) in deuterochloroform and those with excess trifluoroacetic acid. The latters correspond to the spectra of protonated compounds. Thus, the displacement represented by dotted lines may also show the shifts induced by protonation of the nitrogen. In general these diagrams show a tendency for high field shifts.

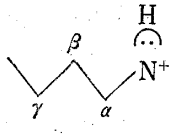
Morishima, *et al.*[8] measured the C-13 chemical shifts induced by protonation of aliphatic amines and N-heterocyclic compounds and reported the following conclusions: (1) On protonation of saturated amines, the C–H bond is polarized producing the C^{-}–H^{+} structure and the electron on the hydrogen atom is transmitted through the carbon skeleton onto the positively charged nitrogen atom. (2) The charge redistribution induced by protonation of the nitrogen may occur either through a "zigzag path" or through a "folded path" as follows:

7) *a*) G.C. Levy and G.L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, John Wiley & Sons, Inc., New York, 1972, p. 44; *b*) M. Tsuda, *Farumashia*, **9**, 756 (1973).

8) I. Morishima, K. Yoshikawa, K. Okada, T. Yonezawa, and K. Goto, *J. Am. Chem. Soc.*, **95**, 165 (1973).



zigzag path



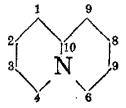
folded path

TABLE II. C-13 Protonation Shifts[a] of Quinolizidine (I), *cis*-(II) and *trans*-4-Methylquinolizidine (III)

Carbon[b]	Position[c]	I	II	III
10	α	2.44	2.79	3.94
4	α	−0.75	3.58	4.12
6	α	−0.75	−0.14	0.54
3	β	−2.56	−3.05	−2.70
1	β	−2.88	−3.10	−2.83
9	β	−2.88	−2.88	−2.70
7	β	−2.56	−2.79	−2.52
2	γ	−2.35	−2.30	−2.12
8	γ	−2.35	−2.17	−2.34
C–CH_3	β		−3.28	1.33

a) The minus sign means a high field shift (in ppm).

b) Carbons are numbered as follows:



c) Positions are counted from the nitrogen atom.

This difference in lone-pair orientation could be responsible for the different feature of the carbon shifts induced by nitrogen protonation. (3) The C–H bond is electronically polarized more readily than the C–C bond by the inductive effect and therefore the C–H carbon has more electron density than the C–C carbon by the protonation. This may be responsible for the observed trend of high field shifts of carbon induced by protonation in the following order: secondary>tertiary>quaternary.

These conclusions are supported by the results on quinolizidines. The values for the protonation shifts on each carbon shown in Table II may be summarized as follows; (1) all carbons show high field shifts except the carbon in the α-position and the C-methyl group of III, (2) the shifts of the β-positions are in the range of *ca.* −2.5——3.0 ppm and (3) in the α-position, the shifts of the C-10 position of I and C-10 and -4 positions of II and III—the tertiary carbon—showed rather low field shifts, while C-4 and -6 of I and C-6 of II and III—the secondary carbon—showed no shift. These results can be explained by the above conclusions,[8] as follows. Taking into account the C–H bond polarization, it seems reasonable that most carbons showed a high field shift. The shifts of the β-position in the range of *ca.* −2.5——3.0 ppm are consistent with the fact that the nitrogen lone-pair is oriented axially and therefore charge redistribution occurs through a "folded path", since the protonation shifts of the β-carbon are in the range of −2.5——3.0 ppm with an axial lone-pair and of −4.5——5 ppm with an equatorial lone-pair.[8] This also supports the conclusion that (III) has a *trans*-fused ring in which the nitrogen lone-pair is axial for both rings. The variation of the α-position is explainable in terms of the difference between the electronic polarizations of C–H and C–C bonds: with a tertiary carbon, decrease in C–H bond polarization is accompanied by decrease in electron density, and low field shifts, rather than high field shifts, are observed.

Although the protonation shift, −3.28 ppm, of the C-methyl—with three C–H bonds—for II is reasonable for the β-position from nitrogen, the low field shift of the same group for III, 1.33 ppm, is unreasonable. However, this abnormal protonation shift seems reasonable

when the direct electronic effect of the nitrogen lone-pair is taken into account as stated above. Namely in III, the abnormally high field shift of the C-methyl group oriented *trans* to the nitrogen lone-pair is decreased by protonation, and consequently this group shows rather a low field shift.

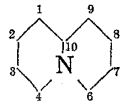
In Table III, the values of $\delta_{trans-cis}$ [(N^+)—for protonated bases— and (N)—for free bases—] are summarized. It can be seen that the $\delta_{trans-cis}$ values for protonated and free bases are similar. This suggests that the conformations of protonated bases are similar to those of free bases.

Table III. Chemical Shift Differences (ppm)[a] between *trans*- and *cis*-4-Methylquinolizidine

Carbon[b]	$\delta_{trans-cis}(N)$[c]	$\delta_{trans-cis}(N^+)$[d]
10	−8.94	−7.79
4	−5.54	−5.00
3	−2.79	−2.44
2	−5.93	−5.75

a) The minus sign means a high field shift.

b) Carbons are numbered as follows:



c) for the free base
d) for the protonated base

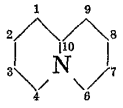
3) C-13 Chemical Shifts of Methiodides

Table IV summarizes the chemical shifts of quinolizidine-(I) and *cis*-4-methylquinolizidine (II) methiodides. In contrast with free bases, the chemical shifts of methiodides result from the sum of the effects of quaternization of the tertiary nitrogen and addition of the methyl group, the effect of the latter being comparable to C-methyl substitution. Thus, when the chemical shifts of protonated bases are subtracted from those of the methiodides, the difference, δ_{N-CH_3}, may be attributed to the substituent effect of N-methylation subtracting the effect of quaternization and be comparable to the substituent effect of C-methylation.

Table IV. C-13 Chemical Shifts of Quinolizidine-(I) and *cis*-4-Methylquinolizidine (II) Methiodide and δ_{N-CH_3} (ppm)

Carbon[a]	I[b]	δ_{N-CH_3}[c]	II[b]	δ_{N-CH_3}[c]	Position[d]
10	71.24	5.66	71.46	5.44	β
4	66.15	10.09	65.44	2.74	β
6	66.15	10.09	62.39	10.58	β
3	20.80	−2.70	29.12	−3.36	γ
1	27.21	−3.54	27.43	−3.72	γ
9	27.21	−3.54	27.43	−3.72	γ
7	20.80	−2.70	21.02	−2.65	γ
2	23.01	0.58	22.74	0.22	δ
8	23.01	0.58	22.74	0.22	δ
C-CH_3			15.18	−2.34	γ
N-CH_3	38.63		37.17		

a) Carbons are numbered as follows:



b) relative to TMS in ppm
c) δ_{N-CH_3} : difference between the chemical shifts of methiodide and protonated base
The minus sign means a high field shift.
d) position from the nitrogen

Table V. Methyl Substituent Parameters[a]

Position[b]	N-CH_3	C-CH_3[c]
$\alpha_{ax.}$	—	1.1
$\beta_{ax.}$	10.3 (CH_2) 5.5 (CH)	5.2
$\gamma_{ax.}$	−3.2	−5.4
$\delta_{ax.}$	0.4	0.1

a) The minus sign means a high field shift.
b) position of the carbon atom from the nitrogen and configuration of the substituent
c) Ref. 7a)

These δ_{N-CH_3} values, determined as described above, are also listed in Table IV. The values for all the carbons except C-4 in the two compounds are similar. The difference in the values for C-4 seems to be because C-4 of I is a secondary carbon whereas that of II is tertiary. These differences correspond well with the observed difference between the values for C-10—a tertiary carbon—and C-6—a secondary carbon.

From these results, the substituent parameters of the axial N-methyl group were estimated to be as shown in Table V. Those for the C-methyl group[7] are also shown.

These parameters show an analogous, through smaller, trend of chemical shifts to those of the C-methyl substituent parameters. They may be useful in analysis of the stereochemistry of the analogous series, although the shift difference between CH_2- and CH-carbons of the β-position is still uncertain.

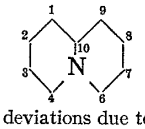
4) C-H Coupling Constants

Table VI summarizes the C–H coupling constants (J_{C-H}) of I, II and III and also the differences of coupling constants induced by protonation (δ).

Table VI. C-H Coupling Constants (Hz) of Quinolizidine (I), *cis*-(II) and *trans*-4-Methylquinolizidine (III)

Carbon[a]	I[b]	δ[c]	II[b]	δ[c]	III[b]	δ[c]
10	133	9*	130*	10	132	11
4	132	8	130*	12	130	10
6	132	8	133	10	133	11
3	130	−1	127	1	131	2
1	127	2	130	−1	126*	2
9	127	2	128	1	126*	2
7	130	−1	130	−2	130*	0
2	130*	2	131	−1	130*	0
8	130*	2	131	−1	129	1
C-CH_3			125	3	125	3

a) Carbons are numbered as follows:



b) Values with an asterisk have large deviations due to long-range coupling and signal-overlap.
c) δ: deviations induced by protonation

Measurement of the coupling constant by the FT NMR technique is somewhat inaccurate: in this experiments, there was an instrumental error of up to 1.2 Hz, ascribed to the data points. Furthermore, it is difficult to obtain the precise J_{C-H} values, because of the line broadens due to long-range coupling and the overlapping of signals. Thus the observed J_{C-H} values may be inaccurate, especially those shown with asterisks. However, the results

do indicate rough trends, and suggest that the coupling constants of α-carbons are rather large. Futhermore, in view of the differences induced by protonation, significant differences being observed in the α-position from nitrogen, these trends of J_{C-H} may be regarded as indicating increase in electronegativity of nitrogen.

No significant deviations in the values for these three bases were observed. This suggests that they have similar conformations with a *trans*-fused ring, and the results are consistent with the idea of a preferential *cis* or *trans* conformation of quinolizidines determined by measurement of the C–H coupling constant of C-10.[9] The small deviation of J_{C-H} of C-4 suggests that substitution of the methyl group and its configuration do not affect the J_{C-H} values of the neighbouring carbon.

9) G. Van Binst and D. Tourwe, *Heterocycles*, **1**, 257 (1973).