Stereochemistry of 13-Hydroxyprotoberberines, Their Derivatives, and a Protopine-Type Alkaloid

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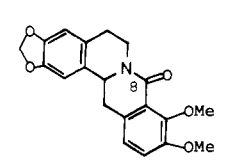
^{13}C NMR and ^{1}H NMR spectral analyses have been used to establish the conformational structure of ophiocarpine (1), epiophiocarpine (2), their acetates and corresponding N-quaternary salts, and allocryptopine (5).

A number of protoberberine-type and protopine-type alkaloids which possess an oxygen function on an aliphatic carbon have been isolated from some *Papaver* species.[1] Oxyberberine has an oxygen function at C-8, and ophiocarpine (1) and berberastine bear an alcoholic hydroxyl group at C-13 and C-5, respectively (Chart I). The protopine-type alkaloids ochrobirine and 13-oxomuramine possess an oxygen function at C-13 in addition to C-14. It is of interest to study the bioconversion of these alkaloids to another class of alkaloids as well as to find the origin of oxygen function and the stage of oxidation. It has been proved that both *cis*- and *trans*-13-methyltetrahydroprotoberberines such as thalictricavine (3) and mesothalictricavine (4), corresponding to ophiocarpine (1) and epiophiocarpine (2) in relative configuration at C-13 and C-14, were converted via their *N*-methyl salts to the protopines, which in turn are the biosynthetic precursors of the benzo[*c*]phenanthridines in the plant and cell cultures.[2] Consequently, examination of the stereochemistry of both the cis and trans isomers of the 13-hydroxytetrahydroprotoberberines and their *N*-methyl salts, as well as the protopines, is important in connection with a study of the biosyntheses.

The relative configurations at C-13 and C-14 and preferred conformations have been assigned to ophiocarpine (1) and epiophiocarpine (2) on the basis of chemical and spectroscopic evidence.[3] Ophiocarpine (1) and its acetate (**1Ac**) are known to have the hydrogens at C-13 and C-14 in a cis relationship to one another and to have the *trans*-quinolizidine system, while the corresponding configurations of epiophiocarpine (2) and its acetate (**2Ac**) have been shown to be trans. However, a rigorous conclusion has not been drawn for their conformations. The conformations of the quaternary *N*-methyl salts of ophiocarpine (1), epiophiocarpine (2), and their acetates have not previously been examined.

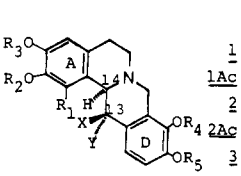
In this paper we describe the conformations of the 13-hydroxy and 13-acetoxytetrahydroprotoberberines and their *N*-methyl salts and protopines. The detection of the conformation of one *trans*-quinolizidine system (conformation A, Chart II)) and two *cis*-quinolizidine systems (conformations B and C) in the tetrahydroprotoberberines has been approached from IR, ^{1}H NMR, and ^{13}C NMR spectroscopic studies.[4] In the ^{13}C NMR spectra of the free

Chart I

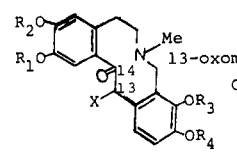


Berberastine

Oxyberberine



	X	Y	R_1	R_2	R_3	R_4	R_5
1	OH	H	H	CH_2		Me	Me
1Ac	OAc	H	H	CH_2		Me	Me
2	H	OH	H	CH_2		Me	Me
2Ac	H	OAc	H	CH_2		Me	Me
3	Me	H	H	CH_2		Me	Me
4	H	Me	H	CH_2		Me	Me
6	H	H	OH	Me	Me	Me	Me
7	H	H	H	CH_2		Me	Me
8	H	H	H	CH_2		CH_2	
9	H	CH_2OH	H	Me	Me	CH_2	



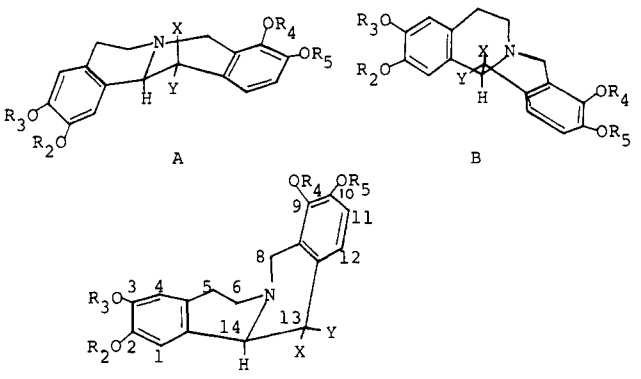
13-oxomuramine

Ochrobirine

5

	R_1	R_2	R_3	R_4	X
	Me	Me	Me	Me	=O
	CH_2		CH_2		OH
	CH_2		Me	Me	H

Chart II



bases existing predominantly in conformations A–C, the C-5 chemical shifts appear at 28.7–29.8 (A), 27.2–28.5 (B),

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Table I. ^{13}C NMR Data on Tetrahydroprotoberberines, Their *N*-Methyl Salts, and Allocryptopine[a]

compd	solvent	conformation	chemical shift, ppm											
			5	6	8	13	14	N-Me	O-Me	O-Me	C-Me	$COCH_3$	OCH_2O	1
1	*c*	A	29.52	50.97	53.94	70.05	64.81		55.84	60.07			100.91	105.66
1Ac	*c*	A	29.50	51.45	53.75	69.41	63.70		55.80	60.16		21.01	100.86	105.45
2	*c*	A	29.71	50.75	52.98	72.51	65.89		55.83	60.22			100.69	107.97
2Ac	*c*	A and B	29.72	49.26	52.41	73.24	61.88		55.75	60.16		21.51	100.76	106.79
1α	*d*	B	25.21	55.30	61.62	68.43	71.48	52.40	56.56	61.27			102.82	108.39
1β	*d*	A	24.77	63.57[b]	63.17[b]	64.11	71.04	44.19	56.56	61.27			102.82	108.39
1Acα	*d*	B	24.73	54.17	61.21	68.25	69.10	52.09	56.52	61.20		20.22	103.03	108.82
1Acβ	*d*	A	24.58	63.33	62.54	65.22	69.82	44.04	56.52	61.20		20.82	103.03	105.95
2α	*d*	B	24.56	54.15	61.30	72.43	71.27	52.04	56.53	61.30			102.98	109.71
2β	*d*	A	25.14	63.63	61.92	68.98	71.43	40.54	56.53	61.33			103.04	108.26
2Acα	*d*	B	24.57	55.61	59.75	72.03	69.63	52.34	56.56	61.39		20.96	103.15	108.40
3α	*c*	B	24.23	53.49	60.25	36.07	68.15	52.14	56.00	61.28	19.25		101.60	107.96
3β	*d*	A	24.86	63.79	64.01	32.94	70.81	44.17	56.60	61.13	18.07		103.08	107.96
4α	*e*	B	23.89	51.98	60.95	38.67	72.94	51.98	56.96	62.06	19.57		102.69	109.92
5[k]	*c*		32.34	57.57	50.19	46.31	193.33	41.17	55.63	60.68			101.16	109.19
	f		31.80	57.32	50.93	46.06	187.44	41.13	55.87	60.97			101.75	109.15
	g		32.37	57.95	50.51	46.57	193.63	41.34	55.72	60.60			101.53	109.02
	d		30.66	56.99	overlap		193.36	41.46	56.33	61.19			102.65	109.07
	h, α	B	23.19	53.77	56.74	39.33	93.22	44.78	55.95	60.61			101.91	105.62
	h, β	A	23.71	55.05	57.22	35.34	92.24	42.41	55.94	60.61			102.03	105.89
	i, α	B	24.27	54.50	57.45	40.55	93.97	45.12	56.53	61.04			103.18	106.64
	i, β	A	24.90	55.55	57.93	36.35	93.18	42.88	56.53	61.04			103.30	107.00
	j, α	B	24.75	56.04	58.61	41.34	95.30	46.40	57.40	62.80			103.94	107.55
5·HCl	*d*, α	B	24.56	54.87	57.74	40.49	94.03	45.71	56.99	61.42			103.32	106.64
	d, β	A	25.13	55.88	58.32	36.50	93.14	43.49	56.99	61.42			103.32	107.08
	e, *l*, α	B	22.29	52.89	55.34	37.81	91.81	43.80	55.34	60.14			101.33	104.70
	e, *l*, β	A	22.67	53.93	55.74	34.07	90.66	41.37	55.34	60.14			101.33	104.96
	j, β	A	25.46	57.35	59.14	36.98	94.27	44.19	57.35	62.80			104.11	107.44

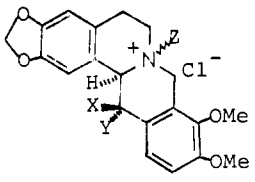
4	11	12	4a	8a	12a	14a	2	3	9	10	C=O
108.54	111.42	125.54	127.41	128.74	131.18	129.54	146.28	146.63	151.83	144.85	
108.40	111.39	126.32	126.47	126.47	129.76	129.33	146.16	146.32	152.31	144.66	171.00
108.34	111.49	123.25	128.41	129.18	131.85	129.42	145.88	146.17	151.16	144.21	
108.85	111.23	123.13	127.87	128.03	129.87	128.70	145.90	146.50	151.54	144.62	170.90
109.24	114.86	126.98	122.33	120.67	127.58	126.76	148.33	149.82	153.71	146.02	
109.40	114.86	127.28	121.79	120.67	128.37	125.88	148.87	149.20	153.62	146.02	
109.14	115.07	126.66	121.51	120.75	126.08	122.58	147.91	149.97	154.28	146.00	170.26
109.84	114.92	126.66	121.78	120.43	126.08	123.86	148.85	149.37	154.38	146.22	171.83
110.03	115.01	124.99	123.38	120.91	127.65	124.66	148.17	150.22	153.66	146.06	
109.25	115.20	125.64	123.90	121.11	128.85	126.05	149.17	149.81	153.62	146.07	
110.05	115.02	125.30	122.75	121.89	128.07	124.33	148.67	150.39	154.42	146.48	171.56
108.36	113.45	123.88	123.38	119.94	128.02	123.38	147.31	148.33	151.10	145.40	
109.87	115.29	125.85	122.61	120.53	130.38	126.39	149.25	149.47	152.49	146.72	
110.23	115.11	124.79	123.54	120.21	129.00	120.57	146.98	149.21	151.74	145.52	
110.41	110.68	127.73	136.48	128.62	129.65	132.87	146.03	148.02	151.60	147.45	
110.60	111.36	128.12	135.80	128.61	129.23	132.66	146.70	148.69	152.02	147.55	
110.68	110.95	128.06	136.48	129.10	130.09	133.31	146.30	148.33	151.89	147.75	
110.75	112.74	128.32	135.84	129.65	131.41	131.41	147.34	150.88	153.54	149.11	
108.28	113.83	124.14	120.02	118.84	122.45	126.90	145.10	149.44	151.33	147.90	
108.39	114.01	125.05	120.39	119.51	123.32	123.95	145.21	149.63	151.33	148.27	
109.61	114.94	125.47	122.46	120.95	125.23	129.21	146.69	150.51	152.56	148.87	
109.39	114.75	126.70	123.06	121.51	125.35	126.18	146.69	150.61	152.69	149.47	
110.73	116.54	128.03	122.34	121.36	125.21	128.58	145.94	151.78	153.70	149.95	
109.73	115.49	125.44	122.70	121.02	125.44	129.11	146.90	150.57	152.57	148.80	
109.51	115.26	126.24	123.14	121.59	125.44	126.77	146.90	150.57	152.57	149.34	
108.27	113.31	124.19	120.57	119.28	123.82	125.90	143.92	147.89	150.23	146.22	
107.87	113.19	125.21	120.82	119.84	123.82	123.58	143.92	148.08	150.23	146.78	
110.44	116.31	128.78	122.63	121.81	125.56	125.82	145.88	152.10	153.51	150.52	

[a] Assignments were made from off-resonance decoupling, selective proton decoupling experiments, and the comparison of the spectra of the related alkaloids. [b] Assignment may be reversed. [c] $CDCl_3$. [d] CD_3OD. [e] D_2O. [f] $CDCl_3$-CD_3OD (3:1). [g] $CDCl_3$-$(CD_3)_2CO$ (3:1). [h] $CDCl_3$-TFA-*d* (19:1); an amount of TFA-*d* 4 times the equivalent weight of allocryptopine was added. [i] CD_3OD-TFA-*d* (19:1); an amount of TFA-*d* 4 times the equivalent weight of allocryptopine was added. [j] TFA-*d*. [k] Concentrations were 0.1 mol/L. [l] CH_3CN was used as an external reference.

and 23.4–24.4 ppm (C), and the C-6 chemical shifts in the corresponding conformations are 51.0–51.6, 45.9–47.2, and 48.3–49.3 ppm.[4f,i,j,l]) The discrimination of conformations A–C can therefore be made from the chemical shifts at C-5 and C-6. In the ^{13}C NMR spectra (Table I) of ophiocarpine (**1**) and its acetate (**1*Ac***) as well as of thalictricavine (**3**)[4i] the chemical shifts at C-6 are typical of the conformation A. In epiophiocarpine (**2**), the chemical shift at C-6 is also indicative of the conformation A in contrast to the predominant conformations B and C in mesothalictricavine (**4**)[4i] and *trans*-13-(hydroxymethyl)tetrahydroprotoberberine (**9**),[4l] respectively, which are the same as epiophiocarpine (**2**) in relative configuration at C-13 and C-14. This indicates that a nonbonded interaction between the hydroxyl group at C-13 and the hydrogen at C-1 is smaller than that between the methyl or hydroxymethyl group at C-13 and the hydrogen at C-1. That is, the *trans*-13-(hydroxymethyl)tetrahydroprotoberberine adopts

predominantly form C due to stabilization by intramolecular hydrogen bonding and also in order to avoid a nonbonded interaction between the hydroxymethyl group at C-13 and the hydrogen at C-1 in form A or that at C-12 in form B. This is supported by the fact that the considerable presence of form C in the *trans*-13-(acetoxymethyl)tetrahydroprotoberberine (**9**, Y = CH_2OAc) was observed in spite of the lack of an intramolecular hydrogen bond.[4l] Mesothalictricavine exists predominantly in form B due to a nonbonded interaction between the methyl group at C-13 and the hydrogen at C-1. The chemical shift at C-6 in epiophiocarpine acetate (**2Ac**) is close to that in capaurine (**6**).[4i] This suggests that epiophiocarpine acetate (**2Ac**) exists as a conformational mixture of forms A and B, and the proportion of the form A is high as that in mesothalictricavine (**4**) and is close to that in capaurine (**6**). This suggests that the nonbonded interaction between the acetoxyl group at C-13 and the hydrogen at C-1 is smaller than that between the methyl group at C-13 and the hydrogen at C-1 and is similar to that between the hydrogen at C-13 and the hydroxyl group at C-1. From the chemical shift at C-5 in the ^{13}C NMR spectrum and the coupling constant between H-13 and H-14 in the ^1H NMR spectrum (Table II), it is suggested that the existence of form C is negligibly small.

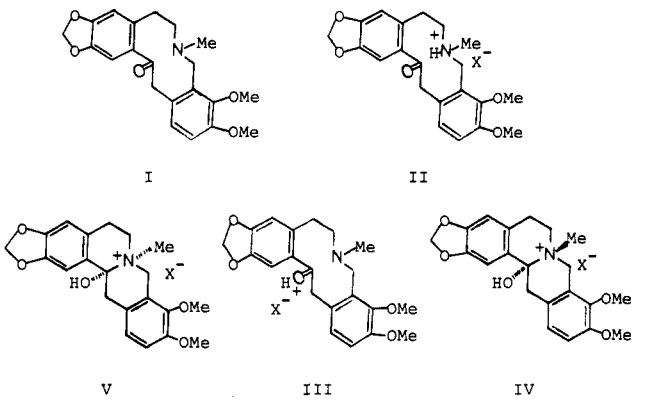
In the *N*-methyl salts bearing conformations A and B, the chemical shifts at C-6 are observed at 61.8–63.8 and 52.1–56.0 ppm and the chemical shifts of the *N*-methyl group at 39.4–44.5 and 50.9–53.3 ppm, respectively, which allow assignment of the two forms.[4i] In the ^1H NMR spectra of the 13-substituted tetrahydroprotoberberines in which the 13,14-hydrogens are trans, the coupling constant between H-13 and H-14 is small (2–3 Hz) in form C and large (7–8 Hz) in forms A and B.[4c,d,l] The distinction between forms C and A or B can be made on the basis of this coupling constant. N-Methylation of ophiocarpine (**1**) and its acetate (**1Ac**) produced two *N*-methyl salts. The ^{13}C NMR spectra (Table I) of their major salts (**1**β and **1Ac**β) showed the C-6 carbon at 63.6 and 63.3 ppm and



	X	Y	Z
1α	OH	H	Me
1β	OH	H	Me
1Acα	OAc	H	Me
1Acβ	OAc	H	Me
2α	H	OH	Me
2β	H	OH	Me
2Acα	H	OAc	Me
3α	Me	H	Me
3β	Me	H	Me
4α	H	Me	Me

the *N*-methyl group at 44.2 and 44.0 ppm, respectively, which are consistent with conformation A. This result is in accord with that previously described for thalictricavine β-*N*-methyl salt (**3**β).[4i] Conformation B was assigned to the minor salts (**1**α and **1Ac**α) on the basis of the chemical shifts of the C-6 (55.3 and 54.2 ppm) and of the *N*-methyl group (52.4 and 52.1 ppm) in the ^{13}C NMR spectra and long-range W coupling between the H-14 and H-6 in the ^1H NMR spectra. In the 200-MHz ^1H NMR spectrum (Table II) of the minor salt of ophiocarpine (**1**α) double-

Chart III



resonance experiments on H-14 at δ 4.77 clearly reduced the apparent 12-line pattern at δ 3.52 to an 8-line pattern and collapsed the H-13 resonance doublet to a singlet. The doublet of doublets (4.0 and 1.5 Hz) of H-14 at δ 4.77 was reduced to a doublet (4.0 Hz) by irradiation of the signal at δ 3.52, which is assigned to H-6. This loss of coupling is ascribed to a long-range W coupling between the H-14 and H-6 expected to conformation B. The same observation was also made in thalictricavine α-*N*-methyl salt (**3**α). N-Methylation of epiophiocarpine (**2**) formed two *N*-methyl salts, while that of epiophiocarpine acetate (**2Ac**) formed only one N-quaternary salt. In the ^{13}C NMR spectrum of the major salt of epiophiocarpine and epiophiocarpine acetate *N*-methyl salt (**2**α and **2Ac**α), the C-6 carbons appear at 54.2 and 55.6 ppm and the *N*-methyls at 52.0 and 52.3 ppm, respectively. ^1H NMR spectra of **2**α and **2Ac**α displayed the C-14 proton as a doublet of doublets at δ 4.42 (8.4 and 1.2 Hz) and 4.86 (7.0 and 1.0 Hz), respectively, as was observed in mesothalictricavine α-*N*-methyl salt (**4**α; 9.7 and 1.5 Hz). The large couplings are ascribed to trans–axial vicinal coupling, and the smaller ones are compatible with a long-range W coupling between the H-6 and H-14. Conformation B was therefore assigned to these salts (**2**α and **2Ac**α). In the ^{13}C NMR spectrum of the minor salt of epiophiocarpine (**2**β) the chemical shifts of the C-6 (63.6 ppm) and the *N*-methyl group (40.5 ppm) indicate that the minor salt (**2**β) adopts the form A. Methylation of ophiocarpine (**1**) and its acetate (**1Ac**) produced the *N*-methyl salt having form A as a major salt, while methylation of epiophiocarpine (**2**) formed that bearing form B as a major salt, and only one *N*-methyl salt having form B resulted from methylation of epiophiocarpine acetate (**2Ac**). This fact might result from the fact that the proportion of form B in a conformational mixture of forms A and B in acetone used in N-methylation increases in the order of the alkaloids **2Ac**, **2**, and **1** and **1Ac**, and the rate of N-methylation is faster in conformation B than in conformation A because the nitrogen atom is less hindered in conformation B.[1] Assignment of the conformation for the 13-hydroxy- and 13-acetoxytetrahydroprotoberberines allows one to estimate the substituent effects by comparing with data[4i] for the corresponding alkaloids unsubstituted at the C-13 and C-14 (tetrahydroberberine **7** and tetrahydrocoptisine **8**; Table III). The α and β effects for quasi-axial and quasi-equatorial hydroxyl or acetoxyl groups are roughly similar to those found for the axial and equatorial hydroxyl and acetoxyl groups of the cyclohexanol derivatives.[5]

It has been suggested from IR and ^1H NMR methods and X-ray analysis[6] that protopine-type alkaloids adopt

(5) Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972; Chapter 5.

Table II. ^{1}H NMR Data on Tetrahydroprotoberberines, Their *N*-Methyl Salts, and Allocryptopine[a]

compd	solvent	conformation	chemical shift, δ									
			H-1, H-4	H-11, H-12[b]	OCH_2O	OMe	H-8[c]	H-13	H-14	NMe	COMe	CMe
1[d]	*i*	A	6.78, 6.60	7.17 d, 6.91 d	5.92 m	3.89, 3.86	4.21 d, 3.54 d	4.97 d (1.8)	3.67 d (1.8)			
1Ac[f]	*g*	A	6.74, 6.61	7.28 d, 6.88 d	5.93 m	3.88 s, 6 H	4.33 d, 3.54 d	6.48 d (2.5)	3.76 br s (W = 6.0 Hz)		1.77	
2[d]	*g*	A	7.40, 6.58	7.24 d, 6.85 d	5.91 m	3.86, 3.83	4.09 d, 3.67 d	4.63 d (8.0)	3.47 d (8.0)			
2Ac[f]	*g*	A and B	6.77, 6.59	6.95 d, 6.85 d	5.90 br s	3.85 s, 6 H	4.08 d, 3.95 d	6.08 d (8.5)	3.84 d (8.5)		2.22	
1α[d]	*h*	B	6.83, 6.80	7.22 d, 7.17 d	5.99 s	3.91, 3.90	5.00 d, 4.81 d	4.97 d (4.0)	4.77 dd (4.0, 1.5)	3.23		
1β[d]	*h*	A	7.00, 6.76	7.37 d, 7.16 d	6.02 s	3.93 s, 6 H	4.94 d, 4.67 d	5.59 d (3.0)	5.04 d (3.0)	3.14		
1Acα[e]	*h*	B	6.92, 6.89	7.18 d, 7.10 d	6.01 br s	3.92 s, 6 H	5.18 d, 5.11 d	6.50 d (4.5)	5.52 d (4.5)	3.34	1.71	
1Acα[d]	*g*	B	6.83, 6.69	6.99 d, 6.96 d	5.97 br s	3.94, 3.88	5.55 d, 5.44 d	6.44 d (5.0)	5.79 d (5.0)	3.69	1.68	
1Acβ[e]	*h*	A	6.87, 6.73	7.34 d, 7.23 d	6.01 br s	3.92 s, 6 H	5.11 d, 5.09 d	7.04 d (3.0)	5.72 d (3.0)	3.23	1.92	
1Acβ[d]	*g*	A	6.72, 6.60	7.29 d, 6.96 d	5.99 br s	3.94, 3.89	5.65 d, 5.45 d	6.88 d (3.5)	5.85 d (3.5)	3.27	1.92	
2α[d]	*h*	B	6.87, 6.78	7.26 d, 7.14 d	6.00 s	3.92, 3.90	4.97 d, 4.92 d	4.74 d (8.4)	4.42 dd (8.4, 1.2)	hidden		
2β[d]	*h*	A	7.75, 6.78	7.47 d, 7.26 d	6.00 m	3.91, 3.90	4.90 d, 4.78 d	5.11 d (9.0)	4.73 d (9.0)	2.88		
2Acα[d]	*h*	B	6.86, 6.80	7.14 d, 7.07 d	6.00 s	3.91, 3.89	4.95 d, 4.90 d	6.82 d (7.0)	4.86 dd (7.0, 1.0)	3.35	2.16	
3α[d]	*h*	B	6.82, 6.78	7.13 s, 2 H	6.01 s	3.90, 3.88	4.94 d, 4.80 d	hidden	4.84 dd (6.5, 1.0)	3.26		1.02 d (7.7)
3β[d]	*h*	A	6.93, 6.82	7.26 d, 7.19 d	6.02 m	3.90, 3.89	4.90 d, 4.68 d	4.15 m	5.19 d (5.5)	3.06		1.38 d (7.5)
4α[d]	*h*	B	6.83 s, 2 H	7.13 br s, 2 H	6.01 s	3.90, 3.88	4.95 d, 4.81 d	3.10 qd (9.7, 6.8)	4.41 dd (9.7, 1.5)	3.19		1.45 d (6.8)
5[p]	*d, g*		6.92, 6.60	6.90 d, 6.81 d	5.91 s	3.84, 3.77	3.74 s, 2 H	3.71 br s, 2 H		1.90		
	α	B	7.04, 6.66	6.99 d, 6.93 d	5.99 m	3.93, 3.90	4.68 d, 4.66 d	3.52 d hidden, 3.46 d hidden		3.13		
	q, j; β	A	7.00, 6.66	7.09 d, 7.06 d	5.99 m	3.91, 3.88	4.71 d, 4.61 d	3.42 d (19.0), 3.32 d (19.0)		3.01		
	r, k; α	B	7.04, 6.60	6.89 d 6.82 d	5.96 m	3.87, 3.84	4.72 d, 4.66 d	3.43 br s, 2 H		3.09		
	r, k; β	A	6.96, 6.60	6.98 br s, 2 H	5.96 m	3.86, 3.83	4.56 d, 4.45 d	3.32 d hidden, 3.23 d hidden		2.94		
	α	B	7.08, 6.75	7.07 d, 6.97 d	5.98 m	3.90, 3.87	4.72 s, 2 H	3.61 d (19.0), 3.45 d (19.0)		3.15		
	q, l; β	A	7.20, 6.79	7.12 s, 2 H	6.03 s	3.92, 3.90	4.64 s, 2 H	3.45 d hidden, 3.37 d hidden		3.04		
	α	B	7.09, 6.76	7.08 d, 6.96 d	5.99 m	3.88, 3.85	4.70 s, 2 H	3.62 d hidden, 3.37 d hidden		3.12		
	r, m; β	A	7.21, 6.80	7.09 s, 2 H	6.01 s	3.90, 3.87	4.62 s, 2 H	3.46 d hidden, 3.33 d hidden		3.00		
	n; β	A	7.20, 6.78	7.19 d, 7.11 d	6.05 s	4.04, 4.00	4.86 d, 4.84 d	3.68 d (19.0), 3.56 d (19.0)		3.26		
5·HCl[p]	*h;* α	B	7.06, 6.74	7.07 d, 6.95 d	5.97 m	3.89, 3.86	4.72 br s, 2 H	overlap		3.13		
	h; β	A	7.20, 6.78	7.10 s, 2 H	6.01 s	3.90, 3.88	4.64 d, 4.62 d	overlap		3.01		
	s, o; α	B	7.08, 6.80	7.14 d, 7.01 d	5.97 m	3.89, 3.84	4.75 d, 4.70 d	overlap		3.16		
	s, o; β	A	7.13, 6.84	7.16 s, 2 H	6.05 s	3.92, 3.86	4.66 s, 2 H	3.42 d (24.0), 3.33 d (24.0)		3.00		
	n; β	A	7.16, 6.79	7.25 d, 7.23 d	6.07 m	4.07, 4.03	4.88 d, 4.80 d	3.63 d (18.0), 3.48 d (18.0)		3.17		
5·CF_3COOH	*n;* β	A	7.14, 6.79	7.25 d, 7.22 d	6.06 m	4.07, 4.03	4.86 d, 4.78 d	3.62 d (18.0), 3.47 d (18.0)		3.16		

[a] Abbreviations: s, singlet; br s, broad singlet; d, doublet; q, quartet; m, multiplet. J values are given in parentheses in hertz. Chemical shifts of H-5 and H-6 are omitted. [b] $J_{11,12}$ = 8.0–9.0 Hz. [c] J_{gem} = 15.7–16.2 Hz. [d] Spectrum was recorded at 200 MHz. [e] Spectrum was recorded at 90 MHz. [f] Spectrum was recorded at 60 MHz. [g] $CDCl_3$. [h] CD_3OD. [i] $CDCl_3$–CD_3OD. [j] $CDCl_3$–TFA-*d* (4:1). [k] $CDCl_3$–TFA-*d* (19:1). [l] CD_3OD–TFA-*d* (4:1). [m] CD_3OD–TFA-*d* (19:1). [n] TFA-*d*. [o] D_2O. [p] Concentrations were 0.1 mol/L. [q] An amount of TFA-*d* of 16 times the equivalent weight of allocryptopine was added. [r] An amount of TFA-*d* of 4 times the equivalent weight of allocryptopine was added. [s] *t*-BuOH was used as an internal reference.

Table III. α- and β-Substituent Effects of Quasi-Axial and Quasi-Equatorial Hydroxyl and Acetoxyl Groups in Free Bases and N-Methyl Salts of Tetrahydroprotoberberines[a]

compds to be compared	orientation of hydroxyl or acetoxyl group	shift, δ C-13 (α)	shift, δ C-14 (β)
7[b]-1	ax′ OH	33.6[c]	5.2[c]
7[b]-2	eq′ OH	36.1[c]	6.3[c]
7[b]-1Ac	ax′ OAc	33.0[c]	4.1[c]
7[b]-2Ac	eq′ OAc	36.8[c]	2.3[c]
8β[b]-1β	ax′ OH	34.1[d]	2.9[d]
8α[b]-1α	ax′ OH	33.8[d]	3.8[d]
8β[b]-2β	eq′ OH	39.0[d]	3.3[d]
8α[b]-2α	eq′ OH	37.8[d]	3.6[d]
8β[b]-1Acβ	ax′ OAc	35.2[d]	1.7[d]
8α[b]-1Acα	ax′ OAc	33.6[d]	1.4[d]
8α[b]-2Acα	eq′ OAc	37.4[d]	1.9[d]

[a] Abbreviations: ax′, quasi-axial; eq′, quasi-equatorial. Positive values indicate downfield shifts. [b] Cited from ref 4i. [c] Determined from data on free bases. [d] Determined from data on N-methyl salts.

the form having the ten-membered ring I (Chart III) in basic medium while they exist as a tricyclic salt (II) and/or an N-quaternary salt (IV or V) in acidic medium. However, the exact structure of the salt in solution is still uncertain. The ^{13}C NMR spectra of allocryptopine in deuteriochloroform, deuteriochloroform–methanol-d_4 (3:1), and methanol-d_4 resemble each other and show the signal for the carbonyl group at 187.4–193.6 ppm. Allocryptopine (5) therefore exists in the form of the ten-membered ring I in these solvent systems. The ^1H NMR spectra of allocryptopine in deuteriochloroform–trifluoroacetic acid-d (19:1 and 4:1) comprised a set of relatively strong signals and of relatively weak signals, indicating the formation of two salts (α and β). The α/β ratio was 1.2:1, which was not changed after the sample was allowed to stand for 1 day. In the ^1H NMR spectra of allocryptopine in methanol-d_4–trifluoroacetic acid-d (19:1 and 4:1) the initial α/β ratio of 5:1 and 7:1 changed to 1.4:1 and 4:1, respectively, after the sample was allowed to stand for 1 h and then to 1:1.3 in both after 1 day. This suggests that the conversion of the α salt to the β salt occurs. The ^{13}C NMR spectra of allocryptopine in deuteriochloroform–trifluoroacetic acid-d (19:1) and methanol-d_4–trifluoroacetic acid-d (19:1) displayed two types of signals having an α/β ratio of 1:1 and showed a quaternary carbon at 93.2 and 92.2 ppm (α and β salts) and at 94.0 and 93.2 ppm (α and β salts) instead of the signal of carbonyl carbon. The ^1H NMR and ^{13}C NMR of allocryptopine (5) in trifluoroacetic acid-d comprise the signals due to the α salt. The evidence for the α salt was substantiated by the comparison of the ^{13}C shifts with those of allocryptopine hydrochloride as described later. The ^1H NMR and ^{13}C NMR spectra of allocryptopine hydrochloride in methanol-d_4 showed almost the same behavior as that of allocryptopine in methanol-d_4–trifluoroacetic acid-d. The α/β ratio estimated from the ^1H NMR spectrum was 1:1.3, and that did not change in the spectrum measured after 1 day. The ^1H NMR and ^{13}C NMR spectra of allocryptopine hydrochloride in D_2O also showed two types of signals. The ratio of β to α estimated from the ^1H NMR spectrum was 2.0. There is no change after the sample was allowed to stand overnight. The ^1H NMR and ^{13}C NMR spectra of allocryptopine in trifluoroacetic acid-d showed the signals due to one type of salt. This spectrum was different from that of allocryptopine hydrochloride in the same solvent. The difference of chemical shifts in both ^{13}C NMR spectra was in accord with that between the α and β salts observed in the spectra of allocryptopine hydrochloride in methanol-d_4 and D_2O. The spectra of allocryptopine and its hydrochloride in trifluoroacetic acid-d were assigned to the α and β salts, respectively, by comparison with the spectra in methanol-d_4 and D_2O. The ^1H NMR spectrum of allocryptopine trifluoroacetate (CF_3COO^- salt) in trifluoroacetic acid-d was consistent with that of allocryptopine hydrochloride in trifluoroacetic acid-d. The ^{13}C NMR spectra of the α and β salts of allocryptopine showed a quaternary carbon in the region of ca. 92.0–95.0 ppm. The IR spectra (KBr and $CHCl_3$) of allocryptopine hydrochloride showed no carbonyl band. The α and β salts therefore adopt a structure having a quaternary nitrogen (IV or V). Except for the different oxygen-containing substituents on the D ring, the α and β salts of allocryptopine correspond to replacement of hydrogen at C-14 in the tetrahydrocoptisine α- and β-N-methyl salts by a hydroxyl group. Conformations A and B were assigned to the β and α salts, respectively, in comparison with the ^{13}C NMR spectra of tetrahydrocoptisine (8) α- and β-N-methyl salts.[4i] The observed shifts (Table IV) are explained by the α-, β-, and γ-substituent effects of the hydroxyl group at the C-14 caused by replacement of the ring-junction hydrogen by the hydroxyl group. The shift found at C-8 in conformation B involves a low-field shift caused by replacement of the methylenedioxy group by methoxy groups at C-9 and C-10.[4i] These results suggest that the salt of allocryptopine readily undergoes a conformational exchange of IV and V via a tricyclic form (III) in methanol, but its exchange may not occur in trifluoroacetic acid and chloroform. Thus detailed analysis of the ^{13}C NMR spectra confirmed the structure assignment of the salts of the protopine-type alkaloids in solution.

Table IV. Shieldings of Allocryptopine Hydrochloride and Tetrahydrocoptisine α- and β-N-Methyl Salts[a]

compds to be compared	shieldings,[b] ppm C-6 (γ)	C-8 (γ)	C-13 (β)	C-14 (α)
5α–8α	1.2 (eq′)	−2.0 (ax′)	5.9 (ax′)	26.3 (ax′ or eq′)
5β–8β	−5.9 (ax′)	−4.6 (ax′)	6.5 (ax′)	25.1 (ax′)

[a] Orientation of hydroxyl group (ax′ = quasi-axial; eq′ = quasi-equatorial) is presented in parentheses. [b] Positive values indicate downfield shifts.

Experimental Section

Melting points are uncorrected. Mass spectra were determined on a JEOL-OIS instrument. ^1H NMR spectra were obtained on a Varian A 60D or a Nippon Electric-Varian Co. NV-21 spectrometer at 22.6 MHz or on a Varian XL-200 (200.06 MHz) spectrometer. ^{13}C FT NMR spectra were measured with an NV-21 spectrometer at 22.6 MHz in an 8-mm tube or a Varian XL-200 spectrometer at 50.31 MHz in a 10-mm tube. Chemical shifts are reported in parts per million relative to Me_4Si as an internal standard, except where noted. The conditions of the FT NMR measurements in an NV-21 and an XL-200 respectively, were as follows: spectral width, 5 and 13 kHz; pulse width, 15–30 and 7 μs (flip angle of about 20–45° and 40°); aquisition time, 0.8 (or 0.4) and 0.6 s; number of data points 8192 and 16K.

Ophiocarpine (1). A solution of dihydroberberine[3b] (3.37 g) in CH_2Cl_2 (100 mL) was added dropwise to a solution of m-chloroperbenzoic acid (2.6 g) in CH_2Cl_2 (100 mL) under N_2 at −70 °C. After warming to room temperature, the solution was washed

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with 5% aqueous $NaHSO_3$ followed by 5% aqueous $NaHCO_3$ and then saturated NaCl solution. The organic layer was dried and the solvent evaporated to yield a yellow-orange solid. The yellow powder was dissolved in a mixture of EtOH (200 mL) and water (40 mL), and $NaBH_4$ (2 g) was added. After 1 h additional $NaBH_4$ (2 g) was added, and the mixture was stirred overnight. The crystals were filtered and recrystallized from $CHCl_3$–MeOH to give ophiocarpine (**1**): 1.75 g; mp 248–252 °C (lit.[3b] 256–258 °C); mass spectrum, *m/e* (relative intensity) 355 (M^+, 2), 180 (11), 177 (14), 176 (100), 165 (10). The filtrate was concentrated, and water was added. The solution was basified with NH_4OH and extracted with $CHCl_3$. The organic layer was dried and the solvent evaporated to give ophiocarpine (1.1 g).

Ophiocarpine Acetate (1Ac). A solution of ophiocarpine (1, 220 mg) in Ac_2O (1 mL) was allowed to stand overnight at room temperature, and then ice–water was added to the reaction mixture. The solution was basified with NH_4OH and extracted with Et_2O. The Et_2O layer was dried and evaporated. The crystals were recrystallized from MeOH–CH_2Cl_2 to afford ophiocarpine acetate (**1Ac**): 160 mg; mp 174–175 °C (lit.[3a] mp 176–177 °C); mass spectrum, *m/e* (relative intensity) 397 (M^+, 10), 355 (22), 337 (35), 180 (100), 179 (46), 176 (26), 165 (20).

Epiophiocarpine (2). Dihydroberberine (2.5 g) was treated with diborane, and the resulting organoborane was oxidized by a method similar to that described in ref 3b. The resulting crystals were recrystallized from $CHCl_3$–MeOH to give epiophiocarpine (**2**): 1.53 g; mp 184–185 °C (lit.[3b] mp 178–179 °C); mass spectrum, *m/e* (relative intensity) 355 (M^+, 2), 180 (11), 177 (13), 176 (100), 165 (14).

Epiophiocarpine Acetate (2Ac). A solution of epiophiocarpine (**2**, 200 mg) in Ac_2O (1 mL) was kept for 5 h at room temperature, and then ice–water was added to the reaction mixture. The solution was basified with NH_4OH and extracted with Et_2O. The Et_2O layer was dried and evaporated. The crystals were recrystallized from acetone to afford epiophiocarpine acetate (**2Ac**): 200 mg; mp 187–190 °C (lit.[3a] mp 185–186 °C); mass spectrum, *m/e* (relative intensity) 397 (M^+, 9), 355 (29), 337 (45), 222 (18), 180 (100), 179 (45), 176 (27), 165 (23).

Ophiocarpine α- and β-*N*-Methyl Chlorides (1α and 1β). Ophiocarpine (**1**, 500 mg) was dissolved in $CHCl_3$ (50 mL) and acetone (50 mL). To this solution was added CH_3I (20 mL), and the reaction mixture was allowed to stand for 4 days at room temperature. The solution was concentrated, and the resulting crystals were filtered to yield the *N*-methyl iodide which was treated with AgCl in MeOH to convert it to ophiocarpine β-*N*-methyl chloride (**1β**): 440 mg; mp 258–260 °C dec.

Anal. Calcd for $C_{21}H_{24}O_5NCl{\cdot}0.5MeOH$: C, 61.20; H, 6.21; N, 3.32. Found: C, 61.32; H, 5.93; N, 3.26.

The filtrate was evaporated, and the residue was crystallized from acetone, giving the *N*-methyl iodide which was treated with AgCl in MeOH to convert it to ophiocarpine α-*N*-methyl chloride (**1α**): 87 mg; mp 210–213 °C dec.

Anal. Calcd for $C_{21}H_{24}O_5NCl{\cdot}H_2O$: C, 59.50; H, 6.18; N, 3.30. Found: C, 59.33, H, 6.00, N, 3.20.

Ophiocarpine Acetate α- and β-*N*-Methyl Chlorides (1Acα and 1Acβ). MeI (1 mL) was added to a solution of ophiocarpine acetate **1Ac** (280 mg) in acetone (20 mL), and the mixture was allowed to stand overnight at room temperature. The resulting crystals were filtered to produce a mixture of the α- and β-*N*-methyl iodides (370 mg) which was converted to a mixture of ophiocarpine acetate α- and β-*N*-methyl chlorides (**1Acα** and **1Acβ**, 1:3; 300 mg) as an oil.

Epiophiocarpine α- and β-*N*-Methyl Chlorides (2α and 2β). A mixture of epiophiocarpine (**2**, 200 mg) in acetone (10 mL) and MeI (0.5 mL) was allowed to stand overnight. The separated crystals were filtered to give the α-*N*-methyl iodide (177 mg) which was converted to epiophiocarpine α-*N*-methyl chloride (**2α**): 123 mg; mp 231–240 °C dec.

Anal. Calcd for $C_{21}H_{24}O_5NCl{\cdot}0.5MeOH$: C, 61.20; H, 6.21; N, 3.32. Found: C, 61.60; H, 5.96; N, 3.40.

The filtrate was evaporated and crystallized from MeOH to produce epiophiocarpine β-*N*-methyl chloride (**2β**): 20 mg; mp 235–242 °C dec.

Anal. Calcd for $C_{21}H_{24}O_5NCl{\cdot}2H_2O$: C, 57.07; H, 6.39; N, 3.17. Found: C, 57.19; H, 6.38; N, 3.45.

Epiophiocarpine Acetate α-*N*-Methyl Chloride (2Acα). MeI (1 mL) was added to a solution of epiophiocarpine acetate (**2Ac**, 127 mg) in acetone (1 mL). After the mixture was allowed to stand for 2 h, the resulting crystals were filtered to afford the α-*N*-methyl iodide (179 mg), which was converted to epiophiocarpine acetate α-*N*-methylchloride (**2Acα**): 128 mg; mp 183–185 °C.

Anal. Calcd for $C_{23}H_{26}O_6NCl{\cdot}0.5MeOH$: C, 60.84; H, 6.08; N, 3.02. Found: C, 60.98; H, 6.10; H, 3.00.

Thalictricavine α- and β-*N*-Methyl Chlorides (3α and 3β). A mixture of thalictricavine (**3**,[7] 400 mg) in acetone (40 mL) and MeI (2 mL) was placed in a glass-stoppered bottle and heated for 16 h at 60 °C. After the mixture cooled, the resulting crystals were filtered to give the β-*N*-methyl iodide (350 mg) which was converted to thalictricavine β-*N*-methyl chloride (**3β**): 190 mg; mp 208–230 °C dec.

Anal. Calcd for $C_{22}H_{26}O_4NCl$: C, 65.42; H, 6.49; N, 3.47. Found: C, 65.59; H, 6.60, N, 3.49.

The filtrate was evaporated, and the residue was treated with AgCl in MeOH to yield thalictricavine α-*N*-methyl chloride (**3α**): 150 mg; mp 177–180 °C dec.

Anal. Calcd for $C_{22}H_{26}O_4NCl{\cdot}MeOH$: C, 63.36; H, 6.94; N, 3.21. Found: C, 63.33; H, 6.60; N, 3.43.

Mesothalictricavine α-*N*-Methyl Chloride (4α). MeI (1 mL) was added to a solution of mesothalictricavine (**4**,[7] 220 mg) in acetone (5 mL). After the mixture was allowed to stand for 3 h, the separated crystals were filtered to yield the α-*N*-methyl iodide: 300 mg; mp 268–270 °C dec.

Anal. Calcd for $C_{22}H_{26}O_4NI$: C, 53.34; H, 5.29; N, 2.83. Found: C, 53.34; H, 5.34; N, 2.92.

The α-*N*-methyl iodide was converted to mesothalictricavine α-*N*-methyl chloride (**4α**): 235 mg; mp 240–243 °C dec.

Allocryptopine (5) Hydrochloride. Allocryptopine (**5**, 200 mg) was dissolved in MeOH (70 mL) and concentrated HCl (2.5 mL). After 30 min, the solution was evaporated to dryness. The residue was recrystallized from MeOH–acetone to give a white salt: 226 mg; 189–195 °C dec; IR Nujol) λ_{max} 3530, 3500 (br), 3360 (br) cm^{-1}. This salt was dissolved in MeOH (37 mL) and concentrated HCl (1.5 mL). The solution was evaporated to dryness. The residue was recrystallized from MeOH–acetone to afford yellow allocryptopine (**5**) hydrochloride: 200 mg; mp 185–195 °C dec; IR (KBr) λ_{max} 3660, 3380 (br), 3300 (br) cm^{-1}; IR ($CHCl_3$) 3450–3050 (br) cm^{-1}.

Anal. Calcd for $C_{21}H_{24}O_5NCl{\cdot}MeOH$: C, 60.34; H, 6.44; N, 3.20. Found: C, 60.63; H, 6.28; N, 3.37.

Allocryptopine (5) Trifluoroacetate. (i) Allocryptopine (**5**, 30 mg) was dissolved in MeOH (0.4 mL) and trifluoroacetic acid (0.1 mL). The solution was concentrated, and the resulting crystals were collected and recrystallized from MeOH to give allocryptopine (**5**) trifluoroacetate: 30 mg; mp 245–246 °C dec.

Anal. Calcd for $C_{21}H_{23}O_5N{\cdot}CF_3COOH$: C, 57.14, H, 5.00; N, 2.90. Found: C, 57.29; H, 4.99; N, 2.76.

(ii) Allocryptopine (**5**, 50 mg) was dissolved in trifluoroacetic acid (0.2 mL). To this solution was added $CHCl_3$ (0.8 mL), and the solvent was evaporated. The resulting crystals were recrystallized from acetone to give allocryptopine (**5**) trifluoroacetate (50 mg).

Registry No. **1**, 18090-55-6; **1α**, 82864-46-8; **1β**, 82838-72-0; **1Ac**, 18090-56-7; **1Acα**, 82838-73-1; **1Acβ**, 82864-47-9; **2**, 18090-57-8; **2α**, 82864-48-0; **2β**, 82864-49-1; **2Ac**, 18090-58-9; **2Acα**, 82864-50-4; **3**, 38969-46-9; **3α**, 82864-52-6; **3β**, 82864-51-5; **4**, 13166-15-9; **4α** Cl, 82864-54-8; **4α** I, 82864-53-7; **5**, 485-91-6; **5**·HCl, 58434-56-3; **5** trifluoroacetate, 82838-74-2; dihydroberberine, 483-15-8.

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