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DEMONSTRATION OF N-EPIMERS IN THE SALT OF A PIPERIDINE DERIVATIVE IN SOLUTION

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The n.m.r. spectrum of 1-ethyl-3-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (free base) differs from that of the corresponding hydrochloride particularly in respect of the 3-methyl and 4-phenyl signals. In the base, the 3-methyl signal is a doublet (τ 9.01, J 7.0 c.p.s.) and the 4-phenyl, a singlet (τ 2.68); in the hydrochloride the 3-methyl signal is a pair of doublets (τ 8.72, J 7.0 c.p.s: τ 9.07, J 6.5 c.p.s.) and the 4-phenyl, a pair of singlets at τ 2.64 and 2.7 [deuteriochloroform solvent in both cases, see Figure 1 (Spectra A and B) which also shows the overlapping triplet due to methyl of the 1-ethyl group]. These differences are interpreted in terms of the salt existing in deuteriochloroform solution in two configurations (I and II) which arise as a result of the basic centre becoming asymmetric upon proton addition. Assuming half-chair conformations, Ia is more likely than Ib since in the former the 1-ethyl group is equatorial and the 3-methyl axial, a favoured position for a 6-alkyl substituent in 1-phenylcyclohexene[1]; in II, (b) is probably the more likely (despite the decrease in resonance energy due to lack of complete planarity of phenyl and double bond) since IIa contains two axial substituents. In conformations Ia and IIb the relative environment of both the methyl and phenyl groups differ, hence the two configurations of the salt in solution exhibit different signals for these two groups.

Since the a-methyl group is close to the positively charged centre its signal should be downfield relative to that of 3-methyl in the free base (τ 9.01); hence the lower field doublet (τ 8.72) is attributed to Ia. Assignment of the higher field doublet (τ 9.07) to 3-methyl (e) in IIb is in accord with this group's further removal from charged nitrogen and with its possible receipt of a positive screening contribution from the phenyl group as a result of the latter's rotation out of the plane of the double bond. The significance of the last aspect is supported by the fact that the 3-methyl doublet suffers a further upfield shift in the 4-o-tolyl analogue (τ 9.13, J 6.5 for free base) in which the aryl group is even further rotated out of the plane of the double bond[2], while the chemical shifts of 3-methyl in the 4-phenyl-and 4-m-tolyl-tetrahydropyridines are identical. The close but separate signals observed for the 4-phenyl group in I and II may be a result of the slight difference in the planarity of phenyl with respect to the double bond in Ia and IIb.

In comparison with the free base, Ia is destabilised by one diaxial hydrogen-methyl interaction and IIb by a decrease in the resonance energy of the conjugated system; the first factor appears to be the slightly greater destabilising influence because the lower (Ia) and higher (IIb) methyl doublets integrate for 1.3 and 1.7 protons respectively (corresponding to approx. 43% Ia and 57% IIb).

The sharp nature of the two 3-methyl doublets and the aromatic pair of singlets indicates that the rate of proton exchange between I and II must be relatively slow in deuteriochloroform. When the rate is accelerated the two methyl doublets collapse to give a single unresolved signal centred at τ 8.95 in deuteriochloroform-pyridine (molar ratio pyridine to the tetrahydropyridine, 1 to 6), and τ 8.58 in deuterium oxide. In these solvents the aromatic signal is one singlet.

Isomerism arising as a result of a basic centre becoming asymmetric upon proton addition has previously been reported for hydrochlorides of 1, 2-dimethylpyrrolidine and pseudotropine.[3,4] Isomers of this type are comparable to N-epimeric quaternary salts[5,6] and differ in the conformation of the N-substituents. In the present example, however, the two epimers differ in respect of the conformation of substituents remote from, rather than attached to, the basic centre.

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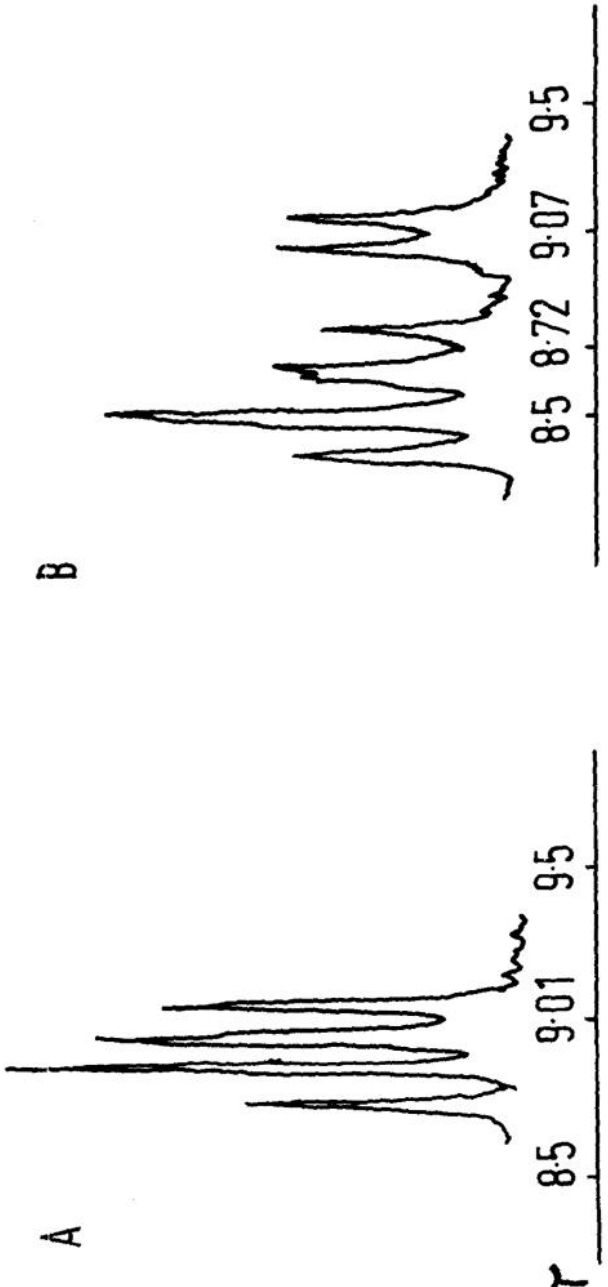


Fig. 1.

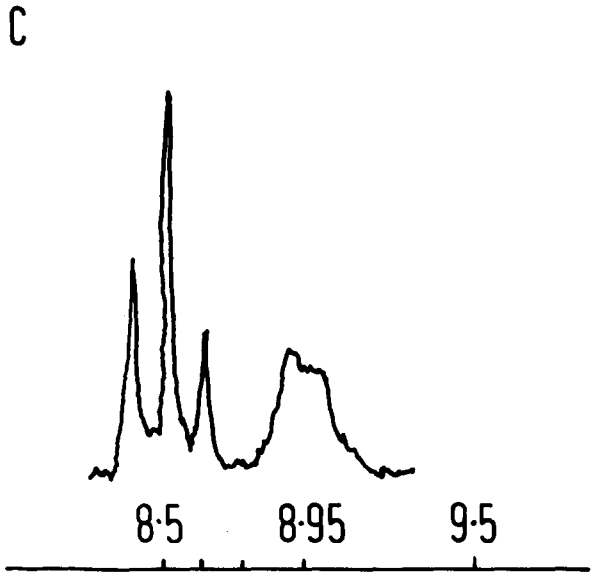
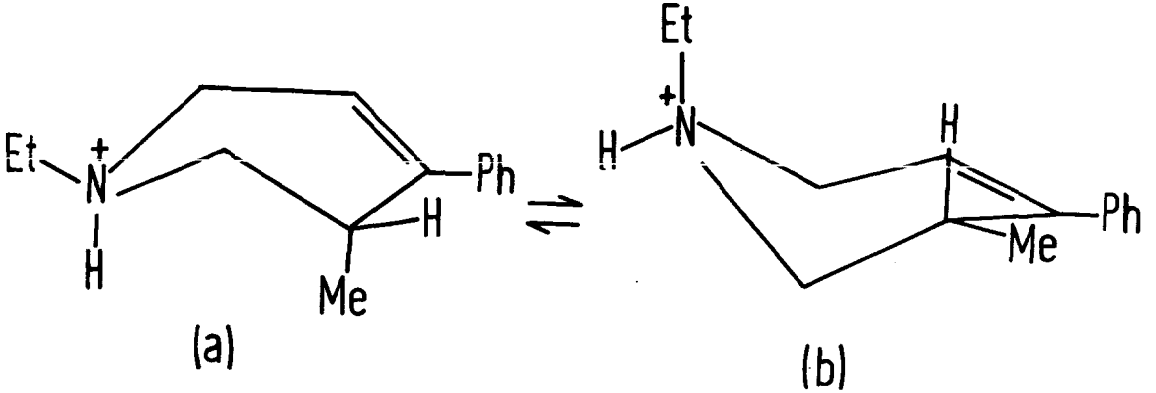


FIGURE 1

Part of the N.M.R. Spectra of 1-ethyl-3-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (recorded on a Varian A60 instrument at room temperature): (A) base in $CDCl_3$; (B) base hydrochloride in $CDCl_3$; (C) base hydrochloride-pyridine (6:1 mole ratio) in $CDCl_3$.



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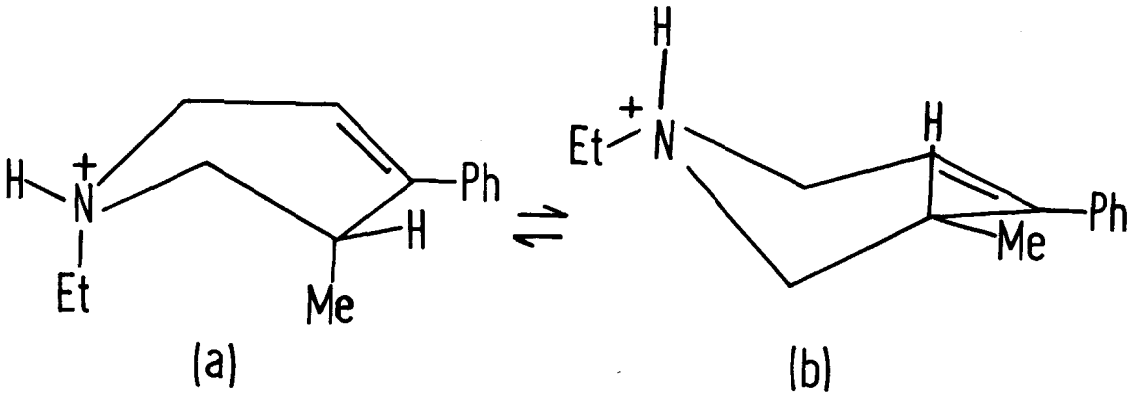

II