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Stereochemistry of Quinolizidines. III.[1] Carbon-13 Magnetic Resonance Spectra of Benzo[*a*]quinolizidines

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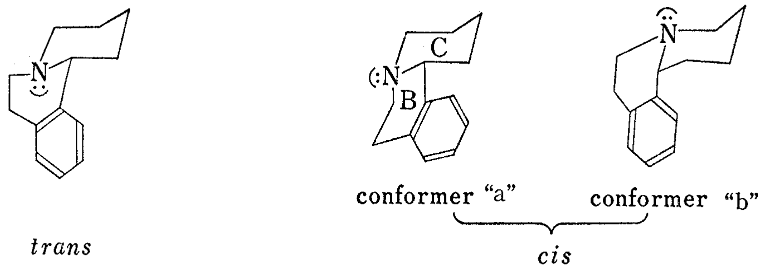
Stereochemistry of benzo[*a*]quinolizidine derivatives (I—VIb) were examined from C-13 magnetic resonance chemical shifts, and C-6 and C-7 shifts of these compounds were found to be reliable as the indications of favoured conformations-*trans*, *cis* "a" or *cis* "b". This treatment is also available for the conformational analyses of tetrahydroprotoberberine type alkaloids.

Keywords——carbon-13 chemical shift; stereochemistry; tetrahydroprotoberberine alkaloid; conformational analysis; benzo[*a*]quinolizidines

Introduction

In the previous papers of this series,[1,3] the relationship between the stereochemistry of quinolizidines and their C-13 chemical shifts was investigated and the usefulness of the C-13 magnetic resonance for the studies of the conformational analyses of quinolizidine analogues was approved. We have extended here our studies to benzo[*a*]quinolizidines.

Benzo[*a*]quinolizidines are interesting subjects as the basic skeleton of various alkaloids, and their conformations have been discussed from infrared and H-1 magnetic resonance spectra or on dehydrogenation rates.[4] Of these compounds, as illustrated in Chart 1, *trans*- and *cis*-fused types are possible, where the latter possesses a *cis*-fused ring with chair and half-chair conformation. Consequently, at room temperature an equilibrium is expected between the conformers "a" and "b" and *trans* form: "a" is formed from *trans* form *via* a configurational change at nitrogen atom, and from "b" by the inversion of ring B and C.[4c] Though, in a strict sense, *trans* form is a diastereomer of "a" and "b", for simplicity's sake the three forms will be referred to henceforth as conformers, and the favoured conformation is the one with least interference between non-bonded atoms. In the two possible *cis* forms, the angular hydrogen is oriented differently with respect to the ring; in conformer "a", 11b hydrogen is



trans

conformer "a" conformer "b"

cis

Chart 1

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[1] Part II: M. Sugiura, N. Takao, and Y. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **25**, 960 (1977).

[2] Location: *a*) *Motoyama-Kitamachi, Higashinada, Kobe*; *b*) *Yamadakami 133–1, Suita, Osaka.*

[3] M. Sugiura and Y. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **24**, 2988 (1976).

[4] *a*) H. Bruderer, M. Baumann, M. Uskoković, and A. Brossi, *Helv. Chim. Acta.*, **47**, 1852 (1964); *b*) M. Uskoković, H. Bruderer, C. Von Planta, T. Williams, and A. Brossi, *J. Am. Chem. Soc.*, **86**, 3364 (1964); *c*) J. Gootjet, A.M. de Roos, and W. Th. Nauta, *Rec. Trav. Chim. Rays-Bas*, **85**, 491 (1966).

pseudo-equatorial to ring B and axial to ring C, whereas in conformer "b", pseudo-axial to ring B and equatorial to ring C.

Uskoković and co-workers[4b)] utilized the chemical shift of 11b hydrogen and its splitting pattern to distinguish three conformers of benzo[*a*]quinolizidines. In *trans* form, 11b hydrogen occupy a *trans* coplaner position with respect to the nitrogen lone-pair and, conseguently, may be expected to be more shielded. In contrast, a low field signal below 3.8 ppm is reported to be characteristic for both *cis* conformation.

On the base of these guides, Uskoković, *et al.*, reported[4a,b)] that *cis*-2-(*p*-chlorophenyl)-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (VIb) prefers the *cis* form "b" and 2-keto-4,4-dimethyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (VII) is the *cis* "a". On the other hand, both isomers of 2-hydroxy-2-(*p*-chlorophenyl)-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (IVa and IVb) have been reported to be the *trans* conformation.[4a)]

As noted above, H-1 magnetic resonance is usefull to distinguish the conformation of benzo[*a*]quinolizidines. It is, however, not always available because of the ambiguous overlapping of proton chemical shift, *etc.* The application of C-13 magnetic resonance to the compounds of these species has been limited mainly to tetrahydroprotoberberine type alkaloids,[5)] and then C-13 magnetic resonance measurement of benzo[*a*]quinolizidine skeleton has not been reported.

Of the C-13 magnetic resonance, chemical shifts are found over a more wide range than H-1 resonance, and it is readily observable to identify the individual resonance shift for each carbon of these compounds. Additional advantages of C-13 chemical shifts are related to the sensitivity for stereochemistry,[3)] and therefore, it appeared of interest to investigate further the correlations between the conformation of these compounds and their C-13 chemical shifts. If characteristic carbon chemical shifts are found, they may be accepted as the indication of those three conformations, *trans*, *cis* "a" and *cis* "b", usefull for the conformational analyses of their related compounds.

In the present paper, for this purpose, we have synthesized the compounds shown in Chart 2, namely 1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (I), 1- or 2-substituted benzo[*a*]quinolizidines (IIa, IIb, III, IVa, IVb, VIa and VIb) and 1,2- or 2,3-dehydro-derivatives

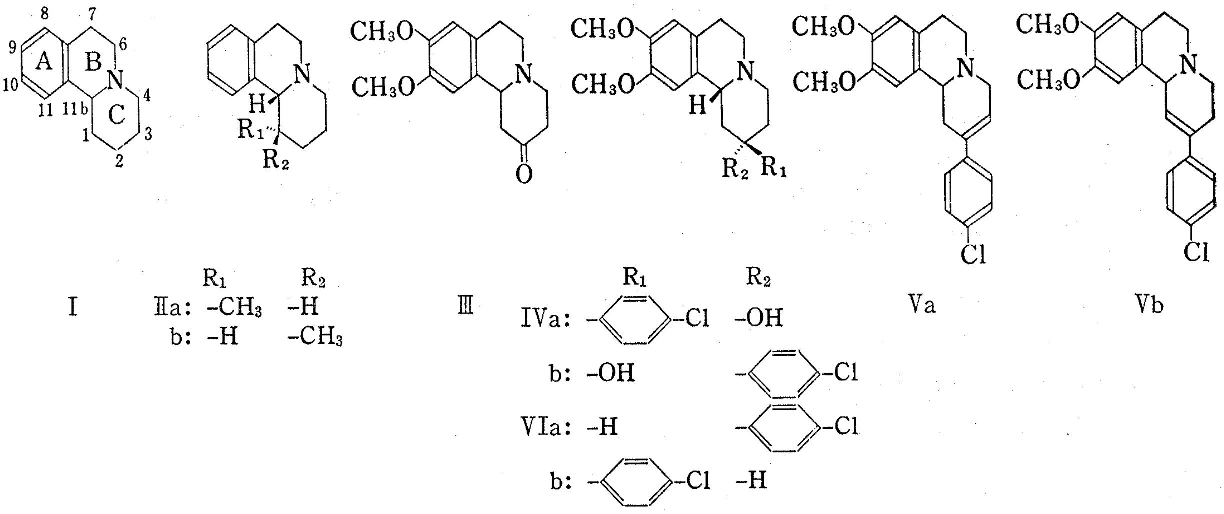

Chart 2

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5) *a*) T. Kametani, A. Ujiie, M. Ihara, K. Fukumoto, and H. Koizumi, *Heterocycles*, 3, 371 (1975); *b*) T. Kametani, K. Fukumoto, M. Ihara, A. Ujiie, and H. Koizumi, *J. Org. Chem.*, **40**, 3280 (1975); *c*) K. Yoshikawa, I. Morishima, J. Kunitomo, M. Ju-ichi, and Y. Yoshida, *Chemistry Letters*, **1975**, 961; *d*) N. Takao, K. Iwasa, M. Kamigauchi, and M. Sugiura, *Chem. Pharm. Bull.* (Tokyo), **25**, 1426 (1977).

(Va and Vb), and examined their C-13 magnetic resonance shifts, and found that C-13 chemical shifts of C-6 and C-7 of these compounds are available to distinguish their conformations.

Experimental

Measurements of C-13 NMR spectra were carried out as described in the preceding papers.[1,3]

Materials——1,2,3,4,6,7-Hexahydro-11bH-benzo[*a*]quinolizine (I) was synthesized by the modified methods of Dyke, *et al.*[6] and Akaboshi, *et al.*[7] MS *m/e*: 187 (M^+).

trans-(IIa) and *cis*-1-Methyl-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (IIb) were prepared by reduction of 1-methyl-1,2,3,4,6,7-hexahydrobenzo[*a*]quinolizinium iodide[8] (VIII) with Zn and HCl. The mixtures of IIa and IIb were separated and purified by column chromatography (silica gel, C_6H_6–ether 4:1—1:4) and preparative thin-layer chromatography (silica gel, C_6H_6–ether). IIa: MS *m/e*: 201 (M^+) IIb: MS *m/e*: 201 (M^+).

2-Keto-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (III), 2-hydroxy-2-(*p*-chlorophenyl)-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (IVa and IVb), 2-(*p*-chlorophenyl)-9,10-dimethoxy-1,4,6,7-tetrahydro-11bH-benzo[*a*]quinolizine (Va), 2-(*p*-chlorophenyl)-9,10-dimethoxy-3,4,6,7-tetrahydro-11bH-benzo[*a*]quinolizine (Vb) and *trans*- and *cis*-2-(*p*-chlorophenyl)-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (VIa and VIb) were prepared by the authentic procedures.[4a]

Results and Discussion

In Table I, all pertinent chemical shifts of compounds I—VIb are summarized. Their chemical shift assignments were made by off-resonance decoupling and from analogy with those of quinolizidines,[3] as well as by comparing chemical shifts of these analogues from each other. On the aromatic carbons, however, ambiguities of the assignment still remain and especially those with asterisks would be reversed.

1) Non-substituted Benzo[*a*]quinolizidine

For free base of non-substituted benzo[*a*]quinolizidine (I), the favoured conformation has been reported to be *trans* form,[4c] even if the nitrogen inversion prevails.

The stick diagram of the chemical shifts of quinolizidine and I is shown in Fig. 1, where both the similarity and distinction between these two compounds are well reflected.

In aliphatic region, large chemical shift differences between these two compounds are appeared at C-1, C-6 and C-7 positions. In I, C-1 proton is close to C-11 proton, and, consequently, the high field shift of C-1 carbon may be interpreted on the so-called steric compression effect. Since C-6 and C-7 are of the ring B, these chemical shifts must reflect the effect of fused aryl ring. In tetralin, compared with cyclohexane, 2.5 ppm deshielding and 3.7 ppm shielding are observed at α- and β-positions, respectively, from aryl ring.[9] Therefore, the chemical shift differences of I from quinolizidine, 3.6 ppm on C-7 and −4.18 ppm on C-6, are reasonable. On the other hand, for the carbons of ring C (C-2, -3, -4 and -11b), little chemical shift differences are observed with quinolizidine.

As above mentioned, for benzo[*a*]quinolizidines with a fused benzene ring, we are able to discuss in a similar manner as quinolizidines and also suggest that I prefers the *trans* conformation as in the case of quinolizidine.

2) 1-Methyl-benzo[*a*]quinolizidines

IIa and IIb obtained by reduction of VIII are isomeric, from each other, with a different configuration of methyl group. These H-1 NMR (Table II) show that IIa has axial methyl and in IIb methyl group takes equatorial configuration. Moreover, H-1 chemical shift of

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[6] D.W. Brown, S.F. Dyke, M. Sainsbury, and W.G.D. Lugton, *Tetrahedron*, **26**, 4985 (1970).

[7] S. Akaboshi, T. Kutsuma, and K. Achiwa, *Chem. Pharm. Bull.* (Tokyo), **8**, 14 (1960).

[8] T. Fujii, M. Nohara, M. Mitsukuchi, M. Ohba, K. Shikata, S. Yoshifuji, and S. Ikegami, *Chem. Pharm. Bull.* (Tokyo), **23**, 144 (1975).

[9] J.B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York, 1972, p. 99.

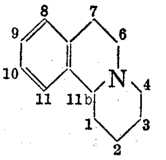
Table I. C-13 Chemical Shifts[a)] of Benzo[*a*]quinolizidine Derivatives (in $CDCl_3$)

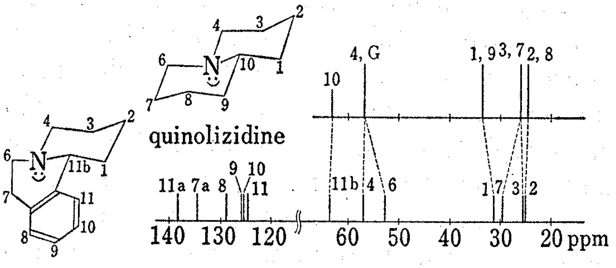
Compound	Carbon[b)]									
	11a	7a	8	9	10	11	1	2	3	4
I	138.39	134.44	128.71	125.75	125.54	124.61	31.37	25.16	25.52	56.92
IIa	138.98	137.02	129.89	126.94	126.62	125.99	32.16	32.16	21.14	58.46
IIb	138.33	135.69	130.17*	127.31	125.47	129.59*	30.31	34.20	21.07	54.42
III	128.75	126.26	111.62	147.90*	147.62*	108.07	47.52	208.17	41.08	54.74
IVa	129.58	126.73	111.77	147.50	147.50	108.21	44.23	72.24	37.64	51.94
IVb	129.36	126.17	111.74	147.74*	147.50*	108.53	43.99	72.04	36.89	52.53
Va	129.76	126.83	111.57	147.66*	147.56*	108.69	35.55	134.41	122.49	55.68
Vb	128.77	126.76	111.94	147.80*	147.58*	109.03	125.66	134.60	28.36	49.27
VIa	129.55	127.08	111.66	147.66*	147.36*	108.17	38.98	42.95	32.92	56.56
VIb	128.56	127.14	112.21	147.87	147.87	108.85	35.50	35.81	31.94	47.44

Compound	Carbon[b)]									
	6	7	11b	C–CH_3	OCH_3		1′	2′	3′	4′
I	52.67	29.60	63.48							
IIa	53.39	30.16	67.98	12.99						
IIb	45.84	28.85	66.22	20.57						
III	50.78	29.39	61.50		55.94	55.83				
IVa	51.94	28.93	57.94		55.94	55.77	132.57	128.30	126.24	147.26
IVb	51.21	28.64	58.95		55.80	55.80	133.54	128.60	127.89	143.34
Va	51.05	29.09	58.71		56.12	55.78	132.75	128.43	126.33	139.41
Vb	50.88	25.66	59.39		56.23	55.87	132.95	128.42	126.51	139.45
VIa	52.39	29.10	62.86		55.99	55.84	129.69	128.96	128.41	144.60
VIb	51.37	24.62	57.06		56.27	55.93	130.84	128.62	128.54	144.00

a) The numbers with asterisks are ambiguous. ppm. relative to TMS

b) Carbons are numbered as follows:





I

Fig. 1. Stick Diagram of C-13 Chemical Shifts of Quinolizidine and 1,2,3,4,6,7-Hexahydro-11bH-benzo[*a*]quinolizine (I)

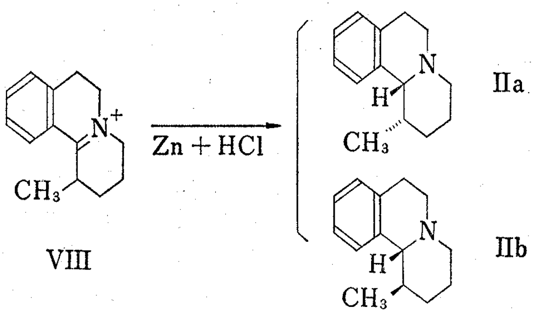


Chart 3

11b hydrogen of IIb is 0.16 ppm shifted to lower field than that of IIa. This observation suggests that IIa prefers *trans* conformation, but, in contrast, IIb takes *cis* "a" conformation to avoid a steric interaction between equatorial 1-methyl group and 11-hydrogen. Though H-1 chemical shift of 11b hydrogen in IIb —3.45 ppm— is shifted higher than 3.8 ppm which is reported to be characteristic for both *cis* conformation,[4b)] the observation of C-13 NMR, as below, suggests the predominance of *cis* "a" conformation.

Table II. H-1 Magnetic Resonances of *trans*- (IIa) and *cis*-1-Methyl-1,2,3,4,6,7,-hexahydro-11bH-benzo-[*a*]quinolizine (IIb) (in $CDCl_3$)

Compound	11b		1[a]	C–CH_3	
	δ (ppm)	*J* (Hz)	δ (ppm)	δ (ppm)	*J* (Hz)
IIa	3.29	*ca.* 2	*ca.* 2.20	0.78	7
IIb	3.45	*ca.* 6.5	*ca.* 1.90	0.95	7

[a] These chemical shifts are determined by spin decoupling

It is reported by Van Binst and Tourwa[10] that in quinolizidines C-H coupling constant (J_{C-H}) of angular carbon adjacent to the nitrogen of *cis* conformation is 6—12 Hz larger than that of *trans* conformation. $J_{C_{11b}-H}$ of IIa and IIb as well as I are listed in Table III. In general, C–H coupling constants are unreliable because of the signal broadning owing to long-range coupling and signal overlap as well as the data point of the computor, but, nevertheless, a significant difference of $J_{C_{11b}-H}$ between IIa and IIb (*ca.* 10 Hz) is apparent. This observation supports the *cis* conformation of IIb in contrast to *trans* conformation of IIa.

Table III. C–H Coupling Constants (Hz) of 11b-Carbon of *trans*- (IIa) and *cis*-1-Methyl-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine(IIb) and 1,2,3,4,6,7-Hexahydro-11bH-benzo[*a*]quinolizine (I)

Compounds	$J_{C_{11b}-H}$ (Hz)
I	125±2
IIa	122±3
IIb	132±2

As noted above, it is established that IIa has the B/C *trans* conformation with an axial methyl and IIb prefers the *cis* conformation with an equatorial methyl. On the basis of this consequence, it is obvious that C-13 chemical shifts (see Table I) reflect the stereochemical differences between these two compounds. The largest chemical shift difference of methyl group (7.58 ppm) indicates the configurational difference—axial and equatorial—of methyl group.[3] The axial methyl group of IIa is in *gauche* situation to C-3 and then, owing to its steric compression effect, may shift higher field than the equatorial methyl group of IIb. The chemical shift difference of C-6 (−7.55 ppm) is explicit as follows; C-6 of IIb is in *gauche* interaction with C-3 and C-1 in *cis* "a" conformation. On the other hand, a small chemical shift difference of the high field shift for C-3 is observed between the two compounds, due to γ-effect of axial methyl group on C-1 of IIa and to *gauche* interaction with C-6 of IIb, respectively. On C-1, high field shift due to the steric interaction with C-11 and small low field shift due to α-substitution effect of axial methyl for IIa and, on the other hand, high field shift due to *gauche* interaction with C-6 and low field shift due to α-effect of equatorial methyl for IIb, are evident, respectively. Consequently, the compensation of their shifts from each other results in a small high field shift on C-1 of IIb. The low field shift on C-11 of IIb may be accepted by lack of the steric compression effect which exists in *trans* conformation of IIa. The higher field shift of C-4 of IIb than IIa reflects their configurational differences; N–C_6 bond is equatorial to ring B of IIa but axial of IIb and then, assuming

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[10] G. Van Binst and D. Tourwa, *Heterocycles*, 1, 257 (1973).

that the N-methylen bond is equivalent to methyl group, the chemical shift of C-4 of IIa is displaced to lower field owing to the difference of β-effects (β_e-effect>β_a-effect).[11]

As discussed above, the chemical shift differences of each carbon between IIa and IIb are quite explicit about their stereochemical difference. It appears of interest that the chemical shift differences between *trans* and *cis* form (Δ_{C-T}) are evaluated quantatively to confirm their conformations.

Previously,[1] we discussed the chemical shift difference between *trans* and *cis* isomers of quaternary salts of quinolizidine by employing the methyl substituent parameters of piperidine.[11] In the similar manner, the chemical shift differences, Δ_{C-T}, of each carbon are approved as the measures of the relative contribution of conformer "a" or "b", respectively. For example, the conformational change from *trans* to *cis* "a" is regarded as the configurational change of N–CH_2 (-6) bond from equatorial to axial at ring C, whereas, at ring B, the change of C-CH_2 (-1) bond on C-11b from equatorial to axial. Assuming that the substituent effect of C-CH_2 is virtually equivalent to that of C-CH_3, these chemical shift differences may be estimated for each carbon by means of methyl substituent parameter.[11] In Table IV, the estimated values of conformer "a" and "b" are summarized, where "γ $(N)_{eq.\to ax.}$" represents the change of equatorial N-CH_2 bond to axial at γ-position.

TABLE IV. Estimated and Observed Value of Δ_{C-T}, Chemical Shift Difference[a] (ppm)

Carbon	$\Delta^{estm.}_{C-T}$ (a)[b]		$\Delta^{obs.}_{C-T}$ (a)[c]	$\Delta^{estm.}_{C-T}$ (b)[d]		$\Delta^{obs.}_{C-T}$ (b)[e]
1	$\gamma(N)_{eq.\to ax.}$:	−5.9	−4.45	$\beta_{eq.\to ax.}$:	−2.4	−3.00
2	$\delta(N)_{eq.\to ax.}$:	0	−0.36	$\gamma_{eq.\to ax.}$:	−5.9	−6.87
3	$\gamma(N)_{eq.\to ax.}$:	−5.9	−5.97	$\delta_{eq.\to ax.}$:	0	−1.09
4	$\beta(N)_{eq.\to ax.}$:	−2.4	−4.04	$\gamma_{eq.\to ax.}(N)$:	−9.0	−9.12
6	$\gamma_{eq.\to ax.}(N)$:	−9.0	−7.55	$\beta(N)_{eq.\to ax.}$:	−2.4	−1.09
7	$\delta_{eq.\to ax.}$:	0	−1.31	$\gamma(N)_{eq.\to ax.}$:	−5.9	−4.60
11b	$\left.\begin{matrix}\alpha_{eq.\to ax.}\\ \beta(N)_{eq.\to ax.}\end{matrix}\right\}$:	−5.0	−4.16	$\left.\begin{matrix}\beta(N)_{eq.\to ax.}\\ \alpha_{eq.\to ax.}\end{matrix}\right\}$:	−5.0	−5.77

a) The minus sign means a high field shift.
b) $\Delta^{estm.}_{C-T}$(a): estimated chemical shift difference between *trans* and *cis* "a" conformation.
c) $\Delta^{obs.}_{C-T}$(a): observed chemical shift difference between *trans* and *cis* "a" conformation calculated from the chemical shifts of IIa and IIb.
d) $\Delta^{estm.}_{C-T}$(b): estimated chemical shift difference between *trans* and *cis* "b" conformation.
e) $\Delta^{obs.}_{C-T}$(b): observed chemical shift difference between *trans* and *cis* "b" conformation calculated from the chemical shift of VIa and VIb.

Since C-1 of IIa and IIb are substituted with axial and equatorial methyl group, the comparison of their chemical shifts, due to the substituent effects of 1-methyl groups, are inadequate for the discussion of the difference between *trans* and *cis* conformation. Therefore, the observed chemical shift differences between *trans* and *cis* "a" are determined from the chemical shift differences between IIa and IIb subtracting an axial and equatorial methyl substituent effects, respectively, symbolized by $\Delta^{obs.}_{C-T}$ (a) as shown in Table IV. In this Table, the observed differences, $\Delta^{obs.}_{C-T}$ (a), are comparable to the estimated values of conformer "a", $\Delta^{estm.}_{C-T}$ (a). Taking into account the errors due to the approximation of methylen to methyl and the distortion of ring B from chair-form, as well as the subtraction of the effects of methyl group on observed value, these relative agreements between the estimated and observed values are appreciable. Above results support the correct assignments of chemical shifts, and reasonable conformations. Thus, it is concluded that IIb prefers *cis* "a" conformation.

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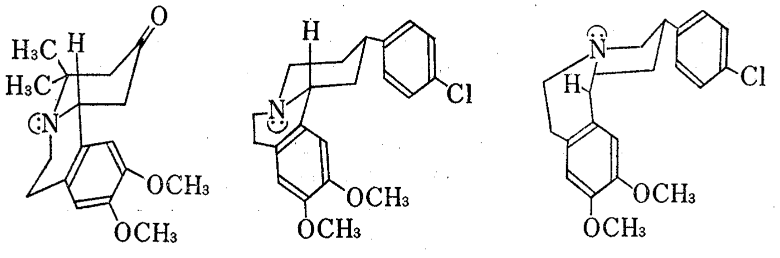
[11] M. Tsuda, *Farumashia*, **9**, 756 (1973).

3) 2-Substituted Benzo[*a*]quinolizidines

As shown Table I, little deviations are observed on the aromatic ring A carbon chemical shifts and the methoxy carbons of III—VI, irrespective of the substituents. In these compounds it is obvious that ring A is not affected by the variation of substituents as well as the conformational change by the variable substituents.

Whereas 2-keto-4,4-dimethyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (VII) was reported[4b] to prefer *cis* "a" conformation, III is suggested to be *trans* conformation by 11b-H chemical shift (3.56 ppm, q.), and C-13 chemical shifts also support above suggestion. Since, as mentioned in the preceding section (see Table IV), C-6 carbon chemical shift reflected the conformational change from *trans* to *cis* "a" conformer, irrespective of substituent on ring C, and the corresponding shift of III (50.78 ppm) suggests rather *trans* conformation. In *cis* "a" conformer, the C-6 chemical shift should be shifted to the high field (*ca.* 46 ppm). In other words, the predominant conformation of III must be *trans*.



VII VIa VIb

Chart 4

It is reported that both IVa and IVb are of *trans* conformations, and that *p*-Cl-C_6H_4-moiety occupies the axial orientation in IVa and equatorial in IVb.[4a] As shown in Table I, in aliphatic region, little difference of chemical shift between IVa and IVb is acknowledged. This observation suggests that these two compounds are of the similar conformation and the substituent effects of -OH and -C_6H_4-Cl group on chemical shifts are comparable to each other.

VIb is reported[4b,c] to have a *cis* "b" conformation when substituent—Cl-C_6H_4—prefers an equatorial orientation rather than axial. All C-13 chemical shifts of IVb appear generally at higher field than its epimer, VIa (see Table I).

Since both VIa and VIb have equatorial Cl-C_6H_4- moieties, the substituent effects are the same in these compounds. Then, the chemical shift differences between VIa and VIb are ascribed only to the conformational change between *trans* and *cis* "b". In other words, these differences are deduced to the observed chemical shift differences between *trans* and *cis* "b", $\Delta_{\text{C-T}}^{\text{obs.}}$ (b). In Table IV, $\Delta_{\text{C-T}}^{\text{obs.}}$ (b) are given together with those of estimated values, $\Delta_{\text{C-T}}^{\text{estm.}}$ (b), and these two kinds of shifts are of the similar magnitudes, which support the reasonable assignment of the chemical shift and conformation, especially *cis* "b" conformation of VIb.

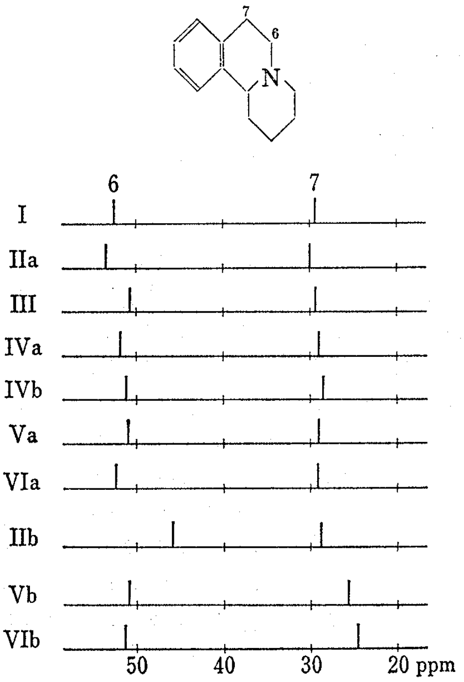


Fig. 2. Stick Diagram of C-6 and C-7 Carbon Chemical Shifts of Benzo[*a*]quinolizidines

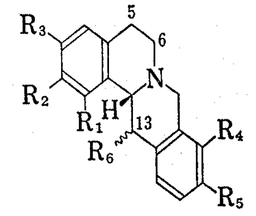
Although Va and Vb have double bonds in the ring C, these compounds are also treated in a same way to other benzo[*a*]quinolizidines to a certain extent. Va, with a double bond between C-2 and C-3, may be taken as a model of tetrahydroprotoberberine type alkaloids. As was expected, the chemical shifts of the ring B at least resemble to other compounds of *trans* conformation very closely.

Vb, with a 11b-H at 4.30 ppm, is suggested *cis* conformation.[4b)] In addition, C-13 chemical shifts of C-6, C-7 and C-4 show comparable values of those of VIb. The high field shift of C-7 carbon, especially, may characterize the *cis* "b" conformation, as mentioned in the following section. From above observation, it is presumed that Vb prefers *cis* "b" conformation, but, in the present step, the reason of the above presumption is not clear.

4) Relationship between C-13 Chemical Shift and Conformation

As mentioned so far, C-13 chemical shifts are correlated to the conformation. As shown in Table IV, chemical shifts afford the characteristic patterns with the conformation of benzo[*a*]quinolizidines, *trans*, *cis* "a" or *cis* "b". Since the compounds dealt with in this work mainly have substituents in ring C, the ring B carbons—C-6 and C-7—might be little affected by the substituents.

The stick diagram of the chemical shifts of C-6 and C-7 of these compounds is presented in Fig. 2, where the conformational regularities are observed. Namely, in the compounds of predominantly *trans* conformation (I, IIa, III, IVa, IVb, Va and VIa), C-6 chemical shifts



	R_1	R_2	R_3	R_4	R_5	R_6
tetrahydropalmatine (IX)	H	OCH_3	OCH_3	OCH_3	OCH_3	H
tetrahydroberberine (X)	H	OCH_2O		OCH_3	OCH_3	H
tetrahydroprotoberberine (XI)	H	H	H	H	H	H
corydaline (XII)	H	OCH_3	OCH_3	OCH_3	OCH_3	$\cdots CH_3$
capaurine (XIII)	OH	OCH_3	OCH_3	OCH_3	OCH_3	H
capaurimine (XIV)	OH	OCH_3	OCH_3	OCH_3	OH	H
methylcapaurine (XV)	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	H
meso-corydaline (XVI)	H	OCH_3	OCH_3	OCH_3	OCH_3	$\blacktriangleleft CH_3$
meso-thalictricavine (XVII)	H	OCH_2O		OCH_3	OCH_3	$\blacktriangleleft CH_3$
meso-13-methyltetrahydroprotoberberine (XVIII)	H	H	H	H	H	$\blacktriangleleft CH_3$

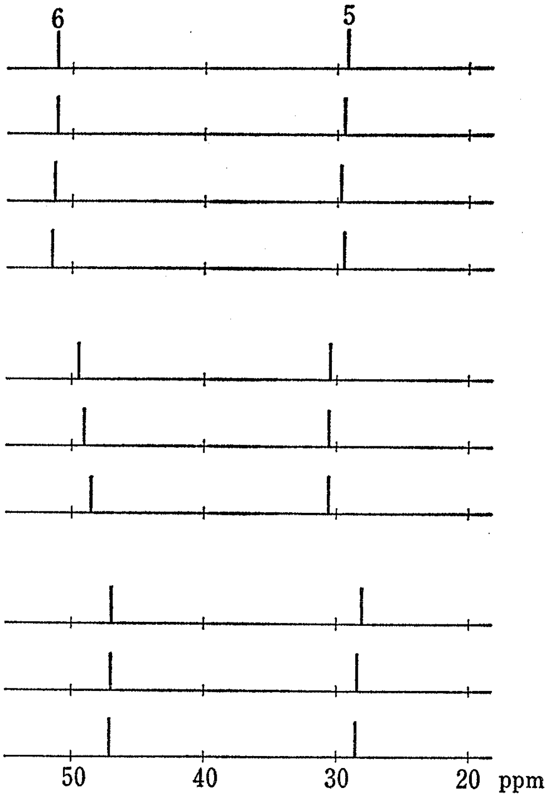


Fig. 3. Stick Diagram of C-6 and C-5 Carbon Chemical Shifts of Tetrahydroprotoberberine Type Alkaloids

are given in the vicinity of 52 ppm and C-7 in *ca.* 29 ppm. On the other hand in *cis* "a" (IIb), the high field shift of C-6 is observed at *ca.* 46 ppm, while little difference on C-7 from *trans* conformer. In *cis* "b" conformer (VIb and Vb), in contrast, a little differences at C-6 (*ca.* 51 ppm) is obvious from *trans* conformer, but C-7 shifts are shifted higher field up to *ca.* 25 ppm. These observations suggest that *cis* "a" conformer is characteristic from another two conformers by C-6 chemical shift, and *cis* "b" is distinguishable by C-7 chemical shift. That is to say, the shifts of C-6 and C-7 may be considered as the measures of the conformation of benzo[*a*]quinolizidines.

In order to check the validity of our approach, above treatments were applied to tetrahydroprotoberberine type alkaloids. Fig. 3 depicts a stick diagram of the chemical shift[5d] of C-6 and C-5, corresponding to C-6 and C-7 of benzo[*a*]quinolizidines, of several tetrahydroprotoberberine alkaloids. In this diagram, regular variations of C-6 rather than C-5 are presented. For four alkaloids (IX, X, XI and XII), which are reported to prefer *trans* conformation, C-6 shifts appear in the vicinity of 51 ppm. In contrast, in three alkaloids (XVI, XVII and XVIII), with *cis* C-13 methyl group for 13a-H, reported to be *cis* "a" conformation, the C-6 shifts are shifted up to *ca.* 47 ppm. These observations support the above treatment as the measures of the conformation of benzo[*a*]quinolizidines. Futhermore, three alkaloids (XII, XIV and XV), with the substituents on C-1, have C-6 shifts in the intermediate region among above two series. This suggests that these alkaloids present the intermediate conformation determined by the equilibrium between *trans* and *cis* "a", which is consistent with the conclusion obtained already from the investigations of infrared spectral data[12] and H-1 and C-13 magnetic resonance spectra.[5d]

It is concluded that, in benzo[*a*]quinolizidines, C-13 chemical shifts of C-6 and C-7 are taken as the measures of these three conformations—*trans*, *cis* "a" or *cis* "b"—and, in addition, these conclusions are available for tetrahydroprotoberberine type alkaloids.

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12) N. Takao and K. Iwasa, *Chem. Bull. Pharm.* (Tokyo), **24**, 3185 (1976).