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STEREOISOMERIC PAIRS OF CYCLIC QUATERNARY AMMONIUM SALTS

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CYCLIC ammonium salts of type $>\overset{+}{N}R_1R_2\ \bar{X}$ may exist in two geometrically isomeric forms if there is appropriate lack of symmetry in the ring system; the hitherto most thoroughly investigated[1] examples have been in the tropine field. The preferred conformation of the alkyl group R in a cyclic base $>NR$ does not of necessity correspond to the configuration of this alkyl group in a derived quaternary salt, and it is at present difficult to predict with assurance the preferred stereochemical course of the quaternisation reactions.

We have been engaged on a study of the preparation, stereochemistry, and differential properties of some such isomeric pairs, and here disclose results obtained with derivatives of camphidine, 2-methyl- and 4-phenylpiperidine, 2-methylpyrrolidine, trans-decahydroquinoline and tropane.

Table I shows the degree of stereoselectivity exhibited under normal preparative conditions in the quaternisation reactions indicated. The symbols 0, +, ++, +++ represent increasing stereoselectivity from approximately equal proportions of isomers to a ratio of about 20:1 or higher (including examples where we believe the reaction to be essentially stereospecific).

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1. Fodor, Tetrahedron (1957) 1, 82; Chem. and Ind. (1961) 1500.

TABLE I

Stereospecificity of Quaternisation Reactions

Base system	>NMe + EtI	>NEt + MeI	>NMe + Pr^nI	>NPr^n + MeI	>NMe + $PhCH_2I$	>NCH_2Ph + MeI
Camphidine	+	+++	+	+++	++	+++
2-methyl-pyrrolidine	+	++	0	+	+	+++
2-methyl-piperidine	+++	+++			++	+++
4-phenyl-piperidine	+++	+++				
Trans-deca-hydroquinoline	0	++				
Tropane	+++	+++				

In some cases (notably with camphidines) fractional crystallisation of mixtures of quaternary iodides or picrates to yield pure isomers was possible; in others an estimate of relative proportions was obtained by N.M.R. spectroscopy.

It is of interest that although mixtures containing approximately equal proportions of isomers were obtained in two reactions, in no case was the obviously predominant product of one quaternisation also that of the reaction sequence in which the alkyl groups were inserted in the reverse order; this parallels the experience of other workers[1,2] with individual base systems. The nomenclature adopted for the isomeric salts may conveniently reflect stereoselectivity in the appropriate quaternisation reaction(s), e.g. with ethyl iodide N-methylcamphidine gives mainly (ca. 70%) N-methylcamphidine ethiodide together with some (ca. 30%) N-ethylcamphidine methiodide.

N.M.R. spectroscopy provided the most important method for determination of structures of individual quaternary salts. The procedure, which is described in the following communication[3], depends essentially on establishment of a spectroscopic relation between the N-methyl hydrochloride (to which a preferred stereo structure must be assigned) and the related quaternary salts; where such a relation cannot be established the method fails. A subsidiary criterion[4] is that the I.R. spectra of salts $\rightarrow \overset{+}{N}MeAlk\ \bar{I}$ in the region 850-900 $cm.^{-1}$

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2. Kocska and Bernath, Chem. and Ind. (1958) 1401.

3. Becconsall and Jones, following communication.

4. (a) Zeile and Schultz, Chem. Ber. (1955) 88, 1078.

   (b) Trojánek, Komrsová, Pospíšek and Čekan, Coll. Czech. Chem. Comm. (1961) 26, 2921.

approx. has a diagnostic band at higher or at lower frequency for N-Me equatorial or axial respectively. Sometimes two significant bands are observed in each spectrum, and in such cases the rule applies to the stronger bands. We find that this rule is generally applicable (in salts derived from 2-methylpyrrolidine cis- and trans-NMe correspond to ax- and eq-NMe respectively), but the application is naturally less clear-cut where configurational or conformational mixtures are examined. A further criterion is that, as might be expected, for axial (or, for 2-methylpyrrolidine, cis) approach of the alkylating reagent to the basic atom, there is often markedly greater stereoselectivity for the reaction >NAlk + MeI than for >NMe + Alk I.

Application of these methods shows that in camphidines (N.M.R.),* 2-methylpiperidine (N.M.R.), 1-phenylpiperidine (I.R.), and trans-decahydroquinoline (I.R., stereoselectivity) in reactions where stereoselectivity is observed the quaternising reagent prefers an axial approach, i.e. the conformation of the base corresponds to the configuration of the salt. The same correspondence is evident for 2-methylpyrrolidine derivatives, where a cis approach is preferred (N.M.R.), but in tropane, as in tropines[1], the approach is mainly equatorial (N.M.R.).

In a recent examination of the quaternisation of camphidine bases, Trojánek et al.[4b] isolated only one isomer in each reaction, and, possibly because they were examining mixtures, found relative intensities for bands at ca. 900 $cm.^{-1}$ and ca. 880 $cm.^{-1}$ which are the reverse of those we have observed in the isomers with equatorial N-Me. They also regard the quaternary salts as probably having skew-boat conformations, but the N.M.R. results (following communication) suggest

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* Where the N.M.R. method could be used no subsidiary criteria are quoted.

that this is unlikely, and in any case such conformations are more probable for boat forms with the normal degree of flexibility, which is considerably reduced in camphidine by the $-CH_2-CH_2-$ bridge. Undoubtedly the piperidine ring will be rather distorted, but we believe it may better be regarded as a distorted chair.

We record in Table II the m.p.'s of pure ($\pm$)-camphidine quaternary salts, which sometimes are markedly higher than those recorded (for the active salts) by Trojánek et al.[4b]. Isolation of pure isomers was the exception rather than the rule for most of the other systems.

TABLE II

Camphidine Quaternary Salts

Salt		Iodide m.p.	Picrate m.p.
N-methylcamphidine	etho salt	255	178-80
N-ethyl "	metho "	244	151
N-methylcamphidine	propo salt	198	132
N-propyl "	metho "	202	130
N-methylcamphidine	benzo salt	206	169
N-benzyl "	metho "	202	148

The rates of ethylene formation by Hofmann degradation in hot alkaline glycol from the isomers $>\overset{+}{N}MeEt\ \bar{I}$ derived from camphidine could not be differentiated with certainty in semiquantitative experiments, but with sodium thiophenoxide we found a rather greater

rate of thioether (mostly PhSMe) formation from the isomer with axial N-Me; with the related 2-methylpyrrolidine salts there was little differentiation. The most striking reactivity differences were observed by examination (N.M.R.) of the ratio of thiophenetole (minor component) to thioanisole in the thioether mixtures from such experiments. Thus proportionally about twice as much thiophenetole was obtained from the $>\overset{+}{N}MeEt\ \bar{I}$ isomer with -NEt axial (for camphidines), cis (for 2-methylpyrrolidines), and equatorial (for tropanes); there is therefore a most interesting stereochemical correspondence in the reactions leading to both attachment and detachment of the ethyl group in all three cases. Thioether analyses are given in Table III.

TABLE III

Thioether Composition from Quaternary Salts with Sodium Thiophenoxide in Diethylene Glycol at 160-180° : Ratios of PhSMe:PhSEt

N-Methylcamphidine ethiodide	3 : 1
N-Ethylcamphidine methiodide	6 : 1
1,2-Dimethylpyrrolidine ethiodide	7 : 1
1-Ethyl-2-methylpyrrolidine methiodide	15 : 1
Tropane ethiodide	5 : 1
N-Ethylnortropane methiodide	10 : 1