The Preferred Steric Course of Quaternisation of 1-Alkyl-4-phenylpiperidines, *N*-Alkylnortropanes, and other Bases

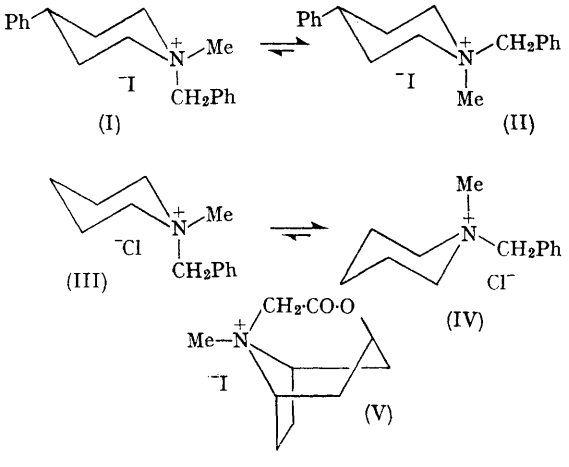
By D. R. BROWN, J. MCKENNA, J. M. MCKENNA, and J. M. STUART
(*Chemistry Department, The University, Sheffield*)
and B. G. HUTLEY
(*College of Technology, Sheffield*)

WE previously concluded[1] that the preferred steric course of quaternisation of 1-alkylpiperidines was usually axial or boat-axial in reactions of marked stereoselectivity, such as methylations or certain benzylations. In the same base systems, other primary alkyl iodides gave lower stereoselectivities, and we have recently shown that the same is true for isopropylations, with striking exceptions in the 2-methylpiperidine and *trans*-decahydroquinoline systems, where in each case the *same* isomeric salt is the highly predominant product for both the reactions $>NMe + Pr^{i}I$ and $>NPr^{i} + MeI$; *i.e.*, we have, atypically, high stereoselectivities in non-stereospecific quaternisations. This unusual result seems to be caused by the strain (*cf.*, cyclohexane analogues[2]) in transition states with *ax*-NPr^{i} groups and *eq*-C-2 substituents.

We have now (hopefully) settled the dispute[1a,3] regarding the preferred steric course of quaternisation of 1-alkyl-4-phenylpiperidines. Epimeric salts

may be identified, and preferred axial quaternisation in reactions of marked stereoselectivity thus deduced, by (a) interconversion of the salts (I) and (II) in $CHCl_3$, the latter predominating (~2 : 1 at 82°) in the near-equilibrium established: this ratio is in encouraging accord with that quoted[3c] (also ~ 2 : 1 in $CDCl_3$) for the conformational equilibrium (III) $\rightleftharpoons$ (IV); (b) cyclisation of PhCH-$(CH_2{\cdot}CH_2Br)_2$ with benzylmethylamine, which gives, we argue,[4] a mixture containing the more stable epimeric quaternary salt in predominance by either kinetic or thermodynamic control, and, (c) application of the earlier[1] i.r. and product-ratio criteria. Our general conclusion agrees with those previously reached[1a,3b,3c,*] for particular epimeric pairs, and accords with the requirement[3b] of a 1-Et_{ax}: 1-Et_{eq} methylation rate-constant ratio of ~ 1·5 : 1 rather than ~ 10 : 1; this ratio, for the *smaller* alkylating agent, should be *less* than the value (~ 3 : 1) for 1-Me_{ax}: 1-Me_{eq} ethylation, deduced from the approximate 1 : 1 product ratio[1a,3b,4] for the ethylation of several simple *N*-methylpiperidines, and the expected[3a] (~ 1 : 3) reactant conformer ratio for such bases.

We find it increasingly difficult to accommodate the conclusion (based ultimately[5] on Fodor's classical work with the tropines) of preferred equatorial quaternisation in the tropane system. Fodor and co-workers sometimes described reaction



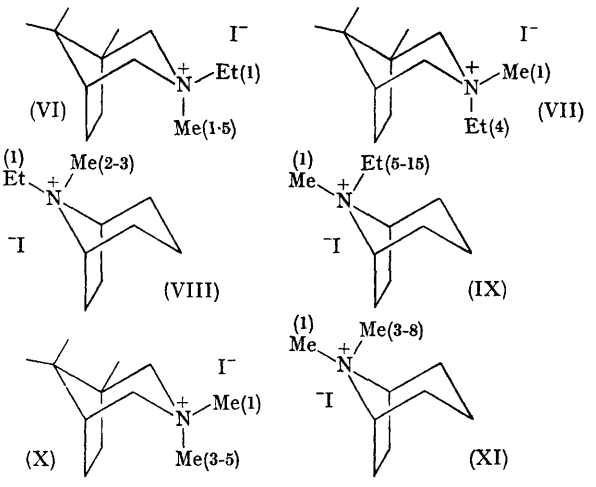


FIGURE. *Relative rates of attack on* axial *and* equatorial N-*alkyl groups by* ~ 0·15 M-*sodium thiophenoxide in diethylene glycol at* 120° (¹⁴C-*labelled* N-*methyl methiodides*), 100° (N-*ethylcamphidinium salts*), [J. McKenna, B. G. Hutley, and J. White, *J. Chem. Soc.*, 1965, 1729] *and* 130° (N-*ethyltropanium salts*). *Ratios are for Me : Me and Et : Et for each salt or diastereoisomeric pair.*

products now known to be mixtures of epimers as homogeneous, and it is not, therefore, quite clear that the lactone (V) is related to the major product from the methylation of the *N*-ethoxycarbonylmethyl-3-hydroxyl base.[6a] A similar ambiguity arises regarding the status of a tropinium salt recently[6b] subjected to *X*-ray analysis. We have found that in the tropane system the reaction $>NPr^i$ + MeI proceeds with much higher stereoselectivity than >NMe + Pr^iI, a result suggestive of preferred *axial* quaternisation† as are the kinetic results shown (with those for camphidinium salts for comparison) in the Figure. In *N*-ethyl-*N*-methylcamphidinium salts (VI; VII) the higher ratio for Et_{ax} : Et_{eq} than Me_{ax} : Me_{eq} and the larger Me_{ax} : Me_{eq} ratio for the *N*-methyl methiodide (X) than for (VI)—(VII), are each ascribed to reactant destabilisation in (VII) (*ax*-Et). Results in the tropane system (VIII; IX; XI) are also more intelligible† on the basis of preferred axial than equatorial quaternisation and thiophenoxide attack

* We emphasize (*cf.* ref. 3c) that our previously published results indicate preferred *axial* benzylation of 1-dideutero-benzyl-4-phenylpiperidine. Otherwise, one would have to assume that factors other than benzene-ring anisotropies would shield the axial methylene group by 0·8—1·3 p.p.m. (depending on the number of conformations considered for the 1-benzyl benziodide) relative to the equatorial.

† *gem*-Dialkyl effects at nitrogen are decidedly difficult (ref. 4) to assess qualitatively in the tropane system, but we believe that a quaternary salt >NMeR⁺X⁻ will be more stable in the configuration with the higher alkyl group R equatorial. Unfortunately, we have not succeeded in equilibrating the *N*-benzyl-*N*-methyl epimers in this system.

as illustrated. We accordingly regard the preferred direction of quaternisation in tropines (3-OH bases) and tropane as an open question which we are endeavouring to settle by further *X*-ray studies.

(*Received, March 6th*, 1967; *Com.* 213.)

[1] (a) J. McKenna, J. M. McKenna, A. Tulley, and J. White, *J. Chem. Soc.*, 1965, 1711; (b) J. McKenna, J. M. McKenna, and A. Tulley, *ibid.*, p. 5439; (c) R. Lygo, J. McKenna, and I. O. Sutherland, *Chem. Comm.*, 1965, 356.

[2] *inter alios*, R. D. Stolow, *J. Org. Chem.*, 1964, **86**, 2170.

[3] (a) J.-L. Imbach, A. R. Katritzky, and R. A. Kolinski, *J. Chem. Soc.* (*B*), 1966, 556; (b) D. R. Brown, B. G. Hutley, J. McKenna, and J. M. McKenna, *Chem. Comm.*, 1966, 719; (c) A. T. Bottini and M. K. O'Rell, *Tetrahedron Letters*, 1967, 423. These authors' argument, that quaternisations which are relatively fast because of certain electronic or coulombic features in particular transition states will have relatively long partial N · · · C bonds to the alkylating agent, and hence will give product ratios relatively near to the reactant-base conformer ratio, is acceptable. The same cannot, however, be said of a converse argument by H. O. House, B. A. Tefertiller, and C. G. Pitt (*J. Org. Chem.*, 1966, 1073) based on the expectation (from an apparently unjustified application of the Hammond postulate) that steric compression on an incoming alkylating agent would, other things being equal, lead to a *shorter* (!) partial N · · · C bond.

[4] D. R. Brown, B. G. Hutley, R. Lygo, J. McKenna, and J. M. McKenna, *J. Chem. Soc.*, forthcoming publications.

[5] *cf.* ref. 1, footnote on p. 1714.

[6] (a) G. Fodor, K. Koczka, and J. Lestyàn, *J. Chem. Soc.*, 1956, 1411; (b) C. H. McGillavry and G. Fodor, *ibid.*, 1964, 597.