# Proton Magnetic Resonance Studies of Cyclic Compounds. Part IX.[1] The Spectra of Protonated Piperidines and Morpholines

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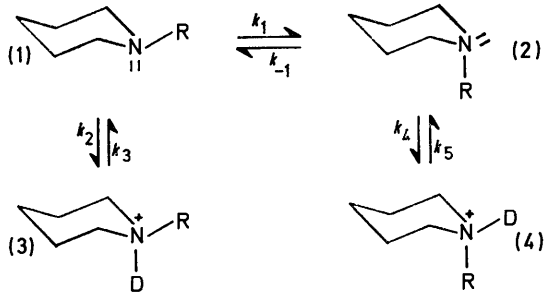
The position of equilibrium, with respect to nitrogen inversion, for *cis*-3,5-dimethylpiperidine (54% lone pair axial, 46% lone pair equatorial) was inferred from the proportions of configurations possessing $\overset{+}{N}$–D (axial) and $\overset{+}{N}$–D (equatorial) which were produced on mixing the amine with an excess of $CF_3 \cdot CO_2D$. The validity of the method was supported by experiments with model compounds, which showed (*a*) that exchange of $H^+$ (or $D^+$) during the mixing period was relatively unimportant, and (*b*) that exchange of $H^+$ (or $D^+$) in piperidine salts dissolved in $CF_3 \cdot CO_2H$ (or $CF_3 \cdot CO_2D$) was exceptionally slow.

THE three solvents most commonly used for n.m.r. spectroscopic measurements on salts of organic bases are deuterium oxide, deuteriochloroform, and trifluoroacetic acid. These will be considered in turn.

(a) *Deuterium Oxide.*—With $D_2O$ as solvent, the $\overset{+}{N}H$ signal of the salt is absent, showing that exchange has occurred, giving largely $\overset{+}{N}D$. Thus the rates of de-



SCHEME

protonation (corresponding to $k_3$ and $k_5$ in the Scheme) are appreciable under these conditions, principally because the solvent acts as a proton acceptor. Also present will be an appreciable concentration of free base (1) ⇌ (2), which can also act as a proton acceptor and therefore facilitate exchange. If the environment of R (*e.g.* R = Me) in the cations (3) and (4) are different, then *two* methyl signals will be seen in the spectrum, provided the overall rate of interconversion of (3) and (4) is appreciably less than the chemical shift difference, in Hz, between methyl protons in (3) and in (4). In effect, cations (3) and (4) are equilibrated in $D_2O$, and the relative proportions of (3) and (4) therefore reflect free energy difference between (3) and (4). The vicinal coupling $CH-\overset{+}{N}D$ is not observed because rapid deuterium exchange ($k_2$, $k_3$, $k_4$, $k_5 \gg J_{CH-\overset{+}{N}D}$) causes the life time of the relevant spin states to be too short.

An example of this behaviour occurs with 1,*c*-2,*r*-6-trimethylpiperidine hydrochloride (5) ⇌ (6) [2,3] where the

relatively slow interconversion of (5) and (6) is due to slow nitrogen inversion ($k_1$ in the Scheme). Indeed, *two* crystalline hydrochlorides, corresponding to (5) and (6) have been isolated and each has been shown to undergo deuterium exchange on the nitrogen without loss of configuration.[4,5] Since (5) was expected to be more stable than (6), the stronger signals in the spectrum of (5) ⇌ (6), in $D_2O$, were assigned to (5), leading to a

[1] Part VIII, H. Booth and A. H. Bostock, *J.C.S. Perkin II*, 1972, 615.
[2] Y. Kawazoe, M. Tsuda, and M. Ohnishi, *Chem. and Pharm. Bull.* (*Japan*), 1967, **15**, 51.
[3] Y. Kawazoe and M. Tsuda, *Chem. and Pharm. Bull.* (*Japan*), 1967, **15**, 1405.
[4] R. E. Lyle, personal communication.
[5] Y. Kawazoe and co-workers, reported in ref. 4.

finding of 66 and 34% for the proportions of (5) and (6) respectively.[2,3]

We have attempted to extend these observations to *c*-3,4,*r*-5-trimethylmorpholine hydrochloride (7) ⇌ (8). Two samples of 3,5-dimethylmorpholine[6] both contained the *cis*-isomer (9; R = H) (see below) to the extent of at least 95%. The spectrum of (9; R = H), measured in a variety of solvents ($CDCl_3$, $CH_2Cl_2$, $CCl_4$, or $C_6H_6$) at 220 MHz, was complicated by the closeness in chemical shift of the 3,5-protons and the 2,6-axial protons. In the six-line signal of the 2,6-equatorial protons (solvent $CCl_4$), the strongest lines were separated by *ca.* 7·7 Hz [$= J_{AX} + J_{BX}$, see (9)]. Making the reasonable assumption that the geminal coupling constant $J_{AX}$ is *ca.* −11 Hz, it follows that $J_{BX}$ is *ca.* 3·3 Hz. However, this value could be due either to $J_{3a,2e}$ in the *cis*-isomer (9; R = H), or to $\frac{1}{2}(J_{3a.2e} + J_{3e.2a})$ in the *trans*-isomer, since the latter will consist of two degenerate and rapidly interconverting conformations. Fortunately, the problem of assigning a configuration to 3,5-dimethylmorpholine was solved by the spectrum of the derived *N*-methyl base (9; R = Me). Full spectral details are given in Table 1, for both $CCl_4$ as solvent (60 MHz, $ABXK_3$ analysis) and $CDCl_3$ as solvent (220 MHz, first-order analysis). The values of the vicinal coupling constants $J_{BX}$ and $J_{AB}$ show that the *C*-methyl substituents are equatorial and, therefore, that the molecule is the *cis*-isomer (9; R = Me).

The hydrochloride (7) ⇌ (8) of *c*-3,4,*r*-5-trimethylmorpholine, dissolved in $D_2O$, gave a spectrum which was unchanged with time. Only one doublet, for *C*-methyl protons and only one singlet for *N*-methyl protons, were evident. The derived coupling constants (see Table 2), which are only approximate because of the first-order treatment, prove the equatorial character of both *C*-methyl groups, but give us no information on the position of equilibrium (7) ⇌ (8), since the most useful parameter $J_{3\text{-H},4\text{-H}}$ is unavailable. In an attempt to gain information on the rate of nitrogen inversion in (9; R = Me), the spectrum was studied at reduced temperatures. However, the spectrum, recorded down to −100° in $CFCl_3$, showed no changes, apart from slight line broadening at −95 to −100°, probably due to an increase in viscosity.

Table 1

Spectral data for *c*-3,4,*r*-5-trimethylmorpholine (9; R = Me) (chemical shifts in τ, *J* in Hz)

| | $CCl_4$ | $CDCl_3$ |
|---|---|---|
| *C*-Methyl | 9·10 | 9·01 |
| *N*-Methyl | 7·85 | 7·74 |
| $H_X$ (2e- or 6e-H) | 6·49 | 6·34 |
| $H_A$ (2a- or 6a-H) | 6·90 | 6·75 |
| $H_B$ (3a- or 5a-H) | 7·90 | 7·75 |
| $J_{AX}$ ($J_{2a,2e}$) | 10·90 | 11·10 |
| $J_{BX}$ ($J_{3a,2e}$) | 3·05 | 3·10 |
| $J_{AB}$ ($J_{2a,3a}$) | 10·25 | 10·50 |
| $J_{CH_3\text{-}CH}$ | 6·0 | 6·5 |

Table 2

Spectral data for *c*-3,4,*r*-5-trimethylmorpholine hydrochloride in $D_2O$ [(7) ⇌ (8); 220 MHz], $CDCl_3$ [(8) ⇌ (10), 100 MHz] and $CF_3{\cdot}CO_2H$ [(8) ⇌ (10), 220 MHz]

| | Chemical shifts (τ) | | |
|---|---|---|---|
| | $D_2O$ | $CDCl_3$ | $CF_3{\cdot}CO_2H$ |
| *C*-Methyl | 8·80 | 8·49 | 8·51 |
| *N*-Methyl | 7·14 | 7·12 | 7·12 |
| 2e-H, 6e-H | 6·00 | 6·13 | 5·70 |
| 2a-H, 6a-H | 6·47 | 5·90 | 5·99 |
| 3a-H, 5a-H | 6·62 | 6·80 | 6·40 |
| | Coupling constants (Hz) | | |
| $J_{2e.2a}$ | 12·5 | 12·7 | 14·0 |
| $J_{2e.3a}$ | 2·5 | 3·55 | 3·0 |
| $J_{2a.3a}$ | 11·8 | 10·95 | 11·0 |
| $J_{CH_3\text{-}CH}$ | 6·5 | 6·5 | 6·5 |
| $J^{+}_{NCH_3\text{-}\overset{+}{N}H}$ | | 4·8 | 5·0 |

(b) *Deuteriochloroform.*—The generally lower solubility of amine salts in $CDCl_3$ (as against $D_2O$) is a disadvantage, but this is offset by the fact that the $\overset{+}{N}H$ signal may be observed at low field, usually τ −2 to +1. For example, the hydrochloride of *cis*-3,5-dimethylpiperidine, m.p. 224—229°, in $CDCl_3$, gave a spectrum showing a broad $\overset{+}{N}H$ resonance at τ 0·6; the hydrochlorides of *cis*- and *trans*-decahydroquinoline each gives two $\overset{+}{N}H$ signals at τ 0·34 and 0·89 (*cis*), and at

[6] Wyandotte Chemicals Corporation, B.P. 835,717 (*Chem. Abs.*, 1961, **55**, 2696).

[7] J. K. Becconsall, R. A. Y. Jones, and J. McKenna, *J. Chem. Soc.*, 1965, 1726; R. E. Lyle and C. R. Ellefson, *J. Amer. Chem. Soc.*, 1967, **89**, 4563; D. R. Brown, R. Lygo, J. McKenna, J. M. McKenna, and B. G. Hutley, *J. Chem. Soc.* (*B*), 1967, 1184; M. J. T. Robinson, *Tetrahedron Letters*, 1970, 691; J. B. Lambert, D. J. Bailey, and F. Michel, *Tetrahedron Letters*, 1970, 691.

τ 0·37 and 0·73 (*trans*). In general, the appearance of the spectrum is a function of the basic strength of the amine and of the purity of the $CDCl_3$ used. In most cases, sufficient proton acceptor (*e.g.* free base or water in solvent) is present to cause $k_3$ and $k_5$ (Scheme) to be appreciable. In this case the protonated species (3) and (4) are equilibrated, although the proportions of (3) and (4) may be different from those measured in $D_2O$ (solvent effect) or may depend on the nature of the anion,[2] or on concentration,[2,8] in the latter case, perhaps, because ion pairs are present. Whether CH–$\overset{+}{N}$H proton coupling is observable depends on the concentration of acid in the system. In acid-free $CDCl_3$, and with pure hydrochloride, CH–$\overset{+}{N}$H proton coupling is not usually observed, because $k_3$ and $k_5$ are relatively large; at higher acid concentrations, CH–$\overset{+}{N}$H proton coupling is observed. When intermediate concentrations cause the signals of protons on carbon atoms α to nitrogen to be undesirably broad, an effective remedy is the introduction of a small quantity of dry HCl gas.

The initially determined spectrum of 1,*c*-2,*r*-6-trimethylpiperidine hydrochloride, m.p. 272°, in a sample of $CDCl_3$ not specially treated, showed only the characteristics of configuration (5), together with CH–$\overset{+}{N}$H proton coupling.

After 5 min, the spectral characteristics of configuration (6) began to appear, but equilibrium was not reached until 30 h had elapsed. At this stage, the proportions of (5) and (6) were 52 and 48% respectively, figures which are different from those obtained in $D_2O$ as solvent (see earlier). The assignment of the low-field *N*-methyl doublet to configuration (5), with *N*-methyl equatorial (see Table 3) is tentative, since the signal for the 2,6-axial protons does not allow an accurate determination of $J_{2a,\overset{+}{N}H}$.

TABLE 3

Chemical shifts (τ) for protons in 1,*c*-2,*r*-6-trimethylpiperidine hydrochloride (60 MHz, $CDCl_3$)

| | Configuration (5) | Configuration (6) |
|---|---|---|
| *C*-Methyl | 8·45 [a] | 8·55 [a] |
| *N*-Methyl | 7·15 [b] | 7·42 [c] |
| 2,6-Axial | 6·85 [d] | 6·55 [d] |

[a] Doublet, *J* 6·0 Hz. [b] Doublet, *J* 5·3 Hz. [c] Doublet, *J* 5·5 Hz. [d] Multiplet.

The spectrum of *c*-3,4,*r*-5-trimethylmorpholine hydrochloride, in $CDCl_3$, at first showed a rather broad singlet for the *N*-methyl protons, but a well-resolved doublet (*J* 4·8 Hz) resulted from treatment of the solution with a trace of dry hydrogen chloride. The 2a-H and 2e-H nuclei form the AB part of an $ABXK_3$ system, and the observed eight-line multiplet was analysed in the usual manner (details in Table 2). Irradiation of the *C*-methyl doublet caused simplification of the broad resonance of the 3,5-axial protons to a clean eight-line pattern containing two large couplings (8·5; 10·7 Hz) and *one* small coupling (3·5 Hz = $J_{3a,2e}$). Of the two large couplings, that of 10·7 corresponds to $J_{2a,3a}$, for which analysis of the AB octet had previously given 10·95 Hz. Therefore $J_{3a,\overset{+}{N}H}$ must be 8·5 Hz, and the exclusive, or dominant, configuration present is likely to be (10), with $\overset{+}{N}$-methyl equatorial and $\overset{+}{N}$–H axial. In view of the appreciable contribution of configuration (6) in the equilibrium (5) ⇌ (6), in $CDCl_3$, the finding that configuration (8) was strongly disfavoured, in the equilibrium (8) ⇌ (10), was unexpected. However, our findings do not exclude from consideration conformation (11), possessing a boat or twist conformation, nor a mixture of (10) and (11). Conformation (11) might allow intramolecular hydrogen bonding between the oxygen and nitrogen atoms. Moreover, this conformation is not expected to be significant when the solvent is $D_2O$ (see earlier) or $CF_3{\cdot}CO_2H$ (see later), since in these cases the oxygen will undergo preferential hydrogen bonding with solvent molecules. In this connection, it is interesting that the spectrum in $CDCl_3$ shows that the 2-proton possessing the smaller vicinal coupling ($H_B$) occurs at higher field than the 2-proton with the larger vicinal coupling ($H_A$, see Table 2). This is opposite to the situation in $D_2O$ and $CF_3{\cdot}CO_2H$ (see Table 2), and lends support to the possibility that change of solvent, to $CDCl_3$, causes the molecule to undergo a marked conformational change. However, a direct solvent effect on chemical shifts, with little or no conformational change, cannot be excluded.

(c) *Trifluoroacetic Acid.*—The strongly acidic nature of $CF_3{\cdot}CO_2H$, and of formic acid,[9] invariably allows the observation of CH–$\overset{+}{N}$H proton–proton coupling in the spectra of amine hydrochlorides. The weakly basic character of the $CF_3{\cdot}CO_2^-$ ion means that rates of proton loss ($k_3$ and $k_5$, Scheme) from the protonated species are negligibly small.

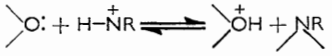
A relatively low exchange rate was originally suggested by the observation of separate signals for $CF_3{\cdot}CO_2\mathit{H}$ (τ −2) and $\overset{+}{N}\mathit{H}_2$ (τ 2—4) in the spectra of piperidines and morpholines, and *N*-alkyl derivatives, dissolved in $CF_3{\cdot}CO_2H$. The spectrum of piperidine itself, dissolved in $CF_3{\cdot}CO_2H$, shows the $\overset{+}{N}H_2$ resonance at about τ 3·1 as a triplet ($J_{N\text{-}H}$ 48 Hz), each peak being broadened considerably. Under the same conditions, morpholine shows a single broad resonance at τ 2·3 for the $\overset{+}{N}H_2$ resonance. The abnormally low rate of proton exchange was confirmed by examination of the spectra of dry piperidine salts dissolved in $CF_3{\cdot}CO_2D$, where no exchange was detectable, even after several months at room temperature. Thus 1,*c*-2,*r*-6-trimethylpiperidine hydrochloride, m.p. 272°, known to have configuration (5) from the initial spectrum in $CDCl_3$ (see above), when dissolved in $CF_3{\cdot}CO_2D$, gives a spectrum including at

[8] H. Booth and R. U. Lemieux, *Canad. J. Chem.*, 1971, **49**, 777.

[9] *Cf.* J. J. Delpuech and C. Gay, *Tetrahedron Letters*, 1966, 2603.

τ 6·95 a doublet ($J$ 5·9 Hz) for the $N$-methyl protons. After 7½ months at room temperature, the solution gave an identical spectrum. Furthermore, since the spectrum of the aged solution shows only one $N$-methyl doublet, and only one $C$-methyl doublet (τ 8·45, $J$ 7·0 Hz), characteristic of (5), it follows that configurations (5) and (6) are not equilibrated under these conditions.

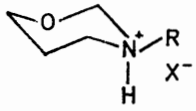
When the molecule contains even weakly basic atoms, such as oxygen, intermolecular, or intramolecular exchange [as in equation (1)] must eventually lead to



(1)

replacement of nitrogen-attached hydrogen by the deuterium of the solvent. For example, the spectrum of *c*-3,4,*r*-5-trimethylmorpholine hydrochloride (7), dissolved in $CF_3{\cdot}CO_2D$, initially gave a doublet ($J$ 5·0 Hz) for the $N$-methyl protons, but within 90 h this had been completely replaced by a singlet. An accurate assessment of $J_{3a,\overset{+}{N}H}$ and, therefore, of the proportions of (8) and (10), was not possible from the spectrum (see Table 2).

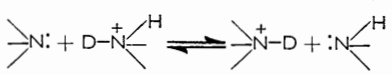
Spectral measurements also indicated rapid exchange of protons on nitrogen for 3-methyltetrahydro-1,3-oxazine hydrochloride (12) [8] in $CF_3{\cdot}CO_2D$ (complete in 90 min) and for 3-ethyltetrahydro-1,3-oxazine hydrobromide (13) [8] in $CF_3{\cdot}CO_2D$ (complete in 5 h).



(12) R = Me, X = Cl
(13) R = Et, X = Br

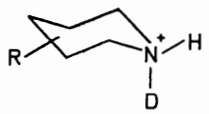
The behaviour of piperidine salts in $CF_3{\cdot}CO_2D$ suggested a possible use of $CF_3{\cdot}CO_2D$ in 'freezing' the conformational equilibrium of a piperidine [(1) ⇌ (2), R = H]. If the rate of nitrogen inversion, $k_1$, is slow compared with the rates of protonation ($k_2$, $k_4$) and if the rates of deprotonation ($k_3$, $k_5$) of the salts produced are negligible, then the rapid protonation of (1) and (2) produces (3) and (4) under conditions where (3) and (4) are not equilibrated, *i.e.* the initially determined proportions of (3) and (4) will reflect the proportions of conformations (1) and (2). However, addition of $CF_3{\cdot}CO_2D$ to the free amine (1) ⇌ (2) to produce (3) and (4) is not equivalent to examination of (3) and (4) in $CF_3{\cdot}CO_2D$. In particular, during the mixing period, local concentrations of free base may be appreciable, and therefore reactions involving proton (or deuterium) abstraction by free base may be significant [equations (2) and (3)].

(2)

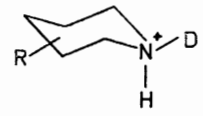


(3)

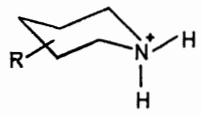
In the case of a piperidine, treated with $CF_3{\cdot}CO_2D$, any significant intrusion of these exchange reactions during the mixing period will lead not only to the expected species (14) and (15), but also to (16) and (17).



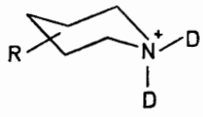
(14)



(15)



(16)



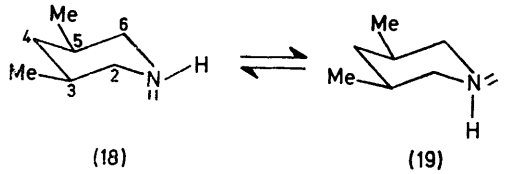
(17)

To determine whether exchange during mixing was significant, a control experiment with di-(n-butyl)amine was carried out. The amine, freshly dried by sodium, was projected in a fine stream into an excess of ice-cold $CF_3{\cdot}CO_2H$ in an n.m.r. sample tube. In the spectrum of the resulting cation $(Me[CH_2]_3)_2\overset{+}{N}H_2$, the methylene protons α to the nitrogen atom appeared as a quintet, the intensities being approximately 1 : 4 : 6 : 4 : 1. Thus the observed signal was that expected from a first-order analysis, the magnitude of $J_{CH-\overset{+}{N}H}$ being similar to that of $J_{CH-CH}$. The experiment was repeated using $CF_3{\cdot}CO_2D$ instead of $CF_3{\cdot}CO_2H$. If exchange reactions during mixing were significant, then an appreciable proportion of $(CH_3[CH_2]_3)_2\overset{+}{N}H_2$ would result, and the outer lines of the 1 : 4 : 6 : 4 : 1 quintet would be observable. In the event, the lowest field signal of the quintet was not seen, even at highest gain; on the high-field side, a weak signal was visible at the expected position, but its intensity was less than 5% of that expected if the ion produced had consisted entirely of $(CH_3[CH_2]_3)_2\overset{+}{N}H_2$. Moreover, the proportion of $CF_3{\cdot}CO_2H$ impurity in the $CF_3{\cdot}CO_2D$ was determined as 3%. It was concluded that the period during which free base and $CF_3{\cdot}CO_2D$ were mixed did not involve significant exchange between unreacted base and deuteriated, or protonated base.

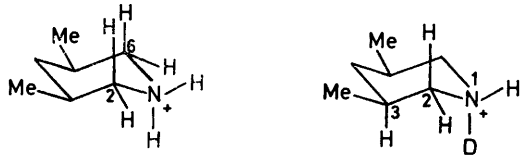
An attempt was then made to determine the position of conformational equilibrium (18) ⇌ (19) in *cis*-3,5-dimethylpiperidine. This base was chosen for two reasons: (*a*) the ring-inversion process is almost completely biased towards that conformation with both methyl substituents equatorial; (*b*) the pronounced shielding effect of equatorial methyl on adjacent, axial hydrogen allows the signals for the 2,6-axial hydrogen to be well shifted from other signals in the spectrum of protonated base (20).

When *cis*-3,5-dimethylpiperidine was dissolved in an excess of $CF_3{\cdot}CO_2H$ the resulting solution, containing (20), gave a spectrum in which the 2,6-axial hydrogen atoms appeared at τ 7·30 as a quartet with separations of about 12 Hz, due to approximately equal couplings with the 1a,2e(6e)- and 3a(5a)-protons. Each signal

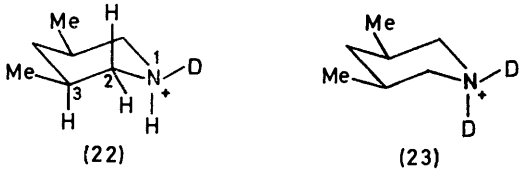
was a doublet (separation 2·5 Hz) due to the further coupling with 1e-H. Next, pure, dry *cis*-3,5-dimethylpiperidine was projected in a fine stream into ice-cold $CF_3{\cdot}CO_2D$. A spectrum obtained on this solution within



(18) (19)



(20) (21)



(22) (23)

10 min showed a group of seven lines centred on τ 7·30. This septet consisted of a triplet and a quartet with identical chemical shifts. The triplet (separations *ca.* 12 Hz) was assigned to the 2,6-axial protons of (21) which are coupled, about equally, to 2e-H(6e-H) and 3a-H(5a-H). The lines of the triplet are broadened by further couplings with 1e-H and 1a-D. The quartet (separations *ca.* 12 Hz) was assigned to the 2,6-axial protons of (22), which are coupled, about equally, to 2e-H(6e-H), 3a-H(5a-H), and 1a-H. Each line is broadened by coupling with 1e-D. As the areas of triplet and quartet constituted, respectively, 54 and 46% of the total, then the mixture contained 54% (21) and 46% (22). Consequently, *cis*-3,5-dimethylpiperidine (18) ⇌ (19) contains 54% (18), with lone pair axial, and 46% (19), with lone pair equatorial. The position of equilibrium, involving nitrogen inversion, for piperidine itself, has been determined using a variety of techniques, and the results, encompassing a wide range of values, have been collected by Jones *et al.*[10]

No change in the relative areas of triplet and quartet was detectable during the seven days following the dissolution of *cis*-3,5-dimethylpiperidine in $CF_3{\cdot}CO_2D$. However, after three weeks the ratio of areas had altered significantly, and in the direction expected from slow deuterium exchange with the solvent: thus the quartet signals were relatively weaker, and the triplet signals were relatively stronger, reflecting the increase in concentration of the fully *N*-deuteriated species (23). Only after 24 months was the exchange practically complete, the signal for 2a-H(6a-H) consisting almost entirely of a 1 : 2 : 1 triplet, with separations of 11 Hz.

We now return to a further consideration of the initial spectrum of *cis*-3,5-dimethylpiperidine in $CF_3{\cdot}CO_2D$, explained as a mixture of (21) and (22). Now the 2,6-axial protons of the ions (20) and (23) would also give rise to a quartet (separations *ca.* 12 Hz) and a triplet (separations *ca.* 12 Hz) respectively, centred on τ 7·30. However, the formation of (20) and (23) is unlikely, in view of the experiment, described earlier, involving di-(n-butyl)amine and $CF_3{\cdot}CO_2D$. The presence of appreciable concentrations of (20) and (23), in the freshly made solution, was excluded by measurements of band-widths. The half-intensity width of the quartets, in the initial spectrum of (18) ⇌ (19) in $CF_3{\cdot}CO_2D$, is significantly less (by 1·4 Hz) than that of the quartets in the spectrum of (18) ⇌ (19) in $CF_3{\cdot}CO_2H$. Also, the decrease in half-intensity width of the triplet peaks, during 24 months after preparation of the sample, is in agreement with the gradual conversion of (21) into (23). The decrease was 1·3 Hz after 5 months, and 2·1 Hz after 24 months, when only the completely deuteriated ion (23) appeared to be present.

Our interpretation of the spectrum of *cis*-3,5-dimethylpiperidine in $CF_3{\cdot}CO_2D$, contained in a preliminary publication,[11] has been criticised,[10,12,13] but we believe that all points of criticism have been answered in the full treatment presented here. McKenna and McKenna [12] assert that ' rapid irreversible acidification of the *N*-alkylpiperidines (for example, with $CF_3{\cdot}CO_2H$) gives configuration ratios for the resulting solutions which are not necessarily the same as the conformer ratios corresponding to *N*-alkyl flip for the neat, liquid bases.' This statement is based on a reasonable argument concerned with partial equilibration of cations during the mixing period, but is unsupported by experimental evidence. Moreover, our experiments with di-(n-butyl)amine support our contention that equilibration during the mixing period is not important under the conditions we describe. McKenna and McKenna, employing $^1H$ spectra, measured the ratios of the configurations of protonated 1-alkylpiperidines, observed in solutions of hydrochlorides in $D_2O$ and $CDCl_3$. These were found to be ' close ' to the ratios observed for solutions of the free bases (neat or in $CDCl_3$) acidified with $CF_3{\cdot}CO_2H$, 2-methylpiperidine being an exception. This work fails to take into account the fact that configurational equilibria between protonated piperidines is almost certainly solvent-dependent (*cf.* ref. 2). Therefore, it is not meaningful to make a simple comparison between the ratio for cations in a solution lacking $CF_3{\cdot}CO_2H$, and the ratio for the same cations in a solution containing $CF_3{\cdot}CO_2H$. Robinson's results [13] for treatment of di-

[10] R. A. Y. Jones, A. R. Katritzky, A. C. Richards, R. J. Wyatt, R. J. Bishop, and L. E. Sutton, *J. Chem. Soc.* (*B*), 1970, 127.

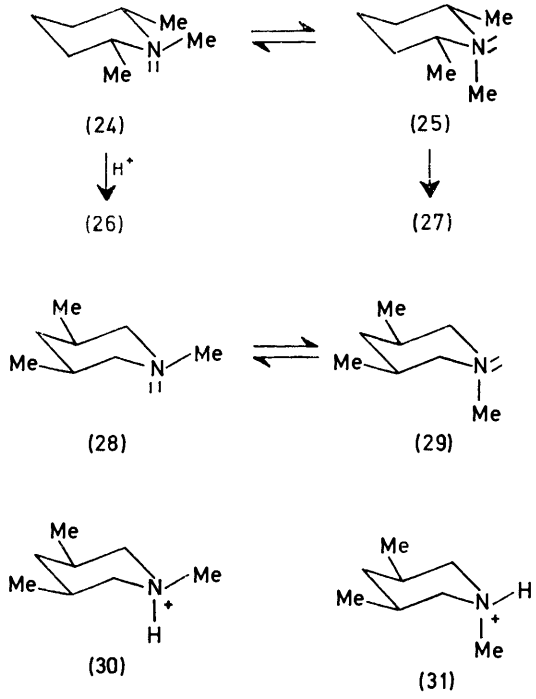
[11] H. Booth, *Chem. Comm.*, 1968, 802.

[12] J. McKenna and J. M. McKenna, *J. Chem. Soc.* (*B*), 1969, 644.

[13] M. J. T. Robinson, in ' Conformational Analysis—Scope and Present Limitations,' p. 635, Butterworths, London, 1971.

methylamine with $CF_3 \cdot CO_2D$ are at variance with our work using di-(n-butyl)amine, and are possibly due to traces of moisture in the system; Robinson obtained results similar to ours when using gaseous methylamine.[13]

Following on this work, the spectra of several amines, dissolved in $CF_3 \cdot CO_2H$, were determined. The spectrum of 1,*c*-2,*r*-6-trimethylpiperidine (24) ⇌ (25) in




$CF_3 \cdot CO_2H$ has been discussed previously.[13-15] Two *N*-methyl doublets, and two *C*-methyl doublets, were observed. If we assign the most intense signals to (26), then the proportions of (26) and (27) were found to be 63 and 37%. Making the same assumptions for this system as for the *cis*-3,5-dimethylpiperidine system considered earlier, we conclude that the equilibrium percentages of (24) and (25) are 63 and 37%. It is worth recalling that the proportions of equilibrated configurations (26) and (27), determined from solutions of the hydrochloride, were 52 and 48% ($CDCl_3$), and 66 and 34% ($D_2O$). Unfortunately, the differences in solvent prevent one from making simple comparisons.

The results just described for 1,*c*-2,*r*-6-trimethylpiperidine are to be contrasted with those for 1,*c*-3,*r*-5-trimethylpiperidine (28) ⇌ (29). Spectral details for this amine are listed in Table 4, and were obtained by a first-order analysis because highly coupled protons were well shifted in the spectrum measured at 220 MHz. The signal for 4a-H at τ 9·51 was a 1 : 3 : 3 : 1 quartet, with separations of *ca.* 13 Hz, whilst the signal for 2a-H, at τ 8·57 was a triplet with separations of *ca.* 11·0 Hz. The diequatorial character (and, therefore, *cis*-relationship) of the two *C*-methyl groups, as in (28), was thus substantiated. Spectral details for the solution of the amine in $CF_3 \cdot CO_2H$ are given in Table 4 (first-order

TABLE 4

Spectral data (220 MHz) for 1,*c*-3,*r*-5-trimethylpiperidine in $CDCl_3$ (28) ⇌ (29) and in $CF_3 \cdot CO_2H$ (30) ⇌ (31)

| | Chemical shifts (τ) | | | Approximate coupling constants (Hz) | |
|---|---|---|---|---|---|
| | $CDCl_3$ | $CF_3 \cdot CO_2H$ | | $CDCl_3$ | $CF_3 \cdot CO_2H$ |
| *C*-Methyl | 9·12 | 8·91 | $J_{2e,2a}$ | 11·5 | 12·0 |
| *N*-Methyl | 7·71 | 6·91 | $J_{2a,3a}$ | 10·5 | |
| 2e-H, 6e-H | 7·15 | 6·36 | $J_{CH_3-CH}$ | 6·5 | 6·5 |
| 2a-H, 6a-H | 8·57 | 7·37 | $J^{+}_{NCH_3-\overset{+}{N}H}$ | | 5·3 |
| 3a-H, 5a-H | 8·26 | 7·91 | | | |
| 4e-H | 8·26 | 7·92 | | | |
| 4a-H | 9·51 | 9·09 | | | |

analysis). It is clear that configuration (30) was dominant. The fact that the 2,6-axial protons (τ 7·37) appeared as a 1 : 3 : 3 : 1 quartet, with separations of *ca.* 11 Hz, establishes the axial orientation of the proton on nitrogen in the dominant configuration (30). However, a low intensity doublet (*J* 5·5 Hz) at τ 6·80, assigned to an *N*-methyl group, and accounting for less than 6% of the total *N*-methyl resonance, could not be explained except on the basis of either unexpected impurity, or configuration (31). Making the usual assumptions, we concluded that conformation (28), with *N*-methyl equatorial, constituted at least 94% of the mixture of (28) and (29). This value is considerably higher than that expected on the basis of the most recently determined Δ*G* value (0·65 kcal $mol^{-1}$) for the *N*-methyl group in *N*-methylpiperidine itself.[16] The unusually high proportion of (25) in the mixture of (25) and (24) is, possibly, a consequence of a greater steric interaction, in this case, between adjacent substituents which are both equatorial, than between substituents of which one is equatorial and one is axial.

Chemical shift data for 1,*t*-3,*r*-5-trimethylpiperidine (32) ⇌ (33) are listed in Table 5; it was not possible to interpret fully the complicated spectrum. The spectrum of the base in $CF_3 \cdot CO_2H$ was capable of a complete first-order analysis, when measured at 220 MHz. The details of Table 6 correspond with configuration (35); signals corresponding with configuration (36), which would follow protonation of (34), were not observed. The result is not unexpected; the severe repulsive interaction between axial methyl groups in (34) should ensure that the base exists almost entirely in conformations (32) and (33), with *N*-methyl equatorial. The assignments of Table 6 were based on existing knowledge of chemical shifts and coupling constants in protonated piperidines, allowing for the shielding and deshielding effects of *C*-methyl groups on adjacent protons.[17]

Attempts to use trifluoroacetic acid to 'freeze' the conformational equilibrium, due to nitrogen inversion,

[14] J. C. N. Ma and E. W. Warnhoff, *Canad. J. Chem.*, 1965, **43**, 1849.
[15] H. Booth and J. H. Little, *Tetrahedron*, 1967, **23**, 291.
[16] R. A. Y. Jones, A. R. Katritzky, A. C. Richards, and R. J. Wyatt, *J. Chem. Soc.* (*B*), 1970, 122.
[17] H. Booth, *Tetrahedron*, 1966, **22**, 615.

of *N*-substituted morpholines gave inconclusive results because signals due to only one species were observed. Now the oxygen atom of morpholines probably facilitates rapid exchange of protons. Thus the observation of only one species is due either to relatively fast nitrogen inversion, leading to fast equilibration of cations or to relatively slow nitrogen inversion, but with the position of equilibrium in the free base so biased that the n.m.r. method is insufficiently sensitive to detect the cation corresponding to the minor species.

TABLE 5

Chemical shifts ($\tau$) for protons in 1,*t*-3,*r*-5-trimethylpiperidine (32) ⇌ (33) ⇌ (34) (220 MHz, $CDCl_3$)

| | |
|---|---|
| *C*-Methyl (doublet, *J* 6·6 Hz) | 9·02 |
| *N*-Methyl (singlet) | 7·76 |
| 4-H | *ca.* 8·7 |
| $H_A$ (doublet, *J ca.* 10 Hz) | 7·59 |
| $H_B$ and 3,5-protons | *ca.* 8·0 |

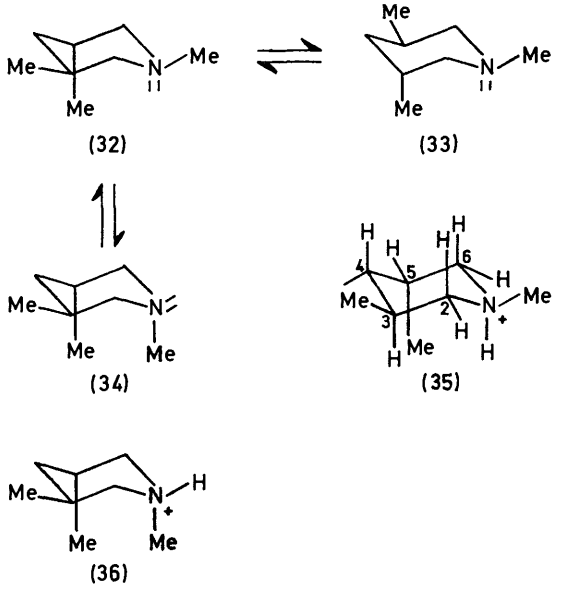



TABLE 6

Spectral data for 1,*t*-3,*r*-5-trimethylpiperidine (35) (220 MHz, $CF_3{\cdot}CO_2H$)

| Chemical shift ($\tau$) | | Coupling constants (Hz) | |
|---|---|---|---|
| *C*-Methyl (e) | 8·92 | $J_{CH_3(e)CH}$ | 6·8 |
| *C*-Methyl (a) | 8·72 | $J_{CH_3(a)CH}$ | 7·5 |
| *N*-Methyl (e) | 6·93 | $J^{+}_{NCH_3\text{-}\overset{+}{N}H}$ | 5·0 |
| 2e-H | 6·37 | $J_{1a,6a}$ | 11 |
| 2a-H | 7·35 | $J_{1a,2a} + J_{2a,3a}$ | 13·5 |
| 6e-H | 6·47 | $J_{2a,2e}$ | 12·5 |
| 6a-H | 6·80 | $J_{3a,4a}$ | 13 |
| 3a-H | 7·69 | $J_{4a,5e}$ | 5 |
| 5e-H | 7·51 | $J_{4e,4a}$ | 14 |
| 4e-H | 8·12 | $J_{5e,6a}$ | 4 |
| 4a-H | 8·51 | $J_{6e,6a}$ | 13 |

Methylation of *cis*-2,6-dimethylmorpholine gave *c*-2,4,*r*-6-trimethylmorpholine (37) ⇌ (38), the configuration of which is confirmed by the vicinal coupling constants deduced from the n.m.r. spectrum (see Table 7). The spectrum of the base in $CF_3{\cdot}CO_2H$ gave data (Table 7, first-order analysis) which represent either weighted averages of those for (39) and (40) (fast *N*-inversion) or a single conformation, (39) or (40), present in ⩾95%, the minor configuration being undetected (slow *N*-inversion). In fact, the high value of 12 Hz for $J_{3a,\overset{+}{N}H}$ suggests that conformation (39) is the major or exclusive configuration present.

A comparable situation occurs with *c*-3,4-*r*-5-trimethylmorpholine which, when dissolved in $CF_3{\cdot}CO_2H$,

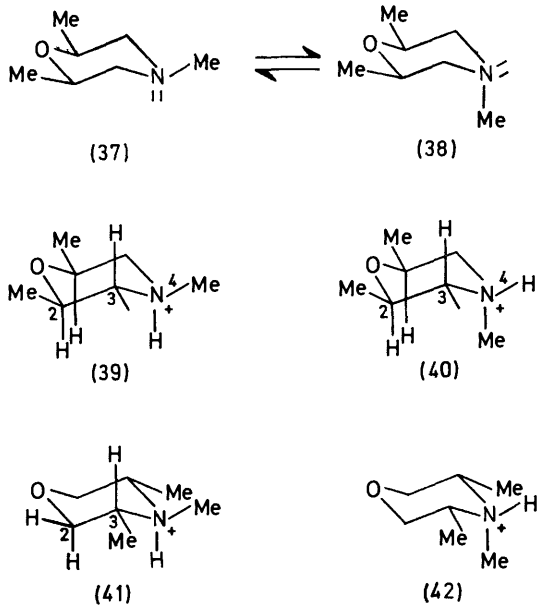



TABLE 7

Spectral data (60 MHz) for *c*-2,4,*r*-6-trimethylmorpholine in $CCl_4$ (37) ⇌ (38) and in $CF_3{\cdot}CO_2H$ (39) ⇌ (40)

| Chemical shifts ($\tau$) | | | Coupling constants (Hz) | | |
|---|---|---|---|---|---|
| | $CCl_4$ | $CF_3{\cdot}CO_2H$ | | $CCl_4$ | $CF_3{\cdot}CO_2H$ |
| *C*-Methyl | 8·95 | 8·60 | $J_{2a,3a}$ | 10·05 | 12·0 |
| *N*-Methyl | 7·88 | 6·92 | $J_{2a,3e}$ | 2·25 | |
| 2a-H, 6a-H | 6·50 | 5·90 | $J_{3e,3a}$ | 11·40 | 12·0 |
| 3e-H, 5e-H | 7·49 | 6·40 | $J_{3a,\overset{+}{N}H}$ | | 12·0 |
| 3a-H, 5a-H | 8·47 | 7·12 | $J_{CH_3\text{-}CH}$ | 6·3 | 6·0 |
| | | | $J^{+}_{NCH_3\text{-}\overset{+}{N}H}$ | | 5·0 |

gives a spectrum containing only one *N*-methyl doublet and only one *C*-methyl doublet. Full analysis of this spectrum was impossible because all ring protons had similar shifts. However, the spectrum obtained using a mixture of $CDCl_3$ (*ca.* 75%) and $CF_3{\cdot}CO_2H$ (*ca.* 25%) was interpretable because, whilst the geminal 2,6-protons now have identical shifts, the 3,5-protons are well shifted from them. The identical shifts of 2e-H and 2a-H lead to a ' deceptively simple ' [18] spectrum, in which the 2e- and 2a-H protons give a doublet (separation *ca.* 7 Hz), and the 3,5-protons appear to be coupled equally to 2,6-equatorial and -axial protons by an averaged coupling of 6·7—7·0 Hz [$= \frac{1}{2}(J_{a,a} + J_{a,e})$]. The further coupling of the 3,5-protons with the methyl protons (*J* 7 Hz) and with the 4-proton ($J_{3a,4H}$ 13—14 Hz) causes the 3,5-proton signal to be a simple septet,

[18] R. J. Abraham and H. J. Bernstein, *Canad. J. Chem.*, 1961, **39**, 216.

with spacings of *ca.* 6·5—7·0 Hz. The value of 13—14 Hz for $J_{3a,4H}$ shows that the dominant or exclusive conformation is (41), with *N*-methyl equatorial.

## EXPERIMENTAL

G.l.c. employed a Perkin-Elmer 800 gas chromatograph (analytical) and a Wilkens Autoprep A700 gas chromatograph (preparative). Columns were packed with Carbowax 20M on a support of alkali-treated Chromosorb W (80—100).

$^1$H N.m.r. were recorded on Perkin-Elmer R10 (60 MHz), Varian HA-100 (100 MHz), and Varian HR-220 (220 MHz) spectrometers.

M.p.s were obtained on a Kofler hot stage. Methylation of secondary amines was carried out using the Eschweiler–Clarke procedure.[19]

The synthesis of 1,*c*-2,*r*-6-trimethylpiperidine, and 1,*t*-2,*r*-6-trimethylpiperidine have already been described.[20]

cis-3,5-*Dimethylpiperidine.*—(i) Sodium (30 g) was added in small pieces, to a boiling solution of 3,5-dimethylpyridine (25 g) in ethanol (500 ml). The mixture was heated under reflux for 3 h, cooled, and acidified with concentrated hydrochloric acid. When ethanol had been removed under reduced pressure, the residue was cooled and basified with sodium hydroxide solution (40%). Extraction with ether, followed by distillation of the dried extracts, gave a mixture (26·8 g), b.p. 138—148°, of *cis*- and *trans*-3,5-dimethylpiperidines (95%, by analytical g.l.c.) together with 3,5-dimethyl-1,2,3,6-tetrahydropyridine (5%). The mixture (10 g), dissolved in ethanol (100 ml) containing concentrated hydrochloric acid (10 ml) was hydrogenated over Adams platinum oxide catalyst (1 g) until uptake of hydrogen ceased. The usual method of recovery gave a mixture (8·0 g), b.p. 139—143°, of *cis*- and *trans*-3,5-dimethylpiperidines.

(ii) 3,5-Dimethylpyridine (10 g) in ethanol (250 ml) was hydrogenated at 180° and 230 atm. initial pressure of hydrogen over Raney nickel W6 catalyst. After 48 h, the mixture was filtered and distilled, giving a mixture (9·2 g), b.p. 138—144°, of *cis*- and *trans*-3,5-dimethylpiperidines. The mixture resisted all attempts at separation by g.l.c. The mixture (4·0 g), dissolved in dry ether (150 ml) was treated with dry hydrogen chloride until no more precipitation occurred. The mixed hydrochlorides were filtered and crystallised several times from acetone–ether, yielding pure cis-3,5-*dimethylpiperidine hydrochloride* (2·1 g), as needles, m.p. 224—229° (Found: C, 56·0; H, 10·8; N, 9·2. $C_7H_{16}ClN$ requires C, 56·2; H, 10·8; N, 9·4%).

Treatment of the hydrochloride with aqueous sodium hydroxide, followed by extraction into ether, gave *cis*-3,5-dimethylpiperidine, b.p. 140—150° (bath-temp.) at 750 mmHg. The *cis*-geometry was established from the n.m.r. spectrum in $CDCl_3$, which showed a doublet (*J ca.* 12 Hz) at τ 7·08 for 2e- and 6e-H, and a triplet (*J ca.* 12 Hz) at τ 7·96 for 2a- and 6a-H.

1,c-3,r-5-*Trimethylpiperidine and* 1,t-3,r-5-*Trimethylpiperidine.*—The mixture of *cis*- and *trans*-3,5-dimethylpiperidines obtained in (i) and (ii) (above) were separately methylated by the Eschweiler–Clarke method, giving mixtures of 1,*c*- and 1,*t*-3,*r*-5-trimethylpiperidines, b.p. 142—146°. Analytical g.l.c. using a 12 ft × 1/8 in column at 70° showed the presence of *cis*-base [68% from (i); 85% from (ii)] and *trans*-base [32% from (i); 15% from (ii)], the latter having the shorter retention time. Separation on the preparative scale was achieved using a 100 ft × 3/8 in column at 85°. 1,*c*-3,*r*-5-Trimethylpiperidine (95% pure, by analytical g.l.c.) had b.p. 143—145° at 760 mmHg and gave a picrate as yellow needles (from EtOH), m.p. 141—142° (lit.,[2] 145—147°). 1,*t*-3,*r*-5-Trimethylpiperidine (95% pure, by analytical g.l.c.) had b.p. 144—145° at 760 mmHg and gave a methiodide as prisms, m.p. 233—235° (lit.,[2] 236—238°). The tertiary amines were also separated by chromatography on alumina, as described.[2]

cis-3,5-*Dimethylmorpholine.*—Commercial 3,5-dimethylmorpholine contained largely (≥95%) one isomer, on the basis of analytical g.l.c. using a 12 ft × 1/8 in column. The base mixture was treated with an excess of carbon disulphide and the precipitated solid was washed with ether and crystallised from ethanol. cis-3,5-*Dimethylmorpholinium* cis-3,5-*dimethylmorpholine*-N-*carbodithioate* had m.p. 156—158° (Found: C, 51·1; H, 8·7; N, 9·1. $C_{13}H_{26}N_2O_2S_2$ requires C, 51·0; H, 8·6; N, 9·2%).

c-3,4,r-5-*Trimethylmorpholine.*—Commercial 3,5-dimethylmorpholine was methylated by the Eschweiler–Clarke method and the resulting mixture was purified by preparative g.l.c. using a 25 ft × 3/8 in column at 120°. *c*-3,4,*r*-5-Trimethylmorpholine (≥99% pure by analytical g.l.c.) had b.p. 146—147° at 760 mmHg. The *picrate*, yellow needles from EtOH, had m.p. 203—205° (Found: N, 15·5. $C_{13}H_{18}N_4O_8$ requires N, 15·6%). The *hydrochloride*, from $Me_2CO$, had m.p. 280° (Found: C, 51·2; H, 9·7; N, 8·2. $C_7H_{16}ClNO$ requires C, 50·9; H, 9·8; N, 8·5%).

c-2,4,r-6-*Trimethylmorpholine and* t-2,4,r-6-*Trimethylmorpholine.*—Commercial 2,6-dimethylmorpholine was separated into *cis*- and *trans*-isomers, as described previously.[21] Each base was converted into its *N*-methyl derivative in the usual manner.

The mixture of *N*-methyl bases obtained by methylation of commercial 2,6-dimethylmorpholine was successfully separated by preparative g.l.c. using a 25 ft × 3/8 in column at 130°. *c*-2,4,*r*-6-Trimethylmorpholine (≥98% pure by g.l.c.) had b.p. 136° at 761 mmHg, and gave a *picrate*, m.p. 156—158° (Found: C, 43·2; H, 4·9; N, 15·5. $C_{13}H_{18}N_4O_8$ requires C, 43·6; H, 5·1; N, 15·6%). *t*-2,4,*r*-6-Trimethylmorpholine (≥98% pure by g.l.c.) had b.p. 138° at 761 mmHg and gave a *picrate*, m.p. 183—184° (Found: C, 43·4; H, 5·1; N, 15·5. $C_{13}H_{18}N_4O_8$ requires C, 43·6; H, 5·1; N, 15·6%).

We are indebted to I.C.I. (Mond) Ltd., and the Wyandotte Chemicals Corporation, for generous gifts of 3,5-dimethylmorpholine. We thank I.C.I. (Runcorn) Ltd., and the S.R.C. 220 MHz Service, for spectra at 220 MHz.

[2/083 *Received*, 14*th January*, 1972]

[19] *Cf.* M. L. Moore, *Org. Reactions*, 1949, **5**, 301.
[20] H. Booth, J. H. Little, and J. Feeney, *Tetrahedron*, 1968, **24**, 279.
[21] H. Booth and G. C. Gidley, *Tetrahedron*, 1965, **21**, 3429.