

STUDIES OF THE ELIMINATION OF 4-ARYL-3-METHYL-4-PIPERIDINOLS—IV¹

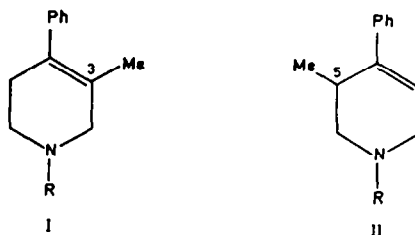
THE STEREOCHEMISTRY OF THE QUATERNIZATION OF SOME 4-ARYL-3 (and 5)-METHYL-1,2,5,6-TETRAHYDROPYRIDINES

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Abstract—The isolation of some isomeric 1-alkyl (and aralkyl)-1,5-dimethyl-4-phenyl-1,2,5,6-tetrahydropyridinium salts is described and their PMR spectra reported. The configurations of isomeric pairs (*cis* or *trans* 1,5-dimethyl) have been assigned by comparing their 1-methyl chemical shifts with those of related 1,3-dimethyl derivatives, and the probable conformations of the salts are discussed. The isomeric ratios obtained are shown to be in accord with a mechanism in which axial approach of the alkylating agent is favoured provided the group already attached to nitrogen is not markedly smaller than the incoming group.

IN PART I of this series the preparation of some 3- and 5-methyl-4-phenyl-1,2,5,6-tetrahydropyridines (I and II) was described.² In this paper the quaternization of these alkenes and the stereochemistry of the products are reported. The reactions were carried out by treating the tetrahydropyridine base with excess of an alkyl (or aralkyl) halide in ether or ether-acetone at either room or the reflux temperature. In the case of 5-methyltetrahydropyridine derivatives, where isomers may result, mixtures of the



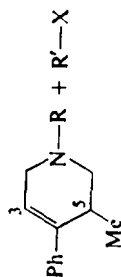
quaternary salts (IV and V, $R \neq \text{Me}$) were obtained both by treating a 1-alkyl (or aralkyl) tetrahydropyridine (II, $R \neq \text{Me}$) with methyl iodide and by treating the 1-methyltetrahydropyridine (II, $R = \text{Me}$) with the corresponding halide (reverse quaternization). A sample of each mixture was reserved for PMR spectroscopy, the bulk being fractionally crystallized to give pure samples of one or both isomeric products. The PMR spectral characteristics of the 5-methyl (IV and V) (mixtures and pure products) and 3-methyltetrahydropyridinium salts (III), recorded in deuteriochloroform, are given in Tables 1 and 2 respectively.

Treatment of a 5-methylalkene (II, $R \neq \text{H}$ or Me) with methyl iodide may give a mixture of two diastereoisomers, one having a *cis*(1,5-diMe) and the other a *trans* configuration [Fig. 2, IV (*cis*) and V (*trans*)]. The methiodide of the 1,5-dimethylalkene (II, $R = \text{Me}$) does not exhibit *cis-trans* isomerism, and the more favoured half-chair

¹ Part III. A. H. Beckett, A. F. Casy and M. A. Iorio, *Tetrahedron*, **22**, 2745 (1966).

² A. F. Casy, A. H. Beckett, M. A. Iorio and H. Z. Youssef, *Tetrahedron*, **21**, 3387 (1965).

TABLE 1. PMR CHARACTERISTICS IN CDCl_3 OF PRODUCTS DERIVED FROM REACTION OF A 4-PHENYL-5-METHYL-TETRAHYDOPYRIDINE (II) AND AN ALKYL HALIDE^a



No.	Reactants		Isomer	m.p.	N-Me ^b	C-3-H' (vinylic)	C-5-Me ^c	Miscellaneous
	-R	R'-X						
1	-Me	MeI	—	212-213°	6.22 6.45	not clear ^a	near 8.95°	—
2	-Me ^d	MeI	—	196°	6.27 6.38* 6.49	4.22	8.98 (J6)	8.33* (3-Me)
3	-Et	MeI	Total product	—	6.5 minor 6.67 major 6.64	4.22	8.96 (J6)	8.48* (J7) (N-CH ₂ Me) 8.47* (J7)
4			A	167-168°	6.5	4.23	8.97 (J6)	(N-CH ₂ Me) 8.52' (N-CH ₂ Me)
5			A and B	124-129°	6.5 6.67	4.22	8.97 (J6)	
6	-Me ^d	EtI	Total product	—	(equal parts) 6.47 major 6.57*	4.22	8.95 (J6)	8.5' (N-CH ₂ Me)
7			B	148°	6.62 minor 6.43	4.2	8.93 (J6)	8.33* (3-Me) 8.5* (J7)
8	-Me ^d	CH ₃ :CH:CH ₂ Br	Total product	—	6.38 slight excess	within allyl signal	8.93 (J7)	4.07' (allyl and vinyl) 8.32* (3-Me)
9			B	232°	6.48* 6.55	within allyl signal	8.93 (J7)	4.13' (allyl and vinyl)
10			A and B	175°	6.42 minor 6.52* trace 6.6 major	within allyl signal	8.97' (J6)	4.13' (allyl and vinyl) 8.32* (3-Me)
11	-CH ₂ :CH:CH ₂	MeI	A (trace of B)	140-142°	6.43 trace 6.6	within allyl signal	8.95 (J6)	4.1' (allyl and vinyl)

12	—CH ₃ Ph	MeI	Total product	—	6.53 minor	not clear ^a	near 9.0 ^c	—
13			A and B	220–222°	6.6 major	4.3	8.92 (J6)	4.6 ^b (N—CH ₃ Ph)
14			A	218–219°	6.54 minor	not clear ^a	9.02 (J6)	4.55 ^b (N—CH ₃ Ph)
15			A (chloride) ^d	218°	6.6 major	4.3	9.03 (J6.5)	4.6 ^b (N—CH ₃ Ph)
16	—Me	PhCH ₂ Cl	Total product	—	6.62	4.2	9.05 (J6)	6.9 ^{b,†} (H ₂ O)
17			B	218–219°	6.5 slight excess	4.17	9.03 (J6)	4.5 ^b (N—CH ₃ Ph)
18			A	218°	6.6	4.3	8.93 (J6)	N—CH ₃ Ph not clear
19	—Me	Me ₂ CHI	Total product	—	6.61	4.2	9.05 (J6)	4.6 ^b (N—CH ₃ Ph)
20			B [†]	236°	6.68 slight excess	not clear ^a	8.88 (J7)	6.8 ^{b,‡} (H ₂ O)
21	—CHMe ₂	MeI	Total product	—	6.77	4.2	8.94 (J6.5)	8.4 ^b (J7)
22			A	220° (softens 196°)	6.6	4.2	8.85 (J6)	(N—CHMe ₂)
					6.7 trace	4.2	8.88 trace	8.4 ^b (J7)
					6.78	4.2	8.95 (J7)	(N—CHMe ₂)
					6.77	4.2	8.93 (J6)	8.4 ^b (J7)
								(N—CHMe ₂)

^a Chemical shifts in τ units, coupling constants in c/s.

^b Singlet.

^c Sparingly soluble compound.

^d Contains 3-methyl isomer.

^e Signal of 3-methyl isomer.

^f Multiplet (centre).

^g Doublet.

^h Triplet.

ⁱ Mid-point of overlapping doublets.

^j Iodide replaced by chloride by means of ion-exchange resin.

^k Absent when D₂O added.

^l In CDCl₃-CHCl₃.

conformation of this compound is (IVa \equiv Va, R = Me), the conformer (IVb \equiv Vb, R = Me) being destabilized because of its diaxial 1,3-Me/Me interaction. Hence the two observed chemical shifts of 1-methyl in the methiodide (IV \equiv V, R = Me) may be taken to represent axial and equatorial environments for this group (for allocation, see later).

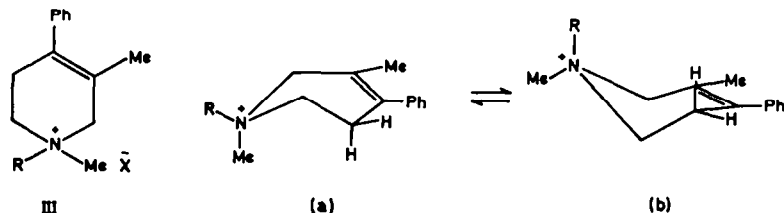


FIG. 1. (Only one enantiomorph shown.)

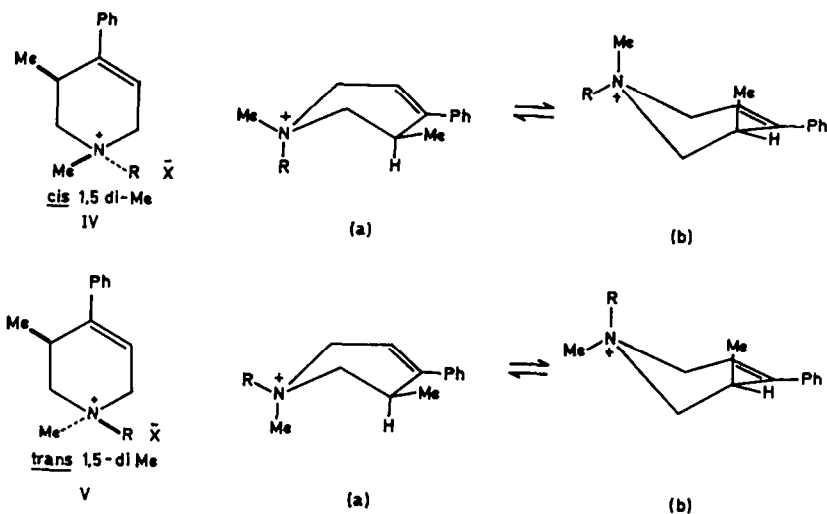


FIG. 2. (Only one enantiomorph shown.)

In the methiodide of the 1,3-dimethylalkene (I, R = Me), the equivalent conformations (IIIa and b, R = Me) will be equi-populated and will undergo rapid interconversion. Hence the 1-methyl chemical shift of this compound should be the mean of the values for axial (as in IIIa) and equatorial 1-methyl (as in IIIb) conformations, these extremes being derived from the PMR spectrum of the 5-methyl isomer (IV, R = Me) as explained above.* In fact the chemical shift of 1-methyl in the quaternary salt (III, R = Me) was τ 6.38, a value exactly half way between those of the two 1-methyl signals (τ 6.27 and 6.49) of the methiodide of the 1,5-dimethylalkene (II, R = Me), in accord with the above arguments (Table 1, No. 2). The higher field signal of the 1,5-dimethyl derivative is assigned to axial methyl on the basis of results obtained for the isomeric methiodides (IV and V, R \neq Me), discussed below.

In the methiodides of the 1-ethyl-5-methylalkene (II, R = Et), the conformations (IVa) and (Va), *cis* and *trans* (1,5-diMe) respectively, are much more favoured than

* It is assumed that the 3-ME contribution to the environments of the N-substituents in (III) is approximately equivalent to that of equatorial-5-Me to the same groups in (IV and V).

the alternative half-chair conformers (IVb) and (Vb), the chemical shift of 1-methyl in the *cis* isomer thus representing an essentially equatorial, and that of 1-methyl in the *trans* isomer, an essentially axial environment. Comparison of these values with those of 1-methyl in the methiodide (III, R = Et) allows conformational assignments to be made, as explained below.*

The two conformations (IIIa and b, R = Et) of the methiodide of the 3-methylalkene (I, R = Et) will not be equi-populated, the 1,3 Et/H interaction of (IIIb) being greater than the 1,3 Me/H interaction of (IIIa). Hence the axial 1-methyl conformer (IIIa, R = Et) will predominate and the 1-methyl signal will tend towards that of axial-methyl in the *trans* 5-methyl isomer (V, R = Et) rather than that of equatorial 1-methyl in the *cis* isomer (IV, R = Et). As the size of the group R in the 3-methyl methiodide (III) increases, the 1-methyl signal should progressively approach that of axial methyl in the corresponding *trans* methiodide of the 5-methyl isomer (II) as a result of the rising population of the axial 1-methyl conformer (IIIa). In extreme cases, when R is a very bulky group, the 1-methyl signal of the methiodides (III) and (V) (axial 1-methyl) should be identical or nearly so. Hence the 1-methyl signal of the 5-methyl isomers (IV and V, R ≠ Me) which is closer to the 1-methyl signal of the corresponding 3-methyl isomer (III, R ≠ Me) may be assigned as arising from an *axial*, and the further removed signal as from an *equatorial* conformation. Such assignments, coupled with the probable identical conformation of 5-methyl (equatorial)† in all the compounds, allow configurational assignments to be made to the *cis* and *trans* isomers (IV and V, R ≠ Me). Individual results will now be described.

The 1-ethylalkene (II, R = Et) with methyl iodide gave a binary mixture of quaternary salts, the PMR spectrum of the total reaction product displaying two N-methyl signals; the isomeric ratio, assessed from integral data, was 9 (higher field) to 1 (lower field signal). Fractional crystallization of the mixture gave a pure sample of the isomer with the higher field N-methyl signal (isomer A)‡, further fractions being mixtures of the two forms in varying proportions (e.g. Table 1, No. 5). The 1-methylalkene (II, R = Me) with ethyl iodide gave a similar mixture of quaternary salts, but in this case the ratio was 3 (higher field) to 7 (lower field);§ isomer B was crystallized from this mixture (Table 1, No. 7).

The chemical shift of the N-methyl signal of the 3-methyl analogue (III, R = Et) was closer to the higher field N-methyl signal of the 5-methylquaternary salts (IV and V, R = Et) (Table 1 No. 6); thus, for the reasons already discussed, isomer A has

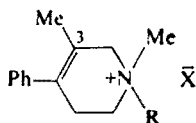
* Evidence of configuration could not be obtained from the N-methyl signals of the hydrochlorides (I and II) because only single peaks were found (cf. McKenna *et al.*).³

† Axial 5-methyl conformations entail unfavourable 1,3-dialkyl interactions in both isomers. PMR evidence for the 5-methyl conformation is presented later.

‡ Throughout this paper "isomer A" denotes the isomeric methohalide with the higher field (greater τ value) N-methyl signal while "isomer B" denotes that with the lower field signal.

§ Because it was difficult to obtain a sample of the 5-methylalkene (II, R = Me) free from the 3-methyl isomer (I, R = Me), the quaternary mixture contained a substantial amount of the 3-methyl quaternary salt (III, R = Et). The spectrum of this mixture (Table 1, No. 6), however, allowed a ready comparison to be made of the relative positions of the three N-methyl signals.

³ J. McKenna, J. M. McKenna, A. Tulley and J. White, *J. Chem. Soc.* 1711 (1965); J. K. Becconsall, R. A. Y. Jones and J. McKenna, *Ibid.* 1726 (1965); J. McKenna, J. M. McKenna and J. White, *Ibid.* 1733 (1965).

TABLE 2. PMR CHARACTERISTICS OF METHOHALIDES OF SOME 4-PHENYL-3-METHYLTETRAHYDROPYRIDINES (I)^a

R	X	N-Me ^a	C-3-Me ^b	Miscellaneous
Me	I	6.37	8.32	—
Et	I	6.57	8.32	8.49 ^c (J6.5) (N-CH ₂ Me)
CH ₂ :CH-CH ₃	I	6.55	8.32	4.08 ^c (allyl)
CH ₂ Ph	Cl	6.6	8.35	4.72 ^c (N-CH ₂ Ph)
Me ₂ CH	I	6.75	8.28	8.45 ^c (J7) (N-CHMe ₂)

Note—Footnotes identical with those of Table 1.

an axial, and isomer B an equatorial N-methyl group in the respective preferred conformations (IVa and Va).

The chemical shifts of the 5-methyl groups in isomers A and B were almost identical indicating the 5-methyl environments to be similar in the two isomers. The values are closer to those of equatorial ($\tau \approx 9.1$) than to axial 5-methyl groups ($\tau \approx 8.7$) in 4-aryl-5-methyl-1,2,5,6-tetrahydropyridine hydrochlorides³ and support the conclusions regarding the preferred equatorial conformation of the 5-methyl group in the quaternary salts (IV and V) already drawn. The slightly lower field value of 5-methyl in isomer B is in accord with the population IVa being probably slightly less than that of Va, in relation to the respective axial 5-methyl conformers, when R is larger than methyl. It follows that isomer A (*a*-1-Me/*e*-5-Me) has the *trans* (1,5 diMe) configuration and isomer B (*e*-1-Me/*e*-5-Me), the *cis*. Similar results were obtained in the allyl series (III–V, R = CH₂:CH:CH₃; Table 1, Nos. 8–11).

The 1-benzylalkene (II, R = CH₂Ph) with methyl iodide gave a binary mixture of quaternary salts in which isomer A predominated. The 5-methyl signal of the mixture was composed of a triplet (two overlapping doublets), in contrast with results already described. The 1,5-dimethylalkene (II, R = Me) gave a binary mixture of quaternary chlorides with benzyl chloride; isomer A was still the major form but the extent of its predominance over isomer B was less than that found with the previous mixture. Fractional crystallization gave pure chlorides of both isomers. Isomer A chloride crystallized with one molecule of water, the resonance signal of the water protons appearing as a sharp singlet, at 10 cycles higher field than the 1-methyl signal (it disappeared in the presence of D₂O). The steric correspondence of isomer A *iodide* and isomer A *chloride* was established by converting the former into the latter by means of an ion-exchange resin; the close similarity of their PMR spectra shows that the two anions do not differ significantly in their influence upon proton resonances in this particular case.

The 1-methyl signal of the methochloride of the 3-methylalkene (I, R = CH₂Ph) occurred at a chemical shift almost identical with that of 1-methyl in isomer A, and on this account the latter is assigned on axial N-methyl substituent and is concluded to

have a *trans* (1,5-diMe) configuration. The *cis* configuration of isomer B follows from its lower field 1-methyl signal but in this case it is not considered that the chemical shift represents an essentially equatorial environment (cf. discussion of the conformation of B isomers in the Et/Me and allyl/Me series), because in this example there is probably an increased population of IVb over that of IVa ($R = CH_2Ph$). The greater significance of conformation IVb in the benzyl/methyl *cis*-isomer as compared with the two previous *cis*-isomer examples is supported by the following evidence:

(1) the 5-methyl signals of the two isomers (IV and V, $R = CH_2Ph$) differ by 8 cycles [in the Et/Me isomers (IV and V, $R = Et$) they are 2.5 cycles apart and in the allyl/Me case (IV and V, $R = CH_2 \cdot CH : CH_2$) they are almost identical]; isomer B (IV, $R = CH_2Ph$) has the lower field value, consistent with a markedly higher population of the axial (more deshielded) 5-methyl conformation (IVb);

(2) the 1-methyl signals of the two isomers (IV and V, $R = CH_2Ph$) differ by 6 cycles, in contrast with those of the Et/Me (IV and V, $R = Et$) and allyl/Me (IV and V, $R = CH_2 \cdot CH : CH_2$) pairs which both differ by 10 cycles; a rise in the population of IVb at the expense of IVa will reduce environmental differences between 1-methyl in the two isomers;

(3) the absorption maximum of isomer B (IV, $R = CH_2Ph$) chloride (λ_{max} 237.5 $m\mu$) occurs at a slightly higher wavelength than that of isomer A (λ_{max} 235.5 $m\mu$), a result consistent with the population of the axial 5-methyl conformation being greater in isomer B (the planarity of the styrenoid chromophore of the tetrahydropyridine is disturbed less by an axial than by an equatorial group⁴).

The increased bulk of the benzyl group over that of allyl and ethyl, responsible for conformational differences between the benzyl/methyl and ethyl (or allyl)/methyl *cis*-isomers, must also account for the near-coincidence of 1-methyl chemical shifts in the *trans*-benzyl/methyl iodide (V, $R = CH_2Ph$) and the 3-methyl isomer (III, $R = CH_2Ph$); in both salts the populations of the conformers (III and Vb, $R =$ axial CH_2Ph) must be very small.

A skew half-boat conformation must also be considered, in addition to conformer (IVb), as an alternative to IVa in *cis*-1-benzyl isomers [the high 1,3 diaxial Me/Me interaction obtaining in (IVb) will certainly be reduced in the former conformation]. The evidence cited in support of IVb is also appropriate to the corresponding skew half-boat since the 5-methyl group in the latter is similarly closer to charged nitrogen and further removed from the styrenoid chromophore than it is in conformer (IVa, $R = CH_2Ph$); in addition, the 1-methyl environment in the skew half-boat is intermediate between that of an axial and equatorial group.

Results with the isopropyl series (III–V, $R = CHMe_2$; Table 1, Nos. 19–22) are similar to those obtained with the benzyl/methyl salts, the isopropyl and benzyl groups being of comparable steric dimensions.

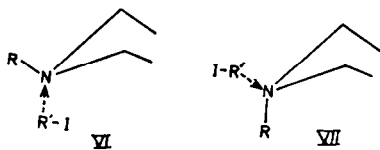
The steric course of quaternization

It is reasonable to assume that the isomer ratios observed in the described methyl/ethyl and methyl/isopropyl series arise, essentially, as a result of differences in the rates of isomer formation, the extent of equilibration probably being insignificant under the mild reaction conditions employed (ether or ether–acetone at room or reflux temperature). The nucleophilic displacements concerned in the equilibration of the ethiodide

⁴ E. W. Garbisch, Jr., *J. Org. Chem.* **27**, 4249 (1962).

of a related N-methylpiperidine derivative (camphidine) have been shown to be very slow under a variety of reaction conditions commonly employed in quaternizations.³ However, the interconversion of several N-benzyl-N-methyl diastereoisomers has been shown to proceed in hot chloroform,³ hence it is probable that some equilibration may take place in the presently studied methyl/benzyl and methyl/allyl series.

An important factor determining the steric course of the reaction between an alkyl halide ($R'X$) and a tertiary base ($>N-R$) is the relative steric requirements of the group being attached (R'), and the group already attached (R) to nitrogen. McKenna *et al.*³ have studied the quaternization of a variety of cyclic bases and, in cases where marked stereoselectivity was observed, have concluded that the incoming group has the lower steric demand (results with tropane were exceptional), with the result that axial



(as in VI), rather than equatorial (as in VII), approach is the preferred reaction pathway. They also found that the degree of selectivity fell as the quaternizing agent became larger, this result being considered as due to an increased tendency for equatorial attack.

The same conclusions may be drawn from the presently reported results (allowance being made, where necessary, for the possible equilibration of isomers), an axial approach for the alkylating agent being favoured provided the group already attached to nitrogen is not markedly smaller than the incoming group. In all cases studied, the reactions of methyl iodide with the 5-methyltetrahydropyridines (II, $R \neq Me$) were highly stereoselective, isomer A (axial methyl) being the predominant product (Table 3). All these salts have the larger N-substituent in the preferred equatorial orientation.

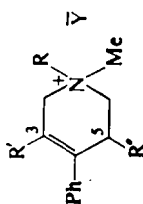
TABLE 3. APPROXIMATE ISOMER RATIOS OBTAINED FROM REACTION BETWEEN THE 4-PHENYL-5-METHYLTETRAHYDROPYRIDINES (II) AND ALKYL HALIDES

R	$>N-R + Me-I$		$>N-Me + R-X$	
	Major isomer	Ratio A:B ^a	Major isomer	Ratio A:B ^a
Et	A	9:1	B	3:7
$CH_2:CH-CH_3$	A	7:1	B	4:5
$PhCH_2$	A	trace of B	A	7:3
Me_2CH	A	7:1.5	A	5:3

^a Estimated from integral of 1-methyl signals.

Reaction between alkyl halides and the 1,5-dimethyltetrahydropyridine (II, $R = Me$) were less stereoselective. Isomer B (equatorial methyl) was the chief product of the reaction involving ethyl iodide but its preponderance was less than that of isomer A over B in the reverse quaternization ($>N-Et + MeI$); this result is in accord with axial approach being less favoured for an ethyl than for a methyl group. In the reaction between the 1,5-dimethylalkene and allyl iodide, a slight excess of isomer B was produced, the increased proportion of isomer A (relative to that produced in the previous case) possibly being due to its partial formation from the less stable isomer B through

TABLE 4. 3 (AND 5)-METHYL-4-PHENYL-1,2,5,6-TETRAHYDROPIRIDINE METHOHALIDES



Isomer	R	R'(C-3)	R'(C-5)	X	M.p.	Mol. formula	Found				Required			
							C	H	N	N	C	H	N	N
—	Me	H	Me	I	192°	C ₁₁ H ₁₀ N	51.1	6.45	4.1	51.1	6.1	4.25	4.25	
—	Me	Me	H	I	184°	C ₁₁ H ₁₀ N	51.0	6.4	4.05	51.1	6.1	4.25	4.25	
A	Et	H	Me	I	167-168°	C ₁₁ H ₁₁ N	52.3	6.6	4.0	52.5	6.5	4.1	4.1	
B	Et	H	Me	I	147-149°	C ₁₁ H ₁₁ N·0.5H ₂ O	51.6	6.7	3.9	51.2	6.9	4.0	4.0	
—	Et	Me	H	I	135-136°	C ₁₁ H ₁₁ N	51.9	6.6	4.1	52.5	6.5	4.1	4.1	
B	CH ₃ :CH:CH ₃	H	Me	Br	232°	C ₁₁ H ₁₁ BrN	62.5	7.15	4.4	62.3	7.2	4.5	4.5	
A	PhCH ₃	H	Me	I	218-219°	C ₁₉ H ₁₄ N	58.8	5.8	3.6	59.3	6.0	3.45	3.45	
B	PhCH ₃	H	Me	Cl	218-219°	C ₁₉ H ₁₄ ClN	76.1	7.6	4.8	76.5	7.7	4.45	4.45	
A	PhCH ₃	H	Me	Cl	218°	C ₁₉ H ₁₄ ClN·H ₂ O	73.3	8.1	4.2	72.3	7.8	4.2	4.2	
—	PhCH ₃	Me	H	I	176-178°	C ₁₉ H ₁₄ N	58.95	6.3	3.5	59.3	6.0	3.45	3.45	
B	Me ₂ CH	H	Me	I	236°	C ₁₁ H ₁₁ N	53.5	6.8	4.3	53.8	6.8	3.9	3.9	
A	Me ₂ CH	H	Me	I	(196°)* 220°	C ₁₁ H ₁₁ N	53.1	6.9	3.8	53.8	6.8	3.9	3.9	
—	Me ₂ CH	Me	H	I	215-216°	C ₁₁ H ₁₁ N	53.6	7.2	4.0	53.8	6.8	3.9	3.9	

* Softens.

equilibration.* In reactions employing the benzyl and isopropyl halides, the large bulk of the incoming groups must be largely responsible for the high proportions of isomers A (the more stable forms†) obtained (approximately 60% for isopropyl and 70% for benzyl) although equilibration may be a contributory factor in the case of the benzyl salts.

EXPERIMENTAL

General procedure for quaternization of the 4-phenyltetrahydropyridines (I and II). A mixture of the tetrahydropyridine base and an alkylhalide (several moles excess) in ether or ether-acetone was left for 1 or 2 days (in some cases the mixture was heated under reflux for 30 min) and the solids which separated recrystallized from acetone, EtOH or mixtures of these solvents with ether. Samples of reaction mixtures, evaporated before crystallization occurred, form the "total products" of Table 1. Analytical and m.p. data are given in Table 4. Amberlite resin I.R.A. 400 (2 g) (treated with 8% NaOH in water for 2 hr, then washed with CO₂-free water till washings showed pH 6 and finally with EtOH) was added to the methiodide of the 5-methyltetrahydropyridine (II, R = CH₃Ph) (0.3 g) in ethanol-CHCl₃ (25 ml, equal parts). The mixture was filtered after 24 hr, the filtrate acidified with ethereal HCl and evaporated. The residue was dissolved in a small volume of EtOH and diluted with ether when the methochloride of the tetrahydropyridine (II, R = CH₃Ph) separated, m.p. 218°, depressed to 175-200° by the corresponding methiodide and undepressed by the methochloride of isomer A (V, R = CH₃Ph) [obtained from the 1,5-dimethyltetrahydropyridine (II, R = Me) and benzyl chloride]. The IR and PMR spectra of the two chlorides were identical. Small quantities of the 1-alkyl and 1-isopropyl-5-methyltetrahydropyridines (II) were obtained by heating a mixture of the secondary base (II, R = H) (0.003 mole), the alkyl halide (0.005 mole) and KOH (0.01 mole) in acetone-water, under reflux for 4 hr. The crude bases, obtained by evaporating the solvents and extracting the residue with ether, were treated with MeI as described above. The PMR spectrum of the isopropyl derivative (II, R = CHMe₂) in CDCl₃-CF₃CO₂H showed a 6-proton signal at τ 8.62 (doublet, J7, Me₂CH) and a 3-proton signal at τ 8.85 and 9.1 (J7, two doublets of 5-methyl epimers).

The PMR spectra were obtained on a 60 Mc Varian A-60 and a Perkin-Elmer R-10 instrument in CDCl₃ with Me₄Si as internal standard.

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* The steric requirements of the N-Et and N-allyl transition states are probably similar in the vicinity of the reaction centre (evidence of models).

† When a mixture of benzyl/methyl salts (IV and V, R = CH₃Ph) was heated under reflux for 4 days, the preponderance of isomer A increased, this result being direct evidence for the greater stability of isomer A.