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THE NUCLEAR MAGNETIC RESONANCE SPECTRUM OF PROTOPINE: RATE OF RACEMIZATION AND RING INVERSION*

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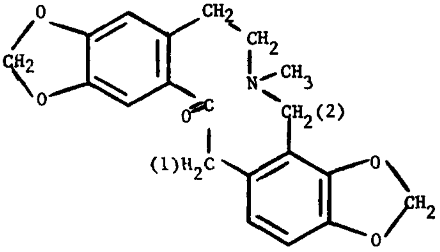
The n.m.r. spectrum (1) of protopine (I) has been assigned on the basis of rapid ring inversion in the ten-membered ring. However, the bands of the methylene protons in that ring are somewhat broader than expected. The broadness of the lines may be due in part to unresolved long-range coupling, but there may also be a contribution from incomplete averaging if ring inversion is, in fact, not very fast.



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* Contribution No. 2123, from the Department of Chemistry, UCLA.

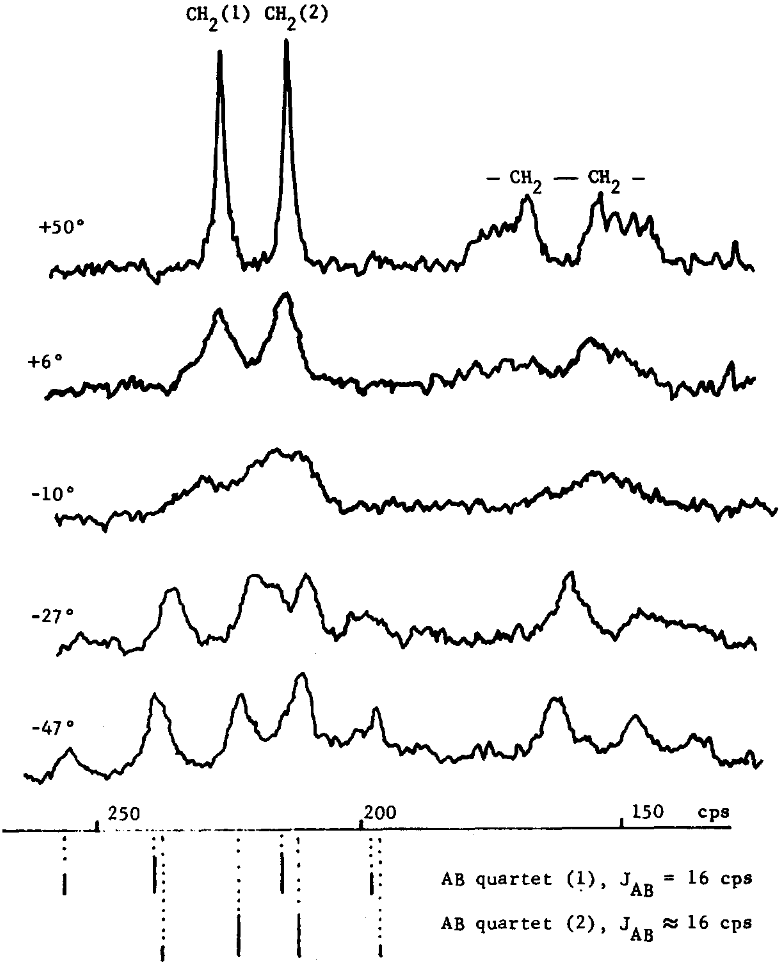

FIG. I

Nmr spectrum (60 Mc/sec.) of the methylene groups in the ten-membered ring of protopine (I) in $CDCl_3$ at various temperatures. The scale is cps downfield from internal TMS. The line spectra shown at the bottom are calculated spectra and refer to the spectrum taken at -47°.

We have found that the n.m.r. spectrum of protopine in $CDCl_3$ solution is temperature dependent and that all the bands of the protons attached to the ten-membered ring broaden greatly as the temperature is lowered (FIG. I). The N-methyl, methylenedioxy, and aromatic bands are unaffected. As the temperature is lowered still more (e.g., -45°), a sharp but very complex spectrum reappears. The singlets of the isolated methylene groups on the ten-membered ring now appear as AB quartets (FIG. I), partly superimposed on one another and on the spectrum of the CH_2-CH_2 protons, which have changed from the symmetrical AA'BB' system at room temperature to a very complex, presumably ABCD system at -45°. Although the low temperature spectrum cannot be analyzed completely, it is entirely consistent with the spectrum expected of I if ring inversion in the ten-membered ring has become slow on the n.m.r. time scale (2). It can be calculated that the rate constant for ring inversion at -10° is about 100 sec.$^{-1}$ and that $\Delta \underline{F}^{\ddagger}$ is about 13 kcal/mole. Because of the complexity of the spectra, attempts were not made to calculate the enthalpy and the entropy of activation (3).

Ring inversion results in a d to l (and vice versa) conversion in I, and is thus a mechanism for racemization. Perkin's (4) failure to resolve cryptopine, a close relative of protopine, is therefore understandable.

The conformation of the ten-membered ring of protopine cannot be deduced from the present results. The known trans-annular (5) carbonyl-amine interaction in this series of alkaloids (3) presumably helps to make ring inversion relatively slow. Ring inversion in ten-membered rings has apparently been detected by n.m.r. only in the case of trans-cyclodecene (6), but this compound bears little resemblance to I.

The published room-temperature spectrum (7) of the alkaloid coulteropine, a methoxy derivative of protopine, shows some broad bands, especially for the methylene protons next to the carbonyl group, for which no really satisfactory explanation has been given. It appears highly likely that this compound will show a temperature-dependent spectrum, as does protopine.

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References

1. N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, NMR Spectra Catalog, Vol. 1, Spectrum No. 339. Varian Associates, Palo Alto (1962).

2. For recent reviews on the application of n.m.r. to conformational problems, see: J. E. Anderson, *Quart. Rev.* (London), **19**, 426 (1966); L. W. Reeves, *Advan. Phys. Org.*, **3**, 187 (1965); C. S. Johnson, Jr., *Advan. Magnetic Resonance*, **1**, 33 (1965).

3. F. A. L. Anet and A. J. R. Bourn, *J. Am. Chem. Soc.*, **89**, 760 (1967).

4. W. H. Perkin, Jr., *J. Chem. Soc.*, **109**, 315 (1916).

5. F. A. L. Anet, A. S. Bailey, and R. Robinson, *Chem. and Ind.*, 944 (1953); E. H. Mottus, H. Schwarz, and L. Marion, *Canad. J. Chem.*, **31**, 1144 (1953); F. A. L. Anet and L. Marion, *ibid.*, **32**, 452 (1954).

6. G. Binsch and J. D. Roberts, *J. Am. Chem. Soc.*, **87**, 5157 (1965).

7. F. R. Stermitz, L. Chen, and J. I. White, *Tetrahedron*, **22**, 1095 (1966).