

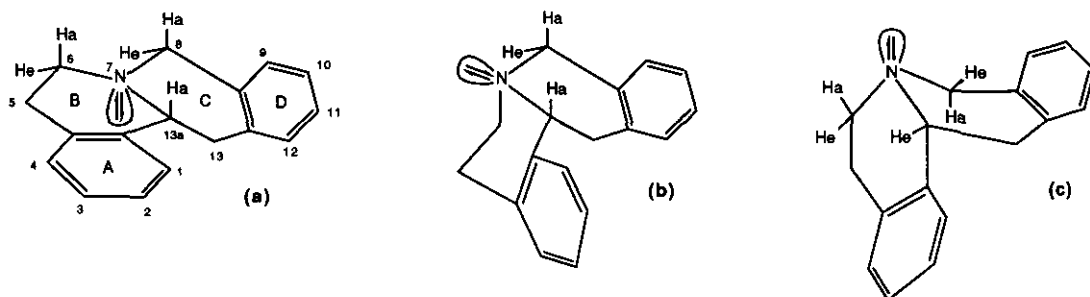
## STEREOCHEMISTRY OF BERBINE AND SOME RELATED COMPOUNDS

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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,  $^1\text{H}$ -nmr,  $^{13}\text{C}$ -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.<sup>1</sup> 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.<sup>2</sup> (Scheme 1)

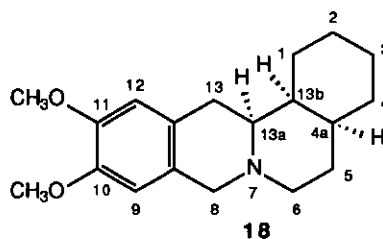
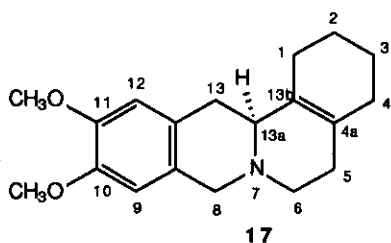
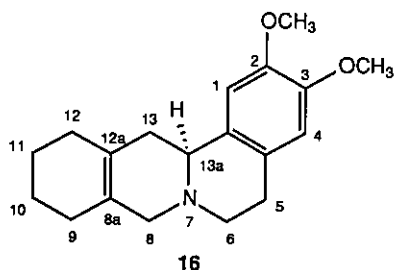
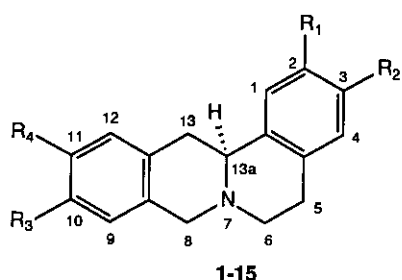


Scheme 1 - Orientations of the nitrogen lone electron pair of *trans*- and *cis*-berbines.

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.<sup>3</sup> We established the

stereochemistry of some compounds (Table 1) on the basis of their ir,  $^1\text{H}$ -nmr and  $^{13}\text{C}$ -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).



N °	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>
1	H	H	H	H
2	H	H	O - CH <sub>2</sub> - O	
3	H	H	H	OH
4	H	H	H	OCH <sub>3</sub>
5	H	H	H	H
6	H	H	H	OCOCH <sub>3</sub>
7	H	H	OH	H
8	H	H	OCH <sub>3</sub>	H
9	H	H	OH	Cl
10	H	H	OCH <sub>3</sub>	Cl
11	H	H	OCH <sub>3</sub>	NH <sub>2</sub>
12	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	NH <sub>2</sub>
13	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	NHCOC <sub>2</sub> H <sub>5</sub>
14	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	Cl
15	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	H

### 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.<sup>4</sup> 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  $\text{cm}^{-1}$ .

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,<sup>5</sup> this method has been applied successfully in the structural assignment of many natural and synthetic alkaloids.<sup>6</sup> In our case all the synthesized quinolizines (Table 1) showed two prominent infrared bands at 2800-2810 and 2750-2760  $\text{cm}^{-1}$  and therefore fulfilled the Bohlmann criterion for a *trans*-B/C ring junction.

### *<sup>1</sup>H-Nmr correlations*

Next to infrared spectroscopy the most widely used physical method in stereoisomeric studies of berbine alkaloids is the <sup>1</sup>H-nmr spectroscopy.<sup>7</sup>

Our <sup>1</sup>H-nmr analyses were concentrated on the chemical shift difference between the two H<sub>8</sub> protons and the angular H<sub>13a</sub> proton signals (Table 2).

Table 2 - <sup>1</sup>H-Nmr chemical shifts ( $\delta$ , 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
$\delta$ H <sub>8eq</sub>	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
$\delta$ H <sub>8ax</sub>	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
$J$ $\delta$ <sub>8eq,8ax</sub>	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
$\delta$ H <sub>13a</sub>	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 <sub>8eq-8ax</sub>	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<sub>3</sub> and b DMSO-d<sub>6</sub>

\* Obscured by other protons

Thus, in all spectra of berbine compounds, excepted for berbane (**16**), the H<sub>8</sub> 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 spectral feature would be smaller (0.10-0.20 ppm).<sup>8</sup> 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<sub>8</sub> protons appeared as a broad singlet at 4.05 ppm.<sup>9</sup> (Scheme 1)

Furthermore the *trans*-B/C junction in these compounds was confirmed by the signal of the angular H<sub>13a</sub> 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.<sup>10</sup> 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<sub>13a</sub> proton signal. In contrast compounds **17** and **18** exhibited an AB quartet of the H<sub>8</sub> 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<sub>8ax</sub> proton compared to **17**. This could be attributed to an optimal orientation of H<sub>8ax</sub> with respect to the nitrogen lone pair in *trans*-diaxial position imposed by the dramatic change of the A/B junction.<sup>11</sup>

### *<sup>13</sup>C-Nmr correlations*

<sup>13</sup>C-Nmr is generally recognized as one of the most useful spectroscopic techniques available for stereochemical assignment and structure elucidation.<sup>12</sup>

In the <sup>13</sup>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.<sup>13</sup> 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  $\gamma$ -steric effects (Table 4).<sup>14</sup>

Table 3 -  $^{13}\text{C}$ -Nmr chemical shifts ( $\delta$ , ppm) of berbine compounds.

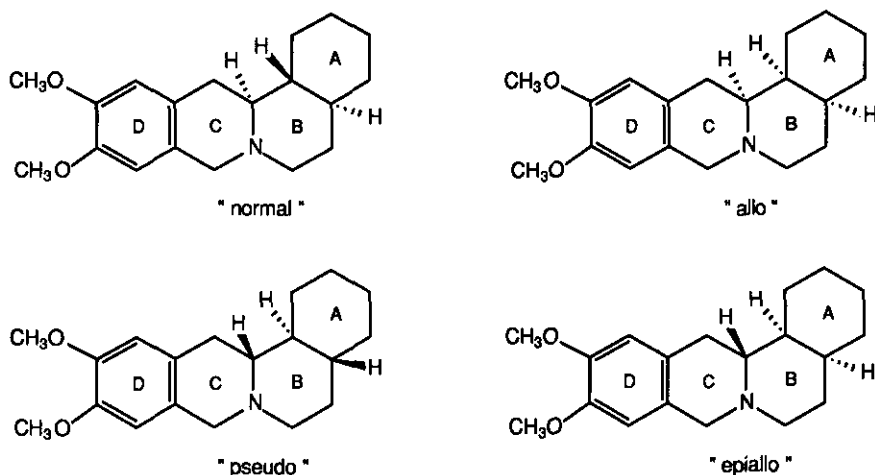
Carbon	Compound						
	1	4	2	12	17	16	18
C - 1	125.4	125.4	125.4	108.6	25.9	108.3	21.2
C - 2	126.0	126.0	126.0	147.4	22.6	147.2	25.0
C - 3	126.0	126.0	126.0	147.4	22.9	147.2	20.9
C - 4	128.8	128.8	128.8	111.3	30.0	111.2	31.7
C - 4a	134.5	134.5	134.5	126.5	127.5	127.0	36.6
C - 5	29.4	29.5	29.5	29.1	30.2	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 <sub>3</sub> O	-	55.2	-	55.8(X3)	55.9(X2)	56.0(X2)	55.9(X2)
O-CH <sub>2</sub> -O	-	-	100.6	-	-	-	-

Table 4 - Characteristic shift ranges ( $\delta$ , ppm) of berbine compounds.

Conformation	<i>cis</i>	<i>trans</i>
Carbon C-6	48.0 $\pm$ 1.0	51.3 $\pm$ 0.2
C-8	55.0 $\pm$ 2.0	57.0 $\pm$ 2.0
C-13	32.5 $\pm$ 0.5	36.5 $\pm$ 0.5
C-13a	55.5 $\pm$ 0.5	59.5 $\pm$ 0.5

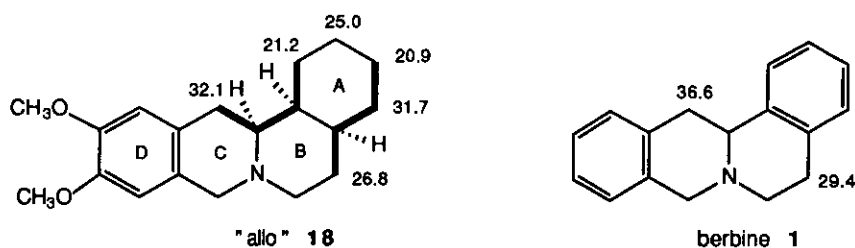
The comparison of these values with the chemical shifts listed in Table 3 showed unambiguously that berbines (1,2,4,12) have a *trans*-B/C junction. And the ring B,C carbon shifts of berbinane (17) and berbane (16) were nearly identical with those exhibited by compounds (1,2,4,12) indicating also a *trans*-B/C quinolizidine 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".<sup>15</sup> (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 <sup>1</sup>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  $\gamma$ -interactions.<sup>16</sup> 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  $\gamma$ -interactions are very weak in planar structures like berbine (1). (Scheme 3)

Scheme 3 - Influence of  $\gamma$ -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.*<sup>17</sup> 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 <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	Kx10 <sup>-4</sup> (25°C)
7	H	H	OH	H	40.0
3	H	H	H	OH	39.2
15	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	H	38.0
16 (berbane)	OCH <sub>3</sub>	OCH <sub>3</sub>	-	-	37.2
1	H	H	H	H	36.0
4	H	H	H	OCH <sub>3</sub>	35.6
8	H	H	OCH <sub>3</sub>	H	34.6
17 (berbinane)	-	-	OCH <sub>3</sub>	OCH <sub>3</sub>	34.0
2	H	H	O-CH <sub>2</sub> -O		32.1
13	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	NHCO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	31.4
12	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	NH <sub>2</sub>	31.2
5	H	H	H	OC <sub>2</sub> H <sub>5</sub>	31.0
11	H	H	OCH <sub>3</sub>	NH <sub>2</sub>	30.0
9	H	H	OH	Cl	29.8
6	H	H	H	OCOCH <sub>3</sub>	28.0
14	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	Cl	27.8
10	H	H	OCH <sub>3</sub>	Cl	26.0
18 (berbinane)	-	-	OCH <sub>3</sub>	OCH <sub>3</sub>	22.9

Initial inspection of this table shows that the rates are of medium magnitude:  $k < 45 \times 10^{-4} \text{ sec}^{-1}$ , which is consistent with a *trans*-B/C conformation.<sup>18</sup> A *cis*-B/C quinolizine reacted at a much faster rate:  $k > 60 \times 10^{-4} \text{ sec}^{-1}$ . 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 withdrawing groups like  $\text{OCOCH}_3$  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:  $k = 22.9 \times 10^{-4} \text{ sec}^{-1}$  compared to **1** ( $k = 36 \times 10^{-4} \text{ sec}^{-1}$ ). These results confirmed our  $^{13}\text{C}$ -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 Bruker AC 200 (nmr) instruments. All the  $^{13}\text{C}$ -nmr spectra were obtained in  $\text{CDCl}_3$  after 10.000 pulses with intervals of 2.5 sec. The  $^{13}\text{C}$ -nmr chemical shifts were measured with respect to internal TMS :  $\delta$  (TMS) = 0 ppm and  $\delta$  ( $\text{CHCl}_3$ ) = 77.2 ppm. The rates of methiodide formation were determined on 5 mg of sample in acetonitrile solution at 25 °C, using a Tacussel CD6 conductivity cell, as described in reference 17.



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