The Conformational Analysis of Saturated Heterocycles. Part LII.[1] The Stereochemical Orientation of the Benzylation of Piperidines [2]

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N-Methyl-, *N*-ethyl-, and *N*-isopropyl-4-phenylpiperidine have been quaternised in acetonitrile, acetone, benzene, and methanol. The product ratios were measured by n.m.r. spectroscopy. For the first two solvents, rate constants were determined and used to calculate individual rates k_a and k_e for axial and equatorial quaternisation. Most of the reactions proceed predominantly by equatorial attack: the individual variations are analysed in terms of k_a and k_e.

THE elucidation and the explanation of the steric course of reaction of tertiary bases with electrophiles has proved difficult and controversial. However, it is now clear that alkylations and *N*-oxidation in the tropane series occur preferentially by equatorial approach.[3] In the simple piperidine series methylation [4] and *N*-oxidation [5] are now agreed to occur by preferential axial

[1] Part LI, R. A. Y. Jones, A. R. Katritzky, D. L. Nicol, and R. Scattergood, *J.C.S. Perkin II*, 1973, 337.

[2] For a preliminary communication see R. P. Duke, R. A. Y. Jones, A. R. Katritzky, J. R. Carruthers, W. Fedeli, F. Mazza, and A. Vaciago, *J.C.S. Chem. Comm.*, 1972, 455.

[3] G. Fodor, R. V. Chastain, jun., D. Frehel, M. J. Cooper, N. Mandava, and E. L. Gooden, *J. Amer. Chem. Soc.*, 1971, **93**, 403.

[4] (*a*) W. Fedeli, R. A. Y. Jones, A. R. Katritzky, F. Mazza, P. G. Mente, and A. Vaciago, *Atti Accad. naz. Lincei, Rend. Classe Sci. fis. mat. nat.*, 1969, **46**, 733; (*b*) R. A. Y. Jones, A. R. Katritzky, and P. G. Mente, *J. Chem. Soc.* (*B*), 1970, 1210; (*c*) W. Fedeli, F. Mazza, and A. Vaciago, *ibid.*, p. 1218; (*d*) R. Brettle, D. R. Brown, J. McKenna, and R. Mason, *Chem. Comm.*, 1969, 339.

[5] M. J. Cook, A. R. Katritzky, and M. Moreno-Mañas, *J. Chem. Soc.* (*B*), 1971, 1330.

approach, but methoxycarbonylmethylation shows a small preference for equatorial approach [6] or yields equal amounts of the two configurational isomers.[7]

The situation regarding benzylation in the piperidine series has not been clear: McKenna *et al.* report zero selectivity for the reaction of benzyl iodide with 1-methyl-4-phenylpiperidine,[8] but in a paper on benzylation they state [9] ' the results accord with preferred axial quaternization (by primary alkylating agents) in all the systems where unambiguous configurational deductions could be made ' (*cf.* also ref. 10). House *et al.*[7] have also concluded that benzyl tosylate and 1-methyl-4-t-butylpiperidine give as the major product (69%) the derivative formed by axial approach. Previous work by ourselves,[4b] by Italian workers,[11] and by Bottini [12] had indicated that preferential *equatorial* approach could occur in benzylation of simple piperidines. However, all these assignments were based on criteria which were less than conclusive.

We now report a study of the reactions of *N*-methyl-, *N*-ethyl-, and *N*-isopropyl-4-phenylpiperidine with benzyl chloride and with *p*-methoxy- and *p*-nitrobenzyl chloride in methanol, acetonitrile, acetone, and benzene. Product ratios were determined by n.m.r. spectroscopy, the two benzyl CH_2-signals being integrated, with precautions against equilibration of the products.[13] Kinetics of the reactions in acetone and acetonitrile were studied conductiometrically using a modification of the previous methods: [4b,14] reactions were studied to from 10—30% completion only because many were too slow to obtain reliable infinity readings. Kinetics were not studied in benzene because of insolubility of the products, and not in methanol because of competitive solvolysis of the benzyl halides.

TABLE 1

Chemical shifts (δ) of benzyl CH_2 resonances in 1-alkyl-1-(substituted benzyl)-4-phenylpiperidinium chlorides

1-Alkyl group	*p*-Substituent		
Me	MeO	4·54 [a]	4·65
	H	4·56	4·66
	NO_2	4·80	4·90
Et	MeO	4·48	4·65
	H	5·50	4·68
	NO_2	4·72	4·90
Pr^i	MeO	4·36	4·76
	H	4·37	4·77
	NO_2	4·60	5·00

[a] Measured as *ca.* 10% solution in trifluoroacetic acid with Me_4Si as internal reference.

Assignment of n.m.r. peaks in Table 1 has been carried out with the aid of *X*-ray crystallography. The methiodide of 1-benzyl-4-phenylpiperidine, prepared in acetone, shows peaks at δ 4·63 (major) and 4·71 p.p.m. (minor) in CF_3CO_2H; the high-field signal has previously been shown to be due to the isomer with equatorial benzyl.[4d] For the ethyl and isopropyl series the *X*-ray analyses were carried out by Vaciago and his collaborators [15] on samples supplied by us (see following paper).

EXPERIMENTAL

Solvents were dried, fractionated, and kept over activated molecular sieves and under nitrogen. Transfers were carried out in a dry box.

Benzyl halides were recrystallised before use and had m.p. in agreement with literature values. Substituted piperidines were prepared as previously described [16] or by applying a general method [17] and characterised by i.r. and n.m.r.

1-*Benzyl*-1-*methyl*-4-*phenylpiperidinium Chloride* (*Mixed Isomers*).—Methyl iodide (1·0 ml) was added to 1-benzyl-4-phenylpiperidine (0·4 g) in dry acetone (10 ml). After 12 h at room temperature the separated crystals of the methiodide were filtered off, dissolved in warm water (25 ml) and shaken with an excess of silver chloride. The precipitate was filtered off, and the filtrate allowed to evaporate, giving crystals of the methochloride, δ (CF_3COOH) 2·1 (CH_2 ring), 3·17 (*Me*-N), 3·6 (CH_2-N ring), 4·63 (N-CH_2-phenyl, major) 4·71 (N-CH_2-phenyl, minor), 7·3 (phenyl) and 7·58 p.p.m. (phenyl).

1eq-*Benzyl*-1ax-*ethyl*-4eq-*phenylpiperidinium Chloride*.—1-Ethyl-4-phenylpiperidine (0·65 g), benzyl chloride (1·0 ml) and AnalaR acetone (10 ml) were heated under reflux for 30 min. Crystals which separated from the cooled solution were recrystallised from acetonitrile to give the *chloride* (0·86 g, 79%), m.p. 276—277° (hot stage; 240—241°, sealed tube), as rhombic crystals (Found: C, 75·8; H, 8·2; N, 4·5. $C_{20}H_{26}ClN$ requires C, 76·1; H, 8·3; N, 4·4%); δ ($CDCl_3$, 220 MHz) 5·25 (s, 2H, PhCH_2); 3·65 (q, 2 H, *J* 7 Hz, MeCH_2), 1·59 (t, 3H, *J* 7 Hz, CH_3); δ (CF_3CO_2H, 100 MHz), 4·48 (s, 2H, PhCH_2), 3·60 (q, 2H, *J* 7 Hz, MeCH_2), and 1·62 p.p.m. (t, 3H, *J* 7 Hz, CH_3).

1eq-*Benzyl*-1ax-*isopropyl*-4eq-*phenylpiperidinium Chloride*.—This *chloride* was prepared by a similar method to that described above; it formed rhombic crystals, m.p. 225—226° (hot stage; 204—205°, sealed tube), from acetonitrile (Found: C, 72·4; H, 8·7; N, 4·3. $C_{21}H_{28}ClN,H_2O$ requires C, 72·5; H, 8·7; N, 4·0%); δ (D_2O) 4·27 (septet, 1H, *J* 7 Hz, Me_2CH), 4·2 (s, 2H, PhCH_2), 1·29 (d, 6H, *J* 7 Hz, $(CH_3)_2CH$); δ (CF_3CO_2H, 100 MHz) 4·57 (septet, 1H, *J* 7 Hz, Me_2CH), 4·36 (s, 2H, PhCH_2), and 1·66 p.p.m. (d, 6H, *J* 7 Hz, $(CH_3)_2CH$).

Product Ratios.—Quaternary salts were formed at room temperature by allowing the amine (0·5 g) in dry solvent (10 ml) to react with the benzyl chloride (1 g). The solvent was removed by freeze drying. Crude solid was dissolved

[6] H. Dorn, A. R. Katritzky, and M. R. Nesbit, *J. Chem. Soc.* (*B*), 1967, 501.
[7] H. O. House, B. A. Tefertiller, and C. G. Pitt, *J. Org. Chem.*, 1966, **31**, 1073.
[8] D. R. Brown, R. Lygo, J. McKenna, J. M. M'Kenna, and B. G. Hutley, *J. Chem. Soc.* (*B*), 1967, 1184.
[9] D. R. Brown, J. M'Kenna, and J. M. M'Kenna, *J. Chem. Soc.* (*B*), 1967, 1195.
[10] D. R. Brown, J. M'Kenna, J. M. M'Kenna, J. M. Stuart, and B. G. Hutley, *Chem. Comm.*, 1967, 380.
[11] M. A. Iorio and S. Chiavarelli, *Tetrahedron*, 1969, **25**, 5235.
[12] A. T. Bottini, personal communication, quoted in ref. 4*b*.
[13] Y. Ogata, M. Okano, and M. Sugawara, *J. Amer. Chem. Soc.*, 1951, **73**, 1715.
[14] M. Shamma and J. B. Moss, *J. Amer. Chem. Soc.*, 1961, **83**, 5038.
[15] J. R. Carruthers, W. Fedeli, F. Mazza, and A. Vaciago, following paper.
[16] J.-L. Imbach, A. R. Katritzky, and R. A. Kolinski, *J. Chem. Soc.* (*B*), 1966, 556.
[17] A. T. Nielsen and E. N. Platt, *J. Heterocyclic Chem.*, 1969, **6**, 891.

in trifluoroacetic acid (0·5 ml) to give *ca.* 10% solution. The n.m.r. spectrum was recorded at 100 MHz and the ratio of the benzyl peak areas determined from repeated (4—9) sweeps (100 MHz) of the appropriate region.

Kinetic Quaternisations.—A modification of the literature method [4b,14] was used. The reactions were followed conductimetrically in a 10 ml Pyrex cell, with 1·2 cm platinum disc electrodes connected in sequence to tungsten, nickel, and copper wires. Electrodes were cleaned with dilute aqua regia, plated by electrolysis of 1% chloroplatinic acid at 10 mA for 10 min (the current direction being reversed every 2 min) and then 2% sulphuric acid for 5 min in each direction, and finally washed with water, ethanol, AnalaR acetone. Benzyl chloride was added to the thermostatted cell using a syringe, through a Suba Seal.

Each cell was standardised by conductance readings for known molarities of 1-benzyl-1-ethyl-4-phenylpiperidinium chloride in each solvent. Solutions were prepared in a dry box and measurements were made at 25·0 ± 0·01° for each solvent used.

Amine (10—30 mg) and solvent (10 ml) were weighed under dry nitrogen (in a dry box) into the tared cell. After equilibration of the cell and benzyl halide at 25·0 ± 0·01°, *ca.* 1 ml of the latter, accurately measured, was added; for *p*-nitrobenzyl chloride a standard solution containing 2·500 g in 10·0 ml of solution was used and a 2 ml aliquot taken. The increase in conductivity was followed up to 10—30% completion using a Wayne Kerr B641 bridge. The pseudo-first-order rate constant was calculated from the least-squares slope of the plot ln $(C_\infty - C_t)$ *vs.* t, where C_t is the conductivity observed at time t seconds; C_∞, the infinity value, was calculated from the known initial molarity of the amine and the calibration line for the cell.

The densities of the solvents, chlorides and the standard solutions of *p*-nitrobenzyl chloride were measured using an Anton Parr digital densimeter DMA02C.

DISCUSSION OF RESULTS

(A) *Peak Area Ratios.*—From the peak area ratios (A_e/A_a, where A_e is the area of the peak deriving from equatorial approach) in Table 2 the following conclusions may be drawn. (*a*) Equatorial attack predominates for all the cases studied except for *p*-methoxybenzylation in acetone solvent.

(*b*) The effect of *p*-substitution in the benzyl chloride is significant; a marked increase in the proportion of equatorial attack in the order OMe < H < NO_2 occurs for each amine and in all solvents.

(*c*) The proportion of equatorial attack is less for methanol than for the other solvents, but varies little with solvent for acetonitrile, acetone, and benzene. This indicates that great caution must be exercised in applying the criterion developed by Bottini [18] which is that if a reaction is carried out in two solvents, a larger proportion of quaternisation of the more stable conformer occurs in the solvent for which the reaction is faster, *i.e.* for the present compounds A_e/A_a would decrease. No such general trend is shown in Table 2.

(*d*) The effect of the *N*-substituent is small and apparently irregular.

TABLE 2

Integrated intensity ratios,[a] rate ratios, and observed rates [b] for quaternisation of *N*-alkyl-4-phenylpiperidines by *p*-substituted benzyl chlorides

Substituent		MeOH		Acetonitrile					Acetone					Benzene	
N-	*P*-	A_e/A_a	k_e/k_a	A_e/A_a	k_e/k_a	log k_{obs}	log k_e	log k_a	A_e/A_a	k_e/k_a	log k_{obs}	log k_e	log k_a	A_e/A_a	k_e/k_a
Me	MeO			1·1	3·3	3·89	4·21	3·69	1·0	3·0	2·62	2·92	2·45	1·6	4·8
	H	1·1 *	3·3	2·0	6·0	3·38	3·81	3·03	2·1	6·3	2·00	2·43	1·63	1·6	4·8
	NO_2	1·6	4·8	2·4	7·2	3·28	3·73	2·87	2·6	7·8	1·92	2·39	1·49	2·3	6·9
Et	MeO			1·3	10·5	3·05	3·76	2·73	0·8 †	6·3	1·70	2·30	1·51	1·3	10·5
	H	1·1	8·9	1·9	15·4	2·32	3·10	1·91	1·7	13·8	0·94	1·70	0·56	1·8	14·6
	NO_2	2·0	16·2	3·4	27·5	1·98	2·83	1·38	2·4	19·4	0·93	1·74	0·45	2·1	17·0
Pr^i	MeO			1·5	28·5	1·57	2·65	1·20	0·9 ‡	16·5	0·52	1·48	0·28	1·8	34·2
	H	1·5	28·5	2·2	41·8	0·86	2·00	0·38	1·9	(36·1)	(−0·30)	(0·81)	(−0·74)		

[a] Values of A_e/A_a given are the mean of 4—9 observations. Standard deviations are ±0·1 or less, except that those marked † and ‡ are 0·03 and 0·04 respectively. [b] Values of k_{obs}, k_e, and k_a are all multiplied by 10^7.

(B) *Gross Observed Reaction Rates.*—Variations in the values of log k_{obs} shown in Table 2 may be generalized as follows. (*a*) All reactions are considerably faster in acetonitrile than in acetone; Δ log k_{obs} is 1·25 ± 0·14.* This increase in rate is expected in view of the greater dielectric constant of acetonitrile (although there is no general correlation of rates with dielectric constant [19]), but in contrast with previous work [20] we do not find any linear diminution in the solvent dependence with the reactivity of the nucleophile. The effects of solvents on the reaction rates of quaternary salt formation have been reviewed.[21,22]

(*b*) As expected, rates vary with the *N*-substituent in the order Me > Et > Pr^i. Substitution of Et for Me causes a rate decrease, Δ log k_{obs}, 1·03 ± 0·16. Substitution of Pr^i for Me causes a rate decrease, Δ log k_{obs}, 2·31 ± 0·17.

(*c*) Again as expected,[23] a *p*-methoxy-substituent causes a large increase of 0·69 ± 0·11 in log k_{obs} and a *p*-nitro-substituent a small decrease of 0·13 ± 0·14, relative to the rates with unsubstituted benzyl chloride.

* Here and elsewhere, arithmetic mean and standard deviation are given.

[18] A. R. Bottini and M. K. O'Rell, *Tetrahedron Letters*, 1967, 423.

[19] H. Hartmann and A. P. Schmidt, *Z. phys. Chem.* (*Frankfurt*), 1969, **66**, 183.

[20] T. Matsui and N. Tokura, *Bull. Chem. Soc. Japan*, 1970, **43**, 1751.

[21] C. Lassau and J. C. Jungers, *Bull. Soc. chim. France*, 1968, 2678.

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

[23] C. Gardner Swain and W. P. Langsdorf, jun., *J. Amer. Chem. Soc.*, 1951, **73**, 2813.

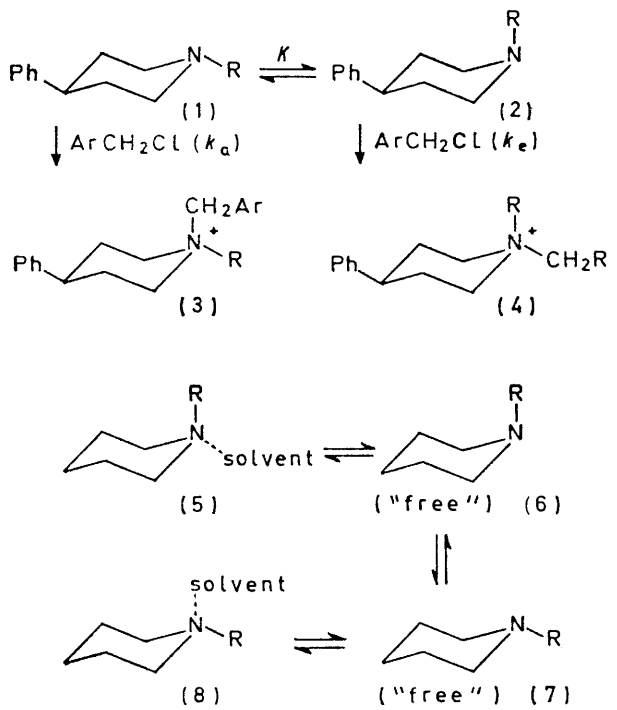
These variations will be discussed in more detail below.

(C) *Conformer Populations in the Various Solvents.*—Knowledge of the conformational equilibrium constant $K = [NR(eq)]/[NR(ax)]$ for the *N*-substituted piperidine substrate would allow us to separate the observed rate constant into the two individual rate constants k_a and k_e for axial and equatorial attack by the electrophile using equations (1) and (2) [*cf.* formulae (1)—(4)]. Even where k_{obs} has not been measured, the ratio k_e/k_a can be obtained using equation (1).

$$k_e/k_a = K(A_e/A_a) \quad (1)$$

$$k_{obs} = k_e/(K + 1) + k_aK/(K + 1) \quad (2)$$

Conformer populations are known for the *N*-alkylpiperidines in cyclohexane solution;[24] recent recalculation of the results using an energy minimisation program to obtain the probable geometry gives [25] for *N*-Me,



N-Et, and *N*-Pr^i 4-phenylpiperidine values of 75%, 89%, and 95% respectively of conformers with lone-pair axial (including an allowance of 1% for conformers with the 4-phenyl group axial). Unfortunately, little is known of the variation of these equilibria with polar solvent although little difference was found between cyclohexane, benzene, and dioxan.[24] However, the following considerations indicate that the use of the cyclohexane equilibrium constants for other solvents is not likely to lead to serious error, and may indeed be preferable. In a solvent which interacts with the nitrogen lone-pair, the equilibrium (5) ⇌ (8) is likely to differ from that found in cyclohexane. However, the solution will also contain some 'free' molecules (6) and (7), and the equilibrium (6) ⇌ (7) should be similar to that found in cyclohexane. Further, these 'free' molecules are expected to react more rapidly than the solvated derivatives with the quaternising agent. If a large proportion of the reaction occurs through (6) and (7), then the use of cyclohexane equilibrium constants would be *more* appropriate than those applying to the polar solvent in question.

In the above discussion the 4-phenyl group has been assumed to be entirely in the equatorial conformation, but in the calculations, a small correction has been made to allow for the *ca.* 1% of 4-axial phenyl present.[26]

(D) *Rate Ratios* k_e/k_a.—The figures in Table 2 show that k_e/k_a ratios lie in the range 3—25. Within this range, as already discussed above in section A(*b*), there is an increase in the ratio for *p*-OMe < H < *p*-NO_2, but now [in contrast to section A(*d*) above] a significant and regular dependence on the *N*-substituent can also be observed: for the same solvent and *p*-substituent the ratios are in the order Me < Et < Pr^i, see Table 3.

TABLE 3

Values of the ratio of (k_e/k_a) for *N*R to (k_e/k_a) for *N*Me

	R = Et			R = Pr^i	
Solvent	*p*-OMe	H	*p*-NO_2	*p*-OMe	H
Methanol		2·70	3·38		8·64
Acetonitrile	3·18	2·57	3·82	8·64	6·97
Acetone	2·10	2·19	2·49	5·50	5·73
Benzene	2·19	3·04	2·46	7·13	

(E) *Individual Rate Constants* k_e *and* k_a.—The rate constants are recorded in Table 2, and incremental log *k* values in Table 4. Results are available only for acetonitrile and for acetone.

(*a*) The effect of solvent is that the reaction is always faster in acetonitrile with $\Delta \log k = 1{\cdot}25 \pm 0{\cdot}14$ when compared with the same reaction in acetone. For the same compound there is no large difference between the solvent effects on k_a and on k_e. The solvent effect does not vary in any regular way with *N*- or *p*-substitution.

(*b*) The effect of changing the *N*-substituent is to slow the rates in order Me > Et > Pr^i; but for any particular compound the effect is significantly greater for k_a than for k_e. In changing from *N*Me to *N*Et, the effect is $1{\cdot}10 \pm 0{\cdot}20$ log *k* units for k_a and $0{\cdot}68 \pm 0{\cdot}15$ for k_e and in changing from *N*Me to *N*Pr^i it is $2{\cdot}42 \pm 0{\cdot}20$ log *k* units for k_a and $1{\cdot}61 \pm 0{\cdot}15$ for k_e. The environment of the reaction site during axial approach (9) is considerably more crowded than during equatorial approach (10), and the effect of replacing the CH_3* by H (Et ⟶ Me) or of the H† by CH_3 (Et ⟶ Pr^i) is correspondingly greater in (9) than (10).

(*c*) As to substitution in the benzyl chloride, *p*-OMe increases the rates substantially, and *p*-NO_2 decreases

[24] R. A. Y. Jones, A. R. Katritzky, A. C. Richards, and R. J. Wyatt, *J. Chem. Soc.* (*B*), 1970, 122.

[25] I. D. Blackburne, R. P. Duke, R. A. Y. Jones, A. R. Katritzky, and K. A. F. Record, *J.C.S. Perkin II*, 1973, 332.

[26] R. J. Bishop, L. E. Sutton, D. Dineen, R. A. Y. Jones, A. R. Katritzky, and R. J. Wyatt, *J. Chem. Soc.* (*B*), 1967, 493.

the rates by a smaller amount. Again the effects are considerably greater for k_a than for k_e; again the rationalisation is that in the more crowded situation the electronic effect is greater. Presumably the transition state during axial approach is more S_N1-like with a longer *N*-electrophile bond.

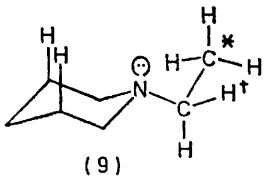
Work.—We conclude that, despite the apparent complexity of the proportions of products formed by equatorial and axial approach, these variations can be explained rationally in terms of the influence of *N*-substituents in the piperidine and *para*-substituents in the benzyl chloride on the individual rate constants.

TABLE 4

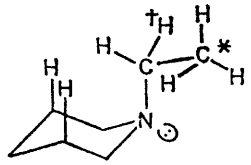
Δ log *k* values for k_e and k_a, effects of solvents, *N*-substituent and *p*-substituent

			Equatorial approach			Axial approach		
	Alkyl group	Solvent	*p*-OMe	H	*p*-NO_2	*p*-OMe	H	*p*-NO_2
$\log\{k(MeCN)/k(Me_2CO)\}$	Me		1·29	1·38	1·34	1·24	1·40	1·38
	Et		1·46	1·40	1·09	1·22	1·35	0·93
	Pr^i		1·17	(1·19)		0·92	(1·12)	
$\log\{k(NMe)/k(NR)\}$	Et	MeCN	0·45	0·71	0·90	0·96	1·12	1·49
		Me_2CO	0·62	0·73	0·65	0·94	1·07	1·04
	Pr^i	MeCN	1·56	1·81		2·49	2·65	
		Me_2CO	1·44	(1·62)		2·17	(2·37)	
$\log\{k(p\text{-subst. benzyl})/k(benzyl)\}$	Me	MeCN	+0·40		−0·08	+0·66		−0·16
		Me_2CO	+0·49		−0·04	+0·82		−0·14
	Et	MeCN	+0·66		−0·27	+0·82		−0·53
		Me_2CO	+0·60		+0·04	+0·95		−0·11
	Pr^i	MeCN	+0·65			+0·82		

(*d*) Comparing the rates of quaternisation k_e for the Pr^i derivative (11) with k_a for the Me analogue (12)

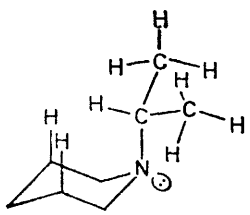


(9)

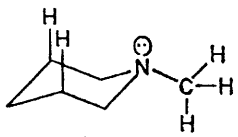


(10)

affords some estimate of the effect of distortion of the CNC angle in (11) as the steric hindrance is otherwise



(11)



(12)

similar. For the three comparisons possible the increments are 1·03, 1·04, and 0·97 log *k* units; the close correspondence in these values is reassuring.

General Conclusions and Comparison with Earlier

It is now possible to examine critically the previous conclusions regarding the orientation of attack in benzylations at piperidine nitrogen atoms. Our previous conclusions [4b] that benzyl chlorides react with 1-methyl-4-phenylpiperidine in acetone predominantly by equatorial approach is confirmed, as are Bottini's results [12] that 4-t-butyl-1-methylpiperidine in acetonitrile is attacked mainly equatorially by *p*-nitrobenzyl chloride, but mainly axially by *p*-methoxybenzyl chloride. Our work supports the conclusion [12] of predominant equatorial attack of benzyl chloride on 4-formyl-1-methyl-4-phenylpiperidine.

As the reactivities as benzylating agents are in the order $PhCH_2Cl < PhCH_2I < PhCH_2OTs$, House's finding [7] that 1-methyl-4-t-butylpiperidine and benzyl tosylate gave mainly axial attack, and McKenna's result [8] of zero selectivity for the reaction of 1-methyl-4-phenylpiperidine with benzyl iodide fit reasonably into the pattern disclosed in this paper.

McKenna's attempted generalisation [9] of *preferred axial quaternisation by primary alkylating agents in all systems* appears to have been based, as regards benzylations, solely on reaction with benzyl iodide: it must now be recognised that the actual situation is far more finely balanced and that a large number of benzylations proceed by predominantly equatorial attack.

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