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Studies in Protoberberine Alkaloids: Part III*—Stereochemistry of 13-Methylprotoberberines

T. R. GOVINDACHARI & K. NAGARAJAN
CIBA Research Centre, Goregaon East, Bombay 63
and
R. CHARUBALA, B. R. PAI & P. S. SUBRAMANIAN
Department of Chemistry, Presidency College, Madras 5

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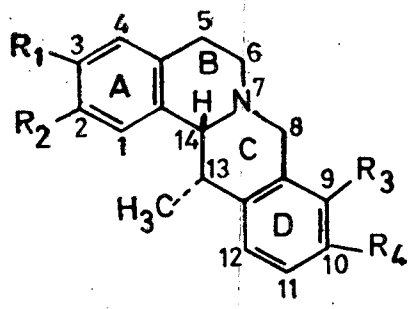
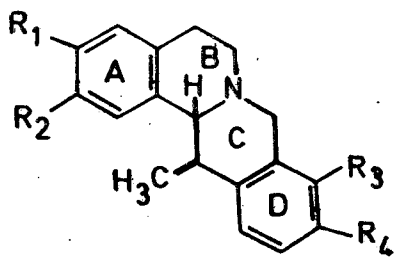
NMR spectral analysis has been used to deduce conformational structure Ia for thalictricavine and VIc for *meso*-thalictricavine.

AMONG the alkaloids belonging to the protoberberine group, the 13-methyl derivatives, thalictricavine (I), corydaline (II) and thalictrifoline (VIII)[1] are of special interest from a stereochemical point of view. The earliest study of their stereochemistry was due to Bersch[2], who assigned a *cis*-C(13), C(14)-configuration for thalictricavine (I) and corydaline (II) and a *trans*-C(13), C(14)-configuration to thalictrifoline (VIII). In a later publication, Kondo[3] assigned *trans*-stereochemistry at these positions in corydaline. In a definitive paper[4] in 1965, Jeffs used IR and Hofmann degradation data to make firm stereochemical assignments to these compounds. Corydaline (II) and the alkaloids thalictricavine (I), corybulbine (III), isocorybulbine (IV) and base II (V), which have been chemically correlated to II, show Bohlmann bands[5] in the IR spectrum, indicative of a *trans*-quinolizidine ring junction. Mesothalictricavine (VI), mesocorydaline (VII) and thalictrifoline (VIII) do not exhibit these Bohlmann bands and, hence, have a *cis*-quinolizidine system. The corydaline group gives Hofmann degradation products by cleavage of C(14)-nitrogen bond and the *meso* series, by cleavage of C(6)-nitrogen bond. The former group was then deduced to have *cis* stereochemistry at C(13) and C(14) in agreement with Bersch. Of the three conformations, viz. IIa, IIb and IIc, possible for II, IIa has the *trans*-quinolizidine ring system, and the *trans*-anticoplanar arrangement of the relevant centres necessary for the observed course of Hofmann elimination. The *meso*-corydaline group having *trans* stereochemistry at C(13) and C(14) can be represented by three conformations VIIa, VIIb and VIIc, in which VIIa with the *trans*-quinolizidine system becomes energetically unfavourable because of severe interaction of the 13-methyl group with the 1-hydrogen. Jeffs thus





I : $R_1,R_2 = CH_2$(O—, O—) ; $R_3 = R_4 = OMe$

II : $R_1 = R_2 = R_3 = R_4 = OMe$

III : $R_1 = OH$; $R_2 = R_3 = R_4 = OMe$

IV : $R_2 = OH$; $R_1 = R_3 = R_4 = OMe$

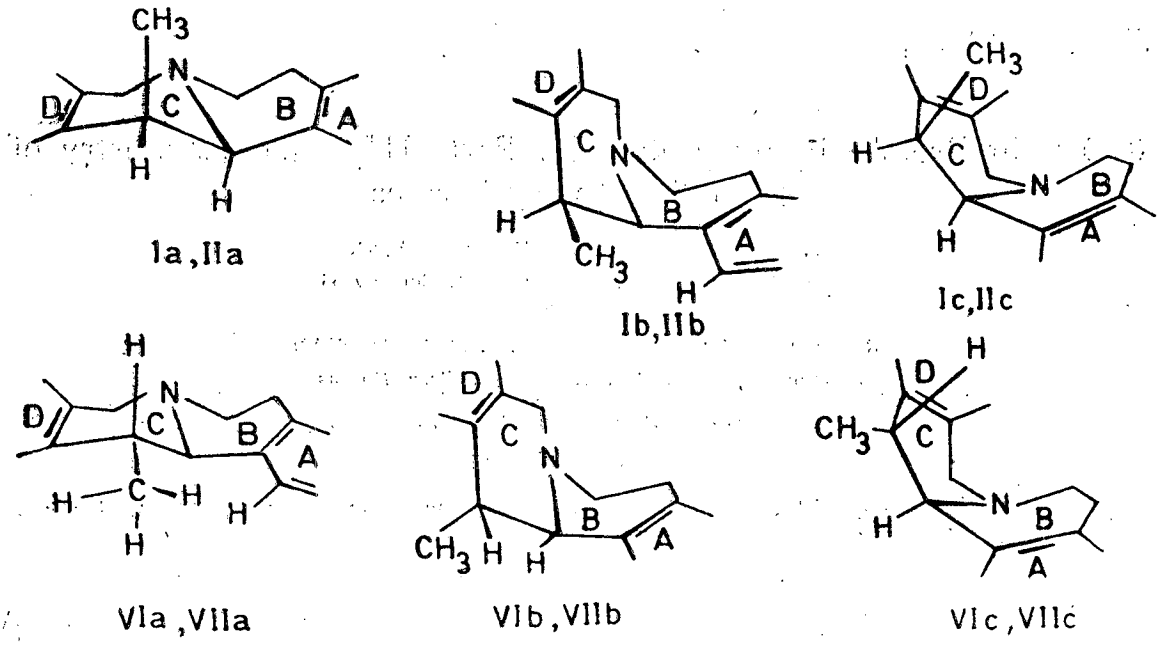
V : $R_1 = R_2 = OMe$; $R_3 = R_4 = CH_2$(O—, O—)

VI : $R_1,R_2 = CH_2$(O—, O—) ; $R_3 = R_4 = OMe$

VII : $R_1 = R_2 = R_3 = R_4 = OMe$

VIII : $R_1 = R_2 = OMe$; $R_3,R_4 = CH_2$(O—, O—)

*Part II, Govindachari, T. R., Nagarajan, K., Charubala, R. & Pai, B. R., *Indian J. Chem.*, 8 (1970), 766.



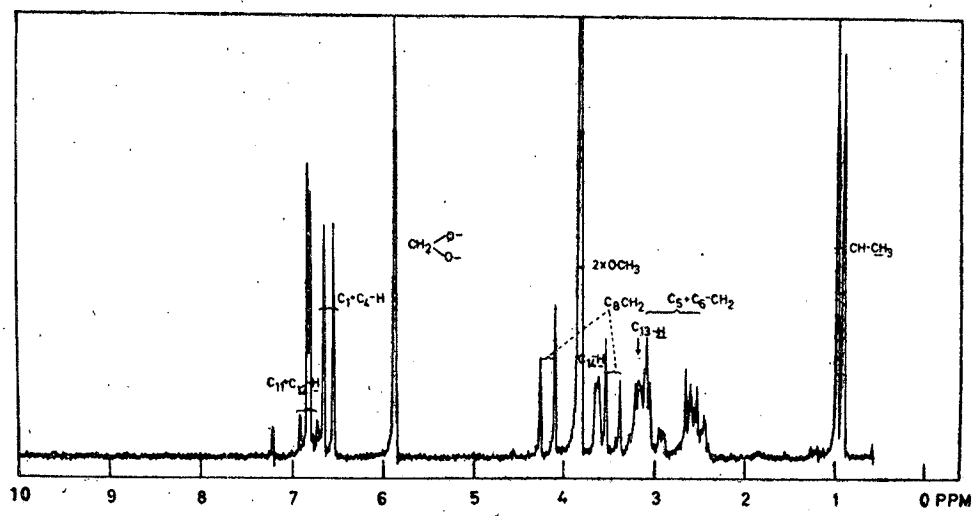


Fig. 1 — 100 MHz NMR spectrum of thalictricavine (I)

deduced the existence of a *cis*-quinolizidine ring junction in the *meso*-corydaline group, but made no choice between conformations VIIb and VIIc.

In a recent publication, Shamma *et al.*[6] have used the rates of methiodide formation of these bases to get an insight into their stereochemistry. Their results have substantiated the relative stereochemistry and conformation IIa for corydaline and allowed the choice of conformation VIIc for the *meso*-corydaline group.

We felt that NMR spectroscopy could be applied to this problem with advantage. The results of our study of the 100 MHz NMR spectra of *dl*-thalictricavine (I) and *meso*-thalictricavine (VI) which serve to confirm these assignments independently are presented in this paper.

The 100 MHz NMR spectra* of I and VI are reproduced in Figs. 1 and 2 respectively along with the proton assignments. In the former, the C(13) proton was found as a multiplet at 3·2 ppm, which was reduced to a doublet ($J = 3$ *cps*) when decoupled from the methyl doublet at 0·93 ppm and to a quartet ($J = 7$ *cps*) when decoupled from the C(14) proton seen as a doublet ($J = 3$ *cps*) at 3·66 ppm. The assignment of the signal due to the C(14) proton was thus secure; its small coupling with its neighbour indicated a *cis* disposition. Coupled with the fact that *dl*-thalictricavine shows the Bohlmann bands, characteristic of a *trans*-

*Spectra were run in $CDCl_3$ solution; chemical shifts are in ppm downfield relative to tetramethylsilane internal standard.

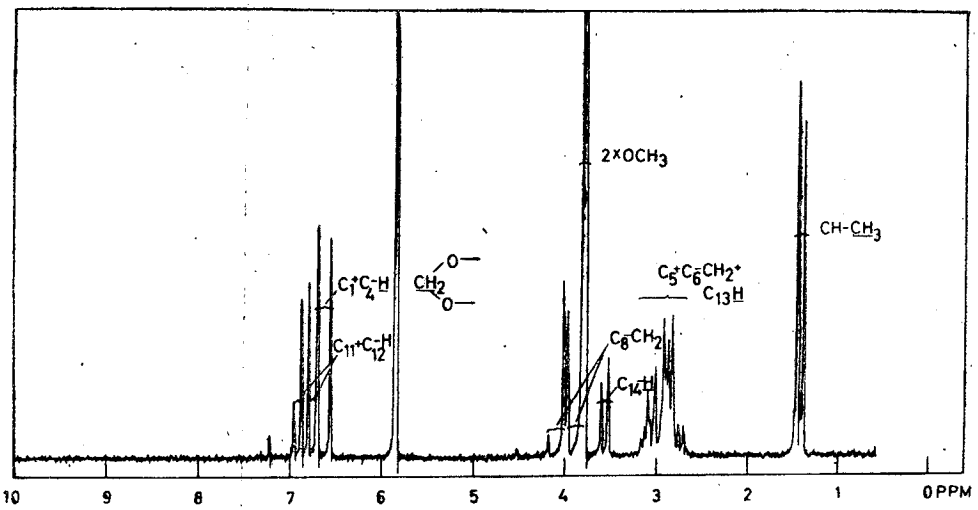


Fig. 2 — 100 MHz NMR spectrum of *meso*-thalictricavine (VI)

quinolizidine ring junction, the NMR data establish the correctness of the conformational assignment Ia to thalictricavine.

The first striking difference in the NMR spectrum of *meso*-thalictricavine (VI) compared to that of I is the attenuation of the chemical shift between the geminal protons at C(8). In I, one of these protons, presumably the *quasi*-equatorial one, is seen as a doublet at 4·16 ppm ($J = 16$ *cps*), while the *quasi*-axial proton, with a *trans*-antiparallel relation to the nitrogen lone pair, is a doublet centred at 3·44 ppm, 0·72 ppm higher field[7]. In VI, the *quasi*-equatorial proton at C(8) is a doublet at 4·08 ppm ($J = 16$ *cps*), while the *quasi*-axial one has moved down to 3·90 ppm. This can happen only if the latter has lost the shielding effect of the nitrogen lone pair and is indicative of the B-C ring junction having *cis* stereochemistry in VI. Although the C(13) proton signal was lost in the multiplet at 2·6-3·2 ppm and could not be located by decoupling techniques, there is no doubt that the C(14) proton signal is the doublet ($J = 8$ *cps*) centred at 3·56 ppm. Its large coupling [presumably with the C(13) neighbour] is indicative of their *trans* disposition to each other. These data confirm the assignment to VI of the conformation VIc.

The difference in the chemical shifts of the methyl group in I (0·93 ppm) and VI (1·43 ppm) deserves comment. Their relative dispositions towards ring D are the same in both Ia and VIc. However, the methyl group appears to be in the shielding region of the ring A current in Ia, while it may be slightly deshielded by the same ring in VIc. Added to this is the possibility that the methyl group, being *pseudo*-axial in Ia but not in VIc, and having a 1,3-diaxial interaction with the nitrogen lone pair, undergoes some further shielding.

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