Characterization of an Unusual Tetrahydroprotoberberine Conformer by Carbon-13 Nuclear Magnetic Resonance Spectroscopy

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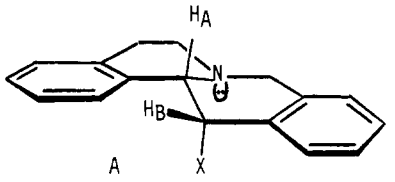
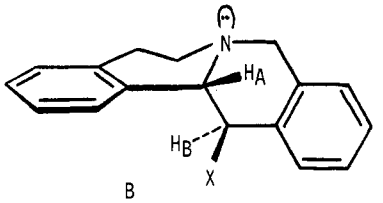
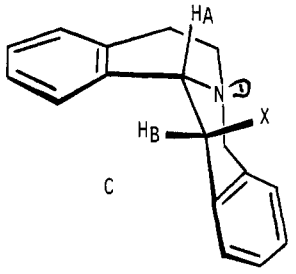
The ^{13}C and ^{1}H NMR spectra of certain 9,10- and 10,11-oxygenated tetrahydroprotoberberines were examined. Both of the two cis-fused as well as the trans-fused quinolizidine conformers were detected. The chemical shift of the C-5 carbon atom was found to be a reliable indicator of the presence of the unusual B/C cis-fused protoberberine conformer.

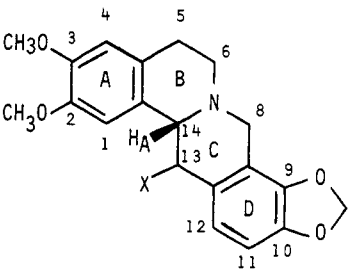
It is well-known that the tetrahydroprotoberberine alkaloids may exist as an equilibrium mixture of one B/C *trans*-quinolizidine (A) and two B/C *cis*-quinolizidine systems (B and C).[1] Although the configuration of the







nitrogen in structure A is opposite of that in B and C, the three systems are usually simply called conformers. The 13-methyltetrahydroprotoberberines such as cavidine (**3**) in which the 13,14-hydrogens are cis exist overwhelmingly in the trans-fused conformation A, while isomers such as thalictrifoline (**6**) in which the 13,14-hydrogens are trans are forced to adopt predominantly the cis-fused conformation B in chloroform solution in order to avoid a severe nonbonded interaction between the C-13 methyl group and the C-1 hydrogen which is present in the trans conformer A. The former formed a *trans*-quinolizidine salt (form A), while the latter formed a *cis*-quinolizidine salt (form B) in chloroform containing trifluoroacetic acid.[2] Tetra-



1, X= ⋯ CH_2OH
2, X= ⋯ CH_2OCOCH_3
3, X= ⋯ CH_3
4, X= ▬ CH_2OH
5, X= ▬ CH_2OCOCH_3
6, X= ▬ CH_3

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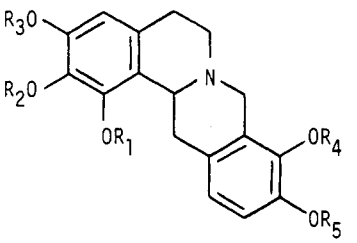
hydroprotoberberines bearing an oxygen substituent at C-1 such as capaurine (**13**) and capaurimine (**14**) derivatives



capaurine (**13**), R_1=H, R_2=R_3=R_4=R_5=CH_3
capaurimine (**14**), R_1=R_5=H, R_2=R_3=R_4=CH_3

exist in solution at room temperature as a mixture of the trans- and cis-fused conformations A and B. The equilibrium did not significantly favor either species. These alkaloids formed the cis salt (form B), and at low temperature the ^{13}C NMR spectra displayed signals for both conformations.[2,3] Conformers A and B have already been well characterized by a variety of IR and NMR methods, as well as by rates of quaternization and circular dichroism.[4] Although all of the naturally occuring protoberberine alkaloids reported to date exist preferentially as conformers A or B, several years ago a 13-(hydroxymethyl)tetrahydroprotoberberine intermediate **10** was synthesized and found to exist in conformation C due to stabilization involving an intramolecular hydrogen bond.[5]

(1) Jeffs, P. W. *Experientia* **1965**, *21*, 690. For previous work related to the study of the conformation of protoberberine alkaloids by NMR, see: Tourwé, D.; Van Binst, G.; Kametani, T. *Org. Magn. Reson.* **1977**, *9*, 341. Hughes, D. W.; Holland, H. L.; MacLean, D. B. *Can. J. Chem.* **1976**, *54*, 2252. Moulis, C.; Stanislas, E.; Rossi, J.-C. *Org. Magn. Reson.* **1978**, *11*, 398.

(2) Takao, N.; Iwasa, K.; Kamigauchi, M.; Sugiura, M. *Chem. Pharm. Bull.* **1977**, *25*, 1426.

(3) Takao, N.; Iwasa, K. *Chem. Pharm. Bull.* **1976**, *24*, 3185.

(4) Shamma, M.; Moniot, J. "Isoquinoline Alkaloids Research 1972-1977"; Plenum Press: New York, 1978; pp 252-253.

(5) Cushman, M.; Gentry, J.; Dekow, F. W. *J. Org. Chem.* **1977**, *42*, 1111.

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Table I. ^{13}C NMR Data on Tetrahydroprotoberberines in $CDCl_3$[a]

compd	major conformation	shift, ppm									
		$COCH_3$ or CH_3	C-5	C-13	C-6	C-8	C-14	CH_2OR	OCH_3	OCH_2O	C-1	C-4
1	A		28.73	43.66	50.91	52.76	63.10	65.72	55.60, 55.82	100.93	108.16	111.22
2	A	20.70	29.00	42.88	50.99	53.03	61.35	66.27	55.67, 55.89	100.98	108.50	111.08
4	C		23.37	40.14	48.29	43.75	59.31	69.72	55.59, 55.72	100.86	108.79	111.63
5	B and C	20.85	25.38	39.58	48.03	46.33	56.98	67.39	55.57, 55.77	100.88	109.06	111.58
6	B	21.96	27.16	33.63	46.26	49.38	63.24		55.28, 55.50	100.52	110.22	111.32
8	A	29.51	29.28	42.87	50.63	57.82	61.67	66.25	55.49, 55.49	100.35	105.36	108.03[b]
10	C		24.39	40.56	49.32	48.02	59.36	68.86	55.54, 55.76	100.35	105.65	108.54[b]
11	B and C	20.68	25.87	39.60	47.59	51.62	57.20	67.03	55.38, 55.55	100.25	105.83	108.45[b]
12	B	21.63	27.88	33.97	45.93	55.42	64.01		55.36, 55.48	100.14	106.84	108.36[b]

[a] The assignments of the ^{13}C chemical shifts were made from off-resonance decoupling and the comparison of the spectra of

Table II. ^{13}C NMR Data on Tetrahydroprotoberberines in $CDCl_3 + CF_3COOD$[a]

compd	major conformation	shift, ppm									
		$COCH_3$ or CH_3	C-5	C-13	C-6	C-8	C-14	CH_2OR	OCH_3	OCH_2O	C-1
2	A	19.97	25.92	39.34	52.54	53.00	64.55	65.96	55.77, 56.18	102.58	109.74
4	B		24.28	40.65	46.26	47.86	58.15	67.68	55.74, 55.79	102.53	109.72
	C		22.67	39.39	48.83	44.56	60.60	67.37	55.96, 55.96	102.32	108.99
5	B	20.31	23.83	40.24	46.33	47.64	58.10	65.40	55.74, 55.91	102.41	109.60[c]
6	B	19.12	23.76	34.39	44.75	48.07	62.81		55.48, 55.60	101.88	110.57
8	A	19.87	26.21	39.44	52.42	56.61	64.55	65.61	55.73, 55.73	101.90	104.42
10	B		24.26	40.83	46.10	52.78	58.39	67.40	55.54, 58.39	101.68	106.42
	C		23.27	39.46	48.56	49.45	60.46	66.76	55.54, 58.39		105.90
11	B	20.21	24.39	40.70	45.45	52.42	57.71	64.19	55.62, 55.74	101.46	106.61
12	B	19.11	24.36	34.95	44.44	53.24	63.24		55.69, 55.69	101.38	107.45

[a] The assignments of the ^{13}C chemical shifts were made from off-resonance decoupling and the comparison of the spectra of

More recently a related intermediate **4** was prepared during a thalictrifoline (**6**) synthesis, and compound **4** was also found to exist in the unusual tetrahydroprotoberberine conformation C.[6] The purpose of the present investigation was to find a ^{13}C NMR parameter which would correlate with conformer C. Such a parameter might be useful in the future to detect form C in the conformational equilibria of other tetrahydroprotoberberine alkaloids.

The ^{13}C NMR spectrum (Table I) of the amino alcohol **1** showed the C-6 signal at 50.91 ppm. The chemical shift of this signal can be used to distinguish clearly between forms A and B.[2,7] In compounds having predominantly conformation A, the C-6 chemical shifts are 51.0–51.6 ppm. The cis amino alcohol **1** as well as the 13-methyltetrahydroprotoberberines such as **3** exist in the trans conformation A. Also consistent with conformation A for compound **1** were the Bohlmann bands and the intramolecular hydrogen bond detected by IR spectroscopy.[8] The ^1H NMR spectrum of the trans amino alcohol **4** displayed a doublet (J_{AB} = 2.13 Hz) at δ 4.33 assigned to the proton at C-14. In addition, the absence of Bohlmann bands and a broad hydroxyl stretching absorption in the 3300–3100-cm^{-1} region, indicating the presence of an intramolecular hydrogen bond, indicate that compound **4** adopts the *cis*-quinolizidine conformation C.[5]

The signals for the aliphatic carbons at C-5, C-6, C-8, C-13, and C-14 in the trans amino alcohol **4** appeared at higher field than the corresponding carbons of the cis amino alcohol **1**. In addition, the carbon bearing the alcohol resonates at lower field in **4** than in **1**. The bond from N to C-8 is axial with respect to ring B in **4** and equatorial in **1**. The difference in β-substituent effects for axial and equatorial bonds therefore explains the higher field shifts at C-6 and C-14 in compound **4**.[9] Similarly,

(6) Iwasa, K.; Gupta, Y. P.; Cushman, M. *Tetrahedron Lett.* **1981**, 2333.

(7) Kametani, T.; Fukumoto, K.; Ihara, M.; Ujiie, A.; Koizumi, H. *J. Org. Chem.* **1975**, *40*, 3280.

(8) Wenkert, E.; Roychaudhury, D. K. *J. Am. Chem. Soc.* **1956**, *78*, 6417. Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157; **1959**, *92*, 1798.

C-9 or C-11	shift, ppm									
	C-12	C-14a	C-4a	C-8a	C-12a	C-2	C-3	C-9 or C-11	C-10	C=O
107.02	120.64	130.73	127.58[b]	116.90	126.05[b]	147.43[c]	147.52[c]	145.12	142.81	
106.17	122.14	130.54	127.84[b]	116.88	126.84[b]	147.21[c]	147.36[c]	145.39	143.06	170.68
106.88	120.69	127.28	126.61[b]	116.80	125.81[b]	146.58[c]	147.58[c]	145.10	143.11	
106.49	121.12	128.04	126.99[b]	116.73	126.26[b]	146.72[c]	147.47[c]	145.19	143.42	170.72
106.27	119.79	129.64	125.61	115.20	132.89	145.87[b]	147.26[b]	144.17	143.13	
108.30[b]	112.18	128.79	127.86[c]	126.31	128.08[c]	145.45	145.82	146.70[d]	147.58[d]	170.30
108.90[b]	110.96	128.19	126.98[c]	124.92	126.62[c]	145.57[d]	145.94[d]	147.55[e]	147.79[e]	
108.94[b]	111.08	129.18	127.28[c]	124.42	126.58[c]	145.27[d]	145.75[d]	147.21[e]	147.30[e]	170.51
108.81[b]	110.24	130.53	126.62	124.80	130.89	144.60[c]	145.67[c]	146.70[d]	147.27[d]	

the related alkaloids. [b-e] Assignments may be reversed within each footnote.

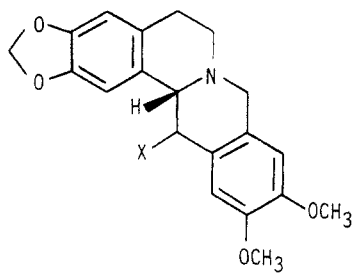
C-4	shift, ppm										
	C-9 or C-11	C-12	C-14a	C-4a	C-8a	C-12a	C-2	C-3	C-9 or C-11	C-10	C=O
111.90	107.85	122.43	124.59[b]	123.21[b]	108.45	118.94	148.64	149.20	147.50	144.00	173.57
111.90	109.72	121.10	121.85[b]	121.37[b]	107.36	122.53[b]	147.91[e]	149.71	147.69[e]	145.49	
111.90	109.25	121.54	122.09[b]	120.03[b]	109.64	123.40[b]	147.96[e]	149.56	147.11[e]	144.10	
111.87	109.93[c]	121.02	122.17[b]	121.90[b]	107.48	122.51[b]	147.71[e]	149.59	147.36[e]	145.19	174.78
111.37	108.92	120.42	122.86[b]	121.54[b]	106.41	127.75	147.38	149.56	146.16	144.52	
108.18[c]	108.96[c]	111.33	125.07	122.74	119.31[d]	119.61[d]	148.31	148.52	149.16[e]	149.25[e]	
109.05[c]	110.11[c]	110.54[c]	123.46[b]	122.40[b]	118.37	121.66[b]	147.52	149.09[e]	149.09[e]	149.52[e]	
109.05	109.05	110.84	124.62[b]	121.04[b]	119.76	121.73[b]	147.52	148.67[e]	148.82[e]	149.40[e]	
108.65	109.69[c]	110.03[c]	123.26[b]	123.04[b]	118.01	121.66[b]	147.04	148.93[e]	148.59[e]	149.54[e]	171.84
109.17	109.45[c]	110.06[c]	122.73[b]	123.86[b]	116.12	126.83	146.52	148.40[e]	148.58[e]	149.34[e]	

the related alkaloids. [b-e] Assignments may be reversed within each footnote.

the fact that the bond from C-14 to the aromatic A ring is equatorial with respect to ring C in **1** and axial in **4** causes C-13 and C-14 to appear at higher field in **4** due to the β- and α-substituent effects.[9] The upfield shift at C-5 in **4** is due to the γ-gauche interaction with C-8. The large upfield shift at C-8 arises from two γ-gauche interactions with C-5 and C-14a. The γ-gauche interaction between the alcohol bearing carbon atom and C-14a in compound **1** which is absent in **4** provides a rationale for the differences in chemical shift observed there.

Thalictrifoline (**6**) exists mainly in conformation B in an equilibrium mixture with the minor form A.[3,10] It is expected that since the effect of the substituent at C-13 on the chemical shifts of C-5, C-6, and C-8 is not significant, the difference in the chemical shifts of these carbons between thalictrifoline (**6**) and the trans amino alcohol **4** reflects the conformational change from form B to C. The signals for C-5 and C-8 in the trans amino alcohol **4** appeared at a higher field than those in thalictrifoline (**6**), while the signal for C-6 was observed at a lower field. The upfield shift of C-5 in **4** arises from the γ-gauche interaction with C-8. The higher field chemical shift of C-8 in compound **4** might result because the upfield shifts due to the γ-gauche interactions with C-5 and C-14a are stronger than the downfield shift caused by the change of the N to C-6 bond from axial in **6** to equatorial in **4**. The C-6 resonance may appear at a lower field in **4** than in **6** due to the loss of the γ-gauche interaction between it and C-8a and C-13 present in form B. This effect must be stronger than that resulting from the change of the N to C-8 bond from equatorial (form B) to axial (form C) which would move the C-6 resonance to higher field in compound **4** (form C). The same considerations explain the ^{13}C chemical shifts of the corresponding 13-substituted 2,3-methylenedioxy-10,11-dimethoxytetrahydroprotoberberine derivatives (**8**, **10**, and **12**). These results indicate that

(9) Dalling, D. K.; Grant, D. M. *J. Am. Chem. Soc.* **1967**, *89*, 6612. Grant, D. M.; Cheney, B. V. *Ibid.* **1967**, *89*, 5315.
(10) Yu, C. K.; MacLean, D. B.; Rodrigo, R. G. A.; Manske, R. H. F. *Can. J. Chem.* **1970**, *48*, 3673. Govindachari, T. R.; Nagarajan, K.; Charubala, R.; Pai, B. R.; Subramanian, P. S. *Indian J. Chem.* **1970**, *8*, 769.



7, X= ⁱⁱⁱⁱ CH_2OH
8, X= ⁱⁱⁱⁱ CH_2OCOCH_3
9, X= ⁱⁱⁱⁱ CH_3
10, X= ▬ CH_2OH
11, X= ▬ CH_2OCOCH_3
12, X= ▬ CH_3

conformation C may be detected by its higher field C-5 chemical shift. The arguments proposed here are in agreement with those previously made in regard to certain benzo[*a*]quinolizidines which were found to adopt a quinolizidine conformation corresponding to form C.[11]

The ^{13}C NMR spectrum of the cis amino acetate **2** is similar to that of the corresponding alcohol **1**. The chemical shift at C-6 (50.99 ppm) is typical of the trans-fused conformation A. In the ^1H NMR spectrum of the trans amino acetate **5** the C-8 protons appear as an AB quartet at δ 3.77 and 3.84, and the C-14 proton appears as a doublet (J_{AB} = 4.90 Hz) at δ 4.09. For the 13-substituted alkaloids having a trans relative configuration at C-13 and C-14, the coupling constant between H-13 and H-14 is small (ca. 3 Hz) in conformation C and large (ca. 8 Hz) in forms A and B. The coupling constant between H-13 and H-14 of the trans amino acetate **5** therefore suggests that this alkaloid exists as a conformational mixture of forms A and C or B and C. The ^{13}C NMR spectra of thalictrifoline (**6**) having form B and the cis amino acetate **2** with form A showed C-5 at 27.16 and 29.00 ppm, respectively, while the signal for the corresponding carbon of the trans amino alcohol **4** possessing conformation C appeared at 23.37 ppm. The C-5 carbon of the trans amino acetate **5** appears at 25.38 ppm, intermediate between the values observed for **2** or **6** and **4**. This also suggests that it exists as a conformational mixture of forms A and C or B and C. However, in conformation A of **5** there is a strong nonbonded interaction between the C-13 substituent and the hydrogen at C-1. Bohlmann bands are also not apparent in its IR spectrum. The proportion of form A is therefore low as in thalictrifoline (**6**). The trans amino acetate **5** is accordingly a 1:1 conformational mixture of B and C. The considerable presence of form C in **5** was observed in spite of the lack of an intramolecular hydrogen bond which stabilizes this conformation in compound **4**. The same conclusions may be derived from study of the ^1H NMR and ^{13}C NMR spectra of the corresponding 10,11-dimethoxy derivatives **8** and **10–12**. The equilibration of forms A and B has previously been proved for capaurine and capaurimine derivatives.[2] The arguments presented above now provide documentation for equilibration of the B and C forms in the trans amino acetates **5** and **11**.

Further evidence was derived from examination of the ^{13}C and ^1H NMR spectra of the salts formed on treatment of the alkaloids with trifluoroacetic acid in chloroform. The distinction between conformations A and B of the salts can be made on the basis of the chemical shift at C-6.[2] These values are 52.8–53.1 ppm for salts of conformation A and 44.5–46.0 ppm for salts of conformation B.[2] The chemical shift of 52.54 ppm for C-6 of the salt of the cis amino acetate **2** is consistent with conformation A. The cis amino alcohol **1** and the *cis*-13-methyltetrahydroprotoberberines such as cavidine **3** also form trans-fused salts (conformation A). On the other hand, the ^1H and ^{13}C NMR spectra of the salts of the trans amino alcohol **4** displayed two types of signals indicating the formation of two salts. The initial B/C ratio was 3:2, but the ^{13}C NMR spectrum recorded after several days showed the overwhelming predominance of the thermodynamically more stable salt. The ^1H NMR spectrum (Table IV) of this salt exhibited a one-proton doublet at δ 4.97 (J_{AB} = 7.38 Hz) which was assigned to the C-14 proton. This coupling constant indicates that the stable salt adopts conformation A or B. Conformation B was assigned to this salt on the basis of the chemical shift of C-6 (46.26 ppm) in its ^{13}C NMR spectrum (Table II). The ^1H NMR spectrum of the minor salt showed the C-14 methine proton as a broad singlet ($W_{1/2}$ = 6 Hz) at δ 5.09, which is consistent only with conformation C. The chemical shift of C-5 was observed at 22.67 ppm in its ^{13}C NMR spectrum. The chemical shifts of C-5 in the trans (form A) and cis (form B) salts appeared at 26.0–26.4 and 24.7–25.8 ppm, respectively.[2] The ^1H NMR spectrum of the salt of the corresponding trans amino acetate **5** displayed the C-14 proton as a doublet (J_{AB} = 7.46 Hz) at δ 4.92, indicating conformations A or B. Its ^{13}C NMR spectrum was in accord with that of the major salt of the trans amino alcohol **4**. The trans amino acetate **5**, as well as thalictrifoline (**6**), form the B/C cis-fused salt having conformation B. Analogous studies on the corresponding 10,11-dimethoxy derivatives **8** and **10–12** led to the same conclusions.

It has previously been noted that in the ^1H NMR spectra of *cis*-9,10-dioxygenated 13-methyltetrahydroprotoberberines having conformation A the C-8 protons appear as an AB quartet with a large chemical shift difference (0.6–0.7 ppm), and in the corresponding trans diastereomers with conformation B the difference in chemical shift is much smaller (0.1–0.2 ppm).[10] In the 10,11-dioxygenated compounds the signals of the C-8 protons are separated by 0.45–0.49 ppm in conformation B and 0.40–0.48 ppm in conformation A.[5,12] It has also been recognized that in 9,10-dioxygenated as well as 10,11-dioxygenated tetrahydroprotoberberines the center of the AB quartet appears downfield in conformation B relative to conformation A by about 0.15–0.20 ppm.[12] It is therefore of interest to compare these parameters with the values observed for conformation C (Table III). In the 9,10-dioxygenated tetrahydroprotoberberines, the center of the AB quartet assigned to the protons at C-8 is observed in conformations A–C at δ 3.84–3.85, 4.00, and 3.69, while the corresponding chemical shift values are seen at δ 3.78–3.83, 3.98, and 3.69 in the 10,11-dioxygenated compounds. In the case of 9,10- and 10,11-dioxygenated tetrahydroprotoberberine salts, the corresponding chemical shifts appear at δ 4.52–4.63 (A), 4.51–4.59 (B), and 4.22 (C) and at 4.55–4.64 (A), 4.48–4.58 (B), and 4.16 (C), respectively (Table IV). These results indicate that the chemical shifts at C-8 in the 9,10-dioxygenated compounds are in accord with those in the alkaloids with 10,11-substitution in each conformation, and the detection of the major form present among confor-

(11) Sugiura, M.; Takao, N.; Iwasa, K.; Sasaki, Y. *Chem. Pharm. Bull.* **1978**, *26*, 1168.

(12) Pai, B. R.; Nagarajan, K.; Suguna, H.; Natarajan, S. *Heterocycles* **1978**, *9*, 1287.

Table III. ^{1}H NMR Data on Tetrahydroprotoberberines in $CDCl_3$[d]

compd	major conformation	shift, ppm: H-1 and H-4	H-9 or H-11 and H-12	OCH_2O	OCH_3	CH_2OR	$COCH_3$ or CH_3	H-8	H-14	other protons
1[a]	A	6.60 (s), 6.63 (s)	6.76 (s, 2 H)	5.95 (m)	3.84 (s), 3.86 (s)	3.55 (d br s, J = 10.4), 3.75 (dd, J = 10.4, 2.10)		3.53 (d, J = 15.1), 4.15 (d, J = 15.1)	4.01 (br s, $W_{1/2}$ = 7.0)	3.25-3.15 (m, 3 H), 2.67-2.55 (m, 2 H)
2[a]	A	6.59 (s), 6.73 (s)	6.70 (d, J = 8.0), 6.73 (d, J = 8.0)	5.95 (m)	3.86 (s), 3.88 (s)	4.07 (s), 4.079 (d, J = 1.91)	1.80 (s)	3.51 (d, J = 15.6), 4.09 (d, J = 15.6)	3.81 (br s, $W_{1/2}$ = 6.0)	3.51-3.47 (m, 1 H), 3.11-3.08 (m, 2 H), 2.59-2.54 (m, 2 H)
3[c]	A	6.68 (s, 1 H), 6.75 (s, 3 H)		6.02 (m)	3.92 (s, 6 H)		0.93 (d, J = 7.0)	3.58 (d, J = 16), 4.12 (d, J = 16)	3.78 (d, $W_{1/2}$ = 6.0)	3.60-2.40 (m, 5 H)
4[a]	C	6.58 (s), 6.59 (s)	6.69 (d, J = 8.0), 6.77 (d, J = 8.0)	5.87 (m)	3.73 (s), 3.81 (s)	3.98 (dd, J = 10.3, 2.88), 4.19 (dd, J = 10.3, 2.88)		3.60 (d, J = 15.8), 3.79 (d, J = 15.8)	4.33 (d, J = 2.13)	3.40 (m, 1 H), 3.37-3.34 (m, 1 H), 3.25-3.19 (m, 1 H), 3.13-3.04 (m, 1 H), 2.75-2.67 (m, 1 H)
5[a]	B and C	6.61 (s), 6.71 (s)	6.68 (d, J = 8.0), 6.74 (d, J = 8.0)	5.92 (m)	3.82 (s), 3.84 (s)	4.38 (dd, J = 11.1, 5.10), 4.51 (dd, J = 11.1, 6.80)	2.08 (s)	3.77 (d, J = 15.9) 3.84 (d, J = 15.9)	4.09 (d, J = 4.90)	3.45 (m, 1 H), 3.17-2.97 (m, 3 H), 2.83-2.74 (m, 1 H)
6[b]	B	6.62 (s, 1 H), 6.71 (s, 3 H)		5.94 (s)	3.85 (s, 6 H)		1.46 (d, J = 6.8)	3.93 (d, J = 16), 3.96 (d, J = 16)	3.65 (d, J = 7.9)	3.60-2.80 (m, 5 H)
7[a]	A	6.58 (s), 6.60 (s), 6.60 (s), 6.73 (s)		5.92 (m)	3.84 (s), 3.86 (s)	3.61 (d br s, J = 10.5, $W_{1/2}$ = 3.8), 3.78 (dd, J = 10.5, 2.0)		3.63 (d, J = 14.5), 4.03 (d, J = 14.5)	3.96 (br s, $W_{1/2}$ = 4.4)	3.20-3.10 (m, 3 H), 2.63-2.54 (m, 2 H)
8[a]	A	6.55 (s, 2 H), 6.71 (s, (s, 1 H), 6.77 (s, 1 H)		5.89 (m)	3.84 (s), 3.86 (s)	4.11 (br s), 4.09 (s)	1.85 (s)	3.60 (d, J = 14.6), 3.96 (d, J = 14.6)	3.77 (br s, $W_{1/2}$ = 6.3)	3.35 (m, 1 H), 3.09-3.01 (m, 2 H), 2.55-2.49 (m, 2 H)
9[c]	A	6.62 (s, 2 H), 6.70 (s, 1 H), 6.73 (s, 1 H)		5.97 (s)	3.87 (s), 3.90 (s)		0.97 (d, J = 7.0)	3.68 (dd, J = 15.0), 3.92 (d, hidden)	3.70 (hidden)	3.40-2.30 (m, 5 H)
10[a]	C	6.42 (s), 6.55 (s), 6.60 (s), 6.73 (s)		5.83 (m)	3.77 (s), 3.86 (s)	4.01 (dd, J = 10.4, 3.60), 4.15 (dd, J = 10.4, 3.0)		3.62 (d, J = 15.0), 3.76 (d, J = 15.0)	4.312 (d, J = 2.10)	3.39-3.32 (m, 1 H), 3.30 (m, 1 H), 3.15-3.10 (m, 1 H), 3.05-2.98 (m, 1 H), 2.75-2.69 (m, 1 H)
11[b]	B and C	6.49 (s), 6.57 (s), 6.69 (s), 6.75 (s)		5.87 (m)	3.81 (s), 3.85 (s)	4.40 (dd, J = 11.0, 4.70), 4.51 (dd, J = 11.0, 6.80)	2.06 (s)	3.58 (d, hidden), 3.69 (d, J = 15.4)	4.06 (d, J = 4.90)	3.47-2.83 (m, 5 H)
12[c]	B	6.60 (s, 1 H), 6.65 (s, 1 H), 6.78 (s, 2 H)		5.97 (s)	3.90 (s, 6 H)		1.45 (d, J = 7.0)	3.80 (d, J = 15.5), 4.17 (d, J = 15.5)	3.67 (d, J = 8.0)	3.50-2.60 (m, 5 H)

[a] Spectrum was recorded at 470 MHz. [b] Spectrum was recorded at 80 MHz. [c] Spectrum was recorded at 60 MHz. [d] The J values are given in hertz.

Table IV. ^{1}H NMR Data on Tetrahydroprotoberberines in $CDCl_3$ + CF_3COOD[d]

compd	major conformation	shift, ppm: H-1 and H-4	H-9 or H-11 and H-12	OCH_2O	OCH_3	CH_2OR	$COCH_3$ or CH_3	H-8	H-14	other protons
1[a]	A	6.71 (s), 6.80 (s)	6.86 (d, J = 8.12), 6.92 (d, J = 8.12)	6.01 (m)	3.90 (s), 3.91 (s)	3.977 (like d, 2 H, J = 1.66),		4.25 (d, J = 15.5), 4.80 (d, J = 15.5)	4.903 (d, J = 3.48)	4.00-3.95 (m, 1 H), 3.66-3.65 (m, 1 H), 3.45-3.33 (m, 2 H), 3.02-2.98 (m, 1 H)
2[a]	A	6.71 (s), 6.77 (s)	6.84 (d, J = 8.10), 6.90 (d, J = 8.10)	6.03 (m)	3.89 (s), 3.90 (s)	4.14 (dd, J = 11.9, 4.20), 4.48 (dd, J = 11.9, 4.80)	1.88 (s)	4.34 (d, J = 15.7), 4.93 (d, J = 15.7)	4.99 (d, J = 3.66)	4.14 (m, 1 H), 4.03 (m, 1 H), 3.46 (m, 1 H), 3.33 (m, 1 H), 3.03 (m, 1 H)
3[c]	A	6.78 (s), 6.83 (s)	6.92 (s, 2 H)	6.07 (m)	3.98 (s, 6 H)		1.08 (d, J = 7.0)	4.38 (d, J = 16.0), 4.88 (J = 16.0)	4.88 (d, J = 2.0)	4.10-2.80 (m, 5 H)
4[a]	B	6.71 (s), 6.73 (s)	6.83 (d, J = 8.10), 6.88 (d, J = 8.10)	6.04 (m)	3.83 (s), 3.86 (s)	4.67 (dd, J = 11.9, 3.67), 4.88 (dd, J = 11.9, 5.36)		4.40 (d, J = 15.8), 4.63 (d, J = 15.8)	4.97 (d, J = 7.38)	overlapping between two salts
	C	6.60 (s), 6.76 (s)	6.850 (s), 6.854 (s)	5.95 (m)	3.76 (s), 3.86 (s)	4.24 (dd, J = 11.4, 3.17), 4.32 (dd, J = 11.4, 2.29)		3.98 (d, J = 15.8), 4.47 (d, J = 15.8)	5.09 (br s, $W_{1/2}$ = 6.0)	overlapping between two salts
5[a]	B	6.70 (s), 6.75 (s)	6.85 (d, J = 8.30), 6.87 (d, J = 8.30)	6.03 (br s)	3.82 (s), 3.87 (s)	4.54 (dd, J = 12.2, 3.39), 4.68 (dd, J = 12.2, 5.24)	2.14 (s)	4.37 (d, J = 15.8), 4.65 (d, J = 15.8)	4.92 (d, J = 7.46)	3.75 (m, 1 H), 3.52 (m, 2 H), 3.32 (m, 1 H), 3.14 (m, 1 H)
6[c]	B	6.75 (s), 6.80 (s)	6.92 (s, 2 H)	6.07 (s)	3.92 (s, 6 H)		1.50 (d, J = 7.0)	4.47 (d, J = 16.0), 4.72 (d, J = 16.0)	4.48 (d, J = 9.0)	3.90-2.90 (m, 5 H)
7[c]	A	6.70 (s, 2 H), 6.87 (s, 1 H)	6.75 (s, 1 H)	6.07 (s)	3.90 (s), 3.93 (s)	4.02 (like d, 2 H, J = 2.0)		4.42 (d, J = 15.5), 4.68 (d, J = 15.5)	4.87 (br s, $W_{1/2}$ = 7.0)	3.80-2.80 (m, 5 H)
8[b]	A	6.70 (s, 1 H), 6.71 (s, 3 H)		6.03 (s)	3.88 (s), 3.91 (s)	4.24 (dd, J = 11.8, 3.80), 4.53 (dd, J = 11.8, 4.0)	1.94 (s)	4.47 (d, J = 15.2), 4.82 (d, J = 15.2)	4.96 (d, J = 2.50)	4.07-3.04 (m, 5 H)
9[c]	A	6.67 (s, 1 H), 6.80 (s, 1 H)	6.72 (s, 2 H)	6.05 (s)	3.88 (s), 3.92 (s)		1.10 (d, J = 7.0)	4.43 (d, J = 15.5), 4.75 (d, J = 15.5)	4.80 (d, J = 3.50)	4.10-2.80 (m, 5 H)
10[a]	B	6.67 (s), 6.68 (s), 6.72 (s), 6.82 (s)		5.98 (m)	3.88 (s, 6 H)	4.63 (dd, J = 11.9, 3.97), 4.96 (dd, J = 11.9, 5.20)		4.27 (d, J = 15.3), 4.70 (d, J = 15.3)	4.878 (d, J = 7.32)	3.70-3.65 (m, 1 H), 3.53 (m, 1 H), 3.36-3.32 (m, 1 H), 3.28-3.06 (m, 1 H), 3.05-3.0 (m, 1 H)
	C	6.50 (s), 6.61 (s), 6.72 (s),		5.94 (m)	3.80 (s), 3.90 (s)	4.25 (dd, J = 11.5, 3.30), 4.31 (dd, J =		3.94 (d, J = 15.2), 4.38 (d, J = 15.2)	4.986 (d, J = 2.30)	4.01-3.83 (m, 1 H), 3.61 (m, 1 H), 3.44-3.38 (m, 1 H), 3.23-

		6.84 (s)			11.5, 2.90)				3.10 (m, 2 H)
11[b]	B	6.65 (s), 6.70 (s), 6.73 (s), 6.86 (s)	5.99 (s)	3.89 (s, 6 H)	4.55 (dd, hidden, J = ca. 10, 3.20), 4.75 (dd, hidden, 5.0)	2.14 (s)	4.30 (d, J = 15.3), 4.72 (d, J = 15.3)	4.88 (d, J = 7.60)	3.64–3.11 (m, 5 H)
12[c]	B	6.72 (s, 3 H), 6.88 (s, 1 H)	6.05 (br s)	3.93 (s, 6 H)		1.53 (d, J = 7.0)	4.35 (d, J = 16.0), 4.82 (d, J = 16.0)	4.42 (d, J = 9.0)	3.80–2.90 (m, 5 H)

[a] Spectrum was recorded at 470 MHz. [b] Spectrum was recorded at 80 MHz. [c] Spectrum was recorded at 60 MHz. [d] The J values are given in hertz.

mations A–C may be accomplished by comparison of the chemical shifts at C-8 in the ^1H NMR spectra. It may also be noted that in the 9,10-dioxygenated compounds, the differences in chemical shifts between the C-8 protons are 0.54–0.62, ca. 0.06, and 0.19 ppm in conformations A–C, while the corresponding values in the compounds with 10,11-substitution are 0.24–0.40, 0.37 and 0.14 ppm (Table III). In the case of 9,10-dioxygenated salts, the differences in chemical shifts between the C-8 protons are 0.40–0.50, 0.23–0.28 and 0.49 ppm in forms A–C. On the other hand, the corresponding values in the 10,11-dioxygenated salts are 0.26–0.35, 0.42–0.47, and 0.44 ppm (Table IV). It can be seen that these values are sensitive to conformational change, and attention should be paid to them during conformational assignment using ^1H NMR.

In the ^{13}C NMR spectra of the 9,10- and 10,11-dioxygenated tetrahydroprotoberberines, the chemical shifts at C-5 appear at 28.73–29.28, 27.16–27.88, and 23.37–24.39 ppm and the C-6 resonances at 50.63–50.99, 45.93–46.26, and 48.29–49.32 ppm in conformations A–C. The chemical shifts at C-8 were observed at 52.76–53.03, 49.38, and 43.75 ppm and at 57.82, 55.42, and 48.02 ppm in forms A–C of the 9,10- and 10,11-dioxygenated alkaloids, respectively. In the case of the salts of the alkaloids with 9,10- and 10,11-substitution, the signals at C-5 appeared at 25.92–26.21, 23.76–24.39, and 22.67–23.27 ppm in conformations A–C, and the corresponding values at C-6 are 52.42–52.54, 44.44–46.33. and 48.56–48.83 ppm. The chemical shifts at C-8 were observed at 53.00, 47.63–48.07, and 44.56 ppm and at 56.61, 52.42–53.24, and 49.45 ppm in the forms A–C of the 9,10- and 10,11-substituted alkaloids, respectively. These data (Tables I and II) allow unambiguous assignment of the three conformations. In conformation B, the C-6 resonance occurs at especially high fields, while in conformation C, the signals for C-5 and C-8 are shifted upfield. In conformation A, none appear at high field.

Experimental Section

The melting points were taken on a Mel-Temp apparatus and are uncorrected. NMR spectra were recorded on a Varian EM-360 60-MHz instrument or on a Vairan FT-80 spectrometer in $CDCl_3$ or $CDCl_3$ containing CF_3COOD. The high-resolution 470-MHz NMR spectra were obtained by using a Nicolet NTC-470 spectrometer and the data accumulated with 32K free-induction decays. ^{13}C NMR spectra were recorded on a JEOL PFT-100 spectrometer with $CDCl_3$ or $CDCl_3$ containing CF_3COOD as the solvent. Chemical shifts are reported in parts per million relative to Me_4Si as an internal standard. IR spectra were recorded on a Beckman IR-33 spectrophotometer. The mass spectra were determined on a CEC 21-110 spectrometer using an ion-source temperature of 190–200 °C and an ionization potential of 70 eV. The preparation of compounds **1**, **3**, **4**, **6**, **7**, **9**, **10**, and **12** has previously been reported.[5,6]

***cis*-2,3-Dimethoxy-9,10-methylenedioxy-13-(acetoxymethyl)tetrahydroprotoberberine (2).** Acetic anhydride (1 mL) and pyridine (1 drop) were added to the cis amino alcohol **1**[12] (175 mg, 0.47 mmol). The reaction mixture was stirred for 3 h at room temperature. Ice, ammonium hydroxide, and Et_2O were then added. The Et_2O extract was separated, dried over K_2CO_3, and evaporated to yield the cis amino acetate **2**: 172 mg (88%); mp 119–121 °C; IR ($CHCl_3$) 2800, 2760, 2740, 1720 cm^{-1}; mass spectrum, m/e (relative intensity) 411 (M^+, 47), 368 (7), 352 (100), 178 (12), 161 (8), 149 (8).

***trans*-2,3-Dimethoxy-9-10-methylenedioxy-13-(acetoxymethyl)tetrahydroprotoberberine (5).** Acetic anhydride (1 mL) and the trans amino alcohol **4** (100 mg, 0.27 mmol) were stirred for 3 h at room temperature. Ice and ammonium hydroxide were added, and the mixture was extracted with $CHCl_3$. The extract was dried over K_2CO_3 and evaporated to afford the trans amino acetate **5**: 100 mg (90%); mp 64–66 °C; IR ($CHCl_3$) 1720 cm^{-1}; mass spectrum, m/e (relative intensity) 411 (M^+, 78), 368

(7), 352 (100), 333 (7), 178 (12), 161 (11), 149 (9).

***cis*-2,3-Methylenedioxy-10,11-dimethoxy-13-(acetoxymethyl)tetrahydroprotoberberine (8).** A solution prepared by dissolving the cis amino alcohol **7** (400 mg, 1.08 mmol) in acetic anhydride (1 mL) was stirred at room temperature for 1 h. After addition of ice and ammonium hydroxide, the mixture was extracted with $CHCl_3$. The extract was dried over K_2CO_3 and evaporated. The residue was recrystallized from acetone–Et_2O to produce the cis amino acetate **8**: 412 mg (93%); mp 184–186 °C; IR ($CHCl_3$) 2800, 2760, 2740, 1725 cm^{-1}; mass spectrum, *m/e* (relative intensity) 411 (M^+, 92), 352 (67), 338 (22), 236 (31), 194 (43), 176 (100).

***trans*-2,3-Methylenedioxy-10,11-dimethoxy-13-(acetoxymethyl)tetrahydroprotoberberine (11).** A mixture of acetic anhydride (1 mL) and the trans amino alcohol **10** (400 mg, 1.08 mmol) was stirred for 1.5 h. Further treatment as above gave the trans amino acetate **11**: 382 mg (86%); mp 162–163 °C; IR ($CHCl_3$) 1723 cm^{-1}; mass spectrum *m/e* (relative intensity) 411 (M^+, 70), 352 (59), 338 (17), 236 (29), 194 (44), 176 (100).

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Conversion of a Primary Amino Group into a Nitroso Group. Synthesis of Nitroso-Substituted Heterocycles[1]

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2-Aminopyridine, 2-amino-4-methylpyridine, 1-aminoisoquinoline, 2-aminopyrimidine, and 2-aminopyrazine have been converted to the corresponding nitroso compounds by reaction with dimethyl sulfide and *N*-chlorosuccinimide, deprotonation of the resulting sulfonium salts with sodium methoxide to the *S,S*-dimethylsulfilimines, and oxidation with *m*-chloroperbenzoic acid. These extremely reactive nitroso compounds condense readily with 1,3-dienes to give 3,6-dihydro-1,2-oxazines and with aromatic amines in the presence of acid to give azo dyes and are smoothly oxidized with ozone or sodium hypochlorite to the corresponding nitro-substituted heterocycles.

Although aromatic nitroso compounds have been known since the early days of organic chemistry,[2] only a few heterocyclic nitroso compounds are known. Direct nitrosation by electrophilic substitution is possible only with electron-rich systems (e.g., many of the five-membered heterocycles and certain six-membered systems which, like 6-aminopyrimidines, react as primary enamines).[3] Some heterocyclic nitroso compounds have been prepared by reduction of the corresponding nitro compounds, but this route is precluded for most electron-poor (π-deficient) heterocycles such as the azines which cannot be nitrated. As a consequence, some of the simplest heterocyclic nitroso compounds were unknown prior to the present study.

It is well-known that cyclic amidines and their vinylogues (e.g., 2- and 4-aminopyridine) react with electrophiles at the ring nitrogen rather than on the exocyclic amino group.[4] It occurred to us that electrophilic attack on the exocyclic amino group should be possible provided that electron density were concentrated at that position; a direct way of assuring this result would be to convert the amino group into a sulfilimine (**1**, Scheme I). Several methods are available for accomplishing this latter transformation.[5] Indeed, the *S,S*-dimethylsulfilimines from various aminopyridines and from 2-aminopyrimidine have been described.[6] These and the other sulfilimines described in this paper are most conveniently prepared from the amino-substituted heterocycle, dimethyl sulfide, and *N*-chlorosuccinimide in methylene chloride followed by deprotonation of the resulting sulfonium salt with sodium methoxide.

These sulfilimines are smoothly converted to the corresponding heterocyclic nitroso compounds (**2**) by oxidation with a slight excess of *m*-chloroperbenzoic acid in dry methylene chloride at 0 °C.[7] The nitroso compounds appear to be monomeric (green) in solution but dimeric (yellow) in the solid state. Some are too unstable to be isolated (see the Experimental Section), but they can be trapped in situ by all of the reactions described below. For example, these heterocyclic nitroso compounds are superb dienophiles and react instantly with dienes such as 2,3-dimethyl-1,3-butadiene or 1,3-diphenylisobenzofuran to

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(7) While the work described herein was in progress, a report appeared[8] which described an inadvertent amino-to-nitroso conversion under similar reaction conditions. In an attempt to prepare *S,S*-dimethyl-*N*-(*p*-nitrophenyl)sulfoximine from the corresponding sulfilimine by oxidation with *m*-chloroperbenzoic acid in the presence of potassium carbonate, *p*-nitrosonitrobenzene was unexpectedly formed. The desired sulfoximine could be obtained provided that the *m*-chloroperbenzoic acid was completely converted into its anion prior to addition of the sulfilimine; in the absence of potassium carbonate, the nitroso compound was formed. No attempt was made to pursue the possible generality of this selective oxidation reaction.

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