The Conformational Analysis of Saturated Heterocycles. Part LXIV.[1] Stereochemical Orientation of the Ethylation of Piperidines

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Rates of reaction of a series of 1-alkyl-4-phenylpiperidines with ethyl iodide in methanol and in acetonitrile and the proportions of the isomeric quaternary salts formed are reported. Axial ethylation predominates for all cases studied, but the equatorial : axial product ratios often approach unity, and the stereoselectivity is intermediate between those found for methylation (preference for axial attack) and benzylation (preference for equatorial attack).

THE steric course of quaternisation of piperidine derivatives, reviewed recently,[2-5] has been the subject of considerable attention. Both axial and equatorial approach occur simultaneously and the isomer ratio depends markedly on solvent, alkylating agent, and substrate structure. Methylations of simple piperidines appear to take place predominantly by axial approach,[2-5] but the larger, less reactive electrophiles benzyl chloride and *p*-nitrobenzyl chloride[6,7] react by predominant equatorial attack. Reversion to zero selectivity (benzyl iodide[8]) or axial attack (benzyl tosylate[9] and *p*-methoxybenzyl chloride[6]) occurs when the reactivity of such alkylating agents is enhanced. To define the limits of this stereochemical 'changeover' we report results with *N*-alkyl-4-phenylpiperidines and ethyl iodide in acetonitrile and in methanol.

The reaction of ethyl iodide with 1-methyl-4-phenylpiperidine in acetone was initially concluded[10] to proceed with a degree of axial stereoselectivity comparable to that of methylation of the *N*-ethyl derivative (*viz. ca.* 85—95%). However, more accurate determination of product ratios[8] showed much less preference for axial attack (50—60%). Quaternisation of 1-methyl-4-t-butylpiperidine with the more reactive ethyl toluene-*p*-sulphonate in acetone[9] gave 83% axial ethylation, whereas 4-formyl-1-methyl-4-phenylpiperidine with ethyl iodide in ether[11] gave 55% axial attack in agreement with McKenna's revised[8] value. Ethylation thus appeared to exhibit a preference for axial attack, but with lower selectivity than for the methylation of the corresponding *N*-ethylpiperidine.

For tropane derivatives, although most evidence[3] favours equatorial approach, its validity has been questioned.[8] Recent chemical and *X*-ray work[12,13] has confirmed that methylation, alkoxycarbonylmethylation, and other quaternisations in the tropane, tropine, tropinone, and pseudotropine series all involve preferential equatorial attack.

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RESULTS

Ratios (A_a/A_e) of axial to equatorial attack were determined from the n.m.r. spectra of the products (Tables 1 and 2). The quaternisation product of 1-methyl-4-phenylpiperidine (1) exhibits two *N*-methyl absorptions (Table 1). The less intense resonance had a chemical shift identical (Table 2) with that of the *N*-methyl absorption of the *ax*-*N*-methyl-*eq*-*N*-ethyl compound (12) of known configuration established by *X*-ray crystallography.[14] The major product from ethylation of 1-methyl-4-phenylpiperidine was therefore assigned the *eq*-1-methyl-*ax*-1-ethyl configuration (7). The ethiodides of 1-benzyl-4-phenylpiperidine (5) showed $PhCH_2$ resonances at δ 4·55 and 4·69 (Table 1). The *eq*-*N*-benzyl-*ax*-*N*-ethyl compound (11) has had its structure verified by *X*-ray crystallography of the chloride;[15] it exhibits $PhCH_2$ absorption at δ ($CF_3 \cdot CO_2H$) 4·50[16] (misprinted in Table 1 of ref. 6 as δ 5·50). The isomer (16), which must therefore have its benzyl group axial, shows $PhCH_2$ signal at δ ($CF_3 \cdot CO_2H$) 4·68.[6] Allowing for the difference in gegenanion, the major ethiodide of (5) is therefore the *eq*-benzyl configuration. Hence axial ethylation predominates in this reaction also.

TABLE 1

Proton chemical shifts [a] for ethiodides

Compound	Acetonitrile [b] Resonance (δ)	Assignment	A_a/A_e [c]	Methanol [b] Resonance (δ)	Assignment	A_a/A_e [c]
N-Me (1)	3·21, 3·29 [d]	*eq* Me	1·3	3·18	*eq* Me	1·4
	3·18, 3·42 [d]	*ax* Me		3·21	*ax* Me	
N-CH_2Ph (5)	4·53	*eq* CH_2Ph	3·6	4·52	*eq* CH_2Ph	4·4
	4·70	*ax* CH_2Ph		4·69	*ax* CH_2Ph	
N-Et (6)	3·45	*eq* Et	1·3	3·47	*eq* Et	1·5
	3·60	*ax* Et		3·61	*ax* Et	
N-Pr^i (17)	3·62 [d]	*eq* Et	1·9	3·63 [d]	*eq* Et	2·0
	3·85 [d]	*ax* Et		3·87 [d]	*ax* Et	

[a] For *ca.* 10% solutions in $CF_3 \cdot CO_2H$. [b] Solvent for quaternisation, containing 1% (v/v) of water. [c] Integrated intensity ratios for products of axial (A_a) and equatorial (A_e) attack; standard deviations ±0·2. [d] Measured in $CDCl_3$.

TABLE 2

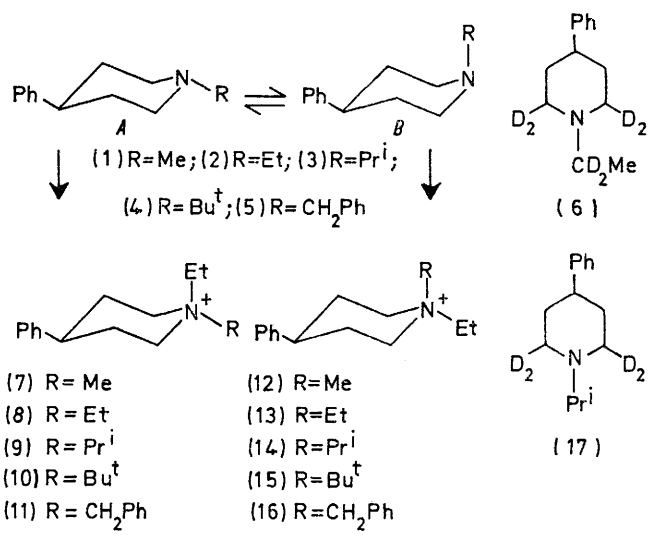
Proton chemical shifts of 1,1-disubstituted 4-*eq*-phenylpiperidinium salts with known configurations

1,1-Substituents *ax*	1,1-Substituents *eq*	Compound no.	Ref. *a*	Ref. *b*	Chemical shift (δ) [c]	Assignment
Me	Et	(12) [d]	*h*	*j*	3·21 [l] (3·38 [m])	*ax* Me
Et	Me	(7) [e]		*j*	3·18 [l] (3·30 [m])	*eq* Me
Et	CH_2Ph	(11) [f]	*i*	*k*	4·50 [n]	*eq* CH_2Ph
CH_2Ph	Et	(16) [g]		*k*	4·68 [n]	*ax* CH_2Ph

[a] To *X*-ray analysis. [b] To chemical work. [c] For 10% solutions in trifluoroacetic acid. [d] Major methiodide of (2) (ref. 14). [e] Minor methiodide of (2) (ref. 14). [f] Major benzochloride of (2) (ref. 15). [g] Minor benzochloride of (2) (ref. 15). [h] Ref. 14. [i] Ref. 17. [j] Ref. 2. [k] Ref. 6. [l] Methiodide prepared and spectrum measured in this work. [m] Measured in $CDCl_4$ (P. G. Mente, Ph.D. Thesis, University of East Anglia, 1967). [n] Ref. 16.

Determination of the ratios of products resulting from the ethyl (2) and the isopropyl (3) compounds presented greater difficulty owing to the complexity of the n.m.r. spectra. Interpretation was facilitated by the use of appropriately deuteriated substrates. Ethylation of 2,2,6,6-tetradeuterio-1-isopropyl-4-phenylpiperidine (3) gave a product mixture exhibiting two quartets at δ ($CDCl_3$) 3·62 and 3·85 attributed to *N*-methylene absorptions. Since the major products from ethylation of the methyl and benzyl analogues have been shown (see above) to be the isomers with axial ethyl groups, the more intense low-field methylene signal may be assigned to the *ax*-ethyl isomer.[17]

The reaction of 2,2,6,6-tetradeuterio-1-(αα-dideuterioethyl)-4-phenylpiperidine (6) with ethyl iodide similarly



gave two isomers showing $N \cdot CH_2$ quartets centred at δ ($CF_3 \cdot CO_2H$) 3·45 and 3·60. The major product is again by analogy assigned the *ax*-ethyl-*eq*-dideuterioethyl configuration.

Kinetics of the reactions were studied at 25° by the previously described methods.[2,6,18] Plots of conductivity *vs.* concentration for some of the product quaternary salts revealed curvature in completely anhydrous solvents, possibly arising from ion-pairing at higher

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concentrations. Linear conductivity–concentration plots were obtained in acetonitrile and in methanol containing a small amount of water and the kinetics were therefore determined for 1% (v/v) aqueous solutions in methanol and in acetonitrile. Measurements were not carried out in acetone since addition of small proportions of water still failed to give a linear relationship. The effect of 1% of water in methanol or acetonitrile is small; for example, quaternisation of (1) with benzyl chloride in 1% aqueous acetonitrile * gave an observed rate constant of $2{\cdot}15 \times 10^{-4}$ (*cf.* $2{\cdot}40 \times 10^{-4}$ reported [6] for acetonitrile) and individual rate constants for equatorial (k_e) and axial (k_a) attack were $5{\cdot}73 \times 10^{-4}$ and $0{\cdot}96 \times 10^{-4}$, respectively (*cf.*[6] $k_e = 6{\cdot}40 \times 10^{-4}$ and $k_a = 1{\cdot}07 \times 10^{-4}$). A further experiment employing 2% aqueous acetonitrile also showed no difference within experimental error. Since ethyl iodide in 1% aqueous acetonitrile develops no conductivity, no solvolysis of the iodide can have occurred.

Rate constants under pseudo-unimolecular conditions were obtained by standard Guggenheim analysis [19] of the data and converted into second-order rate constants by dividing by the concentration of ethyl iodide. Equations (i) and (ii), where K is the equilibrium constant $[A]/[B]$ (see formulae), give the individual rate constants k_e and k_a.[6,20] Values for the populations of

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

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

the conformers (1A) (75%), (2A) (85%), and (3A) (94%) [21] were used as before.[6,†] The benzyl derivative (5) is assumed to be ⩾90% (5A) on the supposition that its conformational equilibrium is intermediate between those of (2) and (3). The t-butyl compound (4) failed to show pseudo-unimolecular reaction kinetics probably because of a competing elimination reaction [22] and is not discussed further. The results are collected in Table 3.

EXPERIMENTAL

Solvents were fractionated and stored over activated molecular sieves. Ethyl iodide was fractionated and stored for short periods at 5° over mercury. Substituted piperidines were prepared by application of general methods; [23] the products possessed i.r. and n.m.r. spectra, elemental analyses, and b.p.s in agreement with literature data.[10,24,25]

2,2,6,6-*Tetradeuterio*-1-(αα-*dideuterioethyl*)-4-*phenylpiperidine*.—3-Phenylglutarimide [26] (1·1 g, 0·005 mol) in anhydrous tetrahydrofuran (THF) (10 ml) was added dropwise to lithium aluminium deuteride (99%, 0·5 g, 0·011 mol) in anhydrous THF (10 ml) during 5 min at 0°. After 30 min at 50—60° it was cooled to 0°, and water (0·5 ml), aq. NaOH (1N; 0·5 ml), and water (1·5 ml) were successively added. The precipitate was removed and the filtrate dried (K_2CO_3) and evaporated to give a pale yellow oil (0·5 g). To this oil in pyridine (at 0°) (2 ml) acetyl chloride (*ca.* 5 ml) was added dropwise. The mixture was poured onto ice and water and extracted with ether, and the ethereal solution dried (K_2CO_3) and evaporated to give an oil (0·5 g). This oil was reduced as before with lithium aluminium deuteride (0·2 g) and the product (220 mg) chromatographed over alumina (neutral; 25 g) with chloroform and methanol to give a pale yellow oil (0·15 g, 4%), δ ($CDCl_3$; 60 MHz) 7·25 (5H, s), 3·30 (1H, m), 2·80 (4H, m), and 1·10 (3H, s).

2,2,6,6-*Tetradeuterio*-1-*isopropyl*-4-*phenylpiperidine*.—3-Phenylglutaric acid [26] (2·08 g, 0·01 mol) in anhydrous ether (40 ml) was added dropwise to lithium aluminium deuteride (1·0 g, 0·024 mol) in anhydrous ether (20 ml) during 5 min. After 3 h under reflux the mixture was cooled and water cautiously added (6 ml), followed by 6N-HCl to dissolve the precipitate (25 ml). The ethereal layer was washed (2 × 10 ml of saturated aq. Na_2CO_3), dried ($MgSO_4$), and evaporated. To the crude diol in pyridine (5 ml) at −10° was slowly added tosyl chloride at such a rate that the temperature remained below −5°. After stirring at 0° for 8 h ice (10 g) was added followed by 6N-HCl (5 ml). The solution was extracted with ether (2 × 10 ml) and the extracts washed successively with 10 ml portions of N-HCl, N-NaOH, and H_2O. When set aside, the ethereal solution gave white prisms, which were boiled in isopropylamine under anhydrous conditions for 3 h. The amine was then removed under vacuum and the oily residue made alkaline with 2N-NaOH (1 ml). The aqueous solution was extracted with ether (2 × 5 ml) and the extracts were dried (Na_2SO_4) Filtration followed by evaporation gave an amber oil which was microdistilled yielding the product (0·2 g, 10%) as an oil, b.p. 100—105° at 0·15 mmHg.

1ax-*Ethyl*-1eq-*isopropyl*-4eq-*phenylpiperidinium Iodide*.—1-Isopropyl-4-phenylpiperidine (1·9 g, 0·01 mol) in dry AnalaR acetone (20 ml) was heated under reflux with ethyl iodide (1·46 g, 0·01 mol) for 20 h. Crystals (1·1 g) which separated from the cooled solution were recrystallised from acetonitrile (×4) and from water (×1) to give the *iodide* (0·23 g, 10%), m.p. 201—203° (hot-stage), as needles (Found: C, 53·1; H, 7·2; N, 4·1. $C_{16}H_{26}IN$ requires C, 53·1; H, 7·3; N, 3·9%).

Product Ratios.—Quaternary salts were formed at 25° by treating the amine (0·10 g) in the appropriate solvent (2 ml) with ethyl iodide (0·8 g) for 2—4 times the reaction half-life. The solvent was removed by freeze-drying and the crude solid dissolved in trifluoroacetic acid to give a *ca.* 10% solution. The n.m.r. spectrum was recorded (100 or 220 MHz) and the product ratio determined from duplicate sweeps of the appropriate region.

* Duplication of quaternisation reported in ref. 6 with 1% aqueous acetonitrile as solvent.

† *Added in proof:* It must be emphasized that the individual k_a and k_e values depend critically on the conformational analysis equilibrium constants for the *N*-alkylpiperidines, which may be considerably more displaced toward the alkyl-equatorial conformer than we have assumed (*cf.* E. L. Eliel and F. W. Vierhapper, *J. Amer. Chem. Soc.*, 1974, **96**, 2257). However, the axial–equatorial product ratios, and the conclusions on the stereoselectivity are not affected.

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Kinetic Quaternisations.—Solutions were prepared under nitrogen and measurements using apparatus previously described [6] made at 25·0 ± 0·01° for each solvent used. Amine (10—30 mg) and freshly prepared 1·0% (v/v) aqueous solvent (10 ml) were weighed under nitrogen into the tared cell. After equilibration of the cell and ethyl iodide at 25·0 ± 0·01°, *ca.* 1 ml of the latter, accurately measured, was added. The increase in conductivity was followed by use of a Wayne Kerr B641 bridge. The pseudo-unimolecular rate constant was calculated from the least squares slope of the plot of ln $(C_{t+T} - C_t)$ *vs.* t (where C_t is the conductivity observed at time t s and T is a time of the order of the reaction half-life) and converted into the second-order rate constant by dividing by [EtI].

Densities of the solvents and ethyl iodide were measured using an Anton Parr digital densitometer DMA O2C.

DISCUSSION

Peak Area Ratios.—For all the piperidines examined, ethylation by axial approach at nitrogen predominates. For the *N*-methyl compound (1) the values of A_a/A_e (1·20 for MeCN; 1·44 for MeOH; see Table 1), the ratio of the peak areas corresponding to axial and equatorial attack agrees with the revised values reported by McKenna *et al.*[8] (1—1·5 : 1).

TABLE 3

Comparative data for quaternisations of 1-alkyl-4-phenyl-piperidines in acetonitrile solution

	N-Alkyl group					
	Me		Et		Pr^i	
Alkylating agent	A_a/A_e	k_e/k_a	A_a/A_e	k_e/k_a	A_a/A_e	k_e/k_a
MeI	4·0	0·7 [a]	2·4	1·8 [a]		
EtI	1·3	2·5 [b]	1·3	6·2 [b]	1·9	10·0 [b]
$PhCH_2Cl$	0·5	6·0 [c]	0·5	15·4 [c]	0·45	41·8 [c]

[a] Ref. 2. [b] This work. [c] Ref. 6.

The effect on A_a/A_e of increasing the size of the *N*-substituent in piperidine requires a compromise between the greater proportion of *eq-N*-alkyl conformer present, which tends to increase A_a/A_e, and the more hindered environment which tends to discourage axial approach, and decrease A_a/A_e. For changing from *N*-methyl to *N*-ethyl, these two effects nearly cancel, and the A_a/A_e ratio does not change appreciably (Table 1). For *N*-isopropyl the A_a/A_e ratio increases to about 65% axial attack in both solvents. For *N*-benzyl the proportion of axial ethylation increases further to around 80% both in acetonitrile and in methanol.

As Table 3 shows, the stereoselectivity of ethylation is intermediate between those of methylation (preference for axial attack) and benzylation (preference for equatorial approach). The proportion of axial attack is less for acetonitrile than for methanol, in which the reaction is slower, and this once again [6] suggests caution in applying Bottini's criterion [27] that quaternisation of the more stable conformer is favoured in solvents for which the reaction is faster. The solvent effects overall are quite small (*cf.* Table 1).

Gross Observed Reaction Rates.—The reactions are found to be considerably faster in acetonitrile than in methanol, as expected.[28,29] In the series *N*-methyl (1), *N*-ethyl (2), and *N*-isopropyl (3) compounds, the difference {log k_{obs} (MeCN) − log k_{obs} (MeOH)} decreases gradually (last column of Table 4), with a slightly larger decrease for the *N*-benzyl compound (5).

The rates vary with *N*-substitution in the order Me > Et > $Pr^i \sim CH_2Ph$, as expected. The incremental rate decrease with substitution is not significantly solvent dependent except perhaps for CH_2Ph: substitution of Et for Me causes a rate decrease (log units) of 0·76 ± 0·04 and of Pr^i for Me, 1·40 ± 0·1. Substitution of CH_2Ph for Me causes a decrease of 1·55 in MeCN and of 1·07 in MeOH.

Rate Ratios k_e/k_a.—The figures in Table 4 show that k_e/k_a values lie in the range 2—10. They are intermediate between those for methylation and for benzylation (Table 3) and confirm that the trend from preferred axial to preferred equatorial attack is derived largely from the change in relative rates of equatorial and axial reaction. The effect of solvent on the ratio is small but regular for the series Me, Et, and Pr^i with equatorial approach slightly more favoured with the faster reactions. The influence of the *N*-substituent is considerable: as previously found for *N*-methylation and for *N*-benzylation (see Table 3), the values of k_e/k_a rise from *ca.* 2 for NMe to *ca.* 10 for NPr^i.

TABLE 4

Rate ratios and observed rates [a] for quaternisation of 1-alkyl-4-phenylpiperidines by ethyl iodide

	Acetonitrile				Methanol				
Compound	k_e/k_a	log k_{obs}	log k_e	log k_a	k_e/k_a	log k_{obs}	log k_e	log k_a	log k_{obs} (MeCN) − log k_{obs} (MeOH)
(1)	2·3	3·65	3·89	3·53	2·1	2·37	2·59	2·26	1·28
(2)	6·2	2·86	3·46	2·66	5·4	1·65	2·21	1·48	1·21
(3)	10·0	2·15	2·98	1·98	9·50	1·08	1·90	0·93	1·07
(4)	2·5	2·10	2·44	2·04	2·1	1·30	1·57	1·26	0·80

[a] Values of k_{obs}, k_e, and k_a are all multiplied by 10^7.

Individual Rate Constants k_e and k_a.—Both equatorial and axial attack are faster in acetonitrile than in methanol, with k_e showing greater solvent dependence. The solvent effect on the individual rates varies in a regular way with *N*-substitution: the effect of changing the *N*-substituent varies both the equatorial and the axial rates in the order Me > Et > Pr^i: but for a

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[29] M. H. Abraham, *J. Chem. Soc.* (*B*), 1971, 299.

particular compound the effect is significantly greater for k_a than for k_e. This parallels the behaviour previously found for benzylation.[6]

General Conclusions.—Axial attack predominates for ethylation under all the conditions studied. However, the equatorial : axial product ratios do approach unity, and the tendency towards axial attack is considerably less than found for methylation [2] although significantly greater than found for benzylation.[6]

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