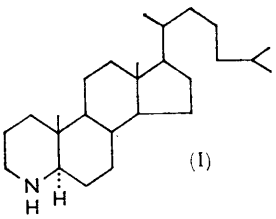
1010. *Stereoisomeric Pairs of Cyclic Quaternary Ammonium Salts. Part V.*[1] *Derivatives of 4-Aza-5α-cholestane* *

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

Stereoselectivity has been observed in the quaternisation of *N*-methyl-4-aza-5α-cholestane with primary alkyl iodides containing alkyl groups other than (and therefore larger than) methyl; the preferred direction of approach of quaternising agent has been shown to be *equatorial* by application of previously developed methods. By contrast, little or no stereoselectivity is observed in the methylation of *N*-alkyl-4-aza-5α-cholestanes. These observations are discussed and compared with previous results obtained in other base systems.

IN this Paper our general study of stereoselectivity in the quaternisation of cyclic *N*-alkyl bases is extended to cover derivatives of 4-aza-5α-cholestane (I). We have shown[1,2] that the degree of stereoselectivity in reactions of cyclic bases of the type >NMe + AlkI and >NAlk + MeI could usually be easily determined by examination of the N^+-methyl signal(s) in the total quaternisation product (most often a mixture of the two possible isomers). Furthermore, four methods have been developed[1,2] for determination of configuration of members of a diastereoisomeric pair $>N^+MeAlkI^-$ (the cyclic base framework being suitably unsymmetrical): (*a*), comparison of the *N*-methyl signals of the diastereoisomeric quaternary salts with those of the *N*-methyl base hydrochloride (a method which in general is applicable only when both configurations of hydrochloride are present in the equilibrium sample); (*b*) empirical examination of the position of certain infrared bands; (*c*) equilibration of *N*-methyl-*N*-benzyl quaternary salts, the isomer with less hindered *N*-benzyl being expected to predominate; and (*d*) consideration of which quaternisation indicated above (with methyl or with higher primary alkyl iodide) gives the higher degree of stereoselectivity; higher selectivity with methyl iodide or with higher alkyl iodide indicates approach of quaternising agent in the more hindered or the less hindered, respectively, of the two relevant space segments around the nitrogen atom, *e.g.*, with piperidine derivatives, axial or equatorial approach.



(I)

N-Methyl-4-aza-5α-cholestane[3] was alkylated with ethyl, n-propyl, or benzyl iodide, and *N*-ethyl-, *N*-n-propyl-, or *N*-benzyl-4-aza-5α-cholestanes were methylated with methyl iodide, all the quaternisations being run in low-boiling organic solvents, usually acetone (see Experimental section). Under these conditions there was no evidence that partial equilibration of products took place, but N^+-methyl group displacement was observed at higher temperatures, as in previous[1] work. N^+-Benzyl displacement is of course an easier process still, but methylation of all three *N*-alkyl bases gave diastereoisomer mixtures in similar proportions (see below) and benzylation of the *N*-methyl base was very fast.

The mixtures of *N*-methyl-*N*-n-propyl[3] and *N*-methyl-*N*-benzyl quaternary salts obtained in the relevant quaternisations could not be separated into component diastereoisomers by fractional crystallisation, although this could be done with some difficulty in the case of mixtures of *N*-methyl-*N*-ethyl salts, which could also be resolved by thin-layer chromatography.

The n.m.r. spectra of the total crude mixtures all showed two *N*-methyl signals (see Table 3) except in the case of the benzylation mixture from the *N*-methyl base;

* *Erratum, Added in Proof.*—Part I, *J.*, 1965, p. 1717, last line of asterisked footnote. *For* confirmation *read* configuration.

[1] Part IV, James McKenna, Jean M. McKenna, and J. White, *J.*, 1965, 1733.

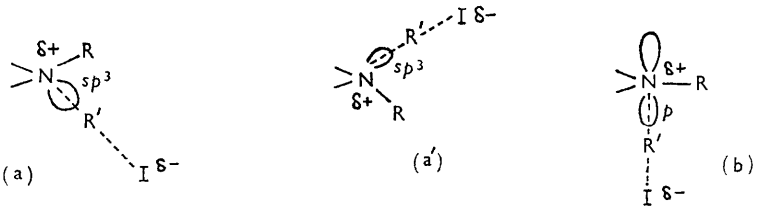
[2] (*a*) James McKenna, Jean M. McKenna, A. Tulley, and J. White, *J.*, 1965, 1711; (*b*) J. K. Becconsall, Richard A. Y. Jones, and James McKenna, *J.*, 1965, 1726.

[3] James McKenna and A. Tulley, *J.*, 1960, 945.

where the signal positions, as obtained from examination of the methylation mixture from the *N*-benzyl base, were so close together that it was evident that resolution of the peaks would not easily be achieved if one was markedly stronger than the other. Benzylation of the *N*-methyl base is therefore probably similar in stereoselectivity to ethylation or n-propylation, where the relevant n.m.r. spectra show clearly that in each case the diastereoisomer ratio is about 2—3 : 1. By contrast, methylation of the *N*-ethyl, *N*-n-propyl, or *N*-benzyl base gave in each case a mixture of approximately equal proportions of the two disatereoisomers.

Configurational assignments for the quaternary salts could not be obtained by comparison of their n.m.r. spectra with that of the *N*-methyl base hydrochloride, as only one (presumably the equatorial) *N*-methyl signal could be seen in the hydrochloride spectrum; but other procedures [1,2] for determining configurations were applicable. Since alkylation of *N*-methyl-4-aza-5α-cholestane gives consistently a higher degree of stereoselectivity than does methylation of the *N*-alkyl bases (where the selectivity is approximately zero) one may deduce that the preferred direction of alkylation of the *N*-methyl base is equatorial, and equilibration experiments with *N*-methyl-*N*-benzyl quaternary salt mixtures confirmed this deduction. In refluxing chloroform, a mixture of approximately equal parts of the two isomers derived from a methylation experiment was slowly converted into a mixed product with the same infrared and n.m.r. characteristics as those corresponding to the product of benzylating the *N*-methyl base; the benzylation mixture, itself, however, remained effectively unchanged by this treatment. The configurational assignments for the *N*-methyl-*N*-ethyl and the *N*-methyl-*N*-benzyl quaternary ammonium salts were further confirmed by application of the empirical rule [2a] relating to infrared band positions: for mixtures of the former salts, increasing intensity in a band at 885 cm.$^{-1}$ relative to one at 872 cm.$^{-1}$ corresponded to a higher proportion of salt with *N*-methyl equatorial; corresponding significant bands in the *N*-methyl-*N*-benzyl quaternary salts were at 885 and 868 cm.$^{-1}$. A suitable pair of bands in the previously defined areas were not seen, however, in the spectra of the *N*-methyl-*N*-n-propyl quaternary salts.

The degree of stereoselectivity observed in quaternisations with the 4-aza-5α-cholestane system is indicated in Table 1 which for comparison includes also a brief summary of results obtained [1,2] in other systems. Views previously expressed [1] on the factors controlling the stereochemistry of the quaternisations may now be appropriately summarised and developed as follows: (*a*) Transition states for quaternisations are likely to involve tetrahedral nitrogen with sp^3- or near sp^3-hybridisation rather than trigonal nitrogen, sp^2-hybridised, with the remaining *p*-orbital used for bond-development to the quaternising agent, *i.e.*, (a), (a′) rather than (b)



This statement depends not only on the known higher energy of trigonal relative to tetrahedral tercovalent nitrogen, and on the better directional quality of the hybrid lone-pair orbital for bond formation, but also on the observation that cyclic bases with one of the two relevant space segments near the nitrogen subject to strong steric compression do not always suffer attack by quaternising agents in the less hindered segment, *e.g.*, with camphidines, transition state (c) would be energetically preferred to (d) corresponding formally to preferred equatorial approach, if such transition states could easily be formed. With competitive transition states of type (a), (a′) the relative steric demands of fully

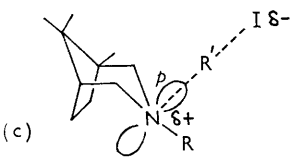
TABLE 1

Characteristic stereoselectivities of quaternisations in acetone [a]

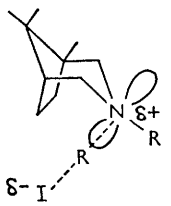
Base system	Characteristic stereoselectivity NMe + AlkI	NAlk + MeI	Preferred direction [b] of quaternisation
2-Methylpiperidine	0	+	Axial
trans-Decahydroquinoline	0	+	Axial
4-Aza-5α-cholestane	+	0	Equatorial
Camphidine	+	+++	Axial
4-Phenylpiperidine [c]	++	++	Axial
Tropane [c]	++	++	Equatorial

[a] Room temperature or reflux as appropriate. For details see Experimental section and ref. 2*a*. [b] *I.e.*, in reactions where stereoselectivity is marked. [c] Only *N*-methyl-*N*-ethyl salts so far examined.

attached R and partly attached R′ are important in determining the relative free energies, which in our present discussion we take as relative potential energies, solvent, and temperature effects on stereospecificity in any cases previously examined [2a] being quite small.



(c)



(d)

(*b*) Further development of the views expressed in paragraph (*a*) is as follows, only reactions not involving additional polar interactions between reagent and substrate being considered. When a three-co-ordinate ring atom becomes tetrahedral one may *in general* expect reagent attack on the less hindered side of the three-co-ordinate atom if that atom has a near-trigonal disposition of full valencies in the transition state. Certain structural arrangements encourage such transition-state geometry, *e.g.*, strong hindrance on one face of a cyclic ketone or inclusion of the relevant ring atom in the framework of an extended π-system, where the relative torsion of one portion relative to the other is likely to be demanding in terms of bonding energy.

On the other hand, if the relevant ring atom is near-tetrahedral in the transition state the relative space demands of the fully and the partly attached exocyclic groups are of major importance* in determining preferred orientation during the reaction, *e.g.*, in quaternisation of ring bases [paragraph (*a*)], or in nucleophilic addition to relatively unhindered cyclic ketones. In some such examples, of course, reagent attack on the less hindered side of the ring atom may be noted, but this *in itself* does not provide a qualitative rationalisation, as *the steric demands of the fully attached exocyclic group in a tetrahedral or near-tetrahedral transition state cannot be ignored.*

Nomenclature previously introduced [4] into the literature may be used in connection with rationalisations relating to the above two transition-state types: one may be said to get *steric approach control* when a 3 ⟶ 4 co-ordinate change at a ring atom involves a transition state with near-trigonal disposition of fully attached groups; one gets *product development control* when the transition states have near-tetrahedral geometry. The notion of preferred "approach from the less hindered side" should be used as a rationalisation *per se* only in the former case.

(*c*) Other things being equal, an incoming quaternising primary alkyl group is effectively larger (bipyramidal geometry in transition state; solvation) than a primary *N*-alkyl group present in the cyclic tertiary base. Variations in this inequality will be

* Except in special cases where the Curtin–Hammett principle is inapplicable.

[4] W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Amer. Chem. Soc.*, 1956, **78**, 2579.

caused by variations in the relative absolute sizes of the two primary alkyl groups concerned.

(*d*) If the nitrogen ring in the neighbourhood of the hetero-atom is relatively flexible, then this flexibility, coupled with the fairly long partial bond between nitrogen and incoming alkyl group in the quaternisation transition state, may, notwithstanding (*c*), result in the incoming rather than the fully attached primary alkyl group being preferentially positioned in what is formally the more hindered of the two relevant space segments near the ring nitrogen atom.

Minimisation of overall potential energy in other systems has been considered by several authors, and the importance of flexing or other bond motions in reducing van der Waals interactions has been emphasised. A good discussion is available in Wiberg's "Physical Organic Chemistry." [5] The activation energy for racemisation of an active 2,2′-dibromobiphenyl, for example, is calculated to be *ca.* 200 kcal. mole^{-1} in a model in which no bending or stretching is permitted, but by the use of suitable parameters for

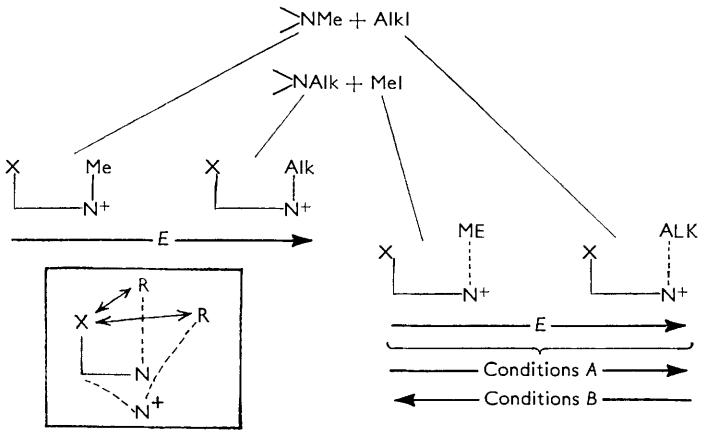


FIGURE 1. Relative potential energies for pairs of diastereoisomeric transition states in quaternisations of cyclic tertiary bases: General pattern

The greater steric demands of partly attached groups (other things being equal) are represented in this Diagram and in Figure 2 by the use of capitals.

Conditions A.—Increased axial interactions and/or reduced flexibility of ring near N-atom.

Conditions B.—Reduced axial interactions and/or increased flexibility of ring near N-atom: the (exaggerated) effect of such increased flexibility is illustrated in the boxed section.

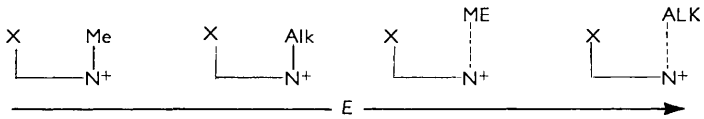
these motions the activation energy is reduced to a calculated 18·2 kcal. mole^{-1}, of which 12·4 kcal. mole^{-1} is attributed to bond bending and stretching. The observed enthalpy of activation is 17·3 kcal. mole^{-1}.

(*e*) In quaternisations of *N*-alkylpiperidines, including bases with the piperidine ring bridged or fused to other rings, diaxial interactions affecting axial alkyl groups fully or partly attached to the nitrogen atom are, in general, more important than interactions affecting fully or partly attached equatorial groups.

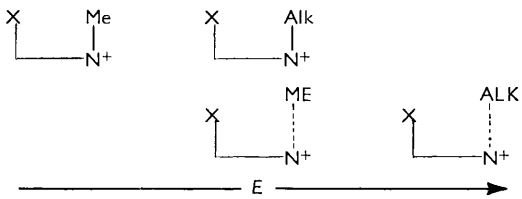
(*f*) A representation of the views expressed in the previous three sections is given in Figure 1. The group(s) X, which cause(s) diaxial interaction with the appropriately oriented group shown at nitrogen, is/are variable but is/are considered to be the same for comparison of any four relevant transition states corresponding to the two reactions indicated in Figure 1. There is no doubt about the direction of increase in potential

[5] K. B. Wiberg, "Physical Organic Chemistry," Wiley, 1964, pp. 364—373.

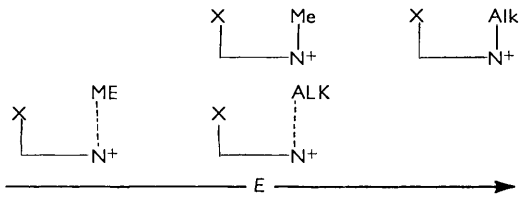
energy E for members of each pair of transition states; this is as shown. What one must consider is how the energy of the pair on the left stands in relation to the pair on the right. If the pair on the left is considered fixed on an energy co-ordinate, the other pair will, because of the operation of the factors discussed above, tend to move relative to the first pair in the directions indicated by the arrows below the horizontal bracket in Figure 1. Specific examples are given in Figure 2; the cases of 4-aza-5α-cholestane and *trans*-decahydroquinoline are most directly comparable as a pair since one of the two relevant parameters, *i.e.*, ring rigidity, is nearly the same for each base system, but there is a major change in the diaxial-interaction parameter. One may say of the quaternisations of *N*-methyl-4-aza-5α-cholestane that the 19-methyl group in the steroid preferentially hinders axial approach of a quaternising agent, but *an* a priori *conclusion that this is so could not have been reached with assurance* (vide, e.g., *results in the camphidine system*) *as the valencies of nitrogen atom are likely to be near-tetrahedrally disposed in the transition states* (*see paragraphs* a *and* b).



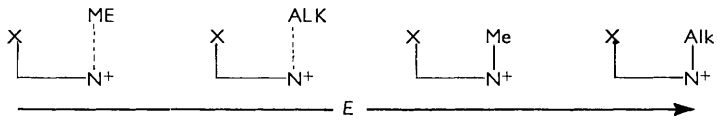
(1) Tropane: relatively low axial interactions but *very low flexbility*



(2) 4-Aza-5α-cholestane: strong axial interactions; moderate flexibility



(3) *trans*-Decahydroquinoline: lower axial interactions than in (2) with approximately the same flexibility



(4) Camphidine: strong axial interactions offset by *relatively high flexibility*

FIGURE 2. Relative potential energies of diastereoisomeric transition states for quaternisations in particular base systems

(*g*) While reactions of groups equatorially attached (by full or partial bonds) to nitrogen have not yet been considered, the zeroth-order treatment given dealing (see paragraph *e*) only with diaxial interactions, these equatorial groups do in fact suffer steric interactions with groups attached either axially or equatorially to the α-carbon atoms. Such interactions might in general be expected to reduce the stereoselectivity of quaternisations controlled in the main by diaxial interactions, and we find (see Table 1) that the

overall stereoselectivity in the 2-methylpiperidine, *trans*-decahydroquinoline, and *N*-methyl-4-aza-5α-cholestane systems is lower than in the camphidine or the 4-phenylpiperidine systems; the tropane system, rather anomalously perhaps, shows relatively high stereoselectivity, possibly because of the over-riding importance of the rigidity parameter in this case.

(*h*) The above theoretical conclusions are sufficiently broadly based to permit predictions regarding stereoselectivity in other base systems, a variety of which are being examined in this laboratory. Additionally, experimental data of a more quantitative nature than has been available previously can be provided, and the possibility of developing a more quantitative rationalisation will be explored.

EXPERIMENTAL

N.m.r. spectra were obtained on an A.E.I. R.S.2 spectrometer, operating at 60 Mc./sec.

Preparation of Bases and Quaternary Salts.—*N*-Acetyl-4-aza-5α-cholestane, *N*-methyl-4-aza-5α-cholestane, and its methiodide have been described previously.[3,6] The *N*-ethyl, *N*-n-propyl, and *N*-benzyl bases were prepared either by reduction of the corresponding *N*-acyl derivatives with lithium aluminium hydride in refluxing ether, or by refluxing the secondary base in acetone with an excess of ethyl, n-propyl, or benzyl iodide in presence of an excess of anhydrous potassium carbonate: some of the *N*-ethyl base ethiodide was also formed in the first case, but neither an n-propyl base propiodide nor a *N*-benzyl base benziodide could be formed even under more forcing conditions (*e.g.*, from the *N*-propyl base with n-propyl iodide at 138° in a sealed tube). Hofmann degradation of the *N*-ethyl base ethiodide by the conventional (Ag_2O: pyrolysis) method also gave a near-quantitative yield of the *N*-ethyl base.

Quaternary salt mixtures containing two different *N*-alkyl groups were prepared from the relevant tertiary base and organic iodide in refluxing methanol (>NEt + MeI), ethanol (>NMe + EtI) or acetone (salts containing *N*-methyl with *N*-n-propyl or *N*-benzyl groups) in presence of an excess of solid potassium carbonate.

Physical properties and analyses for the bases and their derivatives are given in Table 2; corresponding information for quaternary salt mixtures is given in Table 3.

TABLE 2

Physical properties and analyses for *N*-alkyl-4-aza-5α-cholestanes and derivatives

Compound	M. p. (solvent in parentheses)	Analysis (%) Found (upper line) Reqd. (lower line) C	H	N	Cl or I	Molecular formula
N-Ethyl-4-aza-5α-cholestane	86—87°	83·6	12·7	3·5		
	(Et_2O/MeOH)	83·7	12·8	3·5		$C_{28}H_{51}N$
ethiodide	268—269°			2·4	23·1	
	($CHCl_3$/AcMe)			2·5	22·8	$C_{30}H_{56}IN$
hydrochloride	252—258°				8·0	
	(AcMe)				8·1	$C_{28}H_{52}ClN$
N-Propionyl-4-aza-5α-cholestane	112—113°	81·3	11·9			
	(MeOH)	81·1	12·0			$C_{29}H_{51}NO$
N-Propyl-4-aza-5α-cholestane	Oil	83·9	12·7	3·4		
		83·8	12·9	3·4		$C_{29}H_{53}N$
hydrochloride	236—238°				8·0	
	(AcMe)				7·8	$C_{29}H_{54}ClN$
N-Benzoyl-4-aza-5α-cholestane	137—138°	82·7	10·4			
	(AcMe)	83·0	10·8			$C_{33}H_{51}NO$
N-Benzyl-4-aza-5α-cholestane	118—119°	85·1	11·5			
	(AcMe)	85·5	11·5			$C_{33}H_{53}N$

Separation of Diastereoisomeric N-*Methyl*-N-*ethyl Quaternary Ammonium Salts.*—By fractional crystallisation from acetone, mixtures of these salts yielded fractions of m. p. 263—265° (least soluble) and 247—250° (most soluble). The former had an infrared band at 952 cm.$^{-1}$, but none at 945 cm.$^{-1}$, while the latter had the lower-field band but lacked the higher (both bands were displayed in mixtures of the two salts). The higher-melting salt had also a strong band at 885 cm.$^{-1}$ and a weaker one at 874 cm.$^{-1}$, while the lower-melting salt had a

[6] C. C. Bolt, *Rec. Trav. Chim.*, 1938, **57**, 905; U.S.P. 2,227,876/1941.

TABLE 3

Quaternary salt mixtures containing two different *N*-alkyl groups derived from 4-aza-5α-cholestane

Preparative method for mixture	M. p. (crude mixture)	*N*-Methyl signals,[a] n.m.r. (τ scale; tms = 10·0)	Significant i.r. bands (cm.$^{-1}$; KBr discs)	Analysis (%) Found (1st and 2nd lines) Calc. (3rd line) C	H	N	I	Molecular formula
N-Ethyl base + MeI (refluxing MeOH)	See text	6·84[e]; 6·63	885,[bc] 872,[bc] 952,[c] 945[c]	64·3	10·0	2·6	23·5	
				64·3	10·0	2·8	23·6	
N-Methyl base + EtI (refluxing EtOH)	See text			64·1	10·0	2·6	23·3	$C_{29}H_{54}IN$
N-n-Propyl base + MeI (refluxing AcMe)	223—235°	684[e]; 6·57		64·4	10·2	2·6	22·8	
				64·5	10·1	2·4	22·9	
N-Methyl base + n-propyl iodide (refluxing AcMe)	234—244			64·6	10·1	2·5	22·8	$C_{30}H_{56}IN$
N-Benzyl base + MeI (refluxing AcMe)	200—210	6·86[e]; 6·83	885,[bd] 868[bd] 950[d]			2·6	21·2	
				68·0	9·6	2·1	20·8	
N-Methyl base + $PhCH_2I$ (refluxing AcMe)	210—214			67·4	9·3	2·3	21·0	$C_{34}H_{56}IN$

[a] *N*-Me signals at 6·82, 6·42 in dimethiodide and at 7·18 in *N*-methyl base hydrochloride. All solutions in chloroform. [b] Significant bands for application of configurational "i rule" (see text). [c] Significant bands for following progress of separation of mixed isomers. [d] Significant bands for following progress of equilibration of isomers. [e] Axial *N*-Me signals: higher-field signal the stronger in *N*-methyl base ethiodide and n-propiodide mixtures; higher-field signal only one clearly resolved in *N*-methyl base benziodide mixture.

strong band at 874 cm.$^{-1}$ and a weaker one at 885 cm.$^{-1}$. The separation could also be performed by thin-layer chromatography (silica-gel; acetone), the higher-melting solid moving more slowly.

Displacement of N-*Methyl Groups during Alkylations*.—No change was noted in the *N*-methyl base methiodide after it had been refluxed for 4 days in a mixture of ethyl iodide and ethyl alcohol in presence of anhydrous potassium carbonate. Mixtures of the isomeric *N*-methyl-*N*-ethyl quaternary iodides were likewise unchanged in composition (infrared spectra) when solutions in ethanol were refluxed for 4 days with anhydrous potassium carbonate.

However, when the above experiments with the *N*-methyl base methiodide were repeated at 104° and at 158° in sealed tubes, some *N*-methyl-*N*-ethyl quaternary salt was obtained (together with unchanged *N*-methyl base methiodide) in the former case, while the product was chiefly *N*-methyl base in the latter.

Similarly, while quantitative yields of the *N*-methyl-*N*-n-propyl quaternary salt mixtures could be obtained in refluxing acetone (n-propylation of the *N*-methyl base being rather slow, taking several days for completion in typical experiments), evidence of iodide attack on N^+–Me in these salts was obtained in preparative work at higher temperatures. For example, heating the *N*-methyl base in excess of refluxing n-propyl iodide containing a little ethanol in presence of anhydrous potassium carbonate for 4 days gave the n-propyl base (30%) and the quaternary salt mixture (70%). Refluxing the *N*-methyl base methiodide in n-propyl iodide containing a little ethanol in presence of solid potassium carbonate for 4 days gave 40% of the n-propyl base and mixed *N*-methyl-*N*-propyl quaternary salts, together with some unchanged reactant.

Interconversion of N-*Benzyl*-N-*methyl Quaternary Salts in Refluxing Chloroform*.—Mixtures of quaternary salts as obtained from the reactions $>$NMe + $Ph{\cdot}CH_2I$ and $>N{\cdot}CH_2Ph$ + MeI were refluxed in chloroform for 13 days (with an interim examination of products after 4 days). Overall recovery of quaternary salts was *ca.* 80%, the loss being mainly due to transfer operations; a slight odour of benzyl iodide was noted, but no base hydriodide was formed. The quaternary salt mixture from the reaction $>$NMe + $Ph{\cdot}CH_2I$ was unchanged in infrared and n.m.r. spectroscopic appearance by this treatment, but the quaternary salt mixture from the reaction $>N{\cdot}CH_2Ph$ + MeI was altered so that the infrared and n.m.r. spectra, originally different in appearance from the spectra of the other mixture, became identical with these after the 13-day reflux. Thus an infrared peak at 868 cm.$^{-1}$ developed in intensity, while one

at 950 cm.$^{-1}$ became considerably reduced, while an equal-intensity doublet at 6·86 and 6·83 τ (*N*-Me signals) was after 4 days altered to a pair of peaks at the same positions but of different intensities, the higher-field signal having increased in strength relative to the lower. After 13 days, only the higher-field *N*-Me signal was seen. An n.m.r. spectrum showing a similar unequal-intensity pattern at 6·86 and 6·83 τ to that given by the product in the reflux experiment after 4 days was obtained by mixing equal quantities of the quaternary salt mixtures as obtained from the methylation and benzylation quaternisations.

We thank the D.S.I.R. for a Maintenance Grant (to A. T.) and the University of Sheffield for research facilities (to J. M. McK.).

Department of Chemistry, The University, Sheffield 10. [*Received, December 29th*, 1964.]