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STEREOCHEMICAL ASPECTS AND ^{13}C NMR SPECTROSCOPY OF THE BERBAMINE CLASS OF BISBENZYLISOQUINOLINE ALKALOIDS[1]

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Summary: An analysis of the ^{13}C NMR spectra of bisbenzylisoquinoline alkaloids of the berbamine type shows the dependence of spectroscopic properties on preferred conformation.

Apart from the interesting pharmacological activity shown by some members[2], the bisbenzylisoquinoline alkaloids form a particularly attractive group for studying the interrelationship between preferred conformation and spectroscopic properties, as a result of the rather inflexible rings possessed by the majority of these bases. In continuation of our project on isoquinoline alkaloids[3,4], we have accordingly selected the berbamine class for an exhaustive ^{13}C NMR spectroscopic analysis. A correlation of the spectra of phaeanthine 1a, tenuipine 1b, nortenuipine 1c, O-acetylnortenuipine 1e, berbamine 1d, and O-acetylberbamine 1f has allowed an assignment of chemical shift to be made for each carbon in these bases (Table). The assignments were facilitated by comparisons with model compounds, by consideration of the known effects of electron-withdrawing groups (phenyl and acetyl) in a benzene ring[5], and of the multiplicity of the signals in the coupled spectra.

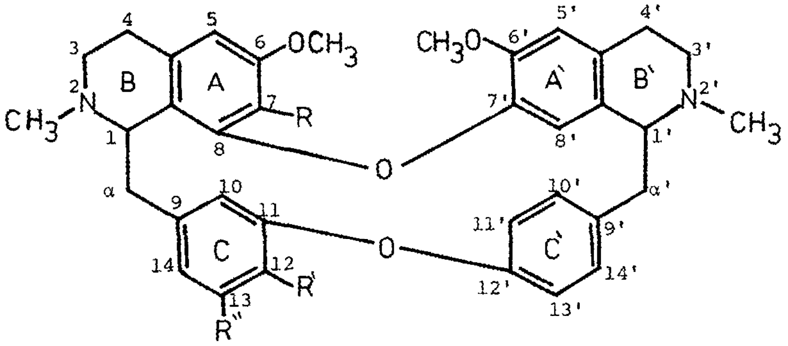
The values for the sp^3 carbon shifts which result from this analysis are of particular interest. The methylene and methine shifts in the case of 1a can be divided into two groups: those with signals at 25.3, 38.3, 45.3 and 63.9 ppm (ring B') and those at 22.1, 41.9, 44.1 and 61.4 ppm (ring B). The first group can be attributed to C-4', C-α', C-3' and C-1' respectively, which show slight shielding as compared to corresponding values for a monobenzyltetrahydroisoquinoline alkaloid[3,8]. It is assumed in these assignments that rings A', B' and C' have a folded conformation closely analogous to that of a monomeric N-methylbenzylisoquinoline alkaloid[6], in which ring B' adopts a half-chair form with the N-methyl group pseudoequatorial, as established for the solid phase by X-ray crystallographic analysis[2] of the enantiomeric alkaloid tetrandrine 1g; that this conformation is largely maintained in solution is suggested by its properties and

TABLE

	1a	1b[π]	1c	1d	1e	1f
C-1	61.4	61.4	61.5	62.0	61.4	62.0
C-3	44.1	44.0	44.0	44.7	43.8	44.8
C-4	22.1	22.0	21.7	23.9	22.0	23.8
C-4a	128.0†	127.5†	123.0ξ	129.0	134.9	127.1
C-5	105.8	105.6	104.7†	105.4	105.6	105.4
C-6	151.2	151.2	145.6	151.7	149.7	151.7
C-7	137.9	136.6	134.3	136.8	130.9	137.8
C-8	148.2	148.3	141.6	147.7	147.0	147.6
C-8a	123.0	122.4	123.0ξ	120.1	122.4	120.3
C-α	41.9	42.2	42.2	37.5	42.7	37.6
C-9	134.9	136.4	136.5	134.0	136.5	137.8
C-10	116.2	110.3	110.3	115.3	110.5	116.9
C-11	146.9	143.1	143.1	143.8	143.1	151.4
C-12	149.3	133.4	133.3	147.3	133.4	141.5
C-13	111.6	148.1	148.2	114.6	148.4	121.2
C-14	122.6	104.5	104.5†	123.5	104.6	123.3
C-1'	63.9	63.7	63.5	63.4	64.1	63.7
C-3'	45.3	45.0	45.0	45.2	45.5	45.9
C-4'	25.3	24.8	25.2	24.8	24.9	25.5
C-4α'	128.1†	127.9†	128.2¶	127.9	128.9	128.5
C-5'	112.7	112.5	112.8	111.1	112.5	111.0
C-6'	148.5	148.5	148.6	149.9	148.7	149.7
C-7'	143.7	143.6	143.3	143.4	142.6	143.3
C-8'	120.0	120.0	120.4	119.7	120.5	119.6
C-8a'	127.8†	127.2†	127.7¶	126.3	127.7	126.6
C-α'	38.3	38.2	37.5	38.2	39.7	38.1
C-9'	134.9	134.9	135.1	134.6	134.9	135.2
C-10'	129.9ξ	129.9ξ	129.9§	130.0†	130.0†	130.1†
C-11'	121.7	121.5	121.4	121.2	121.6	121.9
C-12'	153.6	153.3	153.1	153.9	153.4	153.9
C-13'	121.7	121.5	121.4	121.4	121.6	121.7
C-14'	132.4ξ	132.4ξ	132.3§	132.0†	132.4†	132.1†
NMe	42.3¶	42.0	42.2	42.6ξ	42.2ξ	42.7
NMe'	42.6¶	42.0	42.2	42.0ξ	42.1ξ	42.7
OMe	55.8	55.5	56.0	55.7	55.9	55.7
	56.1	55.5	56.0	55.7	55.7	55.5
OMe(C-7)	60.1	60.0		60.3		60.4
OCH_2O		101.2	101.2		101.3	

(TABLE continued)

The spectra were recorded in the Fourier transform mode on a Varian XL-100-15 spectrometer at 25.2 MHz in $CDCl_3$ solution. The δ values are in ppm downfield from TMS. π: some methanol was added for better solution of the compound. †,ξ,¶,§: signals within the vertical columns may be reversed. δ $\underline{C}OCH_3$ and $CO\underline{C}H_3$ for 1e: 167.5 and 19.7; for 1f: 169.0 and 20.8 respectively.



1a, R = R' = OMe; R'' = H (*R*,*R*)
1b, R = OMe; R' = R'' = $-OCH_2O-$ (*S*,*S*)
1c, R = OH; R' = R'' = $-OCH_2O-$ (*S*,*S*)
1d, R = OMe; R' = OH; R'' = H (*R*,*S*)
1e, R = $-\mathrm{O}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\mathrm{Me}$; R' = R'' = $-OCH_2O-$ (*S*,*S*)
1f, R = OMe; R' = $-\mathrm{O}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\mathrm{Me}$; R'' = H (*R*,*S*)
1g, R = R' = OMe; R'' = H (*S*,*S*)

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reactions[2]. An extended conformation is attributed to rings A,B and C of 1a with ring B in a half-chair form, as for 1g; the N-methyl group and C-α are assigned pseudoaxial conformations, which produces a difference in shift of the methylene carbons associated with ring B as compared to those of B'. This is reflected in the shielding experienced by C-4, which now has a γ-gauche relationship to the N-methyl group; C-3 shows only slight shielding, whereas C-α is considerably deshielded. The shielding observed on C-1 is attributed to the γ-effect of the oxygenated function at C-8. The two N-methyl carbons are practically equivalent (42.3 and 42.6 ppm), and the methoxyl carbon signals appear at normal field (*ca.* 56 ppm), except for that attached to C-7, which being sterically hindered, resonates at 60 ppm. In the ^1H NMR spectrum of 1a, however, the N-2 methyl group and the methoxyls at both C-7 and C-6' are clearly shielded[7], showing the higher sensitivity of proton shifts to anisotropic effects.

The shifts of the sp^3 carbons of tenuipine 1b, nortenuipine 1c, and its acetyl derivative 1e are in good agreement with those in corresponding positions in 1a. These bases belong to an enantiomeric series to 1a, and the main structural difference consists in replacement of the methoxyl in ring C by a methylenedioxy group; the carbon of the latter resonates at normal field

(101.2 ppm). In berbamine 1d, which belongs to a diastereomeric series, the methoxyl and methylimino carbons show shifts corresponding to those for 1a. As far as the methylene and methine carbons are concerned, signals at 24.8, 45.2 and 63.4 ppm were assigned to C-4', C-3' and C-1' respectively, and those at 23.9, 44.7 and 62.0 ppm to C-4, C-3 and C-1. It is apparent that sp^3 carbons in equivalent positions in the two benzylisoquinoline moieties give signals much closer together than in the case of 1a-1c; for C-α and C-α' of 1d, the signals are very similar (37.5 and 38.2 ppm), whereas in the case of 1a, Δδ for C-α and C-α' amounts to 3.6 ppm, while for 1b with a methylenedioxy group in ring C, the difference is even greater (4.0 ppm); similarly, Δδ for C-4 and C-4' of 1d is 0.9 ppm as compared to 3.2 ppm for 1a. These data suggest that there is less steric crowding in the *R*,*S* than in the *R*,*R* or *S*,*S* series, an inference which is supported by the difference in shift of the C-6' methoxy groups (ca. 3.6 and 3.2 ppm) in their respective ^{1}H NMR spectra[7]. It would appear, moreover, that the distinction shown in the *R*,*R* and *S*,*S* series between the completely extended and completely folded conformations of the two coclaurine units is less sharp in the *R*,*S* series.

It is evident that the chemical shifts of the benzylic methylene carbons in these types of bisbenzylisoquinoline alkaloids are especially sensitive to the configurations at the chiral centres, and together with the ^{1}H NMR data, could be of diagnostic value in distinguishing alkaloids of different stereochemistry.

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REFERENCES

1. We have found our results are more easily described in terms of the classical system of numbering (c.f. reference 6, p. 115) rather than the more systematic scheme proposed by M. Shamma and J.L. Maniot in "Isoquinoline Alkaloid Research, 1972-1977", Plenum Press, New York, 1978, p. 71.
2. C.J. Gilmore, R.F. Bryan, and S.M. Kupchan, *J. Amer. Chem. Soc.*, 1976, 98, 1947.
3. A.J. Marsaioli, E.A. Rúveda, and F. de A.M. Reis, *Phytochemistry*, 1978, 17, 1655.
4. A.J. Marsaioli, F. de A.M. Reis, A.F. Magalhães, E.A. Rúveda, and A.M. Kuck, *Phytochemistry*, 1979, 18, 165.
5. H.E. Gottlieb, *Israel J. Chem.*, 1977, 16, 37.
6. M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York, 1972, p. 81.
7. I.R.C. Bick, J. Harley-Mason, N. Sheppard, and M.J. Vernengo, *J. Chem. Soc.*, 1961, 1896.
8. E. Wenkert, B.L. Buckwalter, I.R. Burfitt, M.J. Gasić, H.E. Gottlieb, E.W. Hagaman, F.M. Schell, and P.M. Wovkulich, in "Topics in Carbon-13 NMR Spectroscopy", (G.C. Levy, ed.), vol. 2, Wiley-Interscience, New York, 1976.

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