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CONFORMATIONAL ANALYSIS OF TETRAHYDROPROTOBERBERINES BY CARBON-13 NMR SPECTROSCOPY

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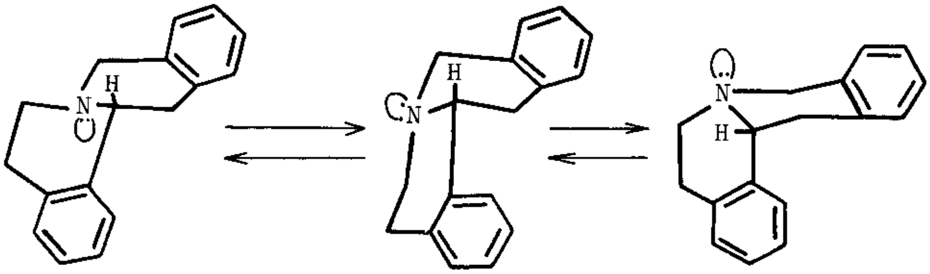
The preferential conformation of tetrahydroprotoberberines is easily assignable by comparison of the chemical shift of C(6) in carbon-13 nmr spectroscopy. It is possible, furthermore, to distinguish the position of substituents in 9,10- and 10, 11-substituted tetrahydroprotoberberines by the difference in chemical shift of C(8).

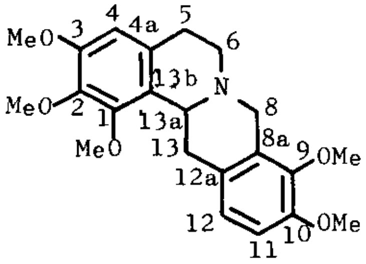
Dibenzo[a,g]quinolizidine is the skeleton of tetrahydroprotoberberine alkaloids. If the B and C rings of dibenzo[a,g]quinolizidine take half-chair conformations, it exists in the equilibrium of one trans (1) and two cis conformations (2 and 3), but mainly as the thermodynamically more stable trans-quinolizidine.[1] X-Ray analyses of the hydrobromides of capaurine and isocapaurimine, and capaurimine p-bromobenzoate revealed that they exist as the cis-quinolizidine form (2) in the crystalline state.[2] It was considered that an energetically unfavorable non-bonded interaction of the C - 1 substituent to the C - 13 hydrogens destabilized the trans form. Such an unfavorable interaction still remains in the other cis form (3), which is the least preferred one.

The ir and nmr spectra are widely used in determination of conformation in quinolizidine type compounds. The presence or absence of Bohlmann bands in the ir spectra is utilized in order to distinguish trans-quinolizidines from cis-quinolizidines.[3] However several workers have found that these bands did not give definite results.[4]

In the nmr spectroscopy of benzo[a]- and indolo[a]quinolizidines, an angular proton of the trans form resonates at a higher field than 3.8 ppm, whereas cis forms are characterized by a downfield signal below 3.8 ppm.[5] Since the signals due to methoxyl groups of tetrahydroprotoberberines appear around 3.8 ppm, it is normally difficult to observe the signal due to the angular proton.[6] Recently ^{13}C-H coupling constants of C-H bonds next to the bridgehead nitrogen in benzo- and indoloquinolizidines were used for determination of the preferential conformation.[7]



(1) (2) (3)



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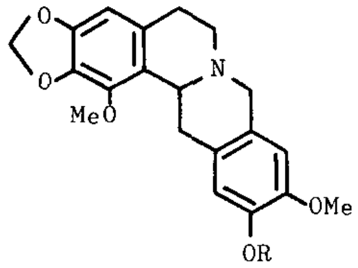
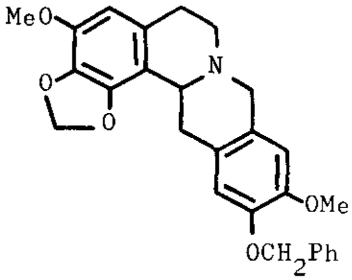


(5) R=CH$_2$Ph

(6) R=H



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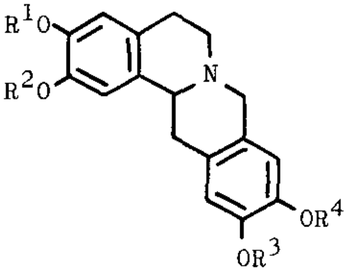
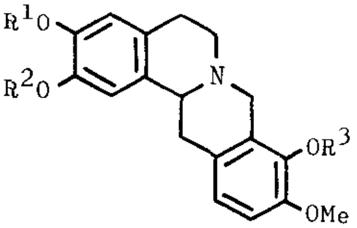


(8) R^1=R^2=R^3=R^4=Me

(9) R^1+R^2=R^3+R^4=CH$_2$



(10) R^1+R^2=CH$_2$, R^3=Me

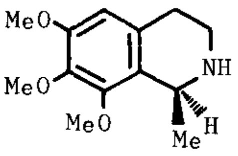
(11) R^1=R^2=Me, R^3=H

In the carbon-13 nmr spectroscopies of some tetrahydroprotoberberines in deuteriochloroform, the assignments of the chemical shifts, based on the comparison of the spectra[8,9] and on splitting patterns recorded under off-resonance decoupled conditions, are shown in Table 1. It was expected that the carbons of *cis*-quinolizidines resonate at a higher region than those of *trans*-quinolizidines owing to steric effects.[10] Although the chemical shifts of C(5), (8), (13) and (13a) in the dibenzo[a,g]quinolizidines would be influenced directly by the substitutents on the adjacent benzene rings, the preferential conformation was firmly determined by comparison of the chemical shift of C(6). Tetrahydroprotoberberines (4,5 and 6) having a methoxyl group at C - 1 position showed the signal due to C(6) at a higher field than 48.3 ppm, a fact which indicated *cis*-quinolizidine conformation. The corresponding signals of tetrahydroprotoberberines (8,9,10 and 11) having one hydrogen at the C-1 position appeared at about 51.3 ppm, even when the substituents on rings A and D were changed. 1,2-Methylenedioxy-3-methoxytetrahydroprotoberberine (7) interestingly showed the signal at 51.1 ppm, indicating the preferential *trans* form, an indication which was supported by the following reasons. In the ir spectrum of this compound in chloroform solution, strong Bohlmann bands were observed. Brossi and coworkers found by X-ray analyses that the C-methyl group is *axial* in O-methylanhalonidine (12) hydrobromide but is *pseudoequatorial* in anhalonine (13) hydrobromide.[11] The latter conformation corresponds to the *trans*-quinolizidine. Thus the distance between the hydrogens at C - 13 and oxygen at C - 1 position in *trans*-quinolizidine of 1,2-methylenedioxy-3-methoxytetrahydroprotoberberine is longer than in the case of 1,2,3-trimethoxytetrahydroprotoberberine derivatives.

Table 1 Carbon-13 Chemical Shifts of Tetrahydroprotoberberines.[12]

(All shifts are in parts per million from TMS:
$*$ and ^{o} represent the signals where the assignments may be reversed)

	Compound							
Carbon	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
C-1	151.9	147.5	147.8	142.4	108.5*	105.6	105.5	109.1
C-2	140.2	134.3	134.5	133.4	147.3	146.1	145.9^o	147.5
C-3	150.1	140.2	140.4	145.3	147.3	146.1	146.1^o	147.5
C-4	107.4	102.9	103.1	107.0	111.3	108.5	108.4	111.5
C-4a	130.6*	128.6	128.5	129.5	126.6	127.9	127.7	127.0
C-5	30.0	30.1	30.1	30.0	29.0	29.6	29.6	29.2
C-6	48.3	47.1	46.9	51.1	51.3	51.3	51.4	51.5
C-8	53.3	57.2	57.3	58.0	58.2	58.7	54.0	53.7
C-8a	128.3*	126.6*	124.8*	126.8*	126.2	127.4	127.7*	121.4
C-9	150.9	109.7	108.7	109.8	109.5*	106.5	150.2	141.6
C-10	145.3	146.6	145.3	146.8	147.3	146.1	145.0	144.2
C-11	110.9	147.9	144.3	148.0	147.3	146.1	110.9	109.1
C-12	124.0	114.3	114.6	114.5	111.3	108.5	123.9	119.3
C-12a	128.6*	127.6*	127.3*	127.8*	126.2	127.4	128.6*	128.1
C-13	33.0	31.9	31.6	34.0	36.3	37.1	36.5	36.5
C-13a	55.5	54.9	54.7	57.1	59.5	59.9	59.6	59.4
C-13b	124.2	123.6	123.9	114.1	129.6	130.9	130.8	129.9
$-O\underline{C}H_3$	60.6(x2) 60.1 55.8(x2)	59.2 56.0	59.5 56.1	56.5 56.3	55.8(x4)		60.1 55.8	56.2(x3)
$-O\underline{C}H_2O-$		100.5	100.7	101.2		100.8(x2)	100.7	
$-O\underline{C}H_2Ph$		70.9		71.2				
$-OCH_2\underline{C}_6H_5$		128.3 127.1 126.4		128.5 127.4 126.8				



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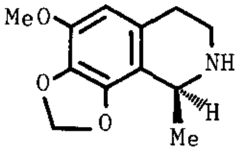

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It is probably worthwhile to mention the difference of the C(8) chemical shifts between the 9,10- and 10,11-substituted tetrahydroprotoberberines. The C(8) of the 9,10-substituted compounds appeared at 54.0 ppm or a higher field. On the other hand, the C(8) of 10,11-substituted ones resonated at a lower field than 57.0 ppm. The steric perturbation by the C - 9 substituent caused this difference, an observation which is useful for structure determination of some natural products.

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6 When the nmr spectra were taken in deuteriotoluene, the signal due to the angular proton was shifted down field and no longer masked by signals of methoxyl groups. Details of the data will be published elsewhere.

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12 The spectra were taken in deuteriochloroform (0.3 - 0.7 M) with a JNM-PFT-100 system equipped with a JNM-PS-100 spectrometer operating at 25.15 MHz.

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