320. *Stereoisomeric Pairs of Cyclic Quaternary Ammonium Salts. Part I.*[1] *Stereospecificity in Quaternisations of* N-*Alkylcamphidines, 2-Methylpyrrolidines, 2-Methyl- and 4-Phenylpiperidines,* trans-*Decahydroquinolines, and Tropanes, and Configurations of the Diastereoisomeric Salts*

By JAMES MCKENNA, JEAN M. MCKENNA, A. TULLEY, and J. WHITE

Quaternisation of *N*-alkyl derivatives of the bases named in the title is usually stereoselective, an axial approach of quaternising agent being apparently preferred for all the six-ring heterocycles except tropane, and an analogous approach *cis* to the 2-methyl group with tertiary 2-methylpyrrolidines. With tropanes, as in the tropines, the preferred approach is equatorial.

Introduction.—The aims of the work initiated by that reported in this group of four Papers are (*a*) an investigation of the degree of stereoselectivity exhibited in quaternisations of reduced cyclic *N*-alkyl tertiary bases with an alkylating agent containing an alkyl group different from that already attached to nitrogen, (*b*) the determination of configuration of the resultant quaternary salts, and (*c*) a study of their differential reactivity in elimination, substitution, and other reactions. An investigation, particularly of the first aspect (and a statement regarding the second), with a series of representative mono- and bi-cyclic bases is reported in the present Paper, while Parts II and III deal respectively with one important method (nuclear magnetic resonance spectroscopy) employed for determination of configuration of the diastereoisomeric quaternary salts and with aspects of differential reactivity for some of the stereoisomers. A general theoretical discussion is given in Part IV. Methods other than the n.m.r. procedure for determining configuration of the isomeric salts are described in this Paper (empirical infrared spectroscopy) and in Part IV (equilibration of methyl–benzyl isomeric pairs; consideration of type of stereoselectivity exhibited).

Previous Work.—Isolated examples of stereoselectivity in the quaternisation of cyclic *N*-alkyl-bases have been from time to time reported by several authors who have examined the process for, *e.g.*, 4-phenylpiperidines [2] and norcodeines.[3] The most extensive work,

[1] This and the following three Papers are regarded as Parts VII—X in the series "Stereochemical Investigations of Cyclic Bases"; Part VI, Jewers and McKenna, *J.*, 1960, 1575.

[2] Mills, Parkin, and Ward, *J.*, 1927, 2613.

[3] Koczka and Bernáth, *Chem. and Ind.*, 1958, 1401.

however, has been carried out in the tropine system chiefly by Fodor and his collaborators,[4] with some contributions from other authors.[5] Fodor found that when *N*-alkylnortropines (hydroxylated derivatives of the tropanes I; R = Me, Et, $CH_2 \cdot CO_2Et$, etc.) were quaternised with the halide R^1X, the reaction led to a product (II), isomeric with that obtained when the groups R, R^1 were introduced in the reverse sequence. Mixtures were obtained in analogous work with oscines, which carry an oxide bridge between the asterisked carbon atoms, but Fodor and his collaborators regarded the quaternisations of tropines as being stereospecific (*i.e.*, yielding in each reaction only one product) rather than merely stereoselective. The work of Closs [6] on the *N*-ethyl-*N*-methylpseudotropinium salts, and our own, reported below, on analogous salts derived from the parent base tropane makes this seem unlikely: quaternisations of all tropines are probably highly stereoselective, but minority proportions of diastereoisomeric quaternary salts in reaction mixtures are often revealed only by n.m.r. spectroscopy. In our own work with salts derived from 2-methylpyrrolidine we have found that samples of constant m. p. and i.r. spectrum from recrystallisation of quaternisation mixtures may be shown by n.m.r. analysis to contain two stereoisomers, each in substantial proportion. These points, and many similar in the literature—*e.g.*, the uncertainties in the characterisation of isomeric *N*-ethyl-*N*-methyltropinium iodides,[4a,5a,b] and probably also the recent work of Trojánek *et al.*[7] in the camphidine field (discussed further below)—emphasize the commonest experimental pitfall facing workers in this field. (A common *theoretical* error in interpretation of the steric course of quaternisations of cyclic *N*-alkyl-bases is discussed in Part IV). We may note finally here the interesting series of isomeric *N*-methylquinolizidinium salts prepared and studied by Katritzky, Schofield, and their collaborators; [8] in these compounds, however, unlike those examined by ourselves, formal interconversion between diastereoisomers is associated with a *cis–trans*-change in ring fusion.

Stereoselectivity of Quaternisations.—Little comment is required on the preparation of the tertiary amines (*N*-alkyl derivatives of the bases named in the title) described in the Experimental section; the oxidative *N*-demethylation of tropane, modelled on a similar process recorded for analogous bicyclic bases,[9] worked surprisingly well, and rendered unnecessary investigation of more specific processes. With all six systems, we examined reaction mixtures obtained by methylating the *N*-ethyl- and ethylating the *N*-methyl-bases; in addition, for four of the systems (camphidine, 2-methylpyrrolidine, 2-methylpiperidine, and *trans*-decahydroquinoline) we obtained a more complete picture of stereoselectivity by using a wider range of *N*-alkyl groups (see Table 1). Quaternisations were carried out in acetone at room temperatures taking from a few minutes to a few hours for effective completion, and some reactions were also performed in refluxing acetone. The camphidines were refluxed, usually for longer periods, with the alkyl iodide in the same solvent. Except in alkylations with the tropanes, where it was omitted for manipulative reasons, anhydrous potassium carbonate was used in the quaternisations to prevent possible competitive formation of base hydriodides.*

Where mixtures of camphidinium quaternary iodides were obtained from quaternisations the components were readily separated by fractional crystallisation, and shown to be

* Hydriodide production especially in a rather slow alkylation with (quite pure) ethyl or higher alkyl iodide may be remarkably extensive even under mild reaction conditions in the absence of inorganic base; where such production is not associated with prior degradation of an unstable quaternary salt (as, *e.g.*, with *N*-6β-cholestanyltrimethylammonium iodide) the reaction is not too readily interpreted, as it seems improbable that the organic base is attacking the iodide in an elimination process under the conditions being employed.

[4] Fodor, (*a*) *Experientia*, 1955, **11**, 129; (*b*) *Tetrahedron*, 1957, **1**, 86; (*c*) *Chem. and Ind.*, 1961, 1500.
[5] *Inter al.* (*a*) Findlay, *J. Amer. Chem. Soc.*, 1953, **75**, 3204; (*b*) Zeile and Schulz, *Chem. Ber.*, 1955, **88**, 1078.
[6] Closs, *J. Amer. Chem. Soc.*, 1959, **81**, 5456.
[7] Trojánek, Komrsová, Pospíšek, and Čekan, *Coll. Czech. Chem. Comm.*, 1961, **26**, 2921.
[8] Moynehan, Schofield, Jones, and Katritzky, *J.*, 1962, 2637.
[9] See Houben-Weyl, " Methoden der Organischen Chemie," 4th edn., Vol. 11/1, p. 976.

TABLE 1

Degree of stereoselectivity of quaternisations in acetone

(?, mixture in unknown proportions; +*, *slight* excess of the isomer which predominates in " reverse " quaternisation; 0, roughly equal proportions; +, *ca.* 2—5 : 1; ++, *ca.* 5—20 : 1; +++, only one isomer found)

Base system	>NMe + EtI	>NEt + MeI	>NMe + Pr^nI	>NPr^n + MeI	>NMe + $PhCH_2I$	>NCH_2Ph + MeI	>NEt + Pr^nI	>NPr^n + EtI
Camphidine [a]	+ (⟶ 0)	+++	+ (⟶ 0)	+++	++	+++	+	+++
2-Methylpyrrolidine [a]					+	++		
2-Methylpyrrolidine [b]	+ (⟶ 0)	++	0	+	+	++	?	?
2-Methylpiperidine [a]					0 (⟶ +*)	+		
2-Methylpiperidine [b]	0 (⟶ +*)	+	0 (⟶ +*)	+	+	++		
4-Phenylpiperidine [b]	++	++						
trans-Decahydroquinoline [a]	0 (⟶ +*)	+	0 (⟶ +*)	+	0 (⟶ +*)	+		
trans-Decahydroquinoline [b]	0 (⟶ +*)	+	?	?				
Tropane	++	++						

[a] Reflux temperatures: except with camphidines, hot solutions of base and quaternising agent initially mixed. [b] Room temperature.

homogeneous by i.r. and especially n.m.r. spectroscopy. Quaternary iodides derived from 2-methylpyrrolidines were partially separated by fractional crystallisation, but the apparently pure specimens were usually shown to be heterogeneous by n.m.r. spectroscopy; isomer proportions in the reaction mixtures were therefore derived from a combination of data. Nearly pure specimens of the isomeric 1-ethyl-1-methyl-4-phenylpiperidinium salts were obtained by fractional crystallisation, in agreement with the observations of Mills and his collaborators,[2] but with derivatives of other base systems total crude quaternisation mixtures were examined by n.m.r. spectroscopy to get an approximate indication of isomer proportions, and in most such cases a measure of supporting evidence was derived from fractional crystallisation (see Table 4). Attempted separation of one pair of " methyl-ethyl " diastereoisomeric iodides (derived from *trans*-decahydroquinoline) by paper chromatography in a butanol–water system failed, although it was possible to separate homologous salts by this method.

For presentation of an overall picture of degree of stereoselectivity in these quaternisations we believe that a symbolism like that adopted in Table 1 is preferable to quotation of percentages or fractional yields, since the quaternisations were carried out under preparative rather than closely controlled kinetic conditions, and analytical techniques have not been refined to give high accuracy; moreover, use of a limited number of symbols emphasizes qualitative similarities between degrees of stereoselectivity found in the quaternisations in the different systems. The data in Table 1 are much more developed than those presented in the corresponding Table in our preliminary communication;[10] the chief differences are that (*a*) we have modified our interpretation of the steric course of some of the quaternisations of 2-methylpiperidines, for reasons stated in the following Paper (Part II), (*b*) the symbol +++ is now used only where there is no available evidence of any kind that more than one isomer is produced, *i.e.*, reactions thus symbolised are stereospecific or virtually so under the reaction conditions employed, and (*c*) a wider range of quaternisations has now been studied.

It is noteworthy that although mixtures containing approximately equal proportions of isomers were obtained in a few reactions, in no case was the *strongly* predominant product of one quaternisation also that of the reaction sequence in which the alkyl groups were inserted in the reverse order.

Configurations of Diastereoisomeric Quaternary Ammonium Salts.—One important method, n.m.r. spectroscopy (see Part II), is applicable only when a spectroscopic relationship can be established between the *N*-methyl hydrochloride (to which a preferred configuration must be assigned) and the related quaternary salts. There is no difficulty in writing down the preferred configuration of any of the *N*-methyl hydrochlorides, since a methyl group is obviously more space-demanding than hydrogen, and relative compressions in the two bonding spaces around each nitrogen atom in the range of bases studied are readily assignable except perhaps in the case of tropane.* Where the relevant spectroscopic relationship cannot be established the n.m.r. method is inapplicable; this was the case with derivatives of 4-phenylpiperidine and *trans*-decahydroquinoline. The close similarity between n.m.r. curves of corresponding derivatives of *trans*-decahydroquinoline and 2-methylpiperidine, however (see Part II) is probably due to analogous configurations in analogous salts derived from each base system—in both cases a 2-alkylpiperidine.

A subsidiary criterion for configurational assignments with the quaternary salts is

* Perhaps the most important evidence for assignment of an *eq*-NMe structure to the hydrochloride of any basic tropine or tropane is the n.m.r. spectroscopic relationship established by Closs [6] between the hydrochloride of pseudotropine and the related *N*-ethyl-*N*-methyl quaternary salts, the configurations of which are known from analogy with Fodor's results and from *X*-ray analysis of *N*-ethylnortropine methobromide.[11] It is clear, therefore, that our configurational assignments for tropane quaternary salts depend ultimately on Fodor's classical work with the tropines, and on the more recent *X*-ray work, and indeed we made these salts mainly for the degradative investigation described in Part III.

[10] McKenna, White, and Tulley, *Tetrahedron Letters*, 1962, 1097.

[11] Quoted by Fodor, ref. 4*c*.

based on i.r. spectroscopy. Zeile and Schulz [5b] found characteristic differences between epimeric pairs in the tropine field in, *inter alia*, the 850—900 cm.$^{-1}$ region, and differences in the same region with camphidine quaternary salts were noted by Trojánek *et al.* A general

TABLE 2

Diagnostic bands in infrared spectra of quaternary iodides

Base system	Isomeric salts	Bands (cm.$^{-1}$)
Camphidine	>NMeEt	878, 898
	>NMePr^n	884, 899
	>NMeCH$_2$Ph	880, 897
2-Methylpyrrolidine	>NMeEt	847, 898
	>NMePr^n	846, 897
	>NMeCH$_2$Ph	865, 890
2-Methylpiperidine	>NMeEt	Not sufficiently well defined
	>NMePr^n	,, ,,
	>NMeCH$_2$Ph	,, ,,
4-Phenylpiperidine	>NMeEt	865, 897
trans-Decahydroquinoline	>NMeEt	Not sufficiently well defined
	>NMePr^n	,, ,,
	>NMeCH$_2$Ph	,, ,,
Tropane	>NMeEt	867, 889

rule, applicable to all our salts with configuration deduced by application of other methods (except those derived from 2-methylpiperidine: see below), is that in the approximate region 840—900 cm.$^{-1}$ there is a diagnostic band at high (>*ca.* 855 cm.$^{-1}$) or at lower frequency for NMe equatorial or axial respectively (or, in the case of 2-methylpyrrolidine derivatives, for NMe respectively *trans* or *cis* to CMe). Often two " diagnostic " bands (and sometimes others) are observed in one spectrum, but in such cases there is a characteristic increase in intensity of diagnostic band in the higher region (*ca.* 885—900 cm.$^{-1}$) and/or an analogous reduction in the lower region (*ca.* 840—885 cm.$^{-1}$) in the spectrum of the salt with *eq*-NMe as compared with that with *ax*-NMe. If the rule is extended to cover derivatives of 4-phenylpiperidine, configurations for quaternary salts in this system may be derived. The application of this rule is less clear-cut, however, with many of the derivatives of *trans*-decahydroquinoline, 2-methylpiperidine, and 2-methylpyrrolidine, perhaps because of the (known) degree of sample heterogeneity in these systems, and we feel unable to quote " diagnostic " bands for the first two of these systems.

Application of these two methods and/or the other two described in Part IV shows that in the camphidine, 2-methyl- and 4-phenyl-piperidine and *trans*-decahydroquinoline systems an *axial* approach of quaternising agent to tertiary base is preferred in reactions of marked stereoselectivity; a *cis* (to CMe) approach (analogous to axial in the above six-membered-ring heterocycles) is preferred in quaternisations of tertiary 2-methylpyrrolidines. In tropane, however, as in tropines, the preferred approach is *equatorial*.

Direct *X*-ray evidence on the configuration of some of the pure quaternary salts described would be of considerable value (see also Part IV) and it is hoped that this may be provided in due course. A preliminary examination [12] of the *N*-benzylcamphidine methiodide led to evaluation of the unit cell parameters, but unfortunately these do not allow an unambiguous configurational assignment.

Work of Trojánek et al.—In a Paper published after our work in the relevant area had been completed, Trojánek *et al.* describe the preparation of a similar range of diastereoisomeric salts related to camphidines, derived in their work from (+)-camphorimide. The quaternisations were carried out at temperatures different from those we used (50 and 100° are quoted in two examples) and in the absence of inert solvent. Only one isomer was obtained in each quaternisation, including several reactions where we isolated both isomers. We have not specifically checked the Czechoslovakian workers' experiments (insufficient details are in any case given in most examples to allow an exact check), but in our own

[12] Smith and White, *Acta Cryst.*, 1963, **16**, 930.

earlier work we have in several reactions shown that use of methyl or ethyl alcohol in place of acetone, using refluxing acetone rather than the same solvent at room temperature (see Table 1), or dispensing with a solvent altogether made little difference to isomer ratio,

TABLE 3

Tertiary bases and derivatives

Compound [a]	B. p.	M. p. (ref. m. p. in brackets); recryst. solvent	Analysis, Found (top line), Reqd. or Calc. (bottom line, opposite molecular formula) C	H	N	Cl	Mol. formula	Ref.
(1) Derivatives of camphidine:								
N-methyl base	91°/28 mm.		78·9	12·7	8·1			
			79·0	12·6	8·4		$C_{11}H_{21}N$	[b]
N-methyl picrate		236° (234) EtOH	51·5	6·2	14·2			
			51·5	6·1	14·1		$C_{17}H_{24}N_4O_7$	[c]
N-methyl hydrochloride		216 (227) Me_2CO			6·8			
					6·9		$C_{11}H_{22}NCl$	[b]
N-*methyl picrolonate* ...		216 EtOH	58·1	6·6	16·0			
			58·5	6·7	16·2		$C_{21}H_{29}N_5O_5$	
N-*ethyl base*	110/28 mm.		79·3	12·9	8·1			
			79·6	12·7	7·8		$C_{12}H_{23}N$	7
N-*ethyl picrate*		178 (155) [n] EtOH	52·5	6·3	13·6			
			52·7	6·3	13·7		$C_{18}H_{26}N_4O_7$	7
N-*ethyl hydrochloride* ...		Sublimes 210—260	66·0	10·9	6·5			
		(m. p. 274) AcMe	66·2	11·0	6·4		$C_{12}H_{24}NCl$	7
N-*propyl base*	180—182		80·2	12·9	7·1			
			80·0	12·8	7·2		$C_{13}H_{25}N$	7
N-*propyl picrate*		168 (168) EtOH	54·1	6·9	13·7			
			53·8	6·6	13·2		$C_{19}H_{28}N_4O_7$	7
N-*benzyl base*	165/30 mm.		84·1	10·3	6·1			
			83·9	10·3	5·8		$C_{17}H_{25}N$	7
N-*benzyl picrate*		154 (156—158)	58·2	6·1	11·8			
		EtOH	58·5	6·0	11·8		$C_{23}H_{28}N_4O_7$	7
N-*n-propylcamphorimide*		57 petrol	69·8	9·4	6·3			
			69·9	9·5	6·3		$C_{13}H_{21}NO_2$	
(2) Derivatives of 2-methylpyrrolidine:								
N-methyl picrate		232 (234) EtOH						[d]
N-*methyl hydrochloride*...		224 AcMe	52·5	10·3		26·1		
			53·1	10·4		26·2	$C_6H_{14}NCl$	
N-ethyl picrate		190 (194) EtOH						[e]
N-*n-propyl picrate*		123 EtOH	46·8	5·7	15·3			
			47·2	5·6	15·7		$C_{14}H_{20}N_4O_7$	
N-benzyl hydrochloride		168 (173) AcMe–Et_2O						[f]
(3) Derivatives of 2-methylpiperidine:								
N-methyl hydrochloride		250 (259) AcMe						[g]
N-ethyl picrate		185 (189) EtOH	47·1	5·9	15·6			
			47·2	5·6	15·7		$C_{14}H_{20}N_4O_7$	[h]
N-n-propyl picrate		112 (113) EtOH						[i]
N-benzoyl	140—142/ 0·5 mm.	40—42 (45)						[j]
N-*benzyl hydrochloride*...		186—188 AcMe	69·2	8·8	6·3			
			69·2	8·9	6·2		$C_{13}H_{20}NCl$	
(4) Derivatives of 4-phenylpiperidine:								
N-methyl base.....	124/10 mm.	16 (9)						2
N-methyl hydrochloride		184 (196—198)	67·9	8·7		16·5		
		EtOH–Et_2O	68·1	8·5		16·8	$C_{12}H_{18}NCl$	2
N-methyl picrate		234 (244) EtOH						2
N-ethyl base	138/0·9 mm.	18 (11)						2
N-ethyl hydrochloride...		192 (203—205)	69·4	9·2	5·9			
		AcMe–Et_2O	69·2	8·9	6·2		$C_{13}H_{20}NCl$	2
Derivatives of 1-ethyl-1,2,3,6-tetrahydro-4-phenyl-1-pyridine:								
hydrochloride		193 (192—194) EtOH–Et_2O						14
picrate		107 EtOH	54·8	5·1	13·1			
			54·8	4·8	13·4		$C_{19}H_{20}N_4O_7$	

TABLE 3 (*Continued*)

Compound [a]	B. p.	M. p. (ref. m. p. in brackets); Recryst. solvent	Analysis, Found (top line), Reqd. or Calc. (bottom line, opposite molecular formula) C	H	N	Cl	Mol. formula	Ref.
(5) Derivatives of *trans*-decahydroquinoline:								
N-methyl picrate		172 (171—173) EtOH	49·9 50·2	5·7 5·7	14·9 14·7		$C_{16}H_{22}N_4O_7$	[k]
N-*methyl hydrochloride*...		186 AcMe–Et_2O	63·1 63·3	10·8 10·5		18·6 18·7	$C_{10}H_{20}NCl$	
N-*ethyl picrate*		112—114 EtOH	51·4 51·5	6·2 6·1	14·1 14·2		$C_{17}H_{24}N_4O_7$	
N-*propyl picrate*		124 EtOH	52·8 52·7	6·6 6·3	13·6 13·7		$C_{18}H_{26}N_4O_7$	
N-*benzyl picrate*		184—186 EtOH	57·4 57·6	5·8 5·7	12·5 12·2		$C_{22}H_{26}N_4O_7$	
(6) Derivatives of tropane:								
tropane hydrochloride...		Sublimes 206 EtOH–Et_2O	59·6 59·5	10·2 9·9		22·3 22·0	$C_8H_{16}NCl$	
tropane picrate		308(*d*) (281) AcMe	47·5 47·4	5·2 5·1	16·0 15·8		$C_{14}H_{18}N_4O_7$	[m]
N-*acetylnortropane*	140—142/ 20 mm.				9·0 9·1		$C_9H_{15}NO$	
N-*ethylnortropane picrate*		236—238 EtOH	48·7 48·9	5·5 5·4	15·3 15·2		$C_{15}H_{20}N_4O_7$	

[a] " New " compounds italicised. [b] Rice and Grogan, *J. Org. Chem.*, 1957, **22**, 185. [c] von Auwers, *J. prakt. Chem.*, 1922, **105**, 108. [d] Löffler, *Ber.*, 1910, **43**, 2046. [e] Signaigo and Adkins, *J. Amer. Chem. Soc.*, 1936, **58**, 709. [f] Stravrovskaya, *J. Gen. Chem. U.S.S.R.*, 1955, **25**, 133. [g] Lipp, *Annalen*, 1896, **289**, 227. [h] Winans and Adkins, *J. Amer. Chem. Soc.*, 1932, **54**, 306. [i] Ladenburg, *Annalen*, 1899, **304**, 76. [j] Bunzel, *Ber.*, 1889, **22**, 1054. [k] Bailey, Haworth, and McKenna, *J.*, 1954, 967. [l] Ladenburg, *Ber.*, 1883, **16**, 1408. [m] Willstätter, *Annalen*, 1901, **317**, 328. [n] All m. p.s of camphidine derivatives quoted in ref. 7 are for active compounds rather than racemic.

and raising the reaction temperature would, if anything, be expected to reduce specificity. We therefore think that the Czechoslovakian workers have failed to identify a second isomer in reaction mixtures where it was the minor component, and this belief is supported by some differences in the 850—900 $cm.^{-1}$ region between their published i.r. curves and ours. The m. p.s of some of our quaternary salts are markedly higher than those recorded by Trojánek *et al.*, but the data are not strictly comparable, as we were working with racemates in all cases. A twisted boat form has been suggested by Trojánek *et al.* for the camphidine quaternary salts. We agree that both a regular chair and a regular boat conformation would be very unlikely because of high internal strains, but we think that since twisting of the camphidine boat is a rather energy-consuming process because of rigidity introduced by the $-CH_2{\cdot}CH_2-$ bridge, a deformed chair conformation (part-way deformed towards the regular boat form) is more likely for the salts;* this suggestion is also supported by the n.m.r. evidence (see Part II). It is clear that the expression " axial approach " (of quaternising agent) used earlier must therefore be interpreted fairly broadly, in its geometrical connotation, in application to the camphidine quaternisations.

EXPERIMENTAL

Preparation of Bases.—*N*-Alkylcamphidines were prepared by reduction of the corresponding camphorimides in ether (NMe; NEt) or tetrahydrofuran (NPr^n; $N{\cdot}CH_2{\cdot}Ph$) with lithium aluminium hydride. 1-Alkyl-2-methylpyrrolidines were obtained from 1,4-dibromopentane

* *Added in Proof:* Recent *X*-ray work (to be published shortly) by Dr. A. J. Smith and Mr. P. L. Jackson of this Department has confirmed this suggestion for the *N*-ethyl base methiodide, which is also shown to have the confirmation (*ax*-NMe) assigned on other grounds in this Paper.

TABLE 4

Quaternisation results

Reaction [a]; Time; Yield [j]	Salt fractions [b] Anion; solvents for fractn. or recryst. m. p. (ref. m. p. in brackets, with ref. superscript)	Structure or compn. of fraction	Analysis Reqd. or Calc. (line opposite mol. formula); Found (other lines) C	H	N	Formula	Name [c] (if " new " compound)
Derivatives of camphidine:							
>NMe + EtI; 36 hr.	I^- fract. *ex* AcMe; AcMe–Et_2O:						
	(1) 245° (238) [7]	Pure III(b)	48·3	8·0	4·1		
			48·3	8·1	4·3	$C_{13}H_{26}IN$	N-*ethyl*-N-*methylcamphidinium iodides*
	(2) 255 (249) [7]	Pure III(a)	48·6	8·1	4·2		
	Picrates [d] *ex* EtOH–Et_2O:						
	151 (159) [7]	Pure III(b)	53·9	6·9	12·9		
			53·8	6·6	13·2	$C_{19}H_{28}N_4O_7$	N-*ethyl*-N-*methylcamphidinium picrates*
	178—180 (177) [7]	Pure III(a)	53·9	6·9	12·9		
>NEt + MeI; 24 hr.	I^- fract. *ex* AcMe; AcMe–Et_2O:						
	(1) 245	Pure III(b)					
	Picrate *ex* EtOH–Et_2O:						
	150	Pure III(b)					
>NMe + Pr^nI; 48 hr.; 90%	I^- fract. *ex* AcMe; AcMe–Et_2O:						
	(1) 202 (184)	Pure III(b)	49·6	8·2	4·1		
			49·8	8·3	4·2	$C_{14}H_{28}IN$	N-*methyl*-N-*propylcamphidinium iodides*
	(2) 198 (193) [7]	Pure III(a)	49·8	8·2	3·9		
	Picrates *ex* EtOH:						
	132	Pure III(b)	54·8	7·1	12·6		
			54·8	6·8	12·8	$C_{20}H_{30}N_4O_7$	N-*methyl*-N-*propylcamphidinium picrates*
	130	Pure III(a)	54·6	7·2	12·7		
>NPr^n + MeI; 24 hr.	I^- fract. *ex* AcMe; AcMe–Et_2O:						
	(1) 202	Pure III(b)					
	Picrate *ex* EtOH:						
	132	Pure III(b)					
>NMe + Ph·CH_2I; minutes	I^- fract. *ex* $CHCl_3$–AcMe; EtOH–Et_2O:						
	(1) 210 (191) [7]	Pure III(a)	56·1	7·3	3·4		
			56·1	7·3	3·6	$C_{18}H_{28}IN$	N-*benzyl*-N-*methylcamphidinium iodides*
	(2) 200 (182) [7]	Pure III(b)	55·9	7·2	3·9		
	Picrate *ex* EtOH:						
	169 (138) [7]	Pure III(a)	59·1	6·1	11·3		N-*benzyl*-N-*methylcamphidinium picrate*
			59·3	6·2	11·5	$C_{24}H_{30}N_4O_7$	
>N·CH_2Ph + MeI; 24 hr.; 75%	I^- fract. *ex* AcMe; AcMe–Et_2O:						
	(1) 202	Pure III(b)					
	Picrate *ex* EtOH:						N-*benzyl*-N-*methylcamphidinium picrate*
	148 (134) [7]	Pure III(b)	59·1	6·2	11·1		

TABLE 4 (*Continued*)

Reaction[a]; Time; Yield[j]	Salt fractions[b] Anion; solvents for fractn. or recryst, m. p. (ref. m. p. in brackets, with ref. superscript)	Structure or compn. of fraction	Analysis Reqd. or Calc. (line opposite mol. formula); Found (other lines) C	H	N	Formula	Name[c] (if " new " compound)
>NEt + Pr^nI; 7 days; 55%	I^- fract. *ex* AcMe–Et_2O:[g]						
	(1) 197	Pure III(c)	51·5	8·7	3·9		
			51·3	8·5	4·0	$C_{15}H_{30}IN$	N-*ethyl*-N-*propylcamphidinium iodides*
	(2) 210	Pure III(d)	50·9	8·5	3·5		
	Picrates *ex* EtOH:						
	118	Pure III(c)	55·6	7·2	12·2		
			55·8	7·1	12·4	$C_{21}H_{32}N_4O_7$	N-*ethyl*-N-*propylcamphidinium picrates*
	121	Pure III(d)	55·6	7·1	12·2		
>NPr^n + EtI; 48 hr.; 55%	I^- fract. *ex* AcMe–Et_2O:[e]						
	(1) 210	Pure III(d)					
	Picrate *ex* EtOH						
	120	Pure III(d)					
Derivatives of 2-methylpyrrolidine:							
>NMe + EtI; minutes	I^- fract. *ex* EtOH–Et_2O:						
	(1) 320	Mixt. mainly IV(a)	37·6	7·4	5·4		
			37·6	7·1	5·5	$C_8H_{18}IN$	
	Picrate *ex* EtOH:						
	294	Possibly pure IV(a)	47·3	5·6	15·7		
			47·2	5·6	15·7	$C_{14}H_{20}N_4O_7$	
>NEt + MeI; seconds	I^- fract. *ex* AcMe; AcMe–Et_2O:						
	(1) 326	Pure IV(b)	37·5	7·1	5·6		
			37·6	7·1	5·5	$C_8H_{18}IN$	1-*ethyl*-1,2-*dimethylpyrrolidinium iodide*
	(2) 316	Mixt. mainly IV(a)					
	Picrates *ex* EtOH:						
	284	Pure IV(b)	47·3	5·6	15·7		1-*ethyl*-1,2-*dimethylpyrrolidium picrate*
			47·2	5·6	15·7	$C_{14}H_{20}N_4O_7$	
	294	Possibly pure IV(a)					
>NMe + Pr^nI; 6 hr.	I^- fract. *ex* EtOH; EtOH–Et_2O:						
	(1) 178	Mixt. mainly IV(b)	40·4	7·3	5·1		
			40·1	7·4	5·2	$C_9H_{20}IN$	
	(2) 206	Mixt. mainly IV(a)	40·2	7·2	5·1		
	Picrates *ex* EtOH:						
	148	Possibly pure IV(b)	48·8	6·2	15·3		
			48·6	5·9	15·1	$C_{15}H_{22}N_4O_7$	
	186	Possibly pure IV(a)	48·4	5·8	14·9		

TABLE 4 (*Continued*)

Reaction [a]; Time; Yield [j]	Salt fractions [b]: Anion; solvents for fractn. or recryst, m. p. (ref. m. p. in brackets, with ref. superscript)	Structure or compn. of fraction	Analysis: Reqd. or Calc. (line opposite mol. formula); Found (other lines) C	H	N	Formula	Name [c] (if " new " compound)
>NPr^n + MeI; minutes	I$^-$ fract. *ex* EtOH; EtOH–Et_2O:						
	(1) 180	Mixt. mainly IV(b)					
	(2) 190	Mixt. mainly IV(a)					
	Picrates *ex* EtOH:						
	144	Possibly nearly pure IV(b)					
	186	Possibly pure IV(a)					
>NMe + Ph·CH_2·I; minutes	I$^-$ fract. *ex* EtOH–Et_2O:						
	(1) 152	Mixt.	49·4	6·2	4·6		
			49·2	6·3	4·4	$C_{13}H_{20}IN$	
	Picrate fract. *ex* EtOH:						
	(1) 152	Possibly pure IV(a)	54·7	5·4	13·5		
			54·5	5·3	13·4	$C_{19}H_{22}N_4O_7$	
	(2) 118	Pure IV(b)	54·7	5·4	13·6		1-*benzyl*-1,2-*dimethylpyrrolidinium picrate*
>NCH_2Ph + MeI; minutes	I$^-$ fract. *ex* AcMe–Et_2O:						
	(1) 126	Pure IV(b)	49·2	6·6	4·4		1-*benzyl*-1,2-*dimethylpyrrolidinium iodide*
			49·2	6·3	4·4	$C_{13}H_{20}IN$	
	Picrate *ex* EtOH:						
	118	Pure IV(b)					
>NEt + Pr^{n}I; 48 hr.; 75%	I$^-$ fract. *ex* AcMe:						
	(1) 266	Mixt.	42·0	7·7			
	(2) 260		42·4	7·8		$C_{10}H_{22}IN$	
	(3) 220						
	Picrates *ex* EtOH:						
	158	Mixt.	49·7	6·2	14·5		
	162		50·0	6·2	14·6	$C_{16}H_{24}N_4O_7$	
>NPr^n + EtI; 24 hr.	I$^-$ fract. *ex* AcMe:						
	(1) 265	Mixt.					
	(2) 256						
	(3) 222						
	Picrates *ex* EtOH:						
	160	Mixt.	49·9	6·4	14·6		
	156						

TABLE 4 (*Continued*)

Reaction [a]; Time; Yield [j]	Salt fractions [b] Anion; solvents for fractn. or recryst. m. p. (ref. m. p. in brackets, with ref. superscript)	Structure or compn. of fraction	Analysis Reqd. or Calc. (line opposite mol. formula); Found (other lines) C	H	N	Formula	Name [c] (if " new " compound)
Derivatives of 2-methylpiperidine:							
>NMe + EtI; minutes	I^- fract. *ex* EtOH–Et_2O:						
	(1) 320	Mixt.					
	Picrates fract. *ex* EtOH:						
	(1) 272	Mixt.					
	(2) 264	Mixt.	48·9	6·1	14·7		
			48·6	5·9	15·1	$C_{15}H_{22}N_4O_7$	
>NEt + MeI; 1 min.	I^- fract. *ex* EtOH–Et_2O:						
	(1) 318	Mixt.	39·7	7·4	46·9 [f]		
			40·1	7·4	47·2	$C_9H_{20}IN$	
	Picrates fract. *ex* EtOH:						
	(1) 264	Mixt.					
	(2) 256	Mixt.					
>NMe + Pr^nI; 24 hr.	I^- fract. *ex* AcMe:						
	(1) 220	Mixt.					
	Picrates fract. *ex* EtOH:						
	(1) 200	Mixt.	49·7	6·1	14·2		
			50·0	6·2	14·6	$C_{16}H_{24}N_4O_7$	
	(2) 134	Mixt.					
>NPr^n + MeI; minutes	I^- fract. *ex* AcMe:						
	(1) 220	Mixt.	42·6	8·1	5·1		
			42·4	7·8	4·9	$C_{10}H_{22}IN$	
	Picrates fract. *ex* EtOH:						
	(1) 157	Mixt.	50·0	6·5	14·6		
			50·0	6·2	14·6	$C_{16}H_{24}N_4O_7$	
	(2) 126	Mixt.	50·1	6·5	14·2		
>NMe + $Ph{\cdot}CH_2I$; minutes	I^- fract. *ex* EtOH–Et_2O:						
	(1) 168	Mixt.	50·5	6·6	38·6 [f]		
			50·8	6·6	38·4	$C_{14}H_{22}IN$	
	Picrates fract. *ex* EtOH:						
	(1) 126	Possibly pure V(b)	55·5	5·7	13·1		
			55·5	5·5	13·0	$C_{20}H_{24}N_4O_7$	
	(2) 156	Possibly pure V(a)	55·2	5·6	12·9		
>$N{\cdot}CH_2Ph$ + MeI: seconds	I^- fract. *ex* EtOH–Et_2O:						
	(1) 172	Mixt.	50·9	6·9	4·4		
			50·8	6·6	4·2		
	(2) 164	Mixt.					

TABLE 4 (*Continued*)

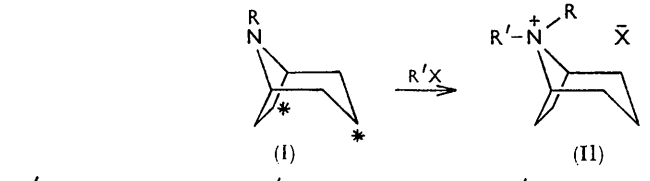
Reaction [a]; Time; Yield [j]	Salt fractions [b] Anion; solvents for fractn. or recryst. m. p. (ref. m. p. in brackets, with ref. superscript)	Structure or compn. of fraction	Analysis Reqd. or Calc. (line opposite mol. formula); Found (other lines) C	H	N	Formula	Name [c] (if " new " compound)
>N·CH_2Ph + MeI: seconds	Picrates fract. *ex* EtOH						
	(1) 126	Possibly pure V(b)					
	(2) 156	Possibly pure V(a)					
Derivatives of 4-phenylpiperidine:							
>NMe + EtI; 2 hr.	I⁻ fract. *ex* AcMe:						
	(1) 168 (170; 181) [2,g]	Nearly pure VI(a)					
	(2) 140 (140; 146) [2,h]	Possibly mainly VI(b)					
	Picrate *ex* EtOH:						
	124	Nearly pure VI(a)			13·1 13·0	$C_{20}H_{21}N_4O_7$	
	114	Possibly mainly VI(b)			13·5		
>NEt + MeI; minutes	I⁻ fract. *ex* AcMe:						
	(1) 142 (140; 146) [2,h]	Pure VI(b)					
	(2) Oily residues						
	Picrate *ex* EtOH:						
	131	Pure VI(b)	55·2 55·5	5·5 5·5	13·2 13·0	$C_{20}H_{24}N_4O_7$	1-*ethyl*-1-*methyl*-4-*phenyl*-*piperidinium picrate*
Derivatives of *trans*-decahydroquinoline:							
>NMe + EtI; 1 hr. [f]	I⁻ fract. *ex* AcMe:						
	(1) 201	Mixt.	46·8 46·6	7·7 7·8	4·3 4·5	$C_{12}H_{24}IN$	
	Picrolonate fract. *ex* EtOH:						
	(1) 112—150 range	Mixt.	58·8 59·3	7·1 7·0	15·6 15·7	$C_{22}H_{31}N_5O_5$	
	Perchlorate fract. *ex* EtOH:						
	(1) 148	Possibly pure VII(b)	51·4 51·2	8·8 8·5		$C_{12}H_{24}NClO_4$	
	(2) 142	Mixt.					
>NEt + MeI; minutes [f]	I⁻ fract. *ex* AcMe:						
	(1) 191	Mixt.	46·8 46·6	7·8 7·8	4·5 4·5	$C_{12}H_{24}IN$	
	Picrate fract. *ex* EtOH:						
	(1) 94—105 range	Mixt.	52·8 52·7	6·5 6·4	13·8 13·7	$C_{18}H_{26}N_4O_7$	

TABLE 4 (*Continued*)

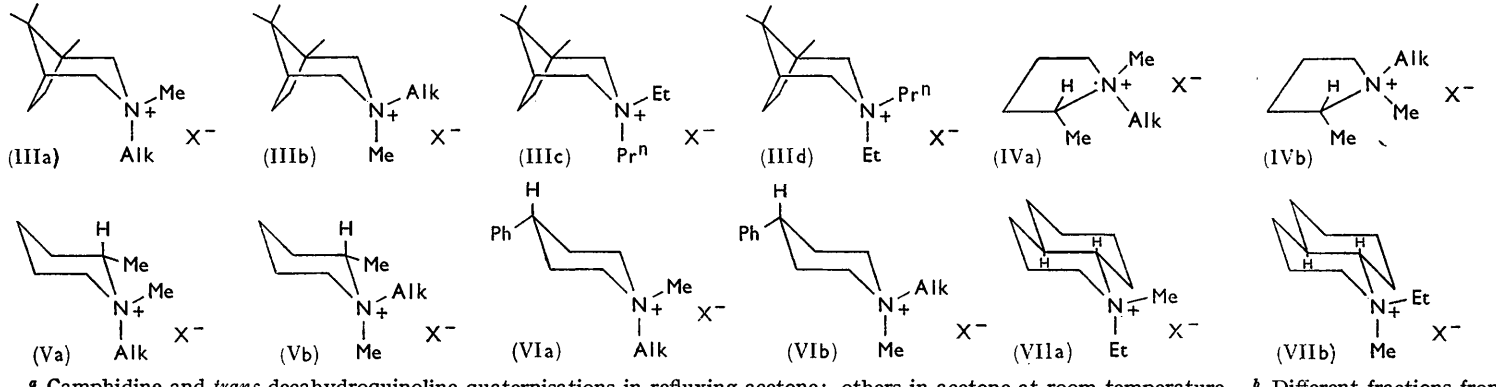
Reaction [a]; Time; Yield [j]	Salt fractions [b]: Anion; solvents for fractn. or recryst. m. p. (ref. m. p. in brackets, with ref. superscript)	Structure or compn. of fraction	Analysis: Reqd. or Calc. (line opposite mol. formula); Found (other lines) C	H	N	Formula	Name [c] (if " new " compound)
>NEt + MeI; minutes [i]	Picrolonate fract. *ex* EtOH: (1) 108—120° range	Mixt.	59·3 59·3	7·3 7·0	15·9 15·7	$C_{22}H_{31}N_5O_5$	
	Perchlorate fract. *ex* AcMe–Et_2O: (1) 148	Possibly pure VII(b)					
	(2) 136—138	Mixt.					
>NMe + Pr^nI [i]; 2 hr.	I^- fract. *ex* AcMe: (1) 199	Mixt.	48·2 48·3	8·2 8·1	4·1 4·4	$C_{13}H_{26}IN$	
	Picrate fract. *ex* EtOH: 91—108 range	Mixt.	53·7 53·8	6·8 6·6	12·8 13·2	$C_{19}H_{28}N_4O_7$	
	Picrolonate fract. *ex* EtOH: 138—160 range	Mixt.	59·7 60·1	7·0 7·2	15·5 15·3	$C_{23}H_{33}N_5O_5$	
>NPr^n + MeI; 2 hr.	I^- fract. *ex* AcMe: (1) 194	Mixt.	48·4 48·3	8·1 8·1	4·4 4·4	$C_{13}H_{26}IN$	
	Picrate fract. *ex* EtOH: (1) 92—104 range	Mixt.	53·5 53·8	6·8 6·6	13·6 13·2	$C_{19}H_{28}N_4O_7$	
	Picrolonate fract. *ex* EtOH: (1) 150—160 range	Mixt.	60·0 60·1	7·4 7·2	14·9 15·3	$C_{23}H_{33}N_5O_5$	
>NMe + $PhCH_2I$; min.	Picrate *ex* aq. EtOH: (1) 113—115	Mixt.					
>N·CH_2Ph + MeI; min.	Picrate *ex* aq. EtOH: (1) 135—138	Mixt.					
Derivatives of Tropane:							
>NMe + EtI; minutes	I^- mixture, not recryst. 359—361	Mixt.	42·2 42·7	7·0 7·1	45·1 [f] 45·2	$C_{10}H_{20}IN$	
	Picrates fract. *ex* EtOH: (1) 334	Possibly pure II (R = Me; R′ = Et)			14·5 14·7	$C_{16}H_{22}N_4O_7$	
	(2) 310	Mixt.					

TABLE 4 (*Continued*)

Reaction [a]; Time; Yield [j]	Salt fractions [b]: Anion; solvents for fractn. or recryst. m. p. (ref. m. p. in brackets, with ref. superscript)	Structure or compn. of fraction	Analysis: Reqd. or Calc. (line opposite mol. formula); Found (other lines) C	H	N	Formula	Name [c] (if " new " compound)
>NEt + MeI; seconds	I^- mixture, not recryst. 354—356	Mixt.	42·3	7·1	45·0 [f]		
			42·7	7·1	45·2	$C_{10}H_{20}IN$	
	Picrates fract. *ex* EtOH: (1) 296	Possibly pure II (R′ = Me; R = Et)	50·0	5·9	14·7		
			50·2	5·8	14·7	$C_{16}H_{22}N_4O_7$	
	(2) 290	Mixt.					



(I) (II)



(IIIa) (IIIb) (IIIc) (IIId) (IVa) (IVb)

(Va) (Vb) (VIa) (VIb) (VIIa) (VIIb)

[a] Camphidine and *trans*-decahydroquinoline quaternisations in refluxing acetone; others in acetone at room temperature. [b] Different fractions from fractional crystallisations are numbered (1), (2), etc., in the order obtained experimentally. [c] All compounds are racemic; the camphidine derivatives described (ref. 7) by Trojánek *et al.* are active. [d] Solubilities of picrates are sometimes in the reverse order to those of the iodides, as in these examples. [e] No n.m.r. spectra: Configurations are assigned on basis of expected preferred axial approach of quaternising agent, as in other quaternisations in same systems. [f] Analysis for iodine. [g] Lower-melting specimen by direct recrystallisation; higher on purification *via* perchlorate. [h] Dimorphous. [i] Details for *trans*-decahydroquinoline salts refer to mixtures prepared by quaternisation at room temperature for the MeEt salts, and in refluxing acetone for the others. [j] Yields essentially theoretical unless otherwise stated.

and the primary alkylamines. Commercial samples of 2-methylpiperidine and *trans*-decahydroquinoline were converted into *N*-methyl derivatives by the Clarke–Gillespie process [13] and into other *N*-alkyl derivatives by reduction of the corresponding *N*-acyl-amines with lithium aluminium hydride in ether. The 4-phenylpiperidines were synthesised *via* the related 1,2,3,6-tetrahydropyridines by a described procedure.[14] Tropane obtained (80%) by the modified [15] Wolff–Kishner reduction of commercial tropinone was (2 g.) oxidised in water (20 c.c.) containing potassium hydroxide (2·3 g.) with potassium permanganate (7 g.) added during 1 hr. with ice-cooling. After a further 12 hr. at room temperature the crude nortropane was isolated and acetylated, and the *N*-acetyl derivative was reduced with lithium aluminium hydride in ether. The resultant *N*-ethylnortropane was shown to be almost free from tropane by g.l.c. analysis, and was finally purified *via* the picrate.

Physical properties and analytical data for the bases, their derivatives, and some synthetical intermediates are given in Table 3.

Preparation and Fractionation of Quaternary Salts.—Quaternary iodides (or mixtures of stereoisomeric iodides) were prepared by treatment of the base with a large excess of the alkyl halide in an equal volume of acetone in presence of finely ground anhydrous potassium carbonate (this was omitted in the tropane quaternisations, where the insolubility of the quaternary salts in organic solvents made their separation from the carbonate difficult). The crude quaternary iodides were extracted with chloroform and fractionated to give the results indicated in Table 4.

Quaternary picrates, picrolonates, and perchlorates were made by appropriate " double decomposition " from the iodides in aqueous solution, in critical cases with stoicheiometric quantities of reagents in the minimum of solvent. Quaternary iodide mixtures in the tropane system were insufficiently soluble for convenient n.m.r. examination, and were accordingly converted in hot aqueous solution into the corresponding chloride mixtures by treatment with silver chloride.

The simple indication " mixt." is given in Table 4 when no reliable information about the composition of a fraction is available from n.m.r. spectroscopy or otherwise, but there is obvious evidence of heterogeneity from attempts at fractional crystallisation. Statements about composition of other salt fractions are made on consideration of fractionation evidence and n.m.r. spectra which were run on pure recrystallised iodides of the camphidine series, nearly pure recrystallised iodides of the 4-phenylpiperidine series, recrystallised but (usually) heterogeneous iodides with some salts of the 2-methylpyrrolidine series, and total crude iodides (chlorides in the tropane system) in other cases.

We thank the D.S.I.R. for maintenance grants (to J. W. and A. T.) and the University of Sheffield for research facilities (to J. M. McK.).

Department of Chemistry, The University, Sheffield 10. [*Received, June 30th,* 1964.]

[13] Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571.
[14] Schmidle and Mansfield, *J. Amer. Chem. Soc.*, 1956, **78**, 425, 1702.
[15] Huang-Minlon, *J. Amer. Chem. Soc.*, 1949, **71**, 3301.