STEREOCHEMISTRY OF BERBINE AND SOME RELATED COMPOUNDS

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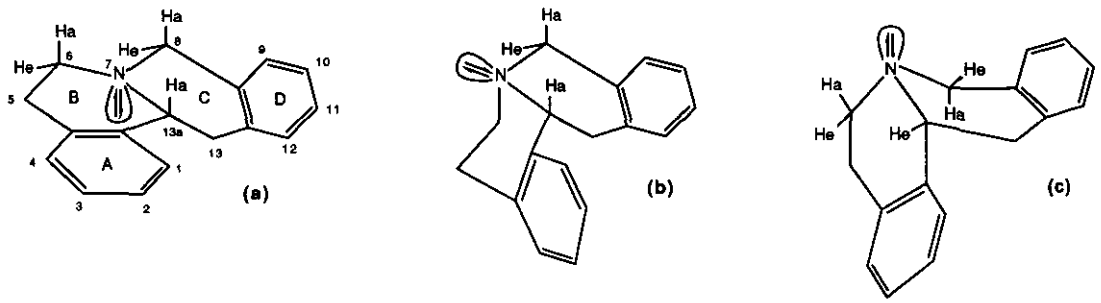
*Abstract - The stereochemistry of berbines (**1-15**) and their berbane (**16**) and berbinanes (**17** and **18**) derivatives was established on the basis of their ir, ^{1}H-nmr, ^{13}C-nmr spectral data and the rates of methiodide formation. All the compounds in this study were found to have a trans-B/C conformation whereas berbinane (**18**) had a cis-A/B configuration.*

Berbines comprise a large group of alkaloids both of natural and synthetic origins.[1] The berbine skeleton is formed by a 5,6,13,13a-tetrahydro-8*H*-dibenzo[*a,g*]quinolizine system which can exist as one *trans* (a) form and two *cis* (b,c) forms according to the B/C ring junction.[2] (Scheme 1)

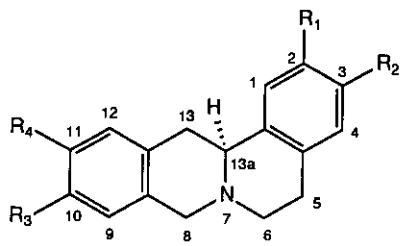


Scheme 1 - Orientations of the nitrogen lone electron pair of *trans*- and *cis*-berbines.

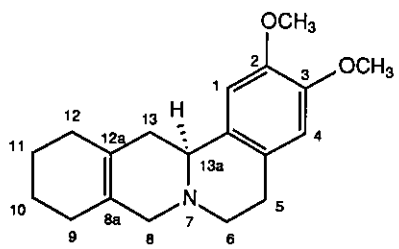
In the course of our recent work on berbine ring system we have synthesized a large number of analogues and some new derivatives saturated in the ring A or D.[3] We established the

stereochemistry of some compounds (Table 1) on the basis of their ir, ^{1}H-nmr and ^{13}C-nmr spectral data and the measurement of the rate of methiodide formation. We report here our findings in this area.

Table 1 - Structure of berbine compounds (**1-18**).



1-15



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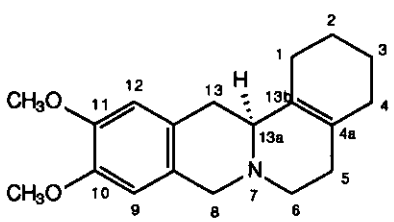
N °	R_1	R_2	R_3	R_4
1	H	H	H	H
2	H	H	O - CH_2 - O	
3	H	H	H	OH
4	H	H	H	OCH_3
5	H	H	H	H
6	H	H	H	$OCOCH_3$
7	H	H	OH	H
8	H	H	OCH_3	H
9	H	H	OH	Cl
10	H	H	OCH_3	Cl
11	H	H	OCH_3	NH_2
12	OCH_3	OCH_3	OCH_3	NH_2
13	OCH_3	OCH_3	OCH_3	$NHCOC_2H_5$
14	OCH_3	OCH_3	OCH_3	Cl
15	OCH_3	OCH_3	OCH_3	H



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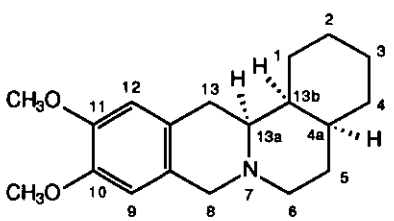


18

Ir correlations

The first spectroscopic criterion utilized to distinguish the *trans*-quinolizines from the *cis*-isomers is the presence or absence of Bohlmann bands in their ir spectra.[4] The *trans*-quinolizines in which

the lone electron pair on the nitrogen is *trans*-diaxial to at least two hydrogen atoms adjacent to it exhibit characteristic infrared bands between 2700 and 2800 cm^{-1}.

Although some authors have shown clearly the limitation of exclusive qualitative dependence on the Bohlmann bands for assignment of stereochemistry for B/C ring junction in quinolizine systems,[5] this method has been applied successfully in the structural assignment of many natural and synthetic alkaloids.[6] In our case all the synthesized quinolizines (Table 1) showed two prominent infrared bands at 2800-2810 and 2750-2760 cm^{-1} and therefore fulfiled the Bohlmann criterion for a *trans*-B/C ring junction.

^{1}H-Nmr correlations

Next to infrared spectroscopy the most widely used physical method in steroisomeric studies of berbine alkaloids is the ^{1}H-nmr spectroscopy.[7]
Our ^{1}H-nmr analyses were concentrated on the chemical shift difference between the two H_8 protons and the angular H_{13a} proton signals (Table 2).

Table 2 - ^{1}H-Nmr chemical shifts (δ, ppm) and coupling constants (*J*, Hz) for compounds (**1-15,17,18**) (5 mg/0.5 ml).

Compound	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*17*	*18*
Solvent °	a	a	b	a	a	a	b	a	b	a	a	a	a	a	a	a	a
δH_{8eq}	3.99	3.92	3.86	3.98	3.98	4.02	3.87	4.01	3.89	3.99	3.93	3.91	3.96	3.99	3.98	3.83	3.81
δH_{8ax}	3.70	3.69	3.47	3.67	3.67	3.71	3.51	3.73	3.51	3.69	3.68	3.65	3.68	3.69	3.70	3.52	3.20
$J_{8eq,8ax}$	14.6	14.7	14.4	14.4	14.4	14.8	15.2	15.1	14.4	15.0	14.4	14.6	14.8	15.3	15.1	14.4	14.9
δH_{13a}	3.67	3.68	-*	3.67	3.67	3.70	-*	3.62	-*	3.65	3.64	3.59	3.57	3.58	3.57	2.88	-*
$\Delta\delta H_{8eq-8ax}$	0.29	0.23	0.39	0.31	0.31	0.31	0.36	0.28	0.38	0.30	0.25	0.26	0.28	0.30	0.28	0.31	0.61

° a $CDCl_3$ and b DMSO-d_6

* Obscured by other protons

Thus, in all spectra of berbine compounds, excepted for berbane (**16**), the H_8 protons appeared as an AB quartet with a large difference in their chemical shifts (0.25-0.61 ppm) characteristic of a *trans*-B/C structure, while in a *cis*-B/C junction the spectal feature would be smaller (0.10-0.20 ppm).[8] This difference has been attributed to the deshielding effect of the electron pair of the nitrogen atom. In a *trans*-fused system only the equatorial proton is deshielded but in a *cis*-fused system both protons are equally affected, since the lone pair bisects the angle between the geminal protons. However some authors have reported that in berbines with a 10,11-substitution pattern the H_8 protons appeared as a broad singlet at 4.05 ppm.[9] (Scheme 1)

Furthermore the *trans*-B/C junction in these compounds was confirmed by the signal of the angular H_{13a} proton which resonated at a higher field than 3.8 ppm (Table 2), whereas a *cis* conformation was characterized by a downfield signal below 3.8 ppm.[10] By this criterion was also confirmed the *trans*-B/C conformation for berbane (**16**) but not for berbinanes (**17** and **18**). In these latter compounds the saturation of the aromatic ring A induced an upfield shift for H_{13a} proton signal.
In contrast compounds **17** and **18** exhibited an AB quartet of the H_8 protons like berbines and their differences in chemical shift (0.31 and 0.61 ppm) agreed with a B/C *trans*-fused system.

Moreover **18** exhibited an upfield shift (0.30 ppm) for the H_{8ax} proton compared to **17**. This could be attributed to an optimal orientation of H_{8ax} with respect to the nitrogen lone pair in *trans*-diaxial position imposed by the dramatic change of the A/B junction.[11]

^{13}C-Nmr correlations

^{13}C-Nmr is generally recognized as one of the most useful spectroscopic techniques available for stereochemical assignment and structure elucidation.[12]

In the ^{13}C-nmr spectra of some berbines and their derivatives (Table 3), the assignments of the chemical shifts are based on the comparison of the spectra and the use of the half-decoupled technique.[13] It was expected that some of the carbons (C-6, C-8, C-13, C-13a) of a *cis*-quinolizine would resonate at a higher field than in a *trans*-quinolizine owing to γ-steric effects (Table 4).[14]

Table 3 - ^{13}C-Nmr chemical shifts (δ, ppm) of berbine compounds.

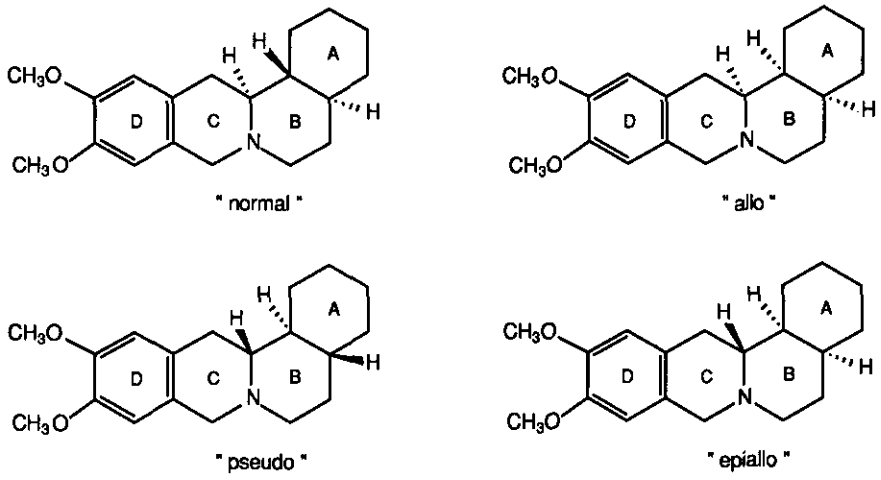
Carbon	Compound						
	1	4	2	12	17	16	18
C - 1	125.4	125.4	125.4	108.6	25.9	108.3	21.2
C - 2	126.0	126.0	126.0	147.4	22.6	147.2	25.0
C - 3	126.0	126.0	126.0	147.4	22.9	147.2	20.9
C - 4	128.8	128.8	128.8	111.3	30.0	111.2	31.7
C - 4a	134.5	134.5	134.5	126.5	127.5	127.0	36.6
C - 5	29.4	29.5	29.5	29.1	30.2	29.4	26.8
C - 6	51.2	51.2	51.1	51.4	50.9	51.2	57.5
C - 8	58.6	58.1	58.6	58.4	58.1	59.2	58.9
C - 8a	134.4	126.7	127.4	124.2	126.7	126.6	126.3
C - 9	125.8	127.0	106.0	108.0	108.9	27.3	108.7
C - 10	126.1	112.2	146.0	146.1	147.1	22.7	147.4
C - 11	126.1	158.0	146.1	134.5	147.2	22.7	147.0
C - 12	128.7	113.2	108.5	114.8	111.4	29.0	110.7
C - 12a	134.4	135.6	127.3	126.7	126.5	126.4	125.7
C - 13	36.6	36.9	36.6	36.1	33.5	38.2	32.1
C - 13a	59.8	59.8	59.8	59.7	61.3	59.5	61.9
C - 13b	137.8	137.8	137.8	130.0	128.4	130.2	40.3
CH_3O	-	55.2	-	55.8(X3)	55.9(X2)	56.0(X2)	55.9(X2)
O-CH_2-O	-	-	100.6	-	-	-	-

Table 4 - Characteristic shift ranges (δ, ppm) of berbine compounds.

Conformation	*cis*	*trans*
Carbon C-6	48.0 ± 1.0	51.3 ± 0.2
C-8	55.0 ± 2.0	57.0 ± 2.0
C-13	32.5 ± 0.5	36.5 ± 0.5
C-13a	55.5 ± 0.5	59.5 ± 0.5

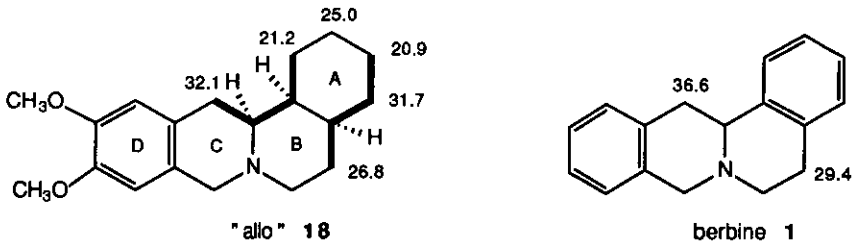
The comparison of these values with the chemical shifts listed in Table 3 showed unambiguously that berbines (**1,2,4,12**) have a *trans*-B/C junction. And the ring B,C carbon shifts of berbinane (**17**) and berbane (**16**) were nearly identical with those exhibited by compounds (**1,2,4,12**) indicating also a *trans*-B/C quinolizine structure.

In contrast berbinane (**18**) has three asymmetric centers (C-4a, C-13a, C-13b), which gives rise to the possibility of four configurations analogous to those of berbanes: "normal", "allo", "epiallo" and "pseudo".[15] (Scheme 2)



Scheme 2 - Possible configurations of berbinane (**18**).

The "pseudo" and "epiallo" stereoisomers were excluded by the downfield shifts of the bridgehead methine (C-13a) and the aminomethylenes (C-8, C-6) which revealed unambiguously a *trans*-B/C structure like berbines (Table 3). This was also confirmed by ^{1}H-nmr and ir results. Furthermore, the differentiation between the "normal" and the "allo" isomers was based on the shielding of certain carbons in this latter configuration owing to γ-interactions.[16] Thus, in the "allo" configuration, because of the A/B *cis*-junction, C-13 and C-5 carbons experienced a large shielding by C-1 and C-3 carbons respectively. These γ-interactions are very weak in planar structures like berbine (**1**). (Scheme 3)



Scheme 3 - Influence of γ-interactions on C-5 and C-13 chemical shifts of berbines.

Rates of methiodide formation

The use of the rates of methiodide formation in the determination of quinolizine alkaloids stereochemistry was introduced by Shamma *et al.*[17] The experimentally observed pseudo first-order rates of *N*-methylation for berbine series are shown in Table 5.

Table 5 - Rates of *N*-methylation for berbine compounds (**1-18**).

Compound	R_1	R_2	R_3	R_4	Kx10^{-4} (25°C)
7	H	H	OH	H	40.0
3	H	H	H	OH	39.2
15	OCH_3	OCH_3	OCH_3	H	38.0
16 (berbane)	OCH_3	OCH_3	-	-	37.2
1	H	H	H	H	36.0
4	H	H	H	OCH_3	35.6
8	H	H	OCH_3	H	34.6
17 (berbinane)	-	-	OCH_3	OCH_3	34.0
2	H	H	O-CH_2-O		32.1
13	OCH_3	OCH_3	OCH_3	$NHCO_2C_2H_5$	31.4
12	OCH_3	OCH_3	OCH_3	NH_2	31.2
5	H	H	H	OC_2H_5	31.0
11	H	H	OCH_3	NH_2	30.0
9	H	H	OH	Cl	29.8
6	H	H	H	$OCOCH_3$	28.0
14	OCH_3	OCH_3	OCH_3	Cl	27.8
10	H	H	OCH_3	Cl	26.0
18 (berbinane)	-	-	OCH_3	OCH_3	22.9

Initial inspection of this table shows that the rates are of medium magnitude: $k < 45 \times 10^{-4}$ sec^{-1}, which is consistent with a *trans*-B/C conformation.[18] A *cis*-B/C quinolizine reacted at a much faster rate: $k > 60 \times 10^{-4}$ sec^{-1}. It is also noted that the rate of methylation was enhanced by the presence of free phenolic hydroxyl groups for **3, 7**, but in contrast is decreased in the presence of chlorine atom for **9,10,14**, or other withdrawning groups like $OCOCH_3$ for **6**. Thus, the effect of substitution pattern on the basicity of nitrogen becomes another important factor besides stereochemical considerations.

In the case of **16,17**, the saturation of the aromatic ring, D or A respectively, did not change the value of k relative to **1**, because of the planarity of the structure which was preserved in both cases. However for **18** which possess an "allo" structure (bended structure), the A/B *cis*-fusion cause a steric hindrance to the nucleophilic nitrogen resulting in a much slower rate of methylation: $k = 22.9 \times 10^{-4}$ sec^{-1} compared to **1** ($k = 36 \times 10^{-4}$ sec^{-1}). These results confirmed our ^{13}C-nmr findings about the stereochemistry of **18** and showed the validity of this physical method as an accessory tool in quinolizine structure determination.

EXPERIMENTAL

Spectroscopic data for all compounds were recorded on Beckmann 4230 (ir) and Brucker AC 200 (nmr) instruments. All the ^{13}C-nmr spectra were obtained in $CDCl_3$ after 10.000 pulses with intervals of 2.5 sec. The ^{13}C-nmr chemical shifts were measured with respect to internal TMS : δ (TMS) = 0 ppm and δ ($CHCl_3$) = 77.2 ppm. The rates of methiodide formation were determined on 5 mg of sample in acetonitrile solution at 25 ^0C, using a Tacussel CD6 conductivity cell, as described in reference 17.

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