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

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

Among the alkaloids belonging to the protoberberine group, the 13-methyl derivatives, thalictricavine (I), corydaline (II) and thalictrifoline (VIII)\(^4\) are of special interest from a stereochemical point of view. The earliest study of their stereochemistry was due to Bersch\(^4\), 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\(^4\) assigned trans-stereochemistry at these positions in corydaline. In a definitive paper\(^5\) 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 Bohmann bands\(^6\) in the IR spectrum, indicative of a trans-quinolizidine ring junction. Mesothalictricavine (VI), mesocorydaline (VII) and thalictrifoline (VIII) do not exhibit these Bohmann 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

\[\begin{align*}
\text{I: } & R_1, R_2 = \text{CH}_2\text{OH} \quad \text{II: } R_1 = R_2 = R_3 = R_4 = \text{OMe} \\
\text{III: } & R_1 = \text{OMe} \quad \text{IV: } R_2 = \text{OH} \\
\text{V: } & R_1 = R_2 = \text{OMe} \quad \text{VI: } R_1, R_2 = \text{CH}_2\text{OH} \\
\text{VII: } & R_1 = R_2 = R_3 = R_4 = \text{OMe} \quad \text{VIII: } R_1 = R_2 = \text{OMe} \end{align*}\]

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. 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. 1 — 100 MHz NMR spectrum of thalictricavine (I)
quino-lizidine ring junction, the NMR data establish
the correctness of the conformational assignment Ia
to thalcticrinave.

The first striking difference in the NMR spectrum
of meso-thalcticrinave (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. 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 indi-
cative of the B-C ring junction having cis stereo-
chemistry in VI. Although the C(13) proton signal
was lost in the multiplet at 2.63-3.2 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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