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SLOW CONFORMATIONAL CHANGE OF A THIAZEPINOQUINOLINE

J.L. Huppatz and G.F. Katekar

C.S.I.R.O. Division of Plant Industry, Canberra, A.C.T. 2601, Australia.

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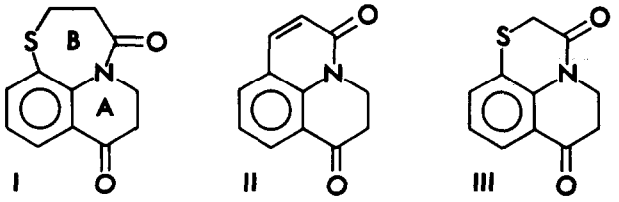
The NMR spectrum of the quinolothiazepine I (1) at 20° shows a broad hump centred about 4.2δ, assigned to the methylene protons adjacent to the nitrogen atom of the quinolone ring. Above +30° the absorption is a triplet, which becomes fully defined at +70°. At -30°C or lower, two principal absorptions appear at 5.2δ and 3.3δ, with fine structure, although the latter signal is hidden under the signal due to the S-CH_2- protons. These signals approximate to an AB system with J_{gem} 12 Hz, with a chemical shift difference of about 1.9δ (Fig. I).



As this chemical shift difference at -50°C is large, it is considered to arise from a non-symmetrical spatial arrangement of the methylene protons relative to the amide carbonyl, with the effect being averaged at +30°C or higher. This being so, these different spatial arrangements may be observable because of slow inversion of ring A with B time averaged, slow conformational changes of ring B, with ring A essentially planar, or rapid inversion of both rings, with a small relative difference in inversion rates. In the pyridoquinoline II (2), the essential features of ring A are maintained, but ring B is now planar. In this system, no non-equivalence of the N-CH_2- protons was observed at temperatures down to -30°C and any line broadening was observed equally with the signals due to both sets of methylene protons in the A ring. This would indicate that the slow inversion of ring A is unlikely to be the cause. That the non-symmetry is due to the steric requirements of the seven membered ring is indicated by the failure of the thiazinoquinoline III (2) to show these effects. The thiazepine ring may give rise to conformational isomers which could be caused by ring inversion, by inversion of the nitrogen atom, and by rotation about the N-CO bond giving rise to non-equivalent conformations where the

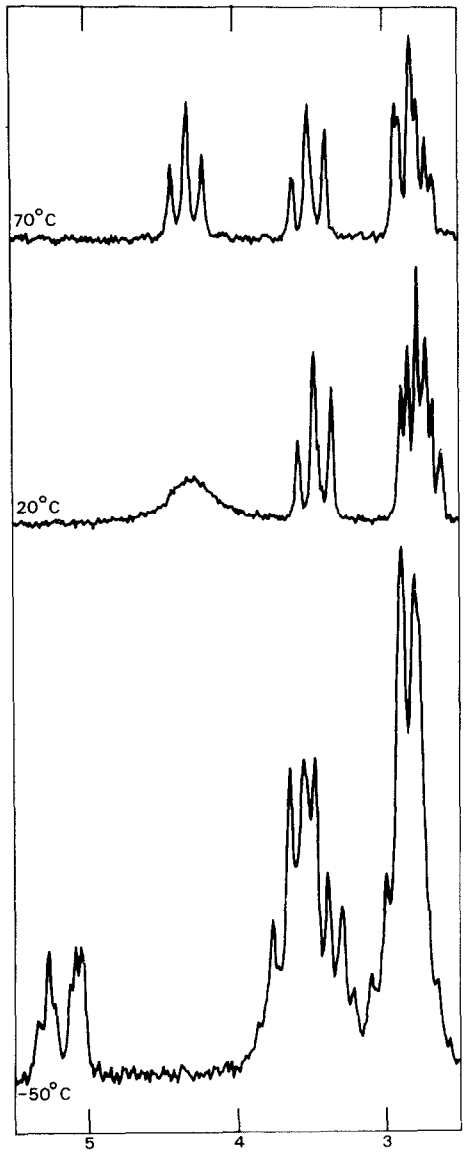


Figure 1

amide group is twisted. As the methylene protons of the 7 membered ring appear as an essentially time averaged A_2B_2 multiplet under conditions where non-equivalence of the α-protons of the A ring is observed, it would appear that slow inversion of ring B could only contribute at lower temperatures.

The effect may therefore be due to slow rotation of the amide (3) or to inversion of nitrogen (4,5,6). With either interpretation, the transition state would occur when the amide function possessed a planar configuration, this planar transition state being destabilised by the steric requirements of the 7 membered ring.

This phenomenon has been observed in other quinolothiazepines and a detailed discussion of these and their synthesis will be presented elsewhere. Spectra were recorded on a Varian A60 and HA60 spectrometers in deuterochloroform solutions. We would like to thank Dr. A.G. Moritz for spectral measurements and valuable discussion.

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