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Studies on the Alkaloids of Papaveraceous Plants. XXIX.[1] Conformational Analysis of Tetrahydroprotoberberines by Carbon-13 Magnetic Resonance Spectroscopy[2]

Narao Takao, Kinuko Iwasa, Miyoko Kamigauchi, and Makiko Sugiura

Kobe Women's College of Pharmacy[3]

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Analyses of CMR spectra at room temperature of the free bases, N-methosalts, and N-protonated salts of tetrahydroprotoberberines indicated that in the chloroform solution, the amount of the B/C-*cis* form in comparison with the B/C-*trans* form increases in the order of the alkaloids (such as tetrahydropalmatine (**1**)) in group I, those (such as capaurine (**9**)) in group II, and those (such as mesocorydaline (**16**)) in group III.

The equilibrium of the B/C-*trans* and B/C-*cis* forms was confirmed by analyses of CMR spectra at low temperatures of tetrahydroprotoberberines in deuteriomethylene-chloride solution and the approximate proportion of the two conformations was determined in acetylcapaurine (**13**), diacetylcapaurimine (**14**), and capaurimine di-*p*-bromobenzoate (**15**).

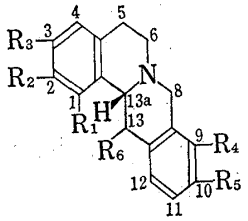
Keywords——CMR spectral analysis of tetrahydroprotoberberines; conformational equilibrium; N-methosalts; N-protonated salts; free bases; tetrahydropalmatine; corydaline; capaurine; mesocorydaline

In previous paper,[4] the conformational equilibrium with respect to the B/C-*trans* and B/C-*cis* ring junctions in tetrahydroprotoberberines in chloroform solution was discussed by analyses of their infrared (IR) spectra. At that time tetrahydroprotoberberines were classified into three groups according to the intensities of their Bohlmann bands (Table I). It was found that the alkaloids of group I, showing the strongest Bohlmann bands, tetrahydropalmatine (**1**), tetrahydroberberine (**2**),tetrahydrocoptisine (**3**), tetrahydroprotoberberine (**4**), corydaline (**5**), thalictricavine (**6**), tetrahydrocorysamine (**7**), and 13-methyltetrahydroprotoberberine (**8**) overwhelmingly take the B/C-*trans* form, while the alkaloids of group III, showing considerably weak Bohlmann bands, mesocorydaline (**16**), mesothalictricavine (**17**), mesotetrahydrocorysamine (**18**), and meso-13-methyltetrahydroprotoberberine (**19**) prefer the B/C-*cis* form, and the alkaloids of group II, showing the Bohlmann bands with intensities between those of group I and III, capaurine (**9**), capaurimine (**10**), capaurimine mono-*p*-bromobenzoate (**11**), O-methylcapaurine (**12**), O-acetylcapaurine (**13**), O,O-diacetylcapaurimine (**14**), and capaurimine di-*p*-bromobenzoate (**15**) do not preferentially take either the B/C-*trans* or B/C-*cis* form.

Recently, conformational analysis of the free bases[5] and the N-methosalts[6] of tetrahydoroprotoberberines by carbon magnetic resonance (CMR) spectroscopy has been reported. independently by other groups. Though these workers studied the CMR spectra of free bases or N-methosalts individually, we examined the CMR spectra of the free bases, N-protonated

1) Part XXVIII: T. Tani and K. Tagahara, *Yakugaku Zasshi*, **97**, 93 (1977).
2) A part of this work was presented at the 95th Annual Meeting of the Pharmaceutical Society of Japan, Nishinomiya, April 1975.
3) Location: *Motoyama-Kitamachi, Higashinada-ku, Kobe, 658, Japan.*
4) N. Takao and K. Iwasa, *Chem. Pharm. Bull.* (Tokyo), **24**, 3185 (1976).
5) *a*) T. Kametani, A. Ujiie, M. Ihara, K. Fukumoto, and H. Koizumi, *Heteroycles*, **3**, 371 (1975); *b*) T. Kametani, K. Fukumoto, M. Ihara, A. Ujiie, and H. Koizumi, *J. Org. Chem.*, **40**, 3280 (1975).
6) K. Yoshikawa, I. Morishima, J. Kunitomo, M. Ju-ichi, and Y. Yoshida, *Chemistry Letters*, **1975**, 961.

TABLE I. Tetrahydroprotoberberine-type Alkaloids[a]



	R_1	R_2	R_3	R_4	R_5	R_6
I group						
tetrahydropalmatine (**1**)	H	OMe	OMe	OMe	OMe	H
tetrahydroberberine (**2**)	H	OCH_2O		OMe	OMe	H
tetrahydrocoptisine (**3**)	H	OCH_2O		OCH_2O		H
tetrahydroprotoberberine (**4**)	H	H	H	H	H	H
corydaline (**5**)	H	OMe	OMe	OMe	OMe	‖‖‖Me
thalictricavine (**6**)	H	OCH_2O		OMe	OMe	‖‖‖Me
tetrahydrocorysamine (**7**)	H	OCH_2O		OCH_2O		‖‖‖Me
13-methyltetrahydroprotoberberine (**8**)	H	H	H	H	H	‖‖‖Me
II group						
capaurine (**9**)	OH	OMe	OMe	OMe	OMe	H
capaurimine (**10**)	OH	OMe	OMe	OMe	OH	H
capaurimine mono-*p*-bromobenzoate (**11**)	OH	OMe	OMe	OMe	OBz[b]	H
O-methylcapaurine (**12**)	OMe	OMe	OMe	OMe	OMe	H
O-acetylcapaurine (**13**)	OAc	OMe	OMe	OMe	OMe	H
O,O-diacetylcapaurimine (**14**)	OAc	OMe	OMe	OMe	OAc	H
capaurimine di-*p*-bromobenzoate (**15**)	OBz[b]	OMe	OMe	OMe	OBz[b]	H
III group						
mesocorydaline (**16**)	H	OMe	OMe	OMe	OMe	◀Me
mesothalictricavine (**17**)	H	OCH_2O		OMe	OMe	◀Me
mesotetrahydrocorysamine (**18**)	H	OCH_2O		OCH_2O		◀Me
meso-13-methyltetrahydroprotoberberine (**19**)	H	H	H	H	H	◀Me

a) ‖‖‖, ◀, These indications express relative configuration at C-13 and C-13a.
b) $Bz=COC_6H_4Br$

TABLE II. Carbon-13 Data on Tetrahydroprotoberberine N-Methosalts in CD_3OD (in ppm from TMS)[a,b]

	$N-CH_3$	C-5	C-13	C-6	C-8	C-13a
I group						
(**3**) N-methochloride β-form	39.4	25.0(+4.8)	30.0(+6.6)	61.8(−10.4)	62.9(−9.8)	68.1(−8.2)
(**4**) N-methiodide β-form	39.6	24.7(+5.0)	30.3(+6.8)	62.6(−11.3)	66.7(−8.0)	67.7(−7.6)
(**8**) N-methiodide β-form	44.5	24.6(+5.2)	33.1(+5.8)	63.5(−12.4)	67.3(−8.3)	71.0(−7.3)
(**6**) N-methochloride β-form	44.2	24.9(+5.0)	32.9(+5.7)	63.8(−12.4)	64.0(−9.5)	70.8(−7.3)
(**3**) N-methochloride α-form	51.4	24.5(+5.3)	34.6(+2.0)	53.7(−2.3)	59.7(−6.6)	67.7(−7.8)
(**4**) N-methiodide α-form	51.9	24.4(+5.3)	35.4(+1.4)	53.3(−2.0)	64.9(−6.2)	67.3(−7.2)
(**8**) N-methiodide α-form	53.3	24.6(+5.2)	38.4(+0.5)	56.0(−4.9)	65.8(−6.8)	70.8(−7.1)
II group						
(**9**) N-methiodide α-form	50.9	24.4(+6.1)	33.3(−0.2)	52.3(−2.9)	62.2(−8.6)	62.7(−6.4)
(**12**) N-methiodide α-form	51.0	24.4(+6.1)	34.3(−1.1)	52.2(−3.7)	62.4(−8.9)	62.9(−7.1)
(**14**) N-methiodide α-form	51.0	24.3(+6.0)	34.4(−0.9)	52.4(−4.1)	62.1(−8.9)	62.4(−7.2)
III group						
(**17**) N-methochloride α-form	52.0	23.9(+4.4)	38.7(−4.2)	52.1(−5.1)	61.6(−11.0)	72.9(−8.5)
(**18**) N-methochloride α-form	52.1	24.0	38.8	52.1	60.4	73.5
(**19**) N-methochloride α-form	51.9	24.2(+4.3)	39.6(−4.4)	52.3(−5.1)	65.9(−9.3)	73.7(−8.5)

a) Assignments were made from off-resonance experiments and by comparing with the spectra of various alkaloids.
b) Values in parentheses present the shift on N-methylation in ppm. Positive sign indicates upfield shift.

salts, and N-methosalts of tetrahydroprotoberberines (Table I) as a whole and its results supported the conformational equilibrium between the B/C-*trans* and B/C-*cis* forms. Further, approximate proportions of the B/C-*trans* and B/C-*cis* forms were estimated on the basis of the CMR spectra at low temperatures.

The CMR spectra (Table II) of the N-methosalts of tetrahydroprotoberberines were measured in order to determine the B/C ring junctions of their salts and to find the carbon indicative of the B/C ring junction among the aliphatic carbons on the B and C rings. It has been reported[7] that N-methylation of the alkaloids of group I gives a mixture of α- and β-methosalts. In Fig. 1, **3** was selected as the representative of group I and the CMR spectra of the pure β-N-methochloride and a mixture of the α- and β-N-methochlorides prepared by N-methylation of **3** are shown. As can be seen from the comparison of these spectra, each set of signals with strong and weak intensities can be assigned to the β- and α-N-methochlorides, respectively. As the representatives of the II and III groups, **12** and **18** were selected. N-Methylation of these afforded only an N-methosalt. Fujii, *et al.* reported[8a] that on the basis of the chemical shifts (in PMR) of quaternary N-methyl signals the α- and β-methiodides of benzo(*a*)quinolizidine derivatives are the *cis* (b and/or c type conformer, Chart 1) and *trans* (a type conformer, Chart 1) isomers, respectively. It has been shown[8b] that the N-methyl signal (in CMR) of β-N-methosalt appears at a higher field than that of α-N-methosalt in quinolizidine derivatives and, as a result, α- and β-N-methosalts are assigned to the B/C-*cis* (b type conformer, Chart 1) and B/C-*trans* (a type conformer, Chart 1) forms, respectively. In a similar manner, α- and β-N-methosalts of the group I alkaloids were assigned to B/C-*cis* and B/C-*trans* forms respectively and N-methosalt of the group II and III alkaloids to B/C-*cis* form (Chart 1). In the cases of *cis* form, two possible b and c

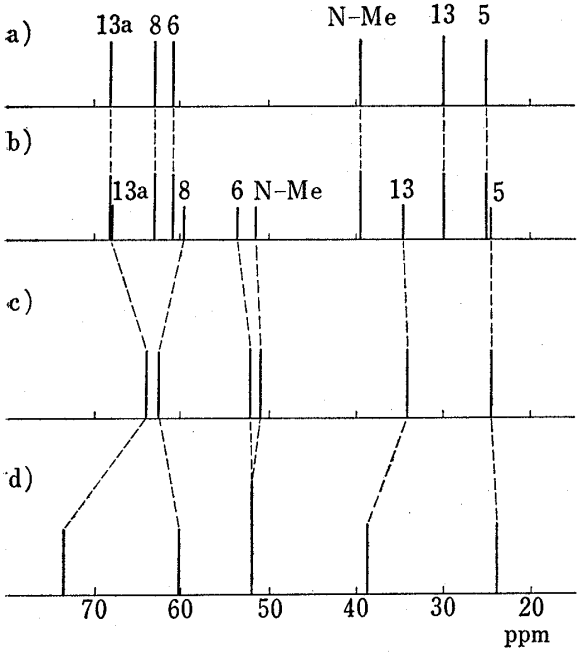


Fig. 1. CMR Spectra of N-Methosalts of Tetrahydroprotoberberines, **3**, **12**, and **18** in CD_3OD

a) β-N-methochloride of **3**
b) α- and β-N-methochlorides of **3**
c) α-N-methiodide of **12**
d) α-N-methochloride of **18**

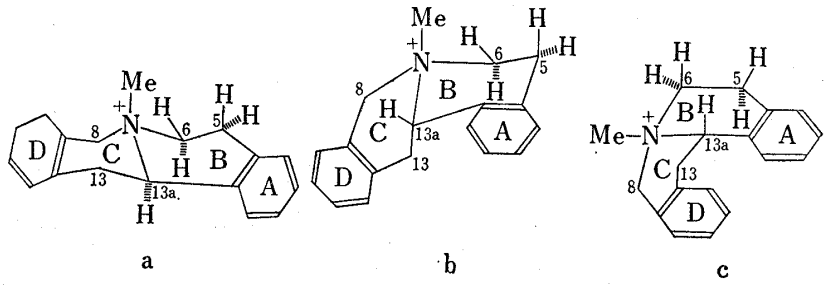


Chart 1

7) H.A.D. Jowett and F.L. Pyman, *J. Chem. Soc.*, **103**, 290 (1913).
8) *a*) T. Fujii, M. Nohara, M. Mitsukuchi, M. Ohba, K. Shikata, S. Yoshifuji, and S. Ikegami, *Chem. Pharm. Bull.* (Tokyo), **23**, 144 (1975); *b*) Y. Arata, J. Aoki, M. Hanaoka, and M. Kamei, *Chem. Pharm. Bull.* (Tokyo), **23**, 333 (1975).

conformers (Chart 1) could be discriminated from the coupling constant[9] between H–13 and H–13a of the alkaloids with the C-methyl group at C–13 (**6** and **17**). In **6** with *cis* hydrogens, the coupling constant is 5.5 Hz, while in the **17**, it is 10 Hz which is expected for the system with *trans* hydrogens. Accordingly, the α-methosalts adopt predominantly the conformer b. In

Table III. Carbon-13 Data on Tetrahydroprotoberberines in $CDCl_3+CF_3COOH$ (in ppm from TMS)[a,b]

		C–5	C–13	C–6	C–8	C–13a
I group						
(**1**)	*trans*-salt	26.0(+3.2)	33.2(+3.2)	53.1(−1.6)	53.8(+0.3)	62.2(−2.9)
(**4**)	*trans*-salt	26.2(+3.3)	33.7(+3.1)	52.8(−1.5)	57.5(+1.2)	62.8(−2.7)
(**6**)	*trans*-salt	26.4(+3.5)	36.3(+2.3)	53.0(−1.6)	54.9(−0.4)	65.8(−2.3)
(**1**)	*cis*-salt	25.1(+4.1)	31.6(+4.8)	46.0(+5.5)	50.5(+3.6)	57.4(+1.9)
(**4**)	*cis*-salt	25.4(+4.3)	32.4(+4.4)	45.8(+5.5)	54.6(+4.1)	57.9(+2.2)
II group						
(**9**)	*cis*-salt	25.7(+4.8)	29.2(+3.9)	45.2(+4.2)	51.2(+2.4)	53.2(+3.1)
(**12**)	*cis*-salt	25.8(+4.7)	30.2(+3.0)	45.1(+3.4)	51.3(+2.2)	53.7(+2.1)
(**13**)	*cis*-salt	25.3(+5.0)	30.0(+3.0)	44.5(+4.0)	52.5(+0.9)	56.2(+0.5)
III group						
(**17**)	*cis*-salt	24.7(+3.6)	34.9(−0.4)	45.4(+1.6)	49.6(+1.0)	63.4(+1.0)
(**19**)	*cis*-salt	24.9(+3.6)	35.7(−0.5)	45.5(+1.7)	54.4(+2.2)	64.3(+0.9)

a) Assignments were made from off-resonance experiments and by compairing with the spectra of various alkaloids.
b) Values in parentheses present the protonation shift in ppm. Positive sign indicates upfield shift.

the conformer a and b, both N-methyl groups are axially oriented with respect to the B ring and, hence the spatial orientation of the N-methyl group with respect to C–6 may be the same. Consequently, the effect caused by N-methylation on the chemical shift of C–6 might essentially be the same between α- and β-N-methosalts. The difference in chemical shift of C–6 between α- and β-N-methosalts of **3**, **4**, and **8** was +8.1, +9.3, and +7.5 ppm, respectively. The upfield shift at C–6 in the α-N-methosalt is interpreted as being due to steric compression in the B/C-*cis* form adopted for α-N-methosalt.

In order to prove the assumption that the chemical shift difference at C–6 results from the difference in the B/C ring junction, CMR spectra were measured in deuteriochloroform ($CDCl_3$) containing a sufficient amount of trifluoroacetic acid (CF_3COOH) to form a salt (Table III). As shown in Fig. 2, the CMR spectrum of the group I alkaloids (*e.g.* **1**) in $CDCl_3$ with CF_3COOH comprised a set of relatively strong signals and that of relatively weak signals, while those of the group II alkaloids (*e.g.* **12**) and of group III alkaloids (*e.g.* **19**) showed signals due to one kind of a salt. This observation indicates that alkaloids

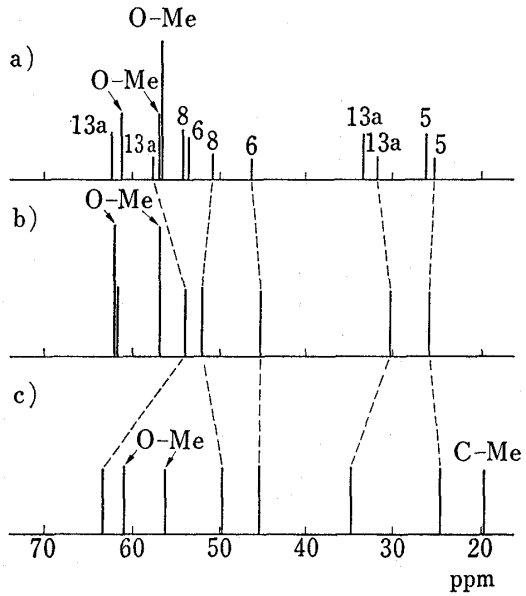


Fig. 2. CMR Spectra of Tetrahydroprotoberberines, **1**, **12**, and **18** in $CDCl_3+CF_3COOH$

a) *cis*- and *trans*-salts of **1**
b) *cis*-salt of **12**
c) *cis*-salt of **19**

9) *a*) T.R. Govindachari, K. Nagarajan, R. Charubala, B.R. Pai, and P.S. Subramanian, *Indian J. Chem.*, **8**, 769 (1970); *b*) C.K. Yu, D.B. MacLean, R.G.A. Rodrigo, and R.H.F. Manske, *Can. J. Chem.*, **48**, 3673 (1970).

of group I form two kinds of salt, while those of group II and III produce only one in analogy with the case of N-methosalts. In the spectra of the group I alkaloids, the set of the strong signals may be assigned to the *trans*-salt and that of weak signals to the *cis*-salt by comparison with the spectra of the corresponding N-methosalts. Each kind of the salt formed from the alkaloids of groups II and III is regarded as a *cis*-salt. The chemical shift differences at C–6

Table IV. Carbon-13 Data on Tetrahydroprobeberines in $CDCl_3$ (in ppm from TMS)[a,b]

	C-CH_3 or $COCH_3$	5	13	6	8	13a	OCH_3 or OCH_2O				C=0	
I group												
1		29.2	36.4	51.5	54.1	59.3	55.8,	56.2,	60.1,	59.3		
2		29.6	36.4	51.4	53.9	59.6	55.8,		60.1			
3		29.8	36.6	51.4	53.1	59.9	100.9,		101.1			
4		29.7	36.8	51.3	58.7	60.1						
5	18.4	29.4	38.5	51.6	54.5	63.2	56.2×2,		56.3,	60.1		
6	18.3	29.9	38.6	51.4	54.5	63.5	56.1,	60.2,	100.8			
7	18.4	29.4	38.5	51.6	54.5	63.2	100.8		101.1			
8	18.3	29.8	38.9	51.1	59.0	63.7						
II group												
9		30.5	33.1	49.4	53.6	56.3	55.8,	56.1,	60.2,	61.0		
10		30.5	32.9	49.1	53.3	56.2	55.9,		60.8,	61.1		
11		30.4	33.3	49.2	53.4	55.8	55.8		60.7	60.9		
12		30.5	33.2	48.5	53.5	55.8	56.1×2,	60.3,	60.8×2			
13	20.8	30.3	33.3	48.5	53.4	55.7	56.1,	60.3×2,	60.8		168.8	
14	20.8	30.3	33.5	48.3	53.2	55.2	56.1,		60.6×2		168.7,	168.8
15		30.3	33.7	48.4	53.1	55.1	55.1,	56.2,	60.8		164.0,	164.3
III group												
16	22.4	28.0	34.5	46.9	50.9	63.9	55.8×2,	56.1,	60.2			
17	22.4	28.3	34.5	47.0	50.6	64.4	55.9,	60.4,	100.0			
19	22.4	28.5	35.2	47.2	56.6	65.2						

	1	4	11	12	4a	8a	12a	14a	2	3	9	10
I group												
1	109.0	111.7	111.2	123.9	127.0	128.0	128.7	130.0	147.6	147.6	150.4	145.3
2	105.6	108.4	111.1	123.9	127.9*	127.9*	128.7	131.0	146.0+	146.1+	150.3	145.2
3	105.7	108.6	106.9	121.2	128.0	117.1	128.7	131.0	145.2*	146.3	146.4*	143.5
4	125.6*	129.0	126.0*	129.0	134.7	134.7	134.7	138.2	126.2*	126.2*	129.0	126.2*
5	109.3	111.6	111.4	124.0	128.7	128.7	135.3	128.7	147.6*	148.0*	150.2	145.2
6	105.8	108.3	111.3	124.1	128.7*	129.5	135.2	129.9*	145.8+	146.5+	150.2	145.2
7	105.7	108.3	106.9	121.4	129.5*	116.9	136.1	129.8*	145.8+	146.5+	144.9+	143.2
8	125.9*	128.3+	125.9*	128.7+	136.3	134.3	141.7	136.8	125.9*	126.2*	129.1+	126.2*
II group												
9	146.7	104.0	111.3	124.2	131.4	128.7*	129.3*	118.3	134.1	150.6+	150.3+	145.6
10	146.5	104.0	114.2	125.3	131.2	127.9*	128.5	118.2	133.9	148.8	146.5	143.6
11	146.6	104.0	121.0	124.6	131.2	129.3	133.9	117.7	135.3	150.5	148.1	140.9
12	152.2	107.7	111.3	124.1	130.8	128.7*	129.0*	124.7	140.6	151.1	150.5	145.7
13	141.8	110.8	111.4	124.0	131.1	128.4	128.7*	123.6	139.6	151.8	150.5	145.8
14	141.2	110.7	121.2	124.4	130.8	129.2	134.3	123.7	139.6	151.8	148.1	141.8
15	142.0	111.0	121.2	124.4	131.0	129.3	134.3	123.9	139.0	152.0	148.5	141.3
III group												
16	111.2	112.2	111.2	123.1	126.5	127.8	133.1	130.7	146.7	148.1	150.2	145.5
17	107.3	108.9	111.2	123.1	127.4*	127.6*	132.9	131.5	145.3+	146.3+	150.3	145.5+
19	126.7*	129.3+	125.3*	127.1+	133.5	134.1	139.8	138.5	125.8*	126.7*	127.9+	126.7*

a) Assignments were made from off-resonance experiments and by comparing with the spectra of various alkaloids.
b) * or + indicate uncertainties in assignment within a given group

between the *cis*- and *trans*-salts of **1** and **4** were +7.1 and +7.0 ppm, respectively (Table III). These values are close to the chemical shift difference at C–6 between the α- and β-N-methosalts. These chemical shift differences in the N-protonated salts, similar to that of N-quaternary salts, are considered to arise from the steric difference in the B/C ring junction.

On the basis of these observations, stereochemistry of the free bases of tetrahydroprotoberberines was examined by using the chemical shift of C–6 as an indicator of the B/C ring juncture. In the CMR spectra in $CDCl_3$, the C–6 resonance appeared at a higher field in the order of the group I, II, and III (Table IV). This indicates that the amount of the B/C-*cis* form in the equilibrium mixture increases in the order of the groups I, II, and III alkaloids, presumably because of increasing repulsive interaction between the substituents at C–1 and C–13. This is consistent with the result obtained from IR spectral analyses.[4]

The differences in chemical shift of the aliphatic carbons on the B and C rings between the group I and III alkaloids were examined. The signals for C–6, C–8, and C–13 in the alkaloids of group III appeared at a higher field relative to the corresponding carbons in the alkaloids of group I, whereas that for C–13a was found in a lower field. Assuming that both B and C rings possess a rigid half-chair conformation,[10] these shifts may be explained as follows, the small upfield shift at C–13 results from the steric compression shift due to the steric interaction with C–6 and the downfield shift due to the α-substituent effect[11] of the quasi-equatorial methyl group (Table V–B). The α- and β-substituent effects of the quasi-axial and quasi-equatorial methyl group in tetrahydroprotoberberines are summarised in Table V–A and V–B. The large upfield shift at C–6 arises from strong steric interation with

Table V. α- and β-Substituent Effects of Quasi Axial and Quasi-Equatorial Methyl Group in Free Bases, N-protonated Salts and N-Methosalts of Tetrahydroprotoberberines

	Compounds to be compared	δ_c (in ppm)[a]	
		C–13 (α)	C–13a (β)
A		quasi-axial methyl substituent effects	
	4—**8**[b]	−2.8	−3.3
	1—**6**[c]	−3.1	−3.6
	1—**5**[d]	−2.1	−3.9
	2—**6**[d]	−2.2	−3.9
	3—**7**[d]	−1.9	−3.3
	4—**8**[d]	−2.1	−3.7
B		quasi-equatorial methyl substituent effects	
	3—**18**[b]	−4.2	−5.8
	4—**19**[b]	−4.2	−6.4
	1—**17**[c]	−3.3	−6.0
	4—**19**[c]	−3.3	−6.4

a) negative values indicate downfield shifts
b) determined from data on N-methosalts in CD_3OD
c) determinded from data on N-protonated salts in $CDCl_3$ and CF_3COOH
d) determined from data on free bases in $CDCl_3$

both C–8a and C–13. The upfield shift at C–8 results from the difference in the β-substituent effect[11] between axial and equatorial C–6 methylene groups. The downfield shift at C–13a results from the upfield shift due to the difference in the β-substituent effect between axial and equatorial C–6 methylene groups and the downfield shift due to the β-substituent effect of the quasi-equatorial methyl group. Thus, the chemical shift differences of the aliphatic

10) N-Methyl group in Chart 1 is replaced by the lone pair.
11) D.K. Dalling and D.M. Grant, *J. Am. Chem. Soc.*, **89**, 6612 (1967).

Table VI. Carbon-13 Data on Tetrahydroprotoberberine-type Alkaloids in

		C-CH_3 or $COCH_3$	5	13	6	8	13a	OCH_3 or OCH_2O					C=0	
1	−30°		29.2	36.5	51.8	54.2	59.3	56.7×x,	60.1					
	−80°		28.9	36.3	51.7	54.5	58.9	55.8×x,	60.1					
9	−30°		30.4	32.7	49.5	—	—	55.6×x,	60.1,	60.7				
	−60°		—	—	—	—	—	—	—	—				
11	−30°		30.4	33.4	49.5	53.4	56.3	55.8,	61.0,	61.3				
	−60°		30.2	—	—	—	—	55.7,	60.8,	61.3				
	−80°		—	—	—	—	—	55.8,	60.8,	61.4				
12	R.T.		30.9	33.8	48.9	53.8	56.2	56.2×2	60.3,	60.8				
	−30°		30.6	33.6	48.8	53.4	55.4	55.7,	55.8,	60.2,	60.8,	60.9		
	−60°		30.5	33.7	48.8	53.4	55.7	56.6,	55.8,	60.2,	60.9,	61.0		
17	−30°	22.5	28.0	34.2	46.2	50.0	63.6	55.6,	60.4,	101.2				
	−80°	22.1	27.6	33.6	46.2	49.5	62.9	55.6,	60.4,	101.3				
13	−0°	21.0	30.5	33.3	48.6	53.4	55.6	55.9,	56.6,	60.2,	60.7		169.2	
	−30°	21.1	30.4	33.5	48.8	53.3	—	55.7,	56.0,	60.2,	60.8		169.4	
	−60°	21.2	30.3*	33.8	49.0*	53.1	55.9	55.9,		60.2,	60.8		169.5*	
			31.3*		47.0*								(169.9)*	
	−80°	21.4	30.4	34.0	49.1	—	—	55.8,		60.2,	60.9		169.6*	
													170.2*	
14	−30°	21.1	30.3	—	—	53.1	—	56.0,		60.8,	61.0		(169.3).	170.0
	−60°	21.3	—	—	—	53.2	—	55.9,		60.9,	61.1		169.4,	170.2
	−80°	21.4	—	—	—	—	—			60.9,	61.1		169.6,	170.4
15	R.T.		30.4	33.8	48.4	53.2	56.1	56.2,		60.8,	61.0		164.1,	164.4
	−10°		30.4	34.1	48.7	53.1	55.3	56.1,		60.9,	61.1			164.5
	−30°		30.3*	34.4	48.7*	53.0	—	—		—	—		164.0,	164.6
			(31.8)*		(47.3)*									
	−60°		—	—	—	—	—	56.0,	60.7,	61.0,	61.3		163.9,	164.6
	−80°		—	—	—	—	—	—	—	61.1,	61.4		164.0	164.6

a) * represents the couple of the signal
b) — hard to read by overlapping or broadening
c) Va ues in parentheses represent the value measured by eye.

carbons between the groups I and III alkaloids may be resulted roughly from the difference in the preferred B/C-*trans* and B/C-*cis* forms. This suggests that the alkaloids of groups I and III exist mainly in the B/C-*trans* and B/C-*cis* forms, respectively. This assumption is consistent with the result obtained from IR spectral analysis.[4)]

The low temperature CMR spectra were measured in order to confirm the conformational equilibrium of the B/C-*cis* and B/C-*trans* forms in solution of tetrahydroprotoberberines and to estimate the approximate proportion of the two conformations (Table VI). The alkaloids measured were **1** in group I ,**9**, **11**, **12**, **13**, **14**, and **15** in group II, and **17** in group III. The CMR spectra of **1**, **9**, **11**, **12**, and **17** in deuteriodichloromethane showed no significant alteration in the region from room temperature to *ca.* −80°, apart from the broadening of some signals. The CMR spectra of **13**, **14**, and **15** showed profound changes at low temperatures.

the Range of Temperature of R.T. to −90° (ppm from TMS, in CD_2Cl_2)[a,b,c]

1	4	11	12	4a	8a	12a	14a	2	3	9	10
109.0	110.9	110.2	124.1	126.7	127.8	129.0	129.6	147.2	147.2	150.4	144.6
107.6	110.5	109.9	124.2	126.5	127.5	128.9	129.2	146.8	146.8	150.2	144.0
147.7	103.2	110.1	124.2	131.4	128.3	128.8	118.7	134.6	151.0	150.0	144.6
147.9	—	—	—	131.4	128.1	128.6	118.9	134.7	151.1	149.9	144.2
147.1	103.4	121.2	124.8	131.6	129.6	133.9	117.8	135.7	150.9	148.0	141.0
147.5	103.0	121.2	124.8	131.5	129.3	134.1	118.0	135.7	151.0	147.9	140.9
147.8	—	—	—	131.5	129.3	134.2	118.3	135.7	151.1	147.9	140.9
152.4	108.0	111.3	124.3	131.3	129.0	129.3	125.3	140.8	151.5	150.6	145.8
152.0	107.1	110.1	124.3	131.3	128.6	128.7	124.1	140.1	151.2	150.2	144.8
151.9	107.0	109.8	124.4	131.4	128.4	128.7	124.0	139.9	151.1	150.1	144.5
107.3	109.0	110.3	123.5	127.6	127.7	132.2	131.4	144.8	146.2	150.2	145.2
107.4	109.1	110.0	123.8	127.5	127.5	131.7	131.0	144.3	146.1	150.1	144.9
141.9	110.3	110.7	124.2	131.5	128.1	128.7	123.8	139.2	151.8	150.5	145.2
141.8	110.0	110.2	124.3	131.6	127.9	128.6	123.5	138.8	151.7	150.4	144.8
141.8	109.9	109.9	124.3	131.9*	127.9*	128.7*	123.3	138.7*	151.6	150.3	144.5
				131.3*	127.1*	128.3*		138.2*			
141.7	109.8	109.8	123.3	132.0*	127.8*	128.7*	123.1	138.5*	151.5	150.2	144.3*
141.3				131.3*	126.9*	128.2		137.9*			144.5*
141.3	110.0	121.3	124.7	131.4	129.5	134.5	123.2	(138.8)	151.7	148.1	141.7
141.2	109.9	121.2	124.9	131.7*	129.5*	134.6*	123.0	138.7*	151.6	147.9	141.7
				(130.9)*	(128.9)*	(133.7)*		(138.0)*			
141.2	109.8	121.2	125.1	131.8*	129.6*	134.7*	122.8*	138.5*	151.5	147.8*	141.6
				131.2*	129.0*	133.8*	123.0*	137.8*		148.0	
142.0	111.0	121.4	124.5	131.4	129.6	134.7	124.0	139.6	152.0	148.5	141.3
141.8	110.5	121.3	124.6	131.5	129.5	134.6	123.6	139.1	151.9	148.3	141.2
141.8	110.3	121.3	124.6	131.3	129.6	134.7*	123.4	139.0	151.8	148.1	141.2
						134.0*					
141.7	110.2	121.1	(124.8)	131.3	129.6	134.7*	123.0*	138.7*	151.7	147.9*	141.2
						133.9*	123.3*	138.1*		148.1*	
141.6	(110.3)	121.2	(125.1)	131.4	129.7	134.8*	122.8*	138.5*	151.6	147.8*	141.2
						133.9*	(123.2)*	137.8		148.0	

When these samples were cooled, the broadening of some signals occurred. Further chilling led to the appearance of some pairs of signals, comprising relatively strong and weak signals (Fig. 3). This observation indicates that the signals due to the B/C-*trans* and B/C-*cis* forms in some carbons appeared at a low temperature. Thus, it was proved that **13**, **14**, and **15** exist in equilibrium of the B/C-*cis* and B/C-*trans* forms in solution. The large difference in the intensities of these pairs of signals indicated that the proportion of the B/C-*trans* and B/C-*cis* forms in the equilibrium mixture is unequal. As shown above, the signal for C–6 in the B/C-*cis* form appears at a higher field than that in the B/C-*trans* form. In the low temperature CMR spectra, the weak signal due to C–6 appeared at a higher field than the strong signal. Consequently, the weak and strong signals might be assigned to the B/C-*cis*

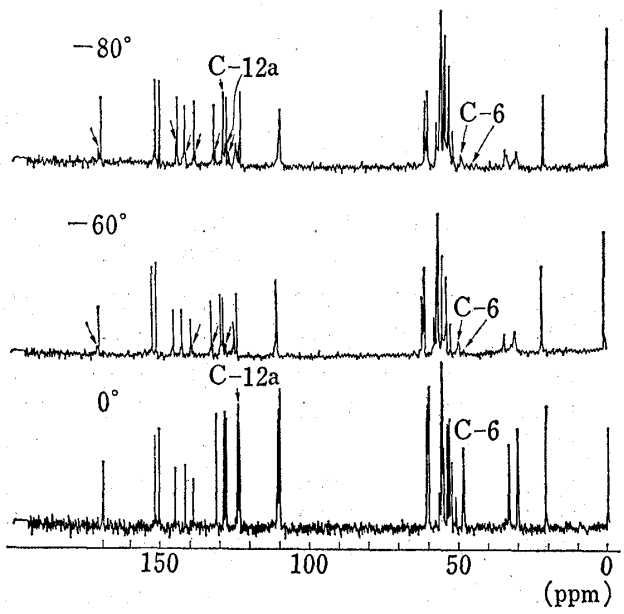


Fig. 3. CMR Spectra of O-Acetylcapaurine (**13**) taken at 0°, −60°, and −80° (in CD_2Cl_2)

and B/C-*trans* forms, respectively. The chemical shift difference of a pair of signals assigned to C–12a was about constant between −60° and −80°. The ratios in the intensities of the strong and weak signals for C–12a in the spectra of **13**, **14**, and **15** at −80° were *ca.* 3.4: 1, *ca.* 3: 1, and *ca.* 2: 1. Accordingly, the amount of the B/C-*cis* form increases in the order of the alkaloids **13**, **14**, and **15**. This agrees with the result obtained from IR spectral analysis.[4]

Thus, analysis of CMR spectra measured at room temperature indicated that the amount of the B/C-*cis* form in comparison with the B/C-*trans* form increases in the order of the groups I, II, and III alkaloids. Analysis of CMR spectra at a low temperture confirmed that **13**, **14**, and **15** exist in equilibrium of the B/C-*cis* and B/C-*trans* forms in solution and allowed estimation of the approximate proportion of the two conformations.

Experimental

CMR pectra were measured with a NEVA-NV-21 spectrometer at 22.6 MHz in 8 mm tube at ordinary probe temperature. The spectra of free bases were determined for solution in $CDCl_3$ containing tetramethylsilane (TMS) as an internal reference (δ_C=O); concentration were *ca.* 0.1—0.5 mole/liter and the spectra were recorded after a sufficinet amount of CF_3COOH to be protonated was added. The samples of methiodides were dissolved in CD_3OD in a concentration of *ca.* 0.1—0.5 mole/liter. The measurement conditions in the fourier transform mode were: spectral width: 5000 Hz, pulse width: 10 or 15 μsec (filipping angles of about *ca.* 20°), aquisition time: 0.4 sec, number of data points: 4096. CMR spectra at low temperature in CD_2Cl_2 containing TMS as an internal reference were measured with Varian CFT-20 spectrometer at 20 MHz.

Preparation of Tetrahydrocoptisine (3) Methochlorides——Tetrahydrocoptisine (3) methochlrides were prepared by the same procedure as that described in our previous paper.[12]

Preparation of Tetrahydroprotoberberine (4) Methiodides——MeI (1.3 ml) was added to a solution of **4** (146 mg) in acetone. After standing for 30 min at room temperature, the separated crystals were collected by filtration and recrystallized from MeOH–acetone to give a mixture of the β- and α-methiodides (188 mg) in 2: 1 ratio, mp 204—207° (decomp.). This mixture was dissolved in MeOH and converted to the chlorides, mp 203—215° (decomp.), with AgCl.

Preparation of Thalictricavine (6) Methochloride——A mixture of **6** (200 mg) in acetone (20 ml) and MeI (1 ml) was placed in a glass-stoppered bottle, and heated for 8 hr in a water bath. The separated crystals were collected by filtration and recrystallized from MeOH–acetone to give the β-methiodide (240 mg), mp 180—200° (decomp.), which was dissolved in MeOH and converted to the chloride, mp 186—195° (decomp.), with AgCl.

Preparation of 13-Methyltetrahydroprotoberberine (8) Methiodides——A mixture of **8** (300 mg) in acetone and MeI (3 ml) was placed in a glass-stoppered bottle and heated for 1 hr in a water bath and the reaction mixture was evaporated *in vacuo*. The residue was recrystallized from MeOH–acetone to give a mixture of β- and α-methiodides (360 mg) in 1.3: 1 ratio, mp 205—225° (decomp.).

Preparation of Capaurine (9) Methiodide——MeI (2 ml) was added to a solution of **9** (100 mg) in acetone (2 ml). After standing for 30 min at room temperature, the separated crystals were collected by filtration and recrystallized from MeOH–acetone to give the α-methiodide (190 mg), mp 230—233° (decomp.).

Preparation of O-Methylcapaurine (12) Methiodide——The α-methiodide (80 mg), mp 235—240° (decomp.), was prepared from **12** (80 mg) in acetone (1 ml) and MeI (0.5 ml) following a procedure similar to that described for capaurine (**1**).

12) N. Takao, K. Iwasa, M. Kamigauchi, and M. Sugiura, *Chem. Pharm. Bull.* (Tokyo), **24**, 2859 (1976).

Preparation of O,O-Diacetylcapaurimine (14) Methiodide——The α-methiodide (100 mg), mp 220—225° (decomp.), was prepared from **14** (90 mg) in acetone (1 ml) and MeI (0.5 ml) following a procedure similar to that described for capaurine (**1**).

Preparation of Mesothalictricavine (17) Methochloride——MeI (100 mg) in acetone (1 ml) was added to a solution of **17** (40 mg) in acetone (1 ml). The reaction mixture was treated in the same procedure as that described for capaurine (**1**) to give the α-methiodide (51 mg), mp 277—282°, which was dissolved in MeOH and converted to the chloride (50 mg), mp 240—243° (decomp.), with AgCl.

Preparation of Mesotetrahydrocorysamine (18) Methochloride——Mesotetrahydrocorysamine methochloride was prepared by the same procedure as described in our previous paper.[12]

Preparation of Meso-13-methyltetrahydroprotoberberine (19) Methochloride——MeI (0.5 ml) was added to a solution of **19** (90 mg) in acetone. The reaction mixture was treated in the same procedure as that described for capaurine (**1**) to give the α-methiodide (180 mg), mp 295—297° (decomp.), which was dissolved in MeOH and converted to the chloride, mp 264—266° (decomp.), with AgCl.

The free bases used for CMR spectral measurement were the samples used for IR spectral analysis in our previous work.[4]

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