# The Conformational Analysis of Saturated Heterocycles. Part LXVI.[1] Stereochemical Orientation of the Methylation of 2-Methylpiperidines

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*cis*- and *trans*-Isomers of 1-methyl-, 1-ethyl-, 1-isopropyl-, and 1-t-butyl-2-methyl-4-phenylpiperidine undergo *N*-methylation to yield metho-salts by both axial and equatorial attack. The stereochemistries of the quaternisation products are assigned, and literature work on the assignment of products for the quaternisation of 1-alkyl-2-methylpiperidines is discussed. The relative and absolute rates of these reactions are determined and related to the expected effects of the 2-methyl group on conformations of the molecules, and on the rate constants for equatorial and axial attack.

The relation of these results to the predominant equatorial quaternisation observed for tropanes is discussed.

In Parts VIII,[2] XXVII,[3] LII,[4] and LXIV[5] we have reported kinetic studies on the quaternisation of piperidine derivatives. The stereochemistry of quaternisation, the subject of considerable attention and dispute, has been reviewed recently.[3,6-8] Solvent, substrate structure, and leaving group of the alkylating agent have a marked influence on the steric course of the reaction, but nevertheless several generalisations may be made: methylations with methyl iodide occur by predominantly axial approach,[3,6-8] larger and/or less reactive alkylating agents, *e.g.* ethyl iodide (ref. 5 and references therein),

[1] Part LXV, R. A. Y. Jones, A. R. Katritzky, A. R. Martin, and S. Saba, preceding paper.
[2] J.-L. Imbach, A. R. Katritzky, and R. A. Kolinski, *J. Chem. Soc.* (*B*), 1966, 556.
[3] R. A. Y. Jones, A. R. Katritzky, and P. G. Mente, *J. Chem. Soc.* (*B*), 1970, 1210.
[4] R. P. Duke, R. A. Y. Jones, and A. R. Katritzky, *J.C.S. Perkin II*, 1973, 1553.
[5] V. J. Baker, I. D. Blackburne, and A. R. Katritzky, *J.C.S. Perkin II*, 1974, 1557.
[6] A. T. Bottini in 'Selective Organic Transformations,' ed. B. S. Thyagarajan, Wiley-Interscience, New York, 1970, pp. 89—142.
[7] J. McKenna, *Topics Stereochem.*, 1970, **5**, (*a*) p. 275; (*b*) p. 301.
[8] J. McKenna in 'Conformational Analysis. Scope and Present Limitations,' ed. G. Chiurdoglu, in the series 'Organic Chemistry. A Series of Monographs,' ed. A. T. Blomquist, Academic Press, New York, 1971, vol. 21, p. 165.

show a reduced tendency for axial attack, and a number of benzylations give mainly products from equatorial approach.[4] However, in the tropane, tropine, tropinone, and pseudotropine series,[9,10] methylation, ethylation, alkoxycarbonylmethylation, and other quaternisations of known orientation all proceed preferentially equatorially.

The factors controlling these stereochemical 'change-overs,' from piperidines to tropanes and from methylations to benzylations, are not well understood and in particular it is not clear whether the two trends are manifestations of similar effects or the consequences of unrelated factors. Behaviour in the tropane series has recently been explained on the basis of steric factors and the nature of the transition state:[9] the flattened piperidine ring and angularly deformed pyrrolidine ring of the tropane nucleus should hinder axial approach through compression of the incoming group with the 2- and 4-axial hydrogen atoms.

The present examination of the methylation of a number of 2-methylpiperidine derivatives was planned to illuminate the degree of involvement of α-substitution in the tropane behaviour.

Studies of the quaternisation of 2-methylpiperidines have previously been reported by McKenna and his co-workers. Diastereoisomer product analyses were based on applications of the criteria advocated by that group.

(i) By the Closs criterion,[11] the more intense of the *N*-methyl signals in the spectrum of 1,2-dimethylpiperidine hydrochloride is assumed to be derived from the *trans*-configuration in which both methyl groups are equatorial.[12] The major and minor peaks thus correspond to equatorial and axial NMe groups and the relative order of their chemical shifts is assumed to apply in the quaternary compounds. However, this criterion has been questioned by other groups,[3,13] and McKenna himself pointed out an added complication with the 2-methyl series: the minor component, *cis*-1,2-dimethylpiperidinium chloride, could exist in comparable proportions in two conformations: 1*ax*,2*eq*- and 1*eq*,2*ax*-dimethyl.

(ii) The i.r. criterion utilises diagnostic bands in the region 840—900 $cm^{-1}$ assigned to the *N*-methyl equatorial (885—900 $cm^{-1}$) and axial (840—885 $cm^{-1}$) situations.[14] Unfortunately, lack of sufficient definition of the bands precluded use of this criterion in the 2-methylpiperidine series.[14]

(iii) *N*-Benzyl quaternary salts undergo thermal isomerisation to afford a greater proportion of the *N*-benzyl equatorial isomer. Observation of the corresponding changes in n.m.r. absorptions enables assignments to be made.[15] However, in the 2-methylpiperidine series the change resulting from the isomerisation of the salts was small, causing, according to McKenna *et al.*, difficulties in interpretation.[16]

(iv) Higher stereoselectivities in the reaction >NAlk + MeI than in the alternative process >NMe + AlkI are usually taken to correspond to preferred axial attack in these systems.[15] However, for 1-isopropyl-1,2-dimethylpiperidinium salts the same isomer is formed predominantly irrespective of the order of introduction of the *N*-alkyl groups.[16] As the criterion is thus inapplicable to the *N*-isopropyl compound, its validity is not assured for the other members of the series.

(v) The chemical shifts of the methylene protons in *N*-benzyl groups can sometimes be calculated. Calculated anisotropies are stated however to be 'too small, in relation to σ-bond induced differential effects, to permit assured configurational assignments' in the *N*-methyl-*N*-benzyl compounds.[17] Use should correctly be confined to the benzylation of *N*-dideuteriobenzyl compounds.[17]

(vi) Dealkylation by sodium benzenethiolate of *N*-methyl-[$^{14}$C]methiodides should remove preferentially the axial *N*-methyl group. However, the results of application to 2-methylpiperidine were inconclusive, according to McKenna *et al.*[18] because 50% recovery of labelled anisole indicated equal attack on equatorial and axial methyl groups.

(vii) The proportions of isomers obtained on cyclisation have also been used as a criterion. Cyclisation of several secondary amines with 1,5-dibromohexane, however, gave products in ratios close to unity, and in the case of the reaction between 1,5-dibromohexane and isopropylmethylamine[19] the predominance of the 'more stable' over the 'less stable' isomer 'could not be demonstrated unambiguously.'

The conclusions of McKenna and his co-workers are summarised in Table 1, with references. They conclude that axial attack predominates for alkylations of 1-alkyl-2-methylpiperidines where the 1-alkyl group is not methyl. However, n-propylation and benzylation of 1,2-dimethylpiperidine show preferred equatorial attack, and for isopropylation the equatorial preference is substantial. Quaternisations of 1-alkyl-2-methylpiperidines are concluded [7b] to show lower preference for axial attack than the corresponding reactions of 1-alkyl-4-phenylpiperidines. The precise criteria on which these conclusions are based are not always clear. However, for reasons outlined later, we believe that his published assignments as summarised in Table 1 are correct.

[9] G. Fodor, R. V. Chastain, jun., D. Frehel, M. J. Cooper, N. Mandava, and E. L. Gooden, *J. Amer. Chem. Soc.*, 1971, **93**, 403.
[10] U. O. De La Camp, A. T. Bottini, C. C. Thut, J. Gal, and A. G. Bellettini, *J. Org. Chem.*, 1972, **37**, 324.
[11] G. L. Closs, *J. Amer. Chem. Soc.*, 1959, **81**, 5456.
[12] J. K. Becconsall, R. A. Y. Jones, and J. McKenna, *J. Chem. Soc.*, 1965, 1726.
[13] A. T. Bottini and M. K. O'Rell, *Tetrahedron Letters*, 1967, 429.
[14] J. McKenna, J. M. McKenna, A. Tulley, and J. White, *J. Chem. Soc.*, 1965, 1711.
[15] J. McKenna, J. M. McKenna, and J. White, *J. Chem. Soc.*, 1965, 1733.
[16] D. R. Brown, R. Lygo, J. McKenna, J. M. McKenna, and B. G. Hutley, *J. Chem. Soc.* (*B*), 1967, 1184.
[17] D. R. Brown, J. McKenna, and J. M. McKenna, *J. Chem. Soc.* (*B*), 1967, 1195.
[18] B. G. Hutley, J. McKenna, and J. M. Stuart, *J. Chem. Soc.* (*B*), 1967, 1199.
[19] D. R. Brown, J. McKenna, and J. M. McKenna, *J. Chem. Soc.* (*B*), 1969, 567.

Data were not previously available for the quaternisation of piperidines with an axial 2-methyl substituent. Further, we wished to provide unambiguous evidence for the influence of an equatorial 2-methyl group where no reaction *via* a ring-inverted form was possible. Therefore, we have now studied the quaternisations of the isomeric *cis* and *trans* * 1-alkyl-2-methyl-4-phenylpiperidines (1)—(8) with methyl iodide, analysing the stereochemistry of quaternisation by linewidth [3] and kinetic [2] criteria. An additional aim was the determination of the orientation of the *N*-alkyl groups in the piperidines (1)—(8): we report $^{13}C$ n.m.r. studies at low temperatures.

TABLE 1

Quaternisations of *N*-alkyl-2-methylpiperidines: McKenna's product ratios and assignment criteria

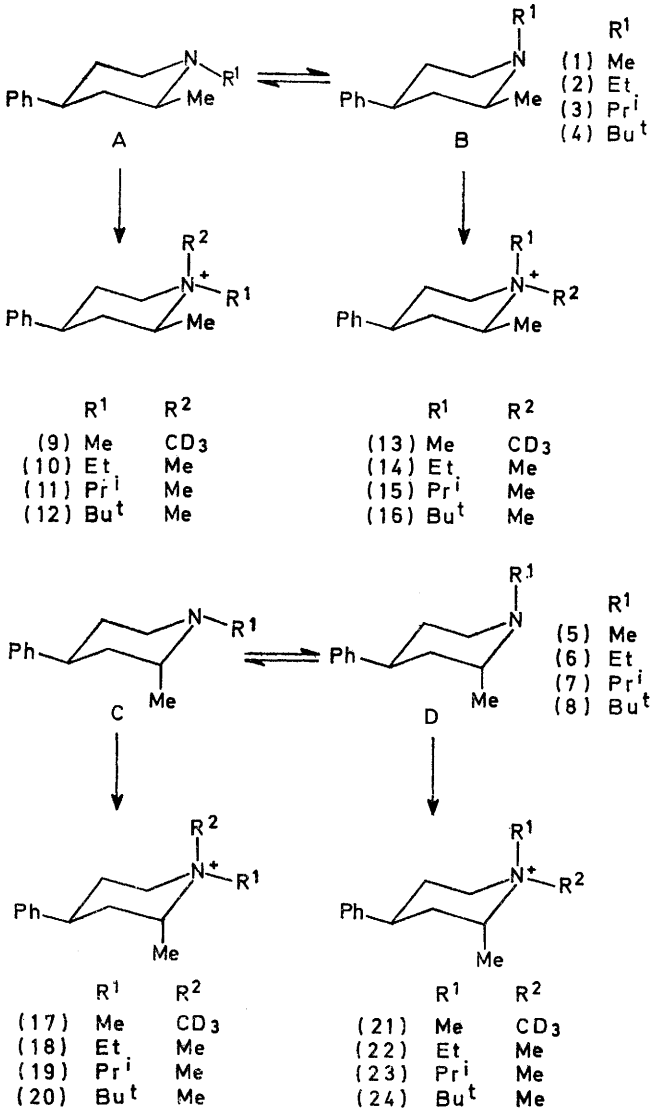
| *N*-Alkyl group | Alkylating agent | Ref. | Peak area ratio *ax* : *eq* attack | Criterion used (see text) |
|---|---|---|---|---|
| Me | $CD_3I$ | 16 | 1—1·5 | (iv) |
| Et | $CH_3I$ | 16 | 2—3 | (iv) |
| | $CH_3I$ | 12, 14 | 2—5 | (i) |
| $Pr^n$ | $CH_3I$ | 12, 14 | 2—5 | (i) |
| | $CH_3I$ | 16 | 2—3 | (iv) |
| Bz | $CH_3I$ | 16 | 2—3 | (iv) |
| $Pr^i$ | $CH_3I$ | 16 | >12 | *a* |
| Me | EtI | 14 | 1 | *b* |
| | $Pr^nI$ | 16 | 0·7—1 | (iv) |
| | $Pr^nI$ | 12, 14 | 0·7—1 | (i) |
| | Bz | 16 | 0·7—1 | (iv) |
| | $Pr^i$ | 16 | 0·1 | *a* |

[a] It is not clear what criterion was used in the assignment. [b] No criterion used as equal amounts found of two isomers.

The only previous work on the 2-methyl-4-phenyl series is the assignment of chemical shifts for the *N*-methyl protons in *cis*- and *trans*-1,1,2-trimethyl-4-phenylpiperidinium salts.[20] Equatorial and axial *N*-methyl groups were assigned on the basis of shifts calculated from the shielding effects of equatorial and axial 2-methyl substituents.[21] The assignments are in agreement with those deduced here.

*Preparation of Compounds.*—Reduction of 5-oxo-3-phenylhexanoic acid [22] with lithium aluminium hydride gave two diastereomeric 3-phenylhexane-1,5-diols (m.p. 93·5—95·5 and 96·0—98·0°) in the ratio 5 : 1, which were separated by fractional crystallisation from benzene and converted into mesylates (m.p. 80·0—81·5 and 57·0—59·0°) by methanesulphonyl chloride in dry pyridine. Heating the mesylates in a sealed tube with $MeNH_2$, $EtNH_2$, $Pr^iNH_2$, or $Bu^tNH_2$, gave the amines (1)—(4) and (5)—(8) in 60—90% yield.[23]

The configurations of the amines (1)—(8) were assigned from the chemical shifts of the 2-protons and 2-methyl groups. The 2-H signals of the piperidines (1)—(4) appeared at higher field (δ 2·0—2·45), than those of the piperidines (5)—(8) (3·25—3·64), indicating the axial position of the 2-proton in compounds (1)—(4). Analogously, the signals of the 2-methyl groups were observed always at lower field in the compounds (1)—(4) than in the compounds (5)—(8) (δ 1·08—1·20 and 1·04—1·15, respectively), thus indicating equatorial methyl groups in the piperidines (1)—(4), and axial methyl groups in the




others. This finding and the assumption of the equatorial position for the phenyl group in both series defines the relative configurations of the 2- and 4-substituents as *cis* for the piperidines (1)—(4) and *trans* for the piperidines (5)—(8).[23]

## EXPERIMENTAL

*Product Ratios.*—Quaternary salts were formed at 25° by treating the amine (0·10 g) in the appropriate solvent (2 ml) with methyl iodide (0·8 g) for 2—4 times the reaction half-life. The solvent was removed by freeze-drying and the

* Throughout this paper *cis* and *trans* refer to the relative configurations of the 2-methyl and the 4-phenyl groups.

[20] A. F. Casy and K. M. J. McErlane, *J.C.S. Perkin I*, 1972, 726.

[21] M. Tsuda and Y. Kawazoe, *Chem. and Pharm. Bull.* (*Japan*), 1970, **18**, 2499.

[22] W. Godhes, *J. prakt. Chem.*, 1929, **123** [2], 169.

[23] R. A. Kolinski, A. Lasota, H. Plenkiewicz, E. Ryzinski, and H. Vollnagel-Neugebauer, *Roczniki Chem.*, submitted for publication.

crude solid dissolved in trifluoroacetic acid to give a *ca.* 10% solution. The n.m.r. spectrum was recorded (Varian HA *100* instrument) and the product ratio determined from duplicate sweeps of the appropriate region.

*Kinetic Quaternisations.*—Solvents were fractionated and stored over activated molecular sieves. Methyl iodide was distilled and stored for short periods at 5° over mercury. The measurements were performed with the apparatus [4] and procedure [5] previously described. The results are given in Table 2.

TABLE 2

Comparative data for the methylations of ring-substituted 1-alkylpiperidine derivatives [a]

| | | Acetonitrile [c] | | Methanol [c] | |
|---|---|---|---|---|---|
| *N*-Alkyl group: | 4-Ph [b] | *cis*-2-Me,4-Ph | *trans*-2-Me,4-Ph | *cis*-2-Me,4-Ph | *trans*-2-Me,4-Ph |
| (i) $A_a/A_e$ | | | | | |
| Me | 4 | 2·1 | 3·8 | 2·9 | 4·0 |
| Et | 2·4 | 2·7 | 3·7 | 3·6 | 3·7 |
| Pr$^i$ | 2 | >15 | 3·2 | >15 | 3·4 |
| Bu$^t$ | | >15 | 8·2 | >15 | |
| (ii) log $k_{obs}$ | | | | | |
| Me | 5·66 [d] | 5·16 | 5·47 | 3·62 | 3·89 |
| Et | 4·99 [d] | 4·75 | 4·63 | 3·25 | 3·24 |
| Pr$^i$ | 4·15 | 3·81 | 3·77 | 2·57 | 2·61 |
| Bu$^t$ | 3·11 | 2·97 | 1·84 | 1·68 | |
| (iii) log $k_{obs}$(MeCN) − log $k_{obs}$(MeOH) | | | | | |
| Me | | 1·54 | 1·58 | | |
| Et | | 1·50 | 1·39 | | |
| Pr$^i$ | | 1·24 | 1·26 | | |
| Bu$^t$ | | 1·29 | | | |
| (iv) log $k_{obs}$(4-Ph) − log $k_{obs}$(2-Me,4-Ph) [e] | | | | | |
| Me | | *ca.* 0·50 | *ca.* 0·19 | | |
| Et | | *ca.* 0·24 | *ca.* 0·36 | | |
| Pr$^i$ | | 0·34 | 0·38 | | |
| Bu$^t$ | | 0·14 | 1·27 | | |
| (v) log $k_e n_A$ | | | | | |
| Me | 5·51 | 4·99 | 5·37 | 3·49 | 3·80 |
| Et | 4·78 | 4·61 | 4·52 | 3·14 | 3·13 |
| Pr$^i$ | 3·97 | *ca.* 3·8 | 3·66 | *ca.* 2·55 | 2·50 |
| Bu$^t$ | | *ca.* 2·95 | 1·79 | *ca.* 1·65 | |
| (vi) log $k_e n_B$ | | | | | |
| Me | 4·90 | 4·67 | 4·79 | 3·03 | 3·20 |
| Et | 4·39 | 4·18 | 3·95 | 2·59 | 2·57 |
| Pr$^i$ | 3·67 | 2·6 | 3·15 | <1·36 | 1·97 |
| Bu$^t$ | | 1·8 | 0·88 | <0·47 | |

[a] Values of $k_{obs}$, $k_e n_B$, and $k_a n_A$ all $\times 10^7$. [b] Refs. 2 and 3—in acetonitrile. [c] Containing 1% (v/v) of water. [d] Extrapolation by Arrhenius plot of data from ref. 2. [e] Comparisons for acetonitrile only.

RESULTS

*Product Ratios for* cis-2-*Methyl*-4-*phenylpiperidines* (1)—(4).—Product ratios, $A_a/A_e$, for axial to equatorial attack were determined by n.m.r. spectroscopy (Table 3), and assignment of the *N*-methyl configurations assisted by linewidth,[3] the Closs,[24] and kinetic criteria. In the piperidine series axial *N*-methyl groups show broader signals ($W_{\frac{1}{2}}$ *ca.* 0·3 Hz) than their equatorial counterparts; the effect arises, amongst other causes, from long-range W-type coupling with 2-axial hydrogen atoms.[3] The quaternisation product of the *cis*-*N*-methylpiperidine (1) with deuteriomethyl iodide exhibits two *N*-methyl absorptions (Table 3), the more intense, narrower resonance occurring at lower field (δ 3·26) than the less intense, broader absorption (δ 3·10). The major product is therefore assigned the *N*-methyl equatorial configuration (9), arising from axial introduction of the $CD_3$ group, and it follows that the minor product has structure (13). The signal of the axial *N*-methyl substituent occurs at higher field than that of its equatorial counterpart, as often found.[6,7] The assignment also agrees with that made by Casy and McErlane [20] and previously cited. Axial attack is also considered to predominate in the quaternisation of 1,2-dimethylpiperidine with $CD_3I$ (Table 1).

Quaternisation of the *cis*-*N*-ethyl compound (2) with methyl iodide gives two products, (10) and (14); the major product shows *N*-methyl absorption at higher field but application of the linewidth criterion is hindered by the error in measurement of the linewidth of the smaller peak caused by baseline variations (Table 2). Our assignment in this case is made mainly on the kinetic criterion (see later), but we note that the chemical shifts are in the expected order, and that predominant axial methylation has also been proposed for 1-ethyl-2-methylpiperidine (Table 1).

The *N*-isopropyl and *N*-t-butyl compounds (3) and (4) each yield a single product of quaternisation (n.m.r. analysis in $CF_3{\cdot}CO_2H$ and $CDCl_3$). As these compounds exist mainly as the *N*-alkyl equatorial conformers [(3A), (4A)] the products are assigned as the axial *N*-methyl isomers (11) and (12), respectively. 1-Isopropyl-2-methylpiperidine is considered to undergo predominant axial methylation (Table 1).

*Product Ratios for* trans-2-*Methyl*-4-*phenylpiperidines* (5)—(8).—Quaternisation of the *trans*-*N*-alkylpiperidines (6)—(8) gives a mixture showing two *N*-methyl peaks in the n.m.r. spectrum, the peak at lower field in each case being the more intense. Treatment of the *N*-methyl compound (5) with $CD_3I$ also gives a mixture showing two peaks, that at higher field being the stronger. In the *trans* series (5)—(8) the linewidth differential was expected to be reduced by the replacement of one of the 2-axial hydrogen atoms by the methyl group. However, Table 2 shows clearly that for the quaternisation products of the *trans*-*N*-ethyl and *N*-isopropyl derivatives the lower-field signal is broader. While the application of the linewidth criterion is inconclusive for the *N*-methyl and *N*-t-butyl derivatives, the relative chemical shifts throughout the series leave little doubt as to their configuration. The assignment for the *N*-methyl compound agrees with that made by Casy.[20]

Application of the Closs criterion further supports the *N*-methyl assignments. Whereas 1-methyl-4-phenylpiperidine and *cis*-1,2-dimethyl-4-phenylpiperidine showed only equatorial *N*-methyl doublets in $CF_3CO_2H$ (at δ 3·05 and δ 3·07, respectively), the *trans*-1,2-dimethyl analogue showed two methyl doublets, at δ 3·08 (30%) and 2·98 (70%). If the small peak is (reasonably) assigned to *N*-methyl axial, this concurs with the assignment suggested for the quaternisation products.

This is the reverse of the general order in piperidine systems but is similar to the behaviour [9,25] in the tropane

[24] J. K. Becconsall and R. A. Y. Jones, *Tetrahedron Letters*, 1962, 1103.

[25] See, for example, ref. 7 in ref. 10.

series which, like the *trans*-compounds (5)—(8), possess 2-axial alkyl residues.

*Kinetic Results.*—Kinetics of the reactions were studied at 25° by the previously described methods.[3,4,26] Solvents containing 1% (v/v) of water to promote ion dissociation were used as before.[5] Pseudo-first-order rate constants were obtained by standard Guggenheim analysis [27] of the data and converted into second-order rate constants by dividing by the concentration of methyl iodide. Where values for $K$, the equilibrium constant [B]/[A], are known, individual rate constants $k_e$ and $k_a$ for equatorial and axial attack follow from equations (i)

$$k_a/k_e = KA_a/A_e \qquad \text{(i)}$$

and (ii), *cf.* earlier discussion in refs. 2 and 3. However, for the 2-methylpiperidines (1)—(8), data for the conformational equilibria of the $N$-alkyl groups are not available and thus $k_e$ and $k_a$ cannot yet be obtained.

$$k_{obs} = k_eK/(K + 1) + k_a/(K + 1) \qquad \text{(ii)}$$

Barriers to inversion at nitrogen are too low for routine accessibility by low temperature $^1$H n.m.r. measurement.[28] We have applied $^{13}$C n.m.r. to these equilibria in view of the larger chemical shift differences expected between the conformers (Table 4). At the lowest temperature currently achieved, *ca.* −80°, no splitting of resonances was observed and $N$-inversion is still fast.

Putting $K = n_B/n_A$, where $n_A$ and $n_B$ are the molar proportions of the conformers A and B, respectively, equation (ii) may be simplified to (iii). Similarly from equation (i) we obtain (iv), whence equation (v) follows. Values for $k_en_B$ and $k_an_A$, which are individual rate constants for equatorial and axial quaternisation as functions of the (unknown) conformer populations, are given in Table 2.

$$k_{obs} = k_en_B + k_an_A \qquad \text{(iii)}$$

$$k_an_A = k_{obs}/(1 + A_e/A_a) \qquad \text{(iv)}$$

$$k_en_B = k_{obs}/(1 + A_a/A_e) \qquad \text{(v)}$$

TABLE 3

Proton chemical shifts for methiodides [a]

| | Acetonitrile [b] | | | | | Methanol [b] | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | NMe axial | | NMe equatorial | | | NMe axial | | NMe equatorial | |
| Compound | $A_a/A_e$ | δ | $W_{\frac{1}{2}}$/Hz | δ | $W_{\frac{1}{2}}$/Hz | $A_a/A_e$ | δ | $W_{\frac{1}{2}}$/Hz | δ | $W_{\frac{1}{2}}$/Hz |
| (1) *cis*, NMe [c] | 2·1 | 3·10 | 1·5 ± 0·05 | 3·26 | 1·2 ± 0·05 | 2·9 | 3·10 | 1·5 ± 0·10 | 3·26 | 1·2 ± 0·05 |
| (2) *cis*, NEt | 2·7 | 3·09 | 2·0 ± 0·05 | 3·18 | 1·95 ± 0·10 | 2·7 | 3·09 | 1·8 ± 0·10 | 3·17 | 1·8 ± 0·10 |
| (3) *cis*, NPr$^i$ | >15 | 3·13 | 1·85 ± 0·05 | | | >15 | 3·13 | 1·9 ± 0·05 | | |
| (4) *cis*, NBu$^t$ | >15 | 3·06 | 1·85 ± 0·05 | | | >15 | 3·05 | 1·85 ± 0·05 | | |
| (5) *trans*, NMe [d] | 3·8 | 3·33 | 1·4 ± 0·05 | 3·16 | 1·2 ± 0·05 | 4·0 | 3·33 | 1·4 ± 0·05 | 3·16 | 1·2 ± 0·05 |
| (6) *trans*, NEt | 3·7 | 3·29 | 1·9 ± 0·05 | 3·07 | 1·6 ± 0·05 | 3·7 | 3·29 | 1·8 ± 0·05 | 3·08 | 1·4 ± 0·10 |
| (7) *trans*, NPr$^i$ | 3·2 | 3·15 | 1·95 ± 0·05 | 2·95 | 1·5 ± 0·10 | 3·4 | 3·12 | 2·0 ± 0·05 | 2·91 | 1·5 ± 0·10 |
| (8) *trans*, NBu$^t$ | 8·2 | 3·28 | 2·0 [d] ± 0·10 | 3·06 | 2·0 [d] ± 0·15 | | | | | |

[a] Measured for *ca.* 10% solution in $CF_3{\cdot}CO_2H$. [b] Containing 1% (v/v) of water. [c] $CD_3I$ as alkylating agent. Methyl resonances correspond to original NMe group. [d] Noisy spectrum.

TABLE 4

$^{13}$C N.m.r. data for $N$-ethylpiperidine derivatives [a]

| | | Unsubstituted | *cis*-2-Methyl | *trans*-2-Methyl |
|---|---|---|---|---|
| Phenyl C atoms | 1′ | 147·6 (s) | 147·5 (s) | 147·7 |
| | 2′(6′), | 129·3 (d, 158), | 129·3 (d, 152) | 129·3, |
| | 3′(5′) | 127·8 (d, 157) | 127·7 (d, 150) | 127·8 |
| | 4′ | 127·0 (d, 160) | 127·0 (d, 157) | 126·9 |
| Ring C atoms | 2 | 55·0 (t, 132) | 47·8 (d, 120) | 46·4 |
| | 6 | 55·0 (t, 132) | 56·8 (t, 123) | 52·4 |
| | 3 | 34·7 (t, 126) | 34·8 (t, 122) | 37·6 |
| | 4 | 43·9 (d, 123) | 44·2 (d, 122) | 41·0 |
| | 5 | 34·7 (t, 126) | 34·8 (t, 122) | 34·8 |
| Ring | $CH_3$ | | 21·6 (q, 120) | 14·0/ 9·3 |
| *N*-Ethyl C atoms | 1″ | 53·5 (t, 132) | 53·1 (t, 128) | 49·3 |
| | 2″ | 13·3 (q, 125) | 11·0 (q, 122) | 9·3/ 14·0 |

[a] Chemical shifts in p.p.m. from $Me_4Si$. Peak multiplicity and $J_{CH}$ values (Hz) in parentheses.

## DISCUSSION

*Peak Area Ratios* [*Table* 2(i)].—With all the 1-alkyl-2-methyl-4-phenylpiperidines (1)—(8) examined, methylation by axial approach predominates, *i.e.* $A_a/A_e > 1$. In the *cis*-series, the trend is for increasing axial preference in the order Me < Et < Pr$^i$ and Bu$^t$, whereas the opposite trend is observed in the *trans*-compounds for all but the $N$-t-butyl derivative. However, except for the *cis*-isopropyl compound (3), the differences from the 2-unsubstituted analogues are small and probably reflect the delicate balance in the dependence of $A_a/A_e$ on both $K$ and $k_a/k_e$ [equation (i)].

The dramatic increase in $A_a/A_e$ on the introduction of an equatorial 2-methyl group in 1-isopropyl-4-phenylpiperidine is striking. In the axial $N$-isopropyl conformation (3B) the 2-methyl group hinders the relief of strain normally achieved by flattening at the nitrogen atom and thus is expected to increase the population of the $N$-isopropyl equatorial conformer (3A). Further the 2-methyl group will hinder the $N$-equatorial attack by alkylating agent in conformation (3A).

The product composition is not greatly dependent on the nature of the solvent; the proportion of axial attack is less for acetonitrile than for methanol, as in ethylations [5] and benzylations.[4]

*Gross Observed Reaction Rates.*—The reactions are

[26] M. Shamma and J. B. Moss, *J. Amer. Chem. Soc.*, 1961, **83**, 5038.

[27] E. A. Guggenheim, *Phil. Mag.*, 1926, **2**, 538.

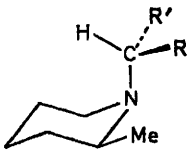
[28] J. B. Lambert, R. G. Keske, R. E. Carhart, and A. P. Jovanovich, *J. Amer. Chem. Soc.*, 1967, **89**, 3761.

found [Table 2(ii)] to be appreciably faster in acetonitrile than in methanol as expected.[29,30] Log $k_{obs}$ (MeCN) — log $k_{obs}$ (MeOH) decreases gradually in the order Me > Et > Pr$^i$ ~ Bu$^t$ and the differences are relatively independent of the 2-methyl group configuration [Table 2(iii)]. For acetonitrile the approximate effect of introduction of the 2-methyl group [Table 2(iv)] is to slow the reactions of the *cis*-series in the order Me > Et ~ Pr$^i$ > Bu$^t$, and of the *trans* series in the reverse sequence, Me < Et ~ Pr$^i$ < Bu$^t$. (Results for NMe and NEt in the 2-unsubstituted series are based on extrapolations of data from lower temperature reactions.) The difference caused by the orientation of the 2-methyl group in the *N*-methyl and *N*-t-butyl series probably reflects the dependence of $k_{obs}$ or $K$. Although for NEt and NPr$^i$ in both solvents, the configuration of the introduced 2-methyl group has little effect on the magnitude of decrease in the reaction rate, this may be merely a cancellation of opposing effects.

As expected, all reactions are slowed by the *N*-alkyl group in the order Me > Et > Pr$^i$ > Bu$^t$.

*Individual Rate Constants* $k_e$ *and* $k_a$.—As described above, these cannot be calculated without knowledge of the conformational equilibrium. However, anticipation of the effect of the introduced 2-methyl group on $k_e$, $k_a$, $n_B$, and $n_A$ does lead to conclusions which support the foregoing diastereoisomer assignments.

An equatorial 2-methyl group in 1-alkyl-4-phenylpiperidines should not greatly affect the state of the conformational equilibrium ($n_B/n_A$) for the *N*-methyl and *N*-ethyl compounds, since the 2-methyl group is *gauche* to both equatorial and axial *N*-alkyl groups. For the same reason, equatorial and axial approach should be similarly hindered, resulting in comparable decreases in $k_e$ and $k_a$. For the *cis*-series, therefore, $k_e n_B$ and $k_a n_A$ should both be less than for the 2-unsubstituted analogues. For the *N*-isopropyl series, the *N*-axial conformer (25) cannot relieve strain by bending the *N*-isopropyl group away, without methyl–methyl steric




(25)

interactions. However, as $n_A$ is already near to unity, it will not be much further affected although $n_B$ will decrease. The observed values of $k_e n_B$ and $k_a n_A$ [Table 2(v) and (vi)] bear out these considerations.

An axial 2-methyl group should displace the conformational equilibrium towards *N*-alkyl axial, *i.e.* $n_B$ increases and $n_A$ decreases in comparison with the 2-unsubstituted compound. The presence of an axial 2-methyl group should have little effect on axial attack but equatorial attack should be inhibited, *i.e.* $k_e$ will decrease. Thus $k_a n_A$ will certainly decrease and, while the change in $k_e/n_B$ is less certain, it will probably also decrease.

Table 5 gives values for log $k_a n_A$ (4-Ph) — log $k_a n_A$ (2-Me, 4-Ph), and the corresponding comparisons of

TABLE 5

Comparative rate data for the effect of 2-substitution [a]

| *N*-Alkyl group | *cis*-2-Methyl | | | *trans*-2-Methyl | | |
|---|---|---|---|---|---|---|
| | $A_a/A_e$ | $\Delta k_a n_A$ [b] | $\Delta k_e n_B$ [c] | $A_a/A_e$ | $\Delta k_a n_A$ [b] | $\Delta k_e n_B$ [c] |
| Me | 2·1 | 0·52 | 0·23 | 3·8 | 0·14 | 0·11 |
| | *ca.* 0·5 | 0·83 | −0·09 | *ca.* 0·3 | 0·72 | −0·47 |
| Et | 2·7 | 0·17 | 0·21 | 3·7 | 0·26 | 0·44 |
| | *ca.* 0·4 | 0·60 | −0·22 | *ca.* 0·3 | 0·83 | −0·13 |
| Pr$^i$ | >15 | *ca.* 0·17 | >1·06 | 3·2 | 0·31 | 0·52 |
| | <0·1 | >1·36 | *ca.* −0·13 | *ca.* 0·3 | 0·82 | 0·01 |

[a] For acetonitrile solutions. [b] $\Delta k_a n_A$ = log $k_a n_A$(4-Ph) — log $k_a n_A$ (2-Me, 4-Ph). [c] $\Delta k_e n_B$ = log $k_e n_B$ (4-Ph) — log $k_e n_B$ (2-Me, 4-Ph).

$k_e n_B$, for both $A_a/A_e > 1$ as listed in Table 2 and for the reciprocal situation corresponding to preferred equatorial attack. The negative values for $\Delta k_e n_B$ corresponding to an increase in $k_e n_B$ for compounds of the *cis*-series if preferred equatorial attack is assumed, is clearly in contradiction of the predicted behaviour.

Distinction is less conclusive for the *trans*-compounds, but support is again given for the assignments already preferred.

*Conclusion.*—The effect of an α-methyl substituent on the methylation of piperidines depends on both the orientation of the α-methyl group and the nature of the *N*-substituent. The variations found in the reaction rates and product stereochemistry can be rationalised by the expected effects of α-substitution on the conformational equilibrium constant $K$ and the individual rate constants $k_a$ and $k_e$.

As no predominance of equatorial quaternisation is observed, we conclude that the predominant equatorial quaternisation found for the tropane series probably stems from factors other than the simple effects of α-substitution.

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