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PROTON MAGNETIC RESONANCE STUDIES OF CYCLIC COMPOUNDS—V*

THE CHEMICAL SHIFTS OF THE 2,6-PROTONS IN C-ALKYL- AND N-ALKYLPIPERIDINES

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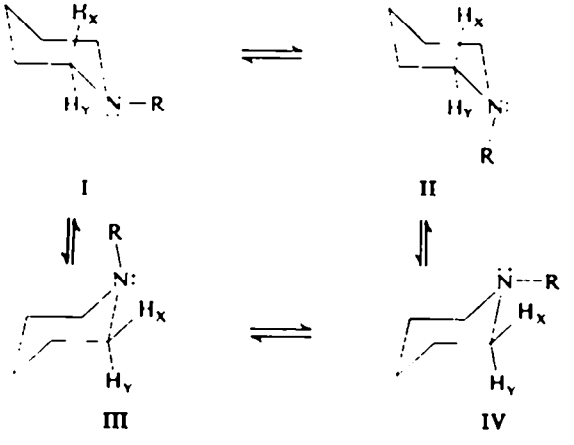
Abstract—Chemical shifts are recorded for the 2,6-protons of both conformationally fixed, and conformationally mobile, C-alkyl and N-alkylpiperidines. The 2,6-protons, especially when axial, suffer a marked shielding after replacement of N—H by N-alkyl. It is suggested that the observed shielding is due to a combination of stereospecific influences: one associated with the orientation of the nitrogen lone pair, and one associated with the orientation of the N-alkyl group.

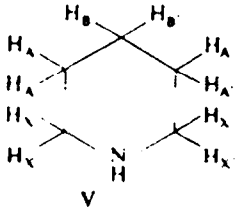
AN INTEREST in the stereochemistry of cyclic bases led us to examine the PMR spectra of a number of simple piperidines. Chemical shift values have already been reported for some piperidines by Roberts and Bottini[1] (40 Mc/s in benzene), by Weitkamp and Korte[2] (25 Mc/s in CCl_4), and by Varian Associates[3] (60 and 100 Mc/s in $CDCl_3$). Our measurements were carried out at 60 Mc/s with CCl_4 as solvent. Since solutions of most piperidines in CCl_4 soon deposit crystalline material, spectra were determined as soon as possible after preparation of the solution.

In general, the ring protons of piperidines give spectra containing complicated line patterns which are not easily interpreted in terms of chemical shifts and coupling constants. Our work has so far only involved the relatively easily interpretable signals due to protons at positions 2 and 6. The deshielding influence of the nitrogen atom causes these signals to appear at low field, in general, compared with signals due to the remaining ring protons.



* Part IV, H. Booth, *Tetrahedron* **22**, 615 (1966).

[1] A. T. Bottini and J. D. Roberts, *J. Amer. Chem. Soc.* **80**, 5203 (1958).
[2] H. Weitkamp and F. Korte, *Chem. Ber.* **95**, 2896 (1962).
[3] Varian Associates, High Resolution NMR Spectra Catalogue Vol. 2 (1963).

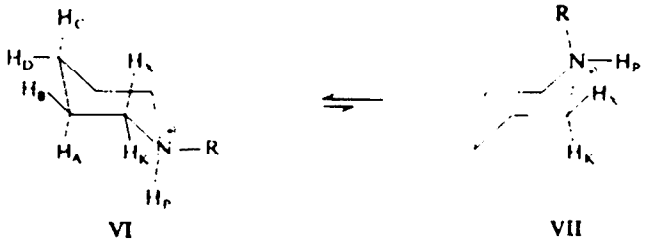


V

In piperidine (I; R = H) and N-alkylpiperidines (I) there is very rapid nitrogen inversion (I $\rightleftharpoons$ II)[1] although conformation (I) is strongly preferred for both R = H and R = Me.[4] Ring inversion (I $\rightleftharpoons$ III and II $\rightleftharpoons$ IV), though not so rapid as nitrogen inversion, is still rapid enough at room temperature to cause an averaging of the chemical shifts. Now $\sigma(H_X)$ in (I) = $\sigma(H_Y)$ in (IV) and $\sigma(H_Y)$ in (I) = $\sigma(H_X)$ in (IV); also $\sigma(H_X)$ in (II) = $\sigma(H_Y)$, in (III), and $\sigma(H_Y)$ in (II) = $\sigma(H_X)$ in (III); thus protons H_X and H_Y are expected to have identical chemical shifts. However, the averaged coupling constants of H_X are unlikely to be the same as those of H_Y. Thus H_X and H_Y are not equivalent in the spin coupling sense, and they should properly be regarded as the $X_2X_2^1$ portion of an $X_2X_2^1A_2A_2^1BB^1$ system (cf. V). In fact, the 2,6-protons of piperidine give, at τ = 7·31, a narrow signal, roughly triplet in character. with half-band width ~10 c/s[5] and of which the centre gives the average chemical shift over conformations I to IV (R = H). A signal of similar character is given by the 2,6-protons of all the N-alkyl derivatives of piperidine examined, even when the alkyl group is t-butyl. Evidently the very rapid nitrogen inversion allows N-t-butylpiperidine to undergo ring inversion between I (R = t-Bu) and IV (R = t-Bu), despite the likelihood that II (R = t-Bu) and III (R = t-Bu) are forbidden, i.e. during the time taken for ring inversion I → III, nitrogen inversion operates to place the t-butyl group in an orientation which causes it to be equatorial in the resulting conformation IV (R = t-Bu).

The chemical shifts of protons at positions 2 and 6 in piperidine and N-alkylpiperidines are recorded in Table 1. The shielding of the 2,6-protons resulting from N-alkylation is interesting, as a similar effect was noted for the α-proton of cyclohexylamines.[6] This effect, the magnitude of which appears to fall in the sequence Me, Et (allyl, benzyl), i-Pr, t-Bu, is discussed later.

In strongly acidic solution, ring inversion of piperidines is still operative, but nitrogen inversion is prevented, so that we are now only concerned with the interconverting



VI VII

[4] R. J. Bishop, L. E. Sutton, D. Dineen, R. A. Y. Jones and A. R. Katritzky, *Proc. Chem. Soc.* 257 (1964); N. L. Allinger, J. G. D. Carpenter and F. M. Karkowski, *Tetrahedron Letters* 3345 (1964).

[5] H. Booth, *J. Chem. Soc.* 1841 (1964).

[6] H. Booth, N. C. Franklin and G. C. Gidley, *Tetrahedron* **21**, 1077 (1965).

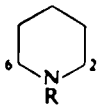


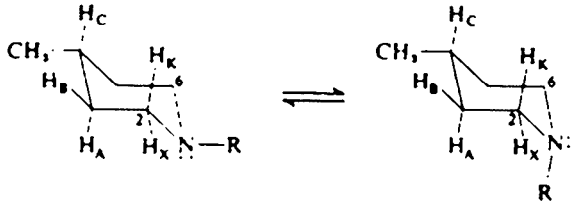
TABLE 1. CHEMICAL SHIFTS OF 2,6-PROTONS IN N-ALKYL DERIVATIVES OF PIPERIDINE

	Chemical Shifts (τ values)			
		CF_3CO_2H		
Alkyl group R	CCl_4	equatorial	axial	$\tau_a - \tau_e$
(hydrogen)	7·31	6·63	6·63	0
methyl	7·76	6·39	7·00	0·61
ethyl	7·71	6·35	7·05	0·70
allyl	7·70	6·35	7·05	0·70
benzyl	7·71	6·38	7·00	0·62
isopropyl	7·61	6·47	7·00	0·53
t-butyl	7·55	6·27	7·12	0·85

conformations VI and VII. For the N-alkyl derivatives of piperidine in CF_3CO_2H (Table 1), separate signals, each representing two protons, are clearly seen in the PMR spectrum, at low field. Since the conformational equilibrium VI $\rightleftharpoons$ VII is expected to favour strongly that conformation with R equatorial, the observed signals mark the approximate chemical shifts of protons which are, respectively, equatorial and axial in conformation VI. This interpretation is confirmed by the fine structure of the two signals, for the latter may be analysed, in a simple first order manner, as the X_2 and K_2 parts of an $X_2K_2A_2B_2CD$ system. Thus the signal for the equatorial protons H_{2e} and N_{6e} ($=H_K$) is a doublet, separation about 12 c/s ($\simeq J_{2e2a} = J_{XK}$ = gem proton–proton coupling constant), each component being broad, due to the further couplings J_{KB}, J_{KA} and J_{KP}, with H_{3e} H_{3a} and HN^+ respectively; each of the latter couplings is probably < 3 c/s, as the dihedral angles involved are in the region of 60°. The signal for the axial protons H_{2a} and H_{6a} ($=H_A$) is a quartet, with separations of about 12 c/s due to three approximately equal couplings J_{XK} (gem-coupling with H_{2e}), J_{XA} (vicinal coupling with H_{3a}, dihedral angle ~180°) and J_{XP} (vicinal coupling with HN^+, dihedral angle ~180°). Each component of the quartet is broad, due to the further small coupling J_{XB} (vicinal coupling with H_{3e}, dihedral angle ~60°). The chemical shifts of the protons at the 2,6-positions of protonated N-alkylpiperidines are given in Table 1, the values recorded being the approximate centres of gravity of the observed doublets (for H_{2e}) or quartets (for H_{2a}). A more refined analysis was not warranted, owing to the broadness of the peaks. Thus the chemical shifts listed may be in error by as much as 0·05 ppm. For some compounds, the signals for H_{2e} or H_{2a} are partially overlapped by other signals, so that interpolation of peaks was necessary to allow the centres of the multiplets to be obtained; however, this was done with confidence, because the correctness of the interpretation was clear from the majority of spectra, in which no overlapping occurs. It is seen that $\tau_a - \tau_e$, the difference in chemical shift between axial and equatorial protons at position 2, lies in the range 0·53 to 0·85 ppm.

Next, piperidines were examined in which the presence of alkyl substituents on

ring carbon atoms produced resistance to ring inversion. By analogy with the situation for methylcyclohexane, which exists to the extent of ~95% in that conformation with methyl equatorial, a C-methylpiperidine is expected to exist almost entirely in a single conformation, as far as the ring is concerned. Nitrogen inversion still persists, however, so that for 4-methylpiperidine, for example, we still have to consider conformations VIII (R = H) and IX (R = H). The spectrum of 4-methylpiperidine, recorded at 60 Mc/s and 100 Mc/s has been published.[3] The signal due to equatorial protons at



VIII IX

positions 2 and 6, and the signal due to axial protons at positions 2 and 6, form the X_2 and K_2 parts, respectively, of an $X_2K_2A_2B_2CP_2$ system. As with the protonated N-alkylpiperidines discussed above, the X_2 and K_2 portions are easily identified from their fine structure, using a first order analysis. Thus the equatorial proton H_{2e} ($=H_X$) appears at lowest field ($\tau = 7{\cdot}1$) as a doublet, separation ~12 c/s ($\sim J_{2e2a} = J_{XK}$), each component being broadened by further small couplings J_{XA} ($=J_{2e3a}$, vicinal coupling with H_A, dihedral angle ~60°) and J_{XB} ($=J_{2e3e}$, vicinal coupling with H_B, dihedral angle ~60°). The axial proton H_{2a} ($=H_K$) appears at $\tau = 7{\cdot}50$ as a triplet (overlapped by other signals in some compounds) with separations of about 12 c/s, due to two approximately equal couplings K_{KX} ($=J_{2e2a}$) and J_{KA} ($=J_{2a3a}$ vicinal coupling with dihedral angle ~180°). Each component of the triplet is somewhat broad, due to the further coupling J_{KB}($=J_{2a3e}$, vicinal coupling with dihedral angle ~60°). The signals due to the 2a and 2e protons are thus easily identified. Similar considerations were applied to the spectra of a number of C-alkylated piperidines, and the results are given in Table 2. For completeness, the Table includes *accurate* chemical shift data for *cis*-2,6- and *cis*-3,5-dimethylpiperidines, the preparation and spectra of which will be fully discussed in a later publication. All the piperidines of Table 2 are expected to be conformationally homogeneous, as far as ring inversion is concerned, to the extent of at east 90%.

It is noteworthy that for the secondary amines, the difference in chemical shift between the protons at position 2, $\tau_a - \tau_e$, lies in the range 0·40 to 0·52, *except* for the 2-protons of 3-methylpiperidine and the 2,6-protons of *cis*-3,5-dimethylpiperidine, where the large differences are clearly due to the preferential shielding of the axial protons at 2 and 6 by the equatorial methyl group(s) on the adjacent carbon atoms(s).[7] The chemical shifts of the equatorial and axial protons at positions 2 and 6 in the N-alkyl derivatives of C-substituted piperidines are also listed in Table 2. The shielding effect caused by N-alkylation is once more evident, and it is now noted that the shielding of the axial proton is much more pronounced than that of the equatorial proton.

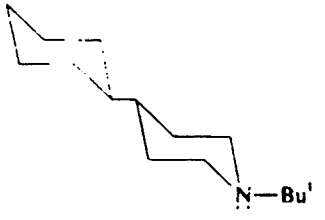
[7] H. Booth, *Tetrahedron* **22**, 615 (1966); E. Eliel, M. H. Gianni, T. H. Williams and J. B. Stothers, *Tetrahedron Letters* 741 (1962).

TABLE 2. CHEMICAL SHIFTS OF 2,6-PROTONS IN C-ALKYL PIPERIDINES AND THEIR N-ALKYL DERIVATIVES

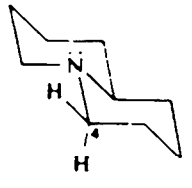
Piperidine derivative	Chemical shifts τ(values)					
	CCl_4			CF_3CO_2H		
	e	a	$\tau_a-\tau_e$	e	a	$\tau_a-\tau_e$
4-Methyl	7·10	7·50	0·40	6·42	6·83	0·41
1,4-Dimethyl	7·32	8·18	0·86	6·38	6·96	0·58
1-Ethyl-4-methyl	7·23	8·18	0·95	6·37	7·05	0·68
1-Allyl-4-methyl	7·21	8·15	0·94	6·37	7·03	0·66
1-Benzyl-4-methyl	7·23	8·10	0·87	6·37	6·95	0·58
1-Isopropyl-4-methyl	7·27	7·90	0·63	6·45	*a*	—
4-Cyclohexyl	6·95	7·47	0·52	*b*	*b*	—
1-t-Butyl-4-cyclohexyl	7·00	8·05	1·05	*b*	*b*	—
2-Methyl	7·07[a]	*a*	—	6·42[a]	*a*	—
1,2-Dimethyl	7·30	> 8·0	> 0·70	*b*	*b*	—
3-Methyl	7·15[c]	7·60[d]	0·45	6·45[c]	*a*	—
	7·15[d]	7·90[d]	0·75	6·45[d]	*a*	—
1,3-Dimethyl	7·38	> 8·10	> 0·72	*b*	*b*	—
cis-2,6-Dimethyl	—	7·44	—	—	6·65	—
cis-1,2,6-Trimethyl	--	> 8·0	—	—	6·35[a]	—
					6·80[a]	
cis-3,5-Dimethyl	7·10	7·95	0·85	*b*	*b*	—
cis-1,3,5-Trimethyl	7·33	8·70	1·37	*b*	*b*	—

[a] not seen clearly
[b] not measured
[c] 6-proton
[d] 2-proton
[e] 2 signals, due to 2 conformations, one with N-Me equatorial and one with N-Me axial.

For example, N-methylation of 4-methylpiperidine causes an upfield shift of 0·22 ppm for the 2-equatorial proton, and 0·68 ppm for the 2-axial proton. This situation naturally leads to an increase in the value of $\tau_a-\tau_e$, compared with that for the related secondary amine. For the N-alkyl derivatives listed, $\tau_a-\tau_e$ lies in the range 0·63 to 1·37 ppm. A value of 1·05 ppm was recorded for $\tau_a-\tau_e$ in 1-t-butyl-4-cyclohexylpiperidine, a molecule which probably exists exclusively in conformation X, since both ring inversion and nitrogen inversion are resisted strongly. The unusually large difference of 1·37 ppm between the chemical shifts of the axial and equatorial protons



X



XI

at position 2 of *cis*-1,3,5-trimethylpiperidine is due largely to the combined shielding effects of N-methyl and the equatorially oriented 3-methyl on the axial proton at position 2.

It has been suggested[8] that the large difference (~0·9 ppm)[8,9] in chemical shift

[8] H. P. Hamlow, S. Okuda and N. Nakagawa, *Tetrahedron Letters* 2553 (1964).
[9] F. Bohlmann, D. Schuman and H. Schulz, *Tetrahedron Letters* 173 (1965).

between axial and equatorial protons at position 4 of quinolizidine (XI) is due to stereospecific shielding of the axial proton by the lone pair situated *trans*-coplanar on the adjacent nitrogen atom. Thus, the fact that N-alkylation of piperidines causes a greater shielding of the axial proton than of the equatorial proton on an adjacent carbon atom may be due to the greater proportion of e.g. VIII (R = alkyl) in the equilibrium VIII $\rightleftharpoons$ IX than of VIII (R = hydrogen) in the equilibrium VIII $\rightleftharpoons$ IX. Certainly the difference $\tau_a - \tau_e$ is smaller when the lone pair is protonated in acid solution (Table 2). However, it is difficult to assess quantitatively the stereospecific shielding effect of the nitrogen lone pair, because there are indications that another effect is involved. Thus, it is noticeable that the average shielding of the axial and equatorial protons at position 2 of N-alkylpiperidines (Table 1) *falls* in the series alkyl = Me, Et(allyl, benzyl), i-Pr, t-Bu. Also in the case of N-alkyl-4-methylpiperidines, the shielding of the axial proton at position 2 due to N-alkylation *falls* in the series alkyl = Me (Et), allyl, benzyl, i-Pr. These trends are opposite to those expected, since increase in the size of the N-alkyl group should increase the proportion of that conformation (e.g. VIII) with lone pair axial. Now it is well established that replacement of an equatorial hydrogen attached to carbon, by an alkyl group, causes a shielding of protons on the adjacent carbon atom which is stronger for the axial than for the equatorial proton.[7] Moreover, the magnitude of this effect was observed to fall in the series Me, Et (n-Pr, n-Bu), i-Pr, t-Bu. The mechanisms of the effect is not known, but it may depend on a mode of electron release similar to that involved in hyperconjugation. There seems to be no reason why this effect should not operate also for alkyl groups attached to nitrogen, and this effect may therefore be superimposed on that due to the lone pair,

The signals due to protons of the N-alkyl and C-alkyl groups are unexceptional, both as regards chemical shifts and splittings, and these details are therefore not included in Tables 1 and 2. In acid solution, the signals of the α-protons of the N-alkyl groups show additional splitting (~5 c/s) due to coupling with the proton attached to nitrogen (cf.[1]).

EXPERIMENTAL

PMR spectra: Perkin–Elmer R10 Spectrometer operating at 60 Mc/s, and using CCl_4 and CF_3CO_2H as solvents, with TMS as internal reference. Piperidine, free from pyridine and 1,2,5,6-tetrahydropyridine, was a gift from Robinson Bros. Ltd. 1,-2,-3,- and 4-Methylpiperidines were obtained from Koch-Light Laboratories, Ltd.

Alkylation of piperidines. The Eschweiler-Clarke procedure[10] was used to methylate piperidines. 1,2-Dimethylpiperidine, 1,3-dimethylpiperidine and 1,4-dimethylpiperidine gave physical constants (b.p. of base, m.p. of picrate) which agreed with literature values.

The following N-alkylpiperidines were prepared by the normal method (piperidine, alkyl bromide or iodide, Na_2CO_3, hot EtOH) and had properties which agreed with those recorded in the literature: 1-ethylpiperidine, 1-isopropylpiperidine, 1-t-butylpiperidine, 1-benzyl-4-methylpiperidine, 1-isopropyl-4-methylpiperidine.

The following are new:

1-*Ethyl-4-methylpiperidine*, b.p. 147°. The *picrate* from EtOH, had m.p. 153°. (Found: C, 47·5; H, 5·7; N, 15·7. $C_{14}H_{20}N_4O_7$ requires: C, 47·2; H, 5·7; N, 15·7%.)

1-*Allyl-4-methylpiperidine*, b.p. 162–164°. The *picrate*, from EtOH, had m.p. 97–98°. (Found: C, 48·6; H, 5·5; N, 15·6. $C_{15}H_{20}N_4O_7$ requires: C, 48·9; H, 5·5; N, 15·2%.)

[10] M. L. Moore, *Organic Reactions* **5**, 301 (1949).

1-*Benzyl-4-methylpiperidine picrate*, from EtOH, had m.p. 137°. (Found: C, 54·7; H, 5·3; N, 13·1. $C_{19}H_{22}N_4O_7$ requires: C, 54·5; H, 5·3; N, 13·4%.)

4-*Cyclohexylpiperidine*. (1) Reduction of 4-phenylpyridine (2 g) with Na (2 g) in boiling EtOH (100 ml), followed by the usual method of isolation (acidification, removal of EtOH, basicification, ether-extraction), gave crude 4-phenylpiperidine (1·8 g). The product (1 g) was dissolved in 30% HCl and hydrogenated at atm press and room temp in the presence of PtO_2 (2·9 moles H absorbed). The soln was filtered, basicified and extracted with ether, giving 4-cyclohexylpiperidine (0·95 g), m.p. 73–75°. Sublimation gave the pure base, m.p. 80–82°.

(2) Hydrogenation of 4-phenylpyridine (1 g) in 30% HCl over PtO_2, at room temp and press (5·8 moles H absorbed), gave 4-cyclohexylpiperidine (0·92 g), m.p. 74–76°, identical with the product of the first preparation. The *picrate*, from EtOH, had m.p. 150–151°. (Found: C, 51·2; H, 6·5; N, 14·4. $C_{17}H_{24}N_4O_7$ requires: C, 51·5; H, 6·1; N, 14·1%.)

1-t-*Butyl-4-cyclohexylpiperidine*. (cf.[11]) A mixture of t-butylamine hydrochloride (28 g), and aqueous formaldehyde (16 g, 40%) was heated on a water bath for 1 hr at 80°. The mixture was cooled to 40° and α-methylstyrene (15 g) was added, with stirring, the temp being kept at about 65°. The mixture was finally kept at 50° for about 2 hr with stirring. MeOH (20 ml) was then added and the soln was stirred for a further 1 hr, and then allowed to stand overnight. The soln was heated to remove MeOH, and then treated with 30% HCl (100 ml) at 100° for 3 hr. The mixture was poured into water (80 ml) and the resulting soln was extracted several times with toluene, the extracts being discarded. The residual aqueous soln was basified with 40% NaOH and extracted several times with toluene. Evaporation of the dried (K_2CO_3) extracts gave a solid, m.p. 109°, probably 4-hydroxy-4-phenyl-1-t-butylpiperidine. The alcohol (2·5 g) was heated with 30% HCl (2 ml.) for 3 hr at 100°. The mixture was then poured into water, basified and extracted with ether. Evaporation of the dried (KOH) extracts gave crude 1-t-butyl-4-phenyl-1,2,5,6-tetrahydropyridine. The PMR spectrum in CCl_4 showed a multiplet at 2·3 to 2·9 (aromatic protons), a multiplet at 3·95 to 4·05 (proton at position 3), a quartet at 6·65 to 6·85 (protons at position 2), complex multiplet at 7·1 to 8·6 (protons at positions 5 and 6), and a singlet at 8·9 (t-butyl protons). The tetrahydropyridine (1·5 g) was dissolved in 10% HCl (15 ml) and hydrogenated over PtO_2 (100 mg) at room temp and press. The usual method of working up gave crude 1-t-butyl-4-cyclohexylpiperidine (0·9 g), m.p. 58–62°. The *picrate*, from EtOH, had m.p. 179–180°. (Found: C, 55·5; H, 6·9; N, 12·4. $C_{21}H_{33}N_4O_7$ requires: C, 55·7; H, 7·1; N, 12·4%.)

Acknowledgement—We are grateful to Messrs. A. J. Eglinton and G. Palmer for help with the experimental work.

[11] C. J. Schmidle and R. C. Mansfield, *J. Amer. Chem. Soc.* **78**, 1702 (1956).