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NMR CHEMICAL SHIFTS AS CRITERIA OF THE CONFORMATION OF THE NITROGEN ATOM IN PIPERIDINES

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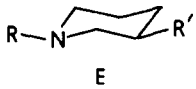
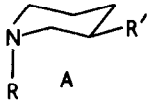
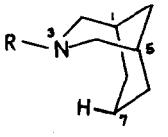
Since Aroney and LeFevre (1) first claimed that the N-hydrogen atom was axial in the preferred conformation IA of piperidine I there have been several attempts to obtain conclusive evidence about this apparent anomaly. Potentially decisive techniques such as microwave spectroscopy (2) and electric dipole moments (3), however, have met with difficulties, although infra-red spectra have now yielded excellent evidence that the preferred conformation is IE (4). Many other experimental (5) and theoretical (6) approaches have been made to the solution of this problem with widely differing results but recently the view that the N-hydrogen atom is axial in piperidine I (and axial even in 3-azabicyclo(3, 3, 1)-nonane V (7)) has been expressed particularly strongly (6, 7). The chemical shift differences δ_{ae} $(= \tau_a - \tau_e)$ between the hydrogen atoms of the methylene groups in 3, 3, 5, 5-d_4-piperidines I-III at low temperatures (7) has been described as "the most definitive" evidence available for this view (6). This Letter has two purposes. Firstly, to point out that the NMR chemical shift differences δ_{ae} cannot (at present) provide valid evidence for the conformation of piperidine I (as distinct from the N-alkylpiperidines II and III), so that the experiments used by Lambert et al. (7) were misconceived and



E



A



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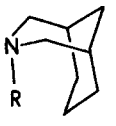


A

I: R = R′ = H

II: R = Me, R′ = H

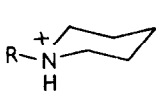
III: R = t-Bu, R′ = H

IV: R = H, R′ = Me

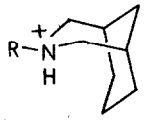
V: R = H

VI: R = Me

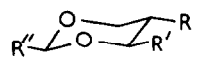
VII: R = H
VIII: R = Me



IX: R = H
X: R = Me

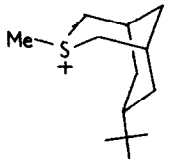


XI: R = H
XII: R = Me

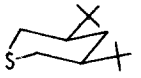


XIII: R = R′ = H, R″ = $C_6H_4NO_2$
XIV: R = Me, R′ = H, R″ = $C_6H_4NO_2$
XV: R = R′ = R″ = H
XVI: R = R″ = H, R′ = Me

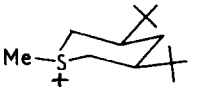
XVII



XVIII



XIX



XX

the conclusion drawn for I are invalid. Secondly, to show by a more detailed examination of the NMR spectra of the 3-azabicyclo(3,3,1)nonanes V and VI that the conclusion of Lambert et al. (7), namely, that the preferred conformation of V is Va, is wrong.

Differential shielding effects of equatorial methyl groups on δ_{ae} values of vicinal methylene groups in six-membered rings.

The use of values of δ_{ae} (2-CH_2) in piperidines as criteria for the conformation of the N-substituent (7,8) depends on two assumptions. The first, implicitly (6,8) or explicitly (7), is that "a small isotropic substituent, e.g., methyl, at the equatorial site of an adjacent atom will have little effect on δ_{ae}, since it is almost equivalently positioned with respect to both the substituents" (7). The second is that an axial unshared pair of electrons on nitrogen causes a selective shielding of vicinal axial hydrogen atoms (8), an idea all too plausibly associated with an explanation (8) of the origin of the 'Bohlmann' bands (5) in the infra-red spectra of certain amines.

The first assumption is not supported by the available evidence. It is apparently general that an equatorial methyl group shields the hydrogen atoms of an adjacent methylene group differently and in all

the unambiguous examples (see Table) the axial hydrogen is the more shielded. The examples cover a wide range of environments for methylene groups and include systems in which a methyl group is added to an unshared pair rather than substituted for a hydrogen atom. In all instances methylation causes a significant change in δ_{ae} but the change for the piperidinium ions IX and X (7) happens to be at the lower end of the range $(|\delta_{ae}| = 0{\cdot}1 - <0{\cdot}9 \text{ppm})$. The data in the Table shows that the N-methyl group in II probably accounts for a substantial part, at least of δ_{ae} for I and II.

The validity of the second assumption is undermined by the results in the following section which indicate that δ_{ae} is not much affected by the axial or equatorial position of the unshared pair in piperidine derivatives.*

The conformation of 3-azabicyclo(3,3,1)nonane.

The predominance of chair-chair conformations in 3-azabicyclo(3,3,1)nonane and those of its derivatives discussed here is not in question (7,12,15). Lambert et al. concluded from the values of δ_{ae} for the 2- and 4-methylene groups in V and VI that the preferred conformations are VA and VIE (7), but as has been shown above such evidence does not define the conformation of piperidines without an N-alkyl group. The spectra of V and VI, however, show two significant features which have not been considered previously (7). Firstly, the chemical shift of the N-hydrogen atom in piperidine I changes from 8.59 τ in chloroform to 8.99 τ in benzene. This is presumably caused by very weak hydrogen bonding between the N-hydrogen atom and the π-electrons of the benzene ring. It is very significant, therefore, that the solvent effect on the chemical shift of the N-hydrogen atom in V (8.59 τ in $CDCl_3$ and 9.23 τ in C_6H_6) is very similar to but somewhat larger than that found for piperidine because in VA hydrogen bonding between the axial N-hydrogen atom and benzene would be very strongly hindered by the 7-methylene group.

The second special feature of the spectra of V and VI is the low τ-values of the endo 7-hydrogen atoms. Qualitatively similar deshielding is found in the 3-oxa- and 3-thia-bicyclo(3,3,1)nonanes (12). This

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* A recent study of derivatives of tetrahydro-1,3-oxazine shows that δ_{ae} for the 4-methylene group is very sensitive to the axial or equatorial conformation of an N-alkyl substituent (9). NMR chemical shifts, therefore, can be used reliably to determine the conformations of N-alkyl-piperidines but not for the reasons previously given (7).

TABLE

The effect of vicinal equatorial equatorial methyl groups on the chemical shifts of axial and equatorial hydrogen atoms in methylene groups in six-membered rings.

Compound	δ_{ae} (p.p.m.)[a]	Compound	δ_{ae} (p.p.m.)[a]	$\Delta\delta_{ae}$	Reference
VII	0.48	VIII	1.17 ± 0.1[b]	0.35[c]	10
I	0.42-0.48 (C-2)[d]	IV	0.79 (C-2)[e] [0.48(C-6)][e]	0.34	7,11
IX	0.35-0.47 (C-2)[d]	X	0.44-0.60 (C-2)[d]	0.1	7
XI	0 (C-2)[f]	XII	0.38 (C-2)[f]	0.38	12
XIII	0.29 (C-4)[e]	XIV	0.69 (C-4)[e]	0.40	13
XV	-0.7 (C-5)[g]	XVI	-0.28 (C-5)[b]	0.4	14
XVII	$\pm$0.69(C-2)[e,h]	XVIII	$\pm$0.16 (C-2)[i]	$\pm$0.85 or $\pm$ 0.53	
XIX	$<\pm$0.3(C-2)[e]	XX	0.60 (C-2)[h,i]	0.3-0.9	

[a] $\delta_{ae} = \tau_a - \tau_e$; where necessary the methylene group is specified by the number of the carbon atom in the ring.

[b] In CCl_4. [c] Effect of each of two adjacent methyl groups. [d] Various solvents, not including $CDCl_3$. [e] In $CDCl_3$. [f] In D_2O. [g] See ref. 14. [h] Relatively insensitive to change of solvent. [i] In CD_3CN.

deshielding effect is attributed to the proximity of an unshared pair on the heteroatom to the endo 7-hydrogen atom because (a) similar effects are found whenever heteroatoms with unshared pairs are close to hydrogen atoms, (b) the effect is not found in salts of V and VI, and (c) the chemical shift of the endo 7-hydrogen atom (but not the others) is very sensitive to the addition of methanol, which causes large shifts to high field, to solutions of V in benzene.* The last is explained by a change in conformation from VE, in which the unshared pair is very hindered, to VA, in which the unshared pair is available for hydrogen bonding but

* Qualitatively similar effects have been observed in $CDCl_3$ solutions but the use of benzene allows the effect of added methanol to be studied over a wider range of concentration.

is not in a position to deshield the endo 7-hydrogen atom. This change in conformation is not accompanied by detectable changes in δ_{ae} for the C-2 and C-4 hydrogen atoms. This provides rather direct evidence that δ_{ae} for a methylene group adjacent to a nitrogen atom in a piperidine is largely unaffected by the position of the unshared pair and further undermines Lambert's conclusions for piperidine (7).

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