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STUDIES IN PROTOBERBERINE ALKALOIDS. XVI[1]. NMR SPECTRAL STUDIES OF 10,11-DIOXYGENATED 13-METHYLTETRAHYDROPROTOBERBERINES

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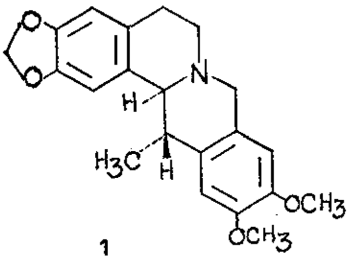
The NMR chemical shift differences of protons at C_{13a} and C_8 and the methyl protons at C_{13} of *cis*- and *trans*-fused 10,11-dioxygenated 13-methyltetrahydroprotoberberines are discussed.

The relative stereochemistry of 13-methyltetrahydroprotoberberines has been established by a study of their NMR spectra[2,3,4]. The chemical shift of the C_{13}-CH_3 group in compounds with *trans*-fused rings B/C and a *cis*-orientation of protons at C_{13} and C_{13a} is between δ 0.90-1.00 while it is near δ 1.40-1.50 in those with *cis*-fused rings B/C and a *trans*-orienta ion of the protons. It has also been observed that in the NMR spectra of *trans*-fused 9,10-dioxygenated 13-methyltetrahydroprotoberberines the C_8-protons appear as an AB quartet with a large chemical shift difference,while in the corresponding *cis* quinolizidines the shift difference is smaller[3,4]. No mention however has been made about 10,11-dioxygenated 13-methyltetrahydroprotoberberines. Recently Cushman *et al.*[5] have pointed out that the C_8 protons of the B/C *cis*-fused 10,11-dioxygenated tetrahydroprotoberberine 1 appeared as two doublets (J=16 Hz) at δ 3.73 and 4.22, with the higher field doublet overlapping the signal for C_{13a} proton. In contrast, the C_8 protons of 2 (*trans*-quinolizidine) were assigned to a broad singlet which appeared at δ 3.72.



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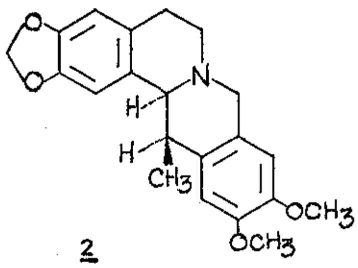

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Our study of the 90 MHz NMR spectra of compounds 3 to 8 (Table I) shows that in the 10,11-dioxygenated 13-methyltetrahydroprotoberberines the C_8 protons are observed as an AB quartet in all cases irrespective of whether the B/C ring fusion is *cis* or *trans*[6]. A scrutiny of the data in Table I and Table II leads to the further conclusion that the centre of the AB quartet appears relatively further downfield in all cases of *cis*-quinolizidines compared to the *trans*-quinolizidines by about 0.15–0.20 ppm*. In the 10,11-dioxygenated compounds the signals of the C_8 protons are separated from each other by about 0.45–0.48 ppm in the *cis* and 0.40–0.48 ppm in the *trans*-quinolizidines, while the corresponding values in 9,10-oxygenated compounds are 0.13–0.18 and 0.55–0.72.

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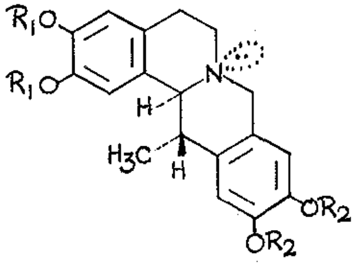
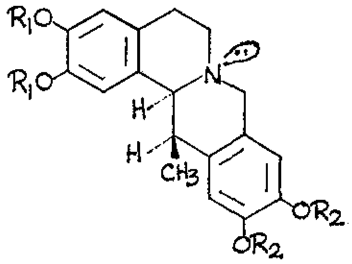
* The difference is somewhat smaller (0.07 ppm) for compounds 7 & 8.



3 $R_1 = CH_3$; $R_2+R_2 = CH_2$

5 $R_1+R_1 = R_2+R_2 = CH_2$

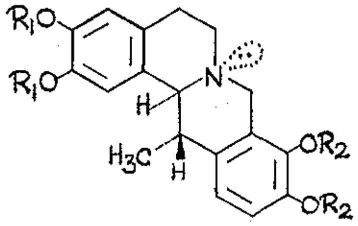
7 $R_1 = CH_3$; $R_2 = H$



4 $R_1 = CH_3$; $R_2+R_2 = CH_2$

6 $R_1+R_1 = R_2+R_2 = CH_2$

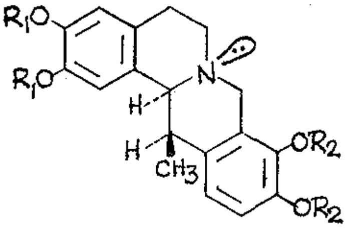
8 $R_1 = CH_3$; $R_2 = H$



9 $R_1 = R_2 = CH_3$
(Meso corydaline)

11 $R_1 = CH_3$; $R_2+R_2 = CH_2$
(Thalictrifoline)

13 $R_1+R_1 = CH_2$; $R_2 = CH_3$
(Meso thalictricavine)



10 $R_1 = R_2 = CH_3$
(Corydaline)

12 $R_1 = CH_3$; $R_2+R_2 = CH_2$
(Cavidine)

14 $R_1+R_1 = CH_2$; $R_2 = CH_3$
(Thalictricavine)

Another point worth mentioning is the chemical shift of the angular proton at C_{13a}. Kametani and coworkers[7] have studied the NMR spectra of a number of 1-substituted tetrahydroprotoberberines and have shown that the angular proton of a trans-quinolizidine resonates upfield from δ 3.80, whereas in the case of a cis-quinolizidine this signal is observed downfield from δ 3.80. This observation was also made in the NMR spectra of caseadine (in $CDCl_3$ as well as in C_6D_6)[8]. This does not seem to be the case for 13-methyltetrahydroprotoberberines.. The tables show that the C_{13a} proton in these compounds generally appears around δ 3.70. Noteworthy is the fact that in each pair the C_{13a} proton of the trans-quinolizidine appears at lower field than in the corresponding cis-quinolizidine.

The most consistent and dramatic differences between the cis- and trans-*quinolizidine series are seen only for the chemical* shifts of the methyl groups at C_{13}. Thus the values range from δ 1.43 to 1.48 for the cis- and from δ 0.88 to 0.99 for the trans-series, showing a difference of about 0.5 ppm.

Based on these observations we conclude that the assignment of stereochemistry of the B/C ring fusion in 10,11-dioxygenated 13-methyltetrahydroprotoberberines should be made on the basis of the chemical shifts of the C_{13} methyl doublets only, which could be further strengthened by an inspection of the chemical shifts for the C_8 protons.

Table I

NMR Chemical Shifts (δ, ppm) of 10,11-Dioxygenated 13-Methyltetrahydroprotoberberines

COMPOUND	C_8-Proton	Centre of AB quartet due to C_8-proton	C_{13a}-H	C_{13}-CH_3	Remark
1	3.73, 4.22	3.98	3.67 (J=8 Hz)	1.48	a
2	3.72 (broad singlet)	3.72	3.88	0.97	a
3	3.75, 4.23 (J=15 Hz)	3.99	3.75(d) (J=8 Hz)	1.49 (J=7 Hz)	b
4	3.62, 4.02 (J=15 Hz)	3.80	3.78(d) (J=2-3 Hz)	0.99 (J=7 Hz)	b
5	3.72, 4.17 (J=15 Hz)	3.95	3.69(d) (J=8 Hz)	1.45 (J=7 Hz)	b
6	3.56, 3.96 (J=15 Hz)	3.76	3.70(d) (J=2-3 Hz)	0.96 (J=7 Hz)	b
7	3.63, 4.09 (J=15 Hz)	3.86	3.59(d) (J=8 Hz)	1.43 (J=7 Hz)	b
8	3.55, 4.03 (J=15 Hz)	3.79	3.78 (J=~2 Hz)	0.88 (J=7 Hz)	b

[a] Data reported by Cushman *et al.*, ref.5; [b] 90 MHz NMR spectrum run in $CDCl_3$, ref.6

Table II

NMR Chemical Shifts (δ, ppm) of 9,10-Dioxygenated 13-Methyltetrahydroprotoberberines

COMPOUND	C_8-Proton	Centre of AB quartet due to C_8-proton	C_{13a}-H	C_{13}-CH_3	Ref.
9	3.97, 4.13	4.05	3.62 (J=7.5 Hz)	1.48	3
10	3.49, 4.19	3.84	3.68 (J=3.0 Hz)	0.97	3
11	3.89, 4.02	3.96	3.68 (J=7.5 Hz)	1.48	3
12	3.52, 4.07	3.80	3.74	0.98	3
13	3.90, 4.08	3.99	3.56	1.43	4
14	3.44, 4.16	3.80	3.66	0.93	4

Acknowledgement

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References and Notes

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6 See Reference 2 for the preparation of compounds **3** and **4** and T.R. Govindachari, K. Nagarajan, S. Natarajan and B.R. Pai, *Indian J. Chem.*, 1971, **9**, 1313 for the preparation of **5** and **6** and M. Shamma and C.D. Jones, *J. Am. Chem. Soc.*, 1970, **92**, 4943 for the preparation of compounds **7** and **8**. The 90 MHz NMR spectra of these compounds were run in $CDCl_3$ in a Bruker Spectrospin NMR instrument and chemical shifts are quoted in ppm downfield from TMS used as internal reference.

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