Magnetic Nonequivalence of Isopropyl Methyl Protons due to Hindered Rotation

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RECENTLY Halpern *et al.*[1] demonstrated experimentally that steric effects may, as expected,[2] contribute to the magnetic nonequivalence of isopropyl methyl protons. We have found further experimental evidence with a series of 1,2,3,4-tetrahydro-1-isopropylisoquinoline derivatives (I and II), which also illustrate that steric hindrance, when combined with the anisotropy effects of a nearby aromatic ring, may give rise to large degrees of nonequivalence of isopropyl methyl protons. The values of "nonequivalence shifts" (Δ) quoted below are the largest yet published for isopropyl groups.

The 60 Mc./sec. resonance trace (Figure) illustrates the magnitude of nonequivalence encountered in the given series of compounds. The proton resonance data (chemical shifts of isopropyl methyl protons, the corresponding Δ values and the coupling constants between isopropyl methine and C-1 protons) are summarised in the Table.

Thus the chemical shift difference of isopropyl methyl protons increases when the free *N*-alkyl bases (Ib, Ic) are converted into their tertiary and quaternary salts (IIb, IIc, IId), or within the series (IIa)—(IId), when the bulkiness of the substituents at the quaternary nitrogen increases. The above changes are best interpreted in terms of increasing steric hindrance accompanied by a simultaneously increasing anisotropy effect of the aromatic ring. The negligible importance of the asymmetry centre at nitrogen in this respect (*e.g.*, in IIb, IId) is readily seen by the results obtained with the symmetrically substituted (IIa) and (IIc).

In the case of free bases the nonequivalence should be ascribed to the presence of asymmetric carbon (C-1) and to the preference of one of the conformations arising from simultaneously occurring internal motions, *i.e.*, rotation of isopropyl group, conformational motion of hetero-ring and inversion at nitrogen. Without a detailed analysis of temperature dependence of the spectra, however, no conclusion can be made concerning the relative importance of these factors, and thus no unequivocal explanation can be given to the differences in the proton resonance characteristics of isopropyl groups either.

Conversion of (I) into (II) makes inversion at nitrogen impossible and, as a consequence of this, the hetero-ring assumes a motionally more defined form with a presumably higher preference to the less-hindered conformation. (In accordance with our other results,[3] this is the *trans-pseudo-equatorial–equatorial* conformation relative to the isopropyl and N-Me group.) Introduction of methyl or ethyl substituent at nitrogen rather than H-atom (IIc and IId, respectively) results in the increase of steric compression which forces the isopropyl group to assume its less hindered rotational conformation.

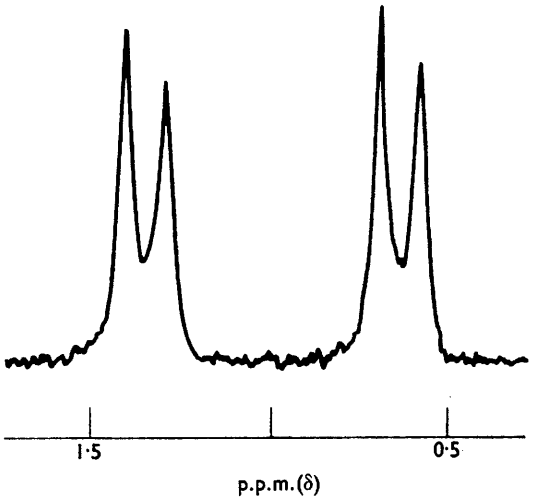


FIGURE. *Isopropyl methyl resonances in* (IIc) *at* 25° (Solvent $CDCl_3$)

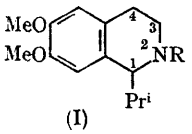
This conclusion is supported by the observed vicinal couplings between C(1)–H and isopropyl methine proton, which—according to the Table—decreases with increasing Δ. In quaternary salts (IIc) and (IId) it is $\leqslant$1·5 c./sec. indicating a dihedral angle of about 90° between the two protons. Examination of molecular models reveals that the less hindered rotational conformation of the isopropyl group in these molecules is indeed the one which follows from this coupling constant. In this conformation one of the isopropyl methyls is placed near the plane of the aromatic ring, while the other one resides "below" it (the isopropyl group being in the *e* position and only one of the optically active forms is considered). Measurements on Dreiding models and use of Johnson–Bovey tables[4]

TABLE

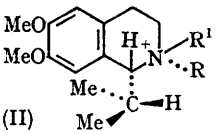
Proton resonance characteristics of isopropyl groups at 25° in $CDCl_3$ solution.

Compound		Chemical shift of Me protons (p.p.m.)		Δ (p.p.m.)	J (c./sec.)
(Ia)	R = H	0·72	1·09	0·37	3·0
(Ib)	R = Me	0·87	0·99	0·12	5·0
(Ic)	R = Et	0·89	1·01	0·12	5·5
(IIa)	R = H, R^1 = H	1·01	1·32	0·31	3·5
(IIb)	R = H, R^1 = Me	0·97	1·33	0·36	~2·5
(IIc)	R = Me, R^1 = Me	0·65	1·36	0·71	≤1·5
(IId)	R = Me, R^1 = Et	0·65	1·38	0·73	≤1·5

allowed us to estimate the nonequivalence shift corresponding to the above conformation. The value thus obtained is 0·6 p.p.m. which, taking into account the approximate nature of these calculations and possible distortions of the hetero-ring, is in good agreement with experiments. At present, it is not possible to decide unequivocally whether this conformation of the isopropyl group represents a highly preferred, or the only sterically possible, rotational conformation. Molecular models and preliminary experiments at elevated temperatures, however, suggest the latter case to be more probable.[5]



(I)



(II)

Further deductions will be made when our variable temperature measurements on these and other tetrahydro-1-isopropylisoquinoline derivatives are completed.

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[1] B. Halpern, J. W. Westley, and B. Weinstein, *Chem. Comm.*, 1967, 160.
[2] M. L. Martin and G. J. Martin, *Bull. Soc. chim. France*, 1966, 2117.
[3] G. Bernáth, M. Kajtár, J. Kóbor, and L. Radics, to be published.
[4] J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution N.m.r. Spectroscopy," Pergamon Press, Oxford, 1965, Vol. I, Appendix B.
[5] Restricted rotation of benzyl group has been suggested recently in *N*-acetyl-1-benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline by G. Fraenkel, M. P. Cava, and D. R. Dalton, *J. Amer. Chem. Soc.*, 1967, 89, 329.