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MAGNETIC ANISOTROPY AND THE INTERPRETATION OF THE NMR SPECTRA OF LACTAMS—I

N-SUBSTITUTED PIPERIDONES

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Abstract—The NMR spectra of a number of N-substituted piperidones have been measured, and an unusually large difference in the chemical shifts of the methylene protons attached to the ring nitrogen has been observed. The magnitude of this difference can be related to the stereochemistry of the ring compound which is also attached to these methylene protons. The explanation of this difference is believed to lie in the shielding effect of the ring keto-group, and this explanation has been confirmed by examining the spectra of a parallel series of compounds in which this keto-group is not present.

IN ORDER to interpretate the reactions of a number of N-substituted piperidines, it was necessary to know the stereochemistry of the N-substituted piperidones which were formed by treatment of the amines with mercury (II) ethylenediamine tetra-acetate,[3] and this paper describes how this has been accomplished using NMR spectroscopy. During these investigations, however, a number of interesting features were observed in the NMR spectra, and these are now reported. The lactams were of the general formula as shown in Fig. 1, and the six compounds shown in Table 1

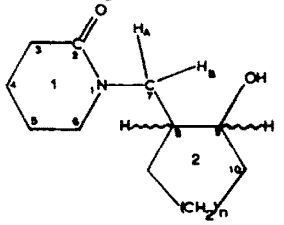

FIG. 1. General formula of the investigated piperidones.

TABLE 1. SUMMARY OF THE INVESTIGATED PIPERIDONES

Compound	Configuration	$n=$	Ring name
I	*cis*	1	cyclopentyl
II	*trans*	1	cyclopentyl
III	*cis*	2	cyclohexyl
IV	*trans*	2	cyclohexyl
V	*cis*	3	cycloheptyl
VI	*trans*	3	cycloheptyl

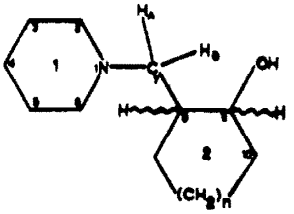

FIG. 2. General formula of the investigated piperidines.

TABLE 2. SUMMARY OF THE INVESTIGATED PIPERIDINES

Compound	Configuration	n =	Ring name
VII	*cis*	1	cyclopentyl
VIII	*trans*	1	cyclopentyl
IX	*cis*	2	cyclohexyl
X	*trans*	2	cyclohexyl
XI	*cis*	3	cycloheptyl
XII	*trans*	3	cycloheptyl

have been investigated. As a comparison compounds of the general formula as shown in Fig. 2, and as set out in Table 2 have also been investigated.

It is well known that NMR spectroscopy can be used to determine the configuration of the OH group in ring 2, when this ring is cyclohexyl, i.e. $n = 2$;[4] and an earlier paper[5] has extended this method to the cyclopentyl system, i.e. $n = 1$. In the case where $n = 3$, it was realized that the greatly increased flexibility of the cycloheptyl ring might make the method rather unreliable, but it was hoped that parallels could be drawn between the NMR spectra of the three types of ring compounds, and this was indeed the case. The NMR results of the lactams are set out in Table 3 (compounds I–VI), and of the amino alcohols in Table 4 (compounds VII–XII).

TABLE 4. SUMMARY OF THE NMR DATA OF THE INVESTIGATED PIPERIDINES

Compound	Configuration	Chemical shift τ	Coupling constants in c/s		B.W.[c] H_9	OH Chem. Shift τ
		H_9	$J_{9/10a}$	$J_{9/10e}$		
VII	*cis*	5·72			17 c/s	4·25
VIII	*trans*	6·26			24 c/s	5·10
IX	*cis*	6·17	5·1	3·2	13 c/s	4·10
X	*trans*	6·63	9·5	4·5	24 c/s	3·40
XI	*cis*	6·05	8·5[b]	4·0[b]	16 c/s	3·95
XII	*trans*	6·50			19 c/s	2·80

[a] Centre of an unresolved multiplet.

[b] Time averaged coupling constants.

[c] Band width (B.W.) measured between the outermost lines. For an explanation of this technique see H. Feltkamp and N. C. Franklin.[6]

TABLE 3. SUMMARY OF THE NMR DATA OF THE INVESTIGATED PIPERIDONES

Compound	Configuration	Chemical shift τ					Coupling constants in c/s					R.W.[1]
		H_{7a}	H_{7b}	H_2	H_3	H_6	J_{7a7b}	J_{2a3}	J_{7a8}	$J_{8/10e}$	$J_{8/10a}$	H_8
I	*cis*	5·87	7·36	6·13	7·62	6·68	14·0	11·0	3·5			9 c/s
II	*trans*	6·52	6·73	6·18	7·62	6·70	13·7	6·5	6·5			19·5 c/s
III	*cis*	5·94	7·57	6·41	7·61	6·72	14·0	11·0	3·4			9 c/s
IV	*trans*	6·13	6·95	6·84	7·61	6·67	14·0	3·9	3·2	9·5	5·0	23 c/s
V	*cis*	5·87	7·55	6·39	7·64	6·69	14·0	11·5	4·0			10 c/s
VI	*trans*	6·23	6·84	6·64[a]	7·64	6·69	14·0	6·5	3·5			~18 c/s

The configuration of the OH group in compounds I, 1-[(*cis*-2-hydroxy-cyclopentyl)methyl]piperidone-(2), and II, 1-[(*trans*-2-hydroxy-cyclopentyl)methyl]piperidone-(2), could be assigned by comparison of the chemical shift[5] and band width of the C_9 proton (Fig. 3A and 3B), for in the *cis* compound I this proton gave rise to a peak at 6·13 τ, band width (B.W.) at $\frac{1}{2}$ band height[6] of 9 c/s, whilst in the *trans* compound the corresponding peak appeared at 6·18 τ, band width 19·5 c/s. It can thus be deduced that in the *cis* compound the OH group is in the quasi-axial position, and in the *trans* compound, in the quasi-equatorial position.

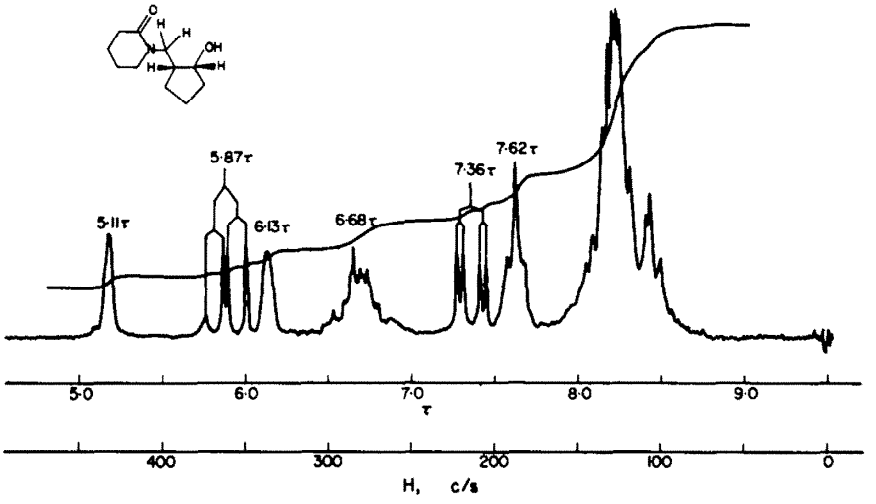

FIG. 3A. The NMR spectrum of 1-[(*cis*-2-hydroxycyclopentyl) methyl] piperidone-(2), (I).

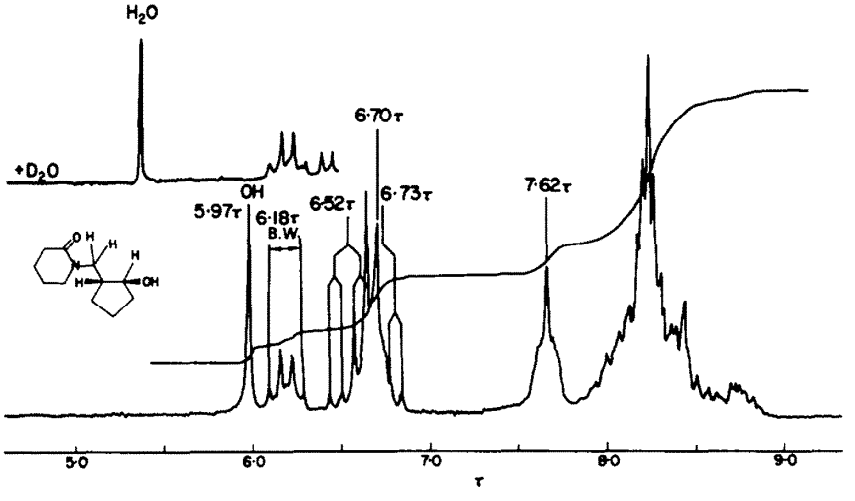

FIG. 3B. The NMR spectrum of 1-[(*trans*-2-hydroxycyclopentyl)methyl]piperidone-(2), (II).

In addition though, there was a considerable difference in the general appearance of the spectra of the *cis* and *trans* compounds. In the *cis* compound I a pair of doublets (1 proton), appeared at 5·87 τ and again at 7·36 τ (1 p), and an ill-defined multiplet at 6·68 τ (2 p); whilst in the *trans* compound a multiplet appeared at about 6·60 τ (4 p). In the *cis* compound I, it seemed that the peaks at 5·87 τ and 7·36 τ were the A and M parts of an AMX system, and this was later confirmed by spin decoupling experiments on the corresponding *cis* cyclohexyl compound III.

Examination of the spectrum of the *trans* compound II showed that the multiplet around 6·60 τ could also be interpreted on the basis of a similar ABX system, the total of 4 protons in this region being due to H_A (6·52 τ) and H_B (6·73 τ) plus two other protons. In both the *cis* and *trans* isomers these peaks were thus due to the protons on C_7, and a detailed analysis of the 2 three-spin systems gave, in the *cis* compound I, the following constants: (it is anticipated that equal signs will be obtained for J_{AX} and J_{BX} because these are vicinal coupling constants), $|J_{AB}| = 14{\cdot}0$ c/s, $J_{AX} = 11{\cdot}0$ c/s, and $J_{BX} = 3{\cdot}5$ c/s, whilst for the *trans* compound II, the values were $J_{AB} = 13{\cdot}7$ c/s, $J_{AX} = 6{\cdot}5$ c/s, and $J_{BX} = 6{\cdot}5$ c/s.

Hence in the *cis* compound I, the 7a proton must be *anti* to the C_8 proton, whilst the 7b proton must be in a *syn* position. In the case of the *trans* isomer II, however, no such clear information can be obtained, because both vicinal couplings have the same value of 6·5 c/s, which, *a priori*, can be the result of either similar dihedral angles or free rotation about C_7–C_8. The reason for the non-equivalence of the two protons on C_7 in both the *cis* I and *trans* II compounds is primarily the asymmetric centre on C_8, but it seems obvious, that this factor alone cannot explain why these C_7 protons in the *cis* compound I possess a much greater degree of magnetic anisotropy than the same C_7 protons in the *trans* isomer II.

It is recognized that magnetic non-equivalence can be due to a number of factors,[7] but it appears that the work of Bohlmann *et al.*[8] leads to a reasonable explanation of these results. If the molecule is fixed in a particular conformation, the spatial arrangement between the methylene protons on C_7 and the keto group can be such that the 7a and 7b protons are differentially shielded by the keto group.

Although it is not absolutely essential for the molecule to be fixed in a particular conformation to give the differential shielding observed, for the preference for a particular rotamer may be quite sufficient, it has been shown that intra-molecular hydrogen bonding does occur by IR measurements.[9] This hydrogen bonding could provide the constraining factor required to fix the molecules in a particular conformation, but there are several possible sites where hydrogen bonding could occur.

If the OH hydrogen bonds to the piperidino-nitrogen as in Fig. 4 a conformation is obtained which could explain many of the observations. It is thought likely that this is the preferred conformation for several reasons; bonding is more likely to

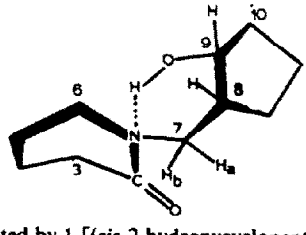

FIG. 4. The conformation adopted by 1-[(*cis*-2-hydroxycyclopentyl) methyl] piperidone-(2), (I).

occur to the piperidino-nitrogen than to the piperidino-keto group, plus the fact that the 6-membered ring formed in the former case is more stable than the 8-membered ring formed in the latter. In addition the 6-membered ring will be less flexible than the 8-membered ring, and hence the spatial relationship between the C_7 protons and the keto group is more fixed giving the large difference in shielding, as observed in the *cis* compound I. It is quite possible to envisage the situation where the 7b proton lies more in the keto de-shielding cone than the 7a proton which might lie more in the C=O plane as shown in Fig. 5.

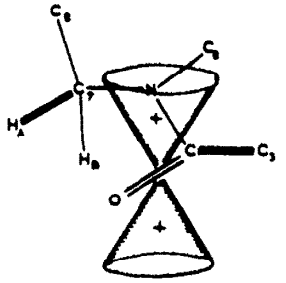

FIG. 5. The spatial relationship between the C_7 protons and the keto-group in 1-[(*cis*-2-hydroxycyclopentyl) methyl] piperidone-(2), (I).

This arrangement is very similar to that found by Bohlmann for the methylene protons on the C_6 atom in quinolizidine,[8a] where magnetic non-equivalence was observed.

In the case of the *trans* compound it is not absolutely necessary to postulate hydrogen bonding and fixation of the molecule to explain the differential shielding for the chemical shift difference between the 7a and 7b protons is sufficiently small to be accounted for by the asymmetric centre on C_8. However, if, as the IR shows, hydrogen bonding is present, then the spatial arrangement could approximate to that shown in Fig. 6, where the 7a and 7b are almost equally effected by the keto group.

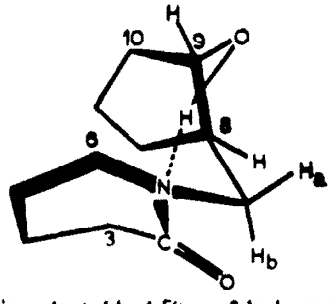

FIG. 6. The conformation adopted by 1-[(*trans*-2-hydroxycyclopentyl)methyl] piperidone-(2), (II).

The remaining characteristic peak in the NMR spectrum was that due to the C_3 protons which in the *cis* cyclopentyl compound appeared at 6·68 τ, and in the *trans* cyclopentyl compound at 6·70 τ.

The NMR spectra of the corresponding cyclohexyl compounds III and IV showed a similar pattern; the configuration of the OH group was determined from the chemical shift and band width of the C_9 proton, which in the *cis* compound III appeared at 6·41 τ, band width 9 c/s, and in the *trans* compound IV at 6·84 τ, band

width about 23 c/s. Although this peak at 6·41 τ was not resolved in the *cis* compound, the narrowness of the band confirmed the equatorial orientation of the C_9 proton which would, under such circumstances, be coupled with its neighbouring protons with small coupling constants, giving rise to the narrow band width. In the *trans* compound IV the peak at 6·84 τ showed the following splittings, 9·5 c/s and 5 c/s and if the reasonable assumption is made that in this system $\nu_A - \nu_B \gg J_{AB}$ then this peak may be analysed as the X approximation, and the splittings equated with the coupling constants. The appearance of the large triplet confirmed the axial orientation of the C_9 protons which thus had two axial neighbours. The equatorial proton on C_{10} resulted in each line of the triplet being further split into a doublet with the smaller coupling constant.

The methylene protons on C_7 also appeared at different fields in the *cis* and *trans* compounds, giving the same type of AMX spectra. From a detailed analysis, the following constants were obtained: *cis* compound III, $H_{7a} = 5{\cdot}94$ τ, $H_{7b} = 7{\cdot}57$ τ, $|J_{7a/7b}| = 14{\cdot}0$ c/s, $J_{7a/8} = 11{\cdot}0$ c/s and $J_{7b/8} = 3{\cdot}4$ c/s, *trans* compound IV, $H_{7a} = 6{\cdot}13$ τ, $H_{7b} = 6{\cdot}95$ τ, $J_{7a/7b} = 14{\cdot}0$ c/s, $J_{7a/8} = 3{\cdot}9$ c/s, and $J_{7b/8} = 3{\cdot}2$ c/s. Thus in the *cis* compound the spatial arrangements of the C_7 and C_8 protons is similar to that found in the corresponding cyclopentyl compound I. In the *trans* compound IV, though there are two noticeable differences when this is compared with the corresponding cyclopentyl compound II. The difference $\nu_{7a} - \nu_{7b}$ is larger, i.e. an increased shielding differential, and the coupling constants are changed. Both these facts could be explained if it is assumed that the *trans* cyclohexyl compound IV exists in the conformation as shown in Fig. 7.

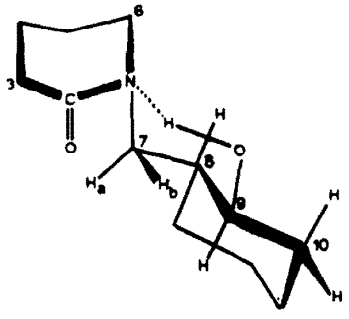

FIG. 7. The conformation adopted by 1-[(*trans*-2-hydroxycyclohexyl) methyl] piperidone-(2), (IV).

In the cycloheptyl compounds V and VI the C_9 proton was only visible in the *cis* compound V at 6·39 τ, band width 10 c/s, whilst in the *trans* compound VI this peak was partially screened by the peak at 6·69 τ due to the C_6 protons, so although it was likely that the configurations were as suggested, confirmation was sought for this. The appearance of the ABX system for the C_7 and C_8 protons removed any further doubts, for in the *cis* compound this appeared as a pair of doublets at 5·87 τ and 7·55 τ, whilst in the *trans* compound these appeared at 6·23 τ and 6·84 τ. The coupling constants in the *cis* compound V were very similar to those found in the other *cis* compounds I and III, and hence the spatial relationship between the C_7 and C_8 protons must be similar. In the *trans* compound though these coupling

constants were $J_{7a/8} = 6{\cdot}5$ c/s, and $J_{7b/8} = 3{\cdot}5$ c/s. It is therefore more than likely that the angle between the planes H_{7a}—C_7—C_8—H_8 is about 0–20° and between the planes H_{7b}—C_7—C_8—H_8 about 110–130°, which agrees with the most favourable conformation for the *trans* compound (Fig. 8) if hydrogen bonding is to occur, and the 7a proton is to be partially de-shielded by the keto group. In this compound, the OH peak appeared as a doublet, suggesting that the OH proton exchanges very slowly due to the hydrogen bonding, and the C_9 proton peak was broadened by coupling with the OH proton.

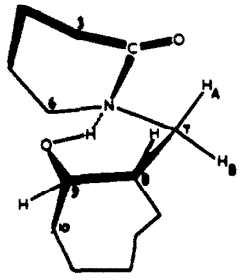

FIG. 8. The conformation adopted by 1-[(*trans*-2-hydroxycycloheptyl) methyl] piperidone-(2), (VI).

Examination of the second group of compounds, the amino alcohols VII–XII confirmed the conclusions reached about the shielding effect of the keto group, and although it was not possible to carry out an unequivocal detailed anaylsis of the spectra of these compounds, certain conclusions could be made.

It was immediately apparent that the removal of the keto group had not resulted in complete magnetic equivalence of the methylene protons on C_7, but this was to be expected due to the retention of the asymmetric centre on C_8. The NMR spectrum of the *cis* amino alcohol VII (*cis*-2-piperidinomethyl-cyclopentanol) showed the following features: a broad band at 4·25 τ (1 p), a quartet at 5·72 τ (1 p), a multiplet about 7·40 τ (3 p), a further multiplet about 7·70 τ (3 p) and a broad peak from 8–9 τ The band width of the peak at 5·72 τ, due to the proton on C_9, was 17 c/s and this suggested that this proton had a preference for the quasi-axial position on the cyclopentyl ring adjacent to the "flap" of the envelope. The corresponding *trans* amino alcohol (*trans*-2-piperidinomethylcyclopentanol, VIII) gave a spectrum where this C_9 proton appeared at 6·26 τ, band width 24 c/s, and so the configuration of the OH group was confirmed, whilst the considerations outlined in the previous paper[4] lead to the conclusion that in this case the OH group is on the "flap" of the envelope in the equatorial position, and the adjacent proton is in the axial position with a "cyclohexane-type" of environment, giving rise to the band width of 24 c/s.

The broad band at 4·25 τ in the *cis* amino alcohol VII and a similar band at 5·10 τ in the *trans* compound suggested that hydrogen bonding could occur in both compounds, and this was confirmed by IR measurements. This is not unlikely bearing in mind the basic nature of the nitrogen. Aaron *et al.*[10] have found in some hydroxyquinolizidines a similar type of hydrogen bonding although an exact comparison cannot be made, because the somehwat more rigid nature of the quinolizidines results in no hydrogen bonding occurring in the 2-hydroxyquinolizidines

which are comparable to the compounds described here. Thus a conformer with hydrogen bonding could be preferred.

An attempt to analyse the multiplets around 7·40 τ and 7·70 τ was made, but no unequivocal assignment could be made. However, it seems highly probable that the peak at 7·40 τ was due to one of the protons on C_7 plus two of the protons adjacent to the conclusion that in these two amino alcohols the magnetic anisotropy of the remaining C_7 proton, and the other two proton adjacent to the nitrogen in the piperidino-ring.

A similar reasoning was applied to assign the signals at about 7·43 τ and about 7·75 τ in the *trans* amino alcohol VIII. Consideration of the above points leads one to the conclusion that in these two aminoalcohols the magnetic anisotropy of the C_7 protons was due to the asymmetric centre on C_8 with possibly a steric contribution if the molecule was in fact fixed in a particular conformer due to hydrogen bonding.

Consideration of molecular models shows that the *cis* compound VII could, with ease, exist in the conformer shown in Fig. 9 and the *trans* compound VIII as in Fig. 10. The features of the spectra which can be interpreted are in agreement with these postulations, but unfortunately there is insufficient evidence to state unequivocally that the two isomers actually do exist in the shown conformers.

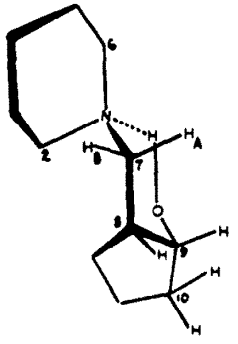

FIG. 9. The conformation adopted by *cis*-2-piperidinomethyl-cyclopentanol. (VII).

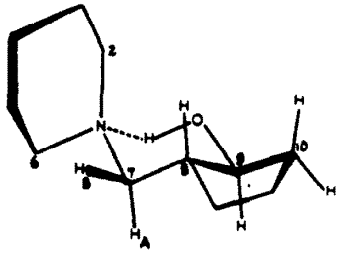

FIG. 10. The conformation adopted by *trans*-2-piperidinomethyl-cyclopentanol. (VIII).

The cyclohexyl amino alcohols (*cis*, compound IX, and *trans*, compound X), gave rather similar spectra (Figs. 11 and 12) to those obtained from the cyclopentyl-amino alcohols. The peak due to the proton on C_9 appeared at lower field (6·17 τ) in the *cis* amino alcohol IX than in the corresponding *trans* compound X, suggesting an equatorial orientation for this proton. Analysis of this peak at 6·17 τ, assuming that the X approximation may be used, confirmed that the larger triplet $J = 5·1$ c/s

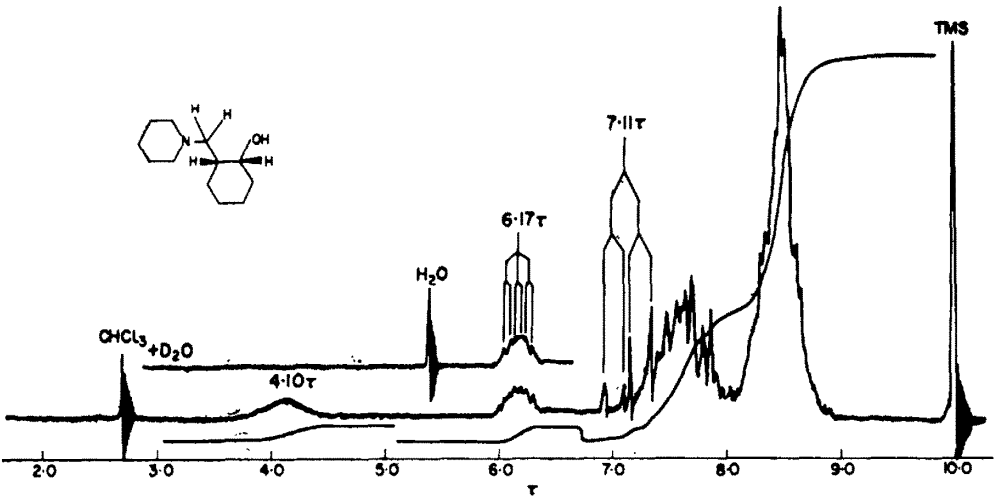

FIG. 11. The NMR spectrum of *cis*-2-piperidinomethyl-cyclohexanol, (IX).

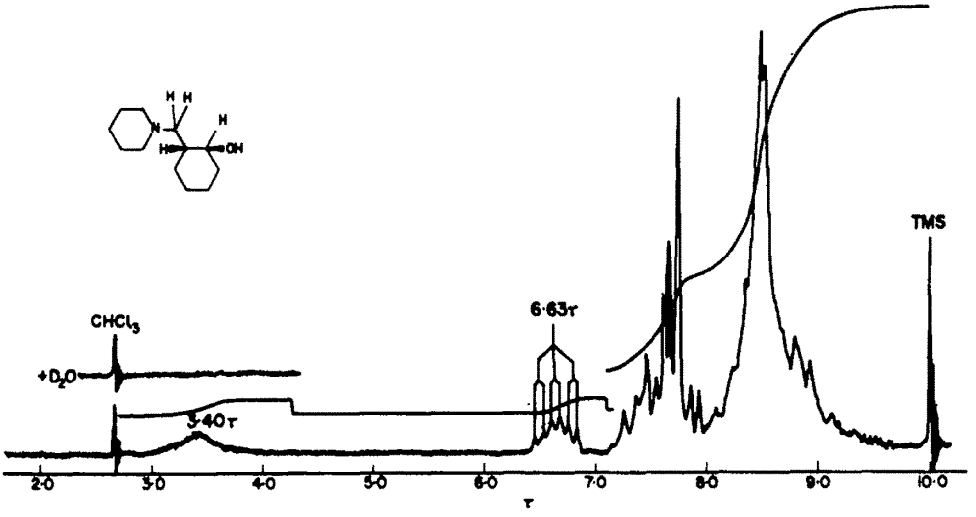

FIG. 12. The NMR spectrum of *trans*-2-piperidinomethyl-cyclohexanol, (X).

was due to this equatorial C_9 proton coupling with two axially oriented neighbours, whilst the equatorial proton on C_{10} split this further into doublets $J = 3{\cdot}2$ c/s. Thus the *cis* configuration of the OH group was confirmed. Although it was thought likely that the four lines centred on 7·11 τ were due to the A part of an ABX system, and hence probably due to one of the protons on C_7, an unequivocal detailed analysis could not be carried out on the remaining visible lines and hence no definite assignments made.

In the *trans* amino alcohol X the C_9 proton appeared at 6·63 τ as a doublet of triplets, and splittings of 9·5 c/s (triplet) and 4·5 c/s (doublet) could be equated with the coupling constants if the X approximation conditions are assumed. These values then confirmed the axial orientation of this proton, and that it had two axial

neighbours and one equatorial neighbour. It was not possible to unequivocally interprete the region from 7·2 τ to 8·0 τ although it did appear as if the 7a and 7b protons appeared at 7·45 τ and 7·75 τ. This, however, was not a unique solution, so that it is not possible to quote these as the definite chemical shifts. In both the *cis* and *trans* compounds (IX and X) the hydroxyl protons appeared at low field, 4·1 τ and 3·4 τ, and this could be in agreement with hydrogen bonding. There was insufficient spectroscopic evidence to propose probable complete conformations for these compounds, but the magnitudes of the coupling constants obtained from the cyclohexyl ring suggests that in both compounds this is fixed.

It was possible to assign the configurations of the cycloheptyl amino alcohols XI and XII by comparison of their spectra with the spectra of the cycloheptyl amino alcohols (IX and X). The C_9 proton in the *cis* compound XI appeared at 6·05 τ, band width 16 c/s, and in the *trans* compound XII this proton appeared at 6·50 τ, band width 19 c/s, which suggested that the C_9 proton was probable equatorial in the *cis* compound and axial in the *trans* compound.

Unfortunately it was not possible to obtain positive confirmation of these assignments, but the general appearance of the spectra, when compared with the corresponding cyclopentyl and cyclohexyl spectra, suggested that the configurational assignments were correct.

Thus on the basis of spectroscopic investigations, the configurations, and in some cases conformations of all twelve investigated compounds have been assigned.

EXPERIMENTAL

The NMR spectra were determined in $CDCl_3$ (approximately 10%) at 60 Mcs. on a Varian A-60A (piperidines) and at 100 Mcs. on a Varian HA-100 (piperidones) at the normal operating temperature. Chemical shifts were measured relative to an internal standard of tetramethylsilane (1%).

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