## 321. *Stereoisomeric Pairs of Cyclic Quaternary Ammonium Salts. Part II.*[1] *Configurational Analysis by Proton Magnetic Resonance Spectroscopy*

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The configurations of the quaternisation products of some cyclic tertiary bases have been analysed by proton magnetic resonance spectroscopy.

Nuclear magnetic resonance spectroscopy is a valuable technique for configurational and conformational analysis of cyclic systems, and has been used by several authors [2-5] for studying the configuration of quaternary salts of cyclic amines. We discuss here the structural analysis of the products of the quaternisations described in the preceding Paper.

The approach is basically that of Closs.[2] If a tertiary methylamine hydrochloride can exist in two configurations its proton magnetic resonance spectrum frequently exhibits two signals associated with the two differently oriented (and hence differently shielded) *N*-methyl groups. One of these signals is likely to be considerably more intense than the other, reflecting the greater stability of one configuration. For example, it is to be expected that *trans*-1,2-dimethylpyrrolidine hydrochloride (Ia) is more stable than its *cis*-isomer (Ib). Of the two *N*-methyl signals (for $\tau$ values see Table) that at lower field is the more intense; therefore in this series differential shielding is such that a *trans*-1-methyl group resonates at lower field than the analogous *cis*-group. The pyrrolidine quaternary iodides (Ia; Ib) all show *N*-methyl signals about $\tau = 6{\cdot}7$ or about $\tau = 7{\cdot}0$ (both signals are of course seen in crude reaction mixtures or samples from fractional crystallisations containing two stereoisomers). If the argument can be transferred from the hydrochlorides to the quaternary salts, the low-field signal is derived from those isomers (Ia) in which the methyl groups are *trans*, and that at high field from the *cis*-isomers. The relative intensities of the signals in the spectrum of a mixture give an indication of the proportions of the two configurations.

A similar situation arises with the tropanes (II). The more intense of the two *N*-methyl signals in tropane hydrochloride is at higher field, presumably corresponding to the configuration (IIa) in which the *N*-methyl group is equatorial [2,6] while the *N*-methyl-base ethochloride ($\tau = 6{\cdot}97$) and the *N*-ethyl-base methochloride ($\tau = 7{\cdot}10$) appear to have axial and equatorial *N*-methyl groups, respectively, as expected.[7] Relative proportions of isomers in reaction mixtures from quaternisations can be assessed as before.

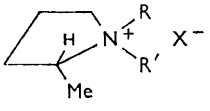
The more intense of the two *N*-methyl signals in the spectrum of 1,2-dimethylpiperidine hydrochloride occurs at lower field, and must be derived from configuration (IIIa) in which both methyl groups are equatorial. Reaction mixtures from the *N*-methyl-base and ethyl or *n*-propyl iodide, or from the *N*-ethyl or *N*-n-propyl-base and methyl iodide, all show two signals in the *N*-methyl region of the spectrum, the signals at higher and at lower field being associated with configurations (IIIb) and (IIIa), respectively.*

These techniques could not always be used for assigning configuration because, in some

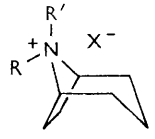
* This statement modifies one made in a preliminary announcement,[8] where the possibility of conformational isomerism with some of the salts was suggested. The error arose partly from an impurity in one of the samples, and partly from an instrumental fault which led to an incorrect calibration.

[1] Part I, McKenna, McKenna, Tulley, and White, preceding Paper.
[2] Closs, *J. Amer. Chem. Soc.*, 1959, **81**, 5456.
[3] Moynehan, Schofield, Jones, and Katritzky, *J.*, 1962, 2637.
[4] Shamma and Moss, *J. Amer. Chem. Soc.*, 1962, **84**, 1739.
[5] Kotake, Kawasaki, Kamoto, Matsutan, Kusomoto, and Kaneko, *Bull. Chem. Soc. Japan*, 1962, **35**, 1335.
[6] Eckert and Le Fèvre, *J. Chem. Soc.*, 1962, 3991.
[7] Fodor, *Tetrahedron*, 1957, **1**, 82; *Chem. and Ind.*, 1961, 1500.
[8] Becconsall and Jones, *Tetrahedron Letters*, 1962, 1103.

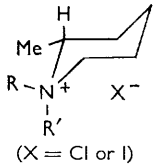
cases, the tertiary *N*-methyl hydrochlorides exhibited only a single peak in the *N*-methyl region of this spectrum, the less stable isomer being present in too small a concentration for detection. This occurred with 1-methyl-4-phenylpiperidine and 1-methyl-*trans*-decahydroquinoline. However, the relative intensities of the two *N*-methyl signals in puaternisation mixtures indicated the proportions of the two stereoisomers formed. Furthermore, apart from the absence of a second *N*-methyl signal in the spectrum of 1-methyl-*trans*-decahydroquinoline hydrochloride, there is a very close similarity in the *N*-methyl region between corresponding spectra of salts of 1-methyl-*trans*-decahydroquinoline and of 1,2-dimethylpiperidine. The similarity covers not only τ-values (see Table) but also, very strikingly, relative peak intensities in crude quaternisation mixtures obtained from the *N*-methyl-bases with ethyl iodide and from the *N*-ethyl-bases with methyl iodide. As also indicated by other evidence (Part IV), therefore, quaternisations with the two base systems are probably stereochemically analogous.



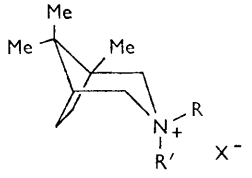
(X = Cl or I)
(Ia; R = Me; R′ = H, Et, $Pr^n$, or $PhCH_2$)
(Ib; R = H, Et, $Pr^n$, or $PhCH_2$; R′ = Me)



(X = Cl or I)
(IIa; R = Me; R′ = H, Me, or Et)
(IIb; R = H, Me, or Et; R′ = Me)



(X = Cl or I)
(IIIa; R = Me; R′ = H, Et, $Pr^n$, or $PhCH_2$)
(IIIb; R = H, Et, $Pr^n$, or $PhCH_2$; R′ = Me)



(X = Cl or I)
(IVa; R = Me; R′ = H, Me, Et, $Pr^n$, or $PhCH_2$)
(IVb; R = Me, Et, $Pr^n$, or $PhCH_2$; R′ = Me)

The spectra of the camphidines (IV) are rather more difficult to interpret. Again, the spectrum of *N*-methylcamphidine hydrochloride has only a single *N*-methyl resonance which appeared as a doublet under suitable conditions (*cf.* ref. 2). Failure to detect the *N*-methyl resonance of the less stable isomer again prevents us from using the hydrochloride spectrum to determine which of the two *N*-methyl configurations has the higher shielding. The actual value of the chemical shift for the more stable isomer observed does not help, because both the *N*-methyl and *N*-methylene protons in the quaternary salts are *ca.* 0·4—0·5 p.p.m. less shielded than those in the hydrochloride, whereas differences between *N*-methyl shieldings in isomeric pairs are only *ca.* 0·2 p.p.m. Configurations can be assigned, however, by considering the relative positions of the *N*-methyl and *N*-methylene resonances, as follows.

In all the compounds examined, the N–C–H region of the spectrum contained two main unresolved multiplets which were assigned to *N*-methylene groups. In each case the sharp signal from the *N*-methyl group was either superimposed on the higher of the two *N*-methylene group signals or was shifted upfield from it by about 0·2 p.p.m. *NN*-Dimethylcamphidinium iodide showed both these peaks; *N*-methylcamphidine hydrochloride (presumably with conformation IVa) only that at higher field. We believe, therefore, that we are justified in assigning the higher signal to an equatorial *N*-methyl group, and structural assignments for the isomeric *N*-alkyl-*N*-methylcamphidinium iodides (in this series pure individual isomers were examined) thus become possible.

The suggestion has been made that the quaternary salts of camphidines (but not the

hydrochlorides) exist with the piperidine ring in a twisted-boat conformation.[9] If this is indeed so then our absolute assignments of structure may no longer be valid, although they would still be relatively correct. However, the spectrum of the *N*-methyl hydrochloride is closely similar to the spectra of the quaternary salts, and this would suggest that such a drastic change in conformation does not occur. The possibility of structural assignments being upset because of gross differences in conformation between the *N*-methyl hydrochloride and the quaternary salts in any other base system examined seems remote.

## Experimental

The spectra of the pyrrolidines were measured in Manchester as solutions in chloroform on a Varian V-4300B spectrometer operating at 40 Mc/sc. Preliminary work (sufficient to permit deductions of configuration) on the camphidines was also done in Manchester, and further measurements with chloroform solutions were made in Sheffield on an A.E.I. model RS 2 spectrometer operating at 60 Mc./sec.; where conditions were otherwise similar, $\tau$-values obtained from measurements on the two instruments agreed closely—those quoted were obtained in Sheffield. With all chloroform solutions tetramethylsilane ($\tau = 10{\cdot}0$) was used as internal reference. The hydrochlorides of *N*-methylcamphidine and 1,2-dimethylpyrrolidine were also examined in Manchester in water and $D_2O$ (see Table).

Proton magnetic resonance spectra of salts of cyclic amines: $\tau$ values for *N*-methyl groups

Salts of 1,2-dimethylpyrrolidine:

| Hydrochlorides * | | >NMeEtI * | | >NMePr$^n$I * | | >NCH$_2$PhMeI * | |
|---|---|---|---|---|---|---|---|
| Ia | Ib | Ia | Ib | Ia | Ib | Ia | Ib |
| 6·97 [a] | 7·27 [a] | 6·72 | 7·02 | 6·65 | 6·98 | 6·77 | 7·06 |

Salts of tropane:

| Hydrochlorides | | >NMe$_2$Cl | >NMeEtCl | |
|---|---|---|---|---|
| IIa | IIb | II | IIa | IIb |
| 7·29 [b] | 7·09 [b] | 6·86 and 7·01 | 7·10 | 6·97 |

Salts of 1,2-dimethylpiperidine:

| Hydrochlorides | | >NMeEtI | | >NMePr$^n$I | | >NCH$_2$PhMeI * | |
|---|---|---|---|---|---|---|---|
| IIIa | IIIb | IIIa | IIIb | IIIa | IIIb | IIIa | IIIb |
| 7·19 [c] | 7·27 [c] | 6·97 | 7·10 | 6·95 | 7·11 | 6·80 | 6·91 |

Salts of 1-methyl-4-phenylpiperidine: [d]

| Hydrochloride | >NMeEtI |
|---|---|
| 7·13 [e] | 6·85, 6·98 |

Salts of 1-methyl-*trans*-decahydroquinoline: [d]

| Hydrochloride | >NMeEtI * | >NMePr$^n$I * | >NCH$_2$PhMeI * |
|---|---|---|---|
| 7·21 [e] | 6·67, 6·83 | 6·60, 6·82 | 6·77, 6·83 |

Salts of camphidine:

| Hydrochloride * | >NMe$_2$I * | >NMeEtI * | | >NMePr$^n$I * | | >NCH$_2$PhMeI * | |
|---|---|---|---|---|---|---|---|
| IVa | IV | IVa | IVb | IVa | IVb | IV [f] | IVb |
| 7·02 [e] | 6·50 and 6·30 | 6·59 | 6·42 | 6·58 | 6·37 | — | 6·30 |

* Asterisked values are for chloroform solutions; other values for aqueous solutions. [a] Doublets, $J = 5{\cdot}3$, because of spin-coupled interaction with the proton on the nitrogen atom. The doublets persisted in aqueous solution, but collapsed to singlets in $D_2O$. [b] Doublets, $J = 5{\cdot}3$, in aqueous solution, collapsing to singlets in $D_2O$. [c] Singlets in aqueous solution, splitting into doublets ($J \simeq 5$—6) at pH $\simeq$ 1. [d] Since the configuration of quaternary salts in these systems may be assigned on other evidence (see Part IV), it may be deduced that the lower field *N*-methyl signal for each epimeric pair is associated with an equatorial *N*-methyl group. [e] Doublet in chloroform ($J = 4{\cdot}4$) and in aqueous solution at pH $\simeq$ 1 ($J = 5{\cdot}3$), collapsing to singlet in neutral aqueous solution and in $D_2O$. [f] The *N*-methyl benziodide was insufficiently soluble in chloroform or water for accurate assignment of band positions.

[9] Trojánek, Komrsová, Popíšek, and Čekan, *Coll. Czech. Chem. Comm.*, 1961, **26**, 2921.

All other spectra were measured in Sheffield; either aqueous solutions were used with an internal reference standard of dioxan [10] ($\tau = 6{\cdot}30$), or chloroform solutions were employed (standardised with tetramethylsilane) as indicated in the Table. Where solubility and sample quantity allowed, the aqueous solutions were 1·5M.

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[10] Jones, Katritzky, Murrell, and Sheppard, *J.*, 1962, 2576.