The Conformational Equilibria of 3-Methyl- and 3,5-Dimethyl-1-t-butyl-4-piperidone: Further Evidence for Steric Requirements of Lone Pairs

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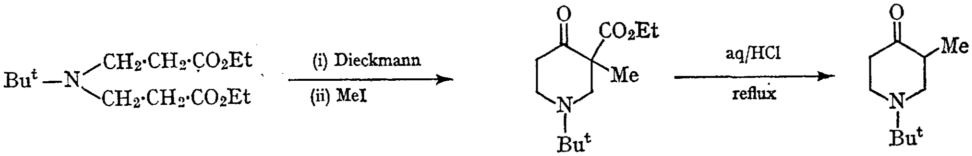
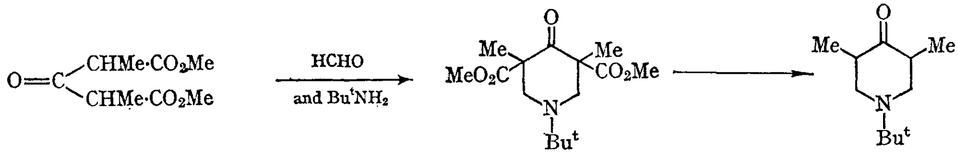
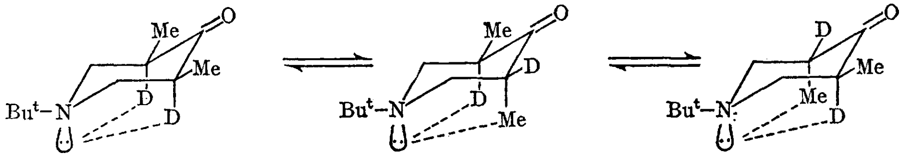
WE prepared the title compounds by the route shown; the second path is a modification of a known[1] method for the preparation of *N*-unsubstituted 4-piperidones. The substituted 4-piperidones were deuterated in the 3- and 5-positions by shaking in carbon tetrachloride with D_2O–NaOD at 25 ± 0·2°; simultaneous equilibration between the *cis*-(III) and *trans*-isomers (IV) occurred for the 3,5-dimethyl derivative. The n.m.r. spectra of the carbon tetrachloride solutions were measured at 60 Mc./sec.



(I)



(II)

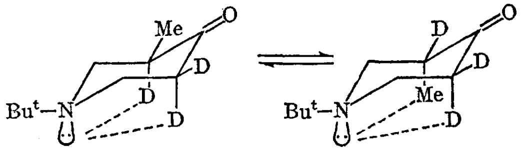


(III) (IVa) (IVb)

The mixture of dimethyl derivatives (III—IV) disclosed two AB systems (see Figure 1). The outer, more intense, peaks are attributed to the α-protons of (III). The α-protons of the conformationally mobile, and energetically less favoured, isomer (IVa ⇌ IVb) show a smaller chemical-shift difference, as is expected because of the time averaging effect. The conformational equilibrium constants (III/IV) obtained from the integrated peak areas are listed in the Table.

3-Methyl-1-t-butyl-4-piperidone exists as an equilibrating pair of conformers (V ⇌ VI). The n.m.r. spectra showed two overlapping AB systems due to time averaging of the 2- and the 6-protons in the different conformations (See Figure 2). Peaks *p* and *q* are the superimposed low-field pairs of lines due to both the 2- and 6-protons, peaks *r* and *s* correspond to the high-field pair due to the 2-protons and peaks *t* and *u* to the high-field pair due to the 6-protons.

The assignment and interpretation of the spectrum will be discussed in detail in the full Paper. Briefly, the AB system ascribed to the 2-protons is a time average of (V) and (VI). The chemical shift differences between the α-protons for two fixed forms are known from the 3,5-dialkyl series, and by interpolation, the conformational equilibrium constant for (V ⇌ VI) may be obtained. The values are listed in the Table with known values



(V) (VI)

TABLE

Compound	K	ΔG	Temp.	ref.
3-Methyl-1-t-butyl-4-piperidone	0·081	1·54	35°	—
3,5-Dimethyl-1-t-butyl-4-piperidone	0·21	0·93	25	—
2,6-Dimethylcyclohexanone	0·076	1·57	34·5	2
2-Methyl-4-t-butylcyclohexanone	0·051	1·81	34·5	2

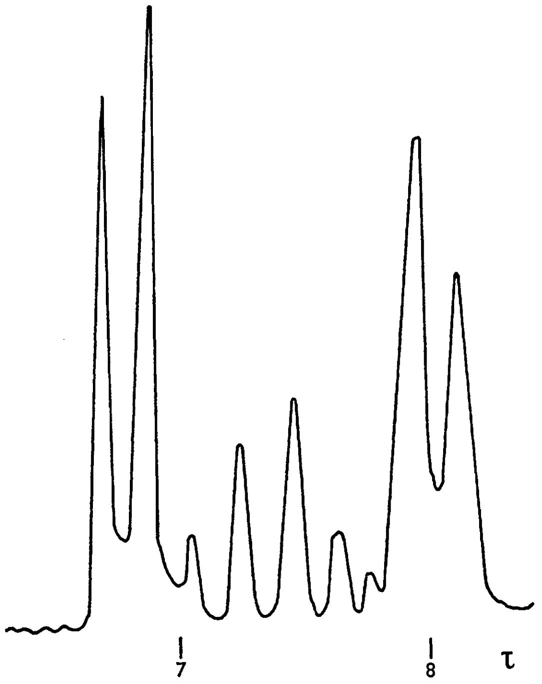


FIGURE 1. *N.m.r. spectrum at* 60 *Mc./sec. of* 3,5 *dideutero*-3,5-*dimethyl*-1-*t*-*butyl*-4-*piperidone.*

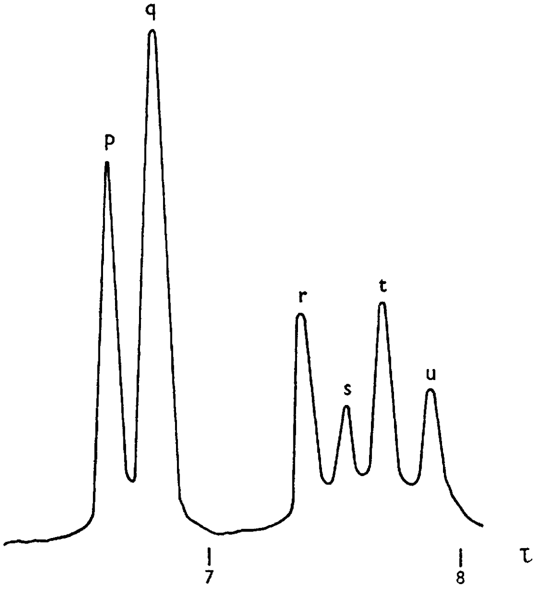


FIGURE 2. *N.m.r. spectrum at* 60 *Mc./sec. of* 3-*methyl*-1-*t*-*butyl*-3,5,5-*trideutero*-4-*piperidone.*

for the corresponding cyclohexanones for comparison.

It is evident that the methyl-axial conformers are more favoured in the piperidones than in the corresponding cyclohexanones. We conclude that, for the non-hydrogen-bonding solvent carbon tetrachloride, the interactions between the axial nitrogen lone pair and an axial methyl group on the same side of the ring in piperidones are less than the corresponding hydrogen–methyl interactions in the geometrically similar methylcyclohexanones. The quantitative significance of these differences will be discussed later.

The present method is well suited to the investigation of steric effects of replacing an sp^3-hybridised carbon atom by a heteroatom. Work is in hand on tetrahydropyrones, tetrahydrothiapyrones and 4-piperidones with a variety of substituents on the nitrogen atom.

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[1] V. Baliah, V. Gopalkrishnan, and T. S. Gorindarajan, *J. Indian Chem. Soc.*, 1954, **31**, 832.

[2] W. D. Cotterill and M. J. T. Robinson, *Tetrahedron*, 1964, **20**, 765.