The Preferred Steric Course of Quaternisation of Certain 1-Alkylpiperidines

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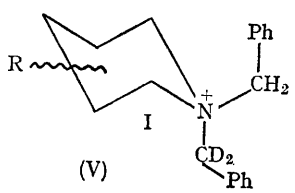
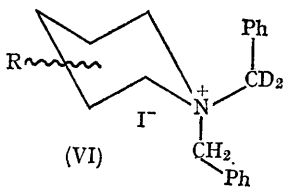
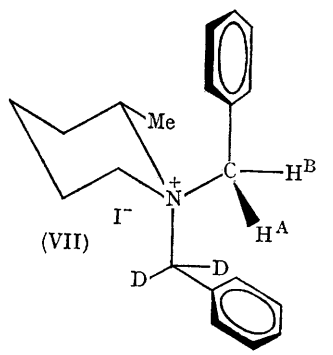
REACTION of the *N*-dideuterobenzyl derivatives of 3-methyl- (I), 4-phenyl- (II) and 2-methyl-piperidine (III) and *trans*-decahydroquinoline (IV) with benzyl iodide in acetone at room temperature gives mixtures of quaternary salts (V and VI; R = biasing group or fused ring) in a ratio of 3—5 : 1 for each system, as shown by n.m.r. spectroscopy. The benzyl-methylene protons in the mixtures are seen as either two singlets [differing in chemical shift by 0·52 and 0·54 p.p.m. for (I) and (II) respectively][1] or AB multiplets (non-equivalent geminal protons: $\delta(H_A-H_B)$, 0·20 and 1·66; 0·16 and 1·78 p.p.m. for mixtures from III and IV respectively).[1] The salt with the higher-field singlet or larger chemical shift



(V)



(VI)



(VII)

difference between the geminal protons is assigned, with assurance, formula (V) in which the benzyl-methylene group is nearer the benzene ring of the dideuterobenzyl group (*cf.*, VI). Calculations based on either the Johnson–Bovey[2] or the point-dipole[3] anisotropy models and the expected preferred conformations support this assignment, *e.g.*, $\delta(H_A-H_B)$ in (VII) $\sim$ 1·6 p.p.m. by the former method. The n.m.r. spectra of the quaternary salt mixtures correspond to preferred *axial* quaternisations for each base system with the primary alkyl iodide, in accordance with previous conclusions.[4]

Katritzky and his co-workers recently[5] reached an opposite conclusion regarding the quaternisation of such simple unhindered piperidines, mainly by extrapolation from the results of a kinetic analysis of the methylation of 1-ethyl-4-phenylpiperidine, the reactivity of individual conformers being evaluated. However, we have found that this analysis is based on an incorrectly determined product-ratio for the overall reaction (taken as 12·5 : 1). In D_2O solution the *N*-methyl peak at $\tau\sim$6·95 includes the signal of *both* isomeric salts; a small downfield signal[5,6] used by Katritzky *et a'*. for product analysis is not due to *N*-methyl. The actual *N*-methyl signals can readily be separated in $CDCl_3$ (τ 6·63; 6·73) and show that product ratios for methylation of 1-ethyl-4-phenylpiperidine and ethylation of the 1-methyl base under a wide

TABLE

Second-order rate constants (l. mole^{-1}sec.$^{-1}$ × 10^4) for reaction of individual conformers of 1-alkyl-4-phenylpiperidines with methyl iodide at 24·5° in acetonitrile.

		Conformer		
		1-Et$_{ax}$	1-Et$_{eq}$	1-Pr$^i_{ax}$
Rate constants	Reference 5	27	and 100	24
		or 410	and 8	or 50
	Recalculated	~110	and ~80	No alteration
		or ~320	and ~30	proposed[a]

[a] Because of the close accord between the appropriate product ratio quoted in ref. 5 and that obtained in our own work.

variety of preparative conditions are ~3 : 1 and 1 : 1—1·5, much lower in each case than prevously supposed.[4,5] Under the conditions used by Katritzky *et al.* for their kinetic runs at 24·5°, the ratio for the former reaction, accurately determined by comparison of the n.m.r. spectra of mixtures of salts obtained with both methyl and trideuteromethyl iodide, is 2·8 : 1. Recalculation of rate constants for important individual conformers now gives the figures shown in the Table, Katritzky's figures being also given for comparison. With the new values, it is not possible to choose between alternatives, and hence decide by the kinetic-analysis method the preferred direction of alkylation for the base, using either the chief criterion previously proposed[5]—that the rate constant for the 1-Pr$^i_{ax}$ conformer must be lower than that for the 1-Et$_{ax}$ analogue (see Table)—or the necessarily very rough analysis[5] of a wider range of rate constants on the basis of numbers of *gauche*-butane interactions in transition states.

(*Received, September 7th*, 1966; *Com.* 668.)

[1] Values for $CDCl_3$ solutions. A thorough study of related salts (derivatives of 2-methylpyrrolidine) reveals no qualitative changes in AB multiplet patterns over a very wide range of solvents and conditions.

[2] C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, 1958, **29**, 1012.

[3] H. M. McConnell, *J. Chem. Phys.*, 1957, **27**, 226.

[4] J. McKenna, J. M. McKenna, and A. Tulley, *J. Chem. Soc.*, 1965, 5439, and earlier papers. By a somewhat similar analysis of the n.m.r. spectra of isomeric *N*-benzyl-*N*-methylcamphidinium salts, in which the effects of the benzene ring on the signals of bridge-methyl and -methylene protons are examined, the previously assigned configurations for these salts have also been confirmed.

[5] J.-L. Imbach, A. R. Katritzky, and R. A. Kolinski, *J. Chem. Soc.* (*B*), 1966, 556.

[6] J. K. Becconsall, R. A. Y. Jones, and J. McKenna, *J. Chem. Soc.*, 1965, 1726.