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PMR STUDIES OF N-SUBSTITUTED-2,5-DIMETHYL-4-PIPERIDONES

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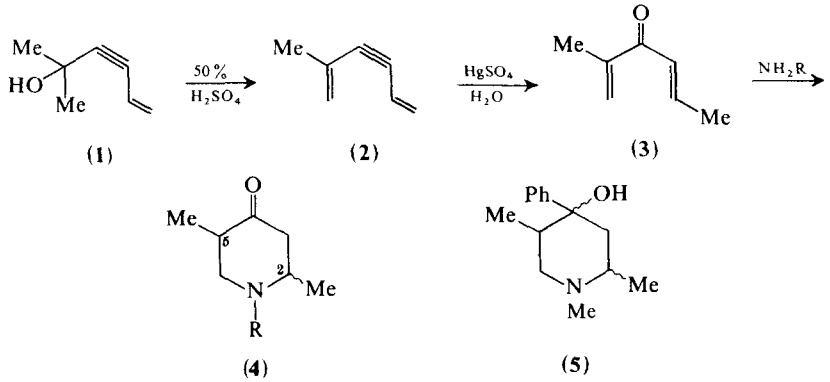
Abstract—PMR characteristics of some isomeric 1-substituted-2,5-dimethyl-4-piperidones are reported and major isomers shown to have a *trans* 2,5-dimethyl configuration. Differences between benzylic methylene signals of isomeric 1-benzyl analogs provide evidence of the preferred conformation of the *cis* derivative. Evidence of the D/H exchange of α-protons in 1,2,5-trimethyl-4-piperidone base and of addition of D_2O to the carbonyl group of the corresponding hydrochloride and methiodide salts is also demonstrated. The effect of a 2-methyl substituent upon the chemical shifts of *N*-methyl groups in some piperidine methiodides is discussed.

THE SYNTHESIS 1-alkyl-2,5-dimethyl-4-piperidones (**4**), based on vinyl acetylene chemistry, has been developed in Russia (see **1** to **4**).[1] The ketones **4** are assumed to be mixtures of *cis* and *trans* isomers because more than two isomeric products result when a third asymmetric centre is created at C-4 e.g. reaction of **4a** with lithium phenyl yields three of the four possible isomeric 4-phenyl-4-piperidinols (**5**),[2] and



(**a**) R = Me
(**b**) R = CH_2Ph
(**c**) R = $(CH_2)_2Ph$
(**d**) R = C_6H_{11}

separations of isomeric ketones have been reported.[3] This PMR study was undertaken to obtain more direct evidence of the stereochemistry of these cyclic ketones and to extend investigation of the deuteration and hydration of 4-piperidones.[4]

Spectral data and analyses

Each isomeric form of the ketone **4a** should give rise to distinct 2- and 5-methyl PMR signals, hence the presence of at least three doublets in the C-methyl resonance

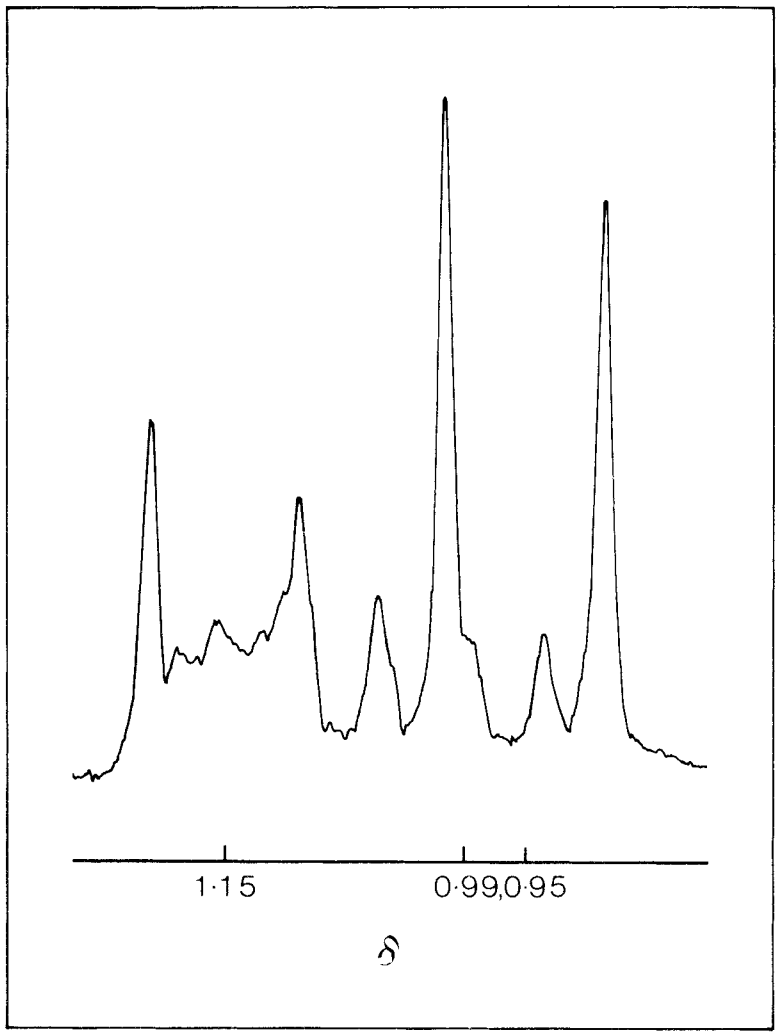
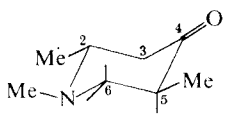


FIG. 1. Secondary methyl region of the 60 MHz PMR spectrum of the 1,2,5-trimethyl-4-piperidone isomeric mixture in $CDCl_3$ (100 Hz sweep width).

region of the PMR spectrum of a commercial sample of **4a** establishes it to be a mixture (Fig. 1). One component must preponderate because two of the doublets (those centred at δ0·95 and 1·15) are intense while the third (at δ0·99) is weak; the strong signals are attributed to the major and the weak signal to the minor isomer. The second doublet of the minor form is not well resolved but is probably responsible for the shoulder apparent at the base of the highest field doublet (Fig. 1). These assignments were confirmed by examining the spectra of the base derived from a recrystallized hydrochloride of **4a** and that of the base enriched in the minor isomer by treatment with alumina.[3] The secondary methyl signal at δ0·99 was of reduced intensity in the spectrum of the former and of enhanced intensity in that of the latter sample in comparison with intensities of the δ0·95 and 1·15 signals. A singlet at

δ2·4 (probably due to *N*-Me) is also associated with the minor isomer since its intensity variations follow those of the δ0·99 doublet in the three samples examined.

Spectral analysis of signals due to the major isomer is consistent with its *trans* 2,5-dimethyl configuration **6**. This analysis was aided by study of the fully deuterated analog **7**, obtained by treating the ketone in carbon tetrachloride with Na–D_2O



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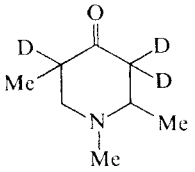
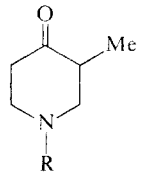


(7)

(see Experimental); this treatment did not disturb the isomeric composition as seen by the spectral identity of **4a** before and after treatment with CCl_4–Na–H_2O. Specific points in the analysis are as follows:

(a) the quartet near δ3 and the triplet at δ2 collapse to doublets with a typical *geminal* coupling constant ($J \sim 10$ Hz in the normal and 11·5 Hz in the deuterated ketone) after deuteration (Fig. 2), and are thus due to the C-6 methylene protons. The higher field signal is assigned to the axial member because it displays the larger vicinal coupling constant (5·5 for the lower and 11 Hz for the higher field signal), the near equality of J_{gem} and J_{vic} in this case leading to the observed triplet (a quartet was apparent at higher resolution). The higher field chemical shift of the axial C-6 proton must be due to its being flanked by two equatorial methyl groups, the screening influence of these groups upon the equatorial C-6 proton being less; in addition, the axial proton will be shielded by the lone pair on nitrogen.[6] After D/H exchange the higher field doublet showed fine structure not seen in the lower field signal; this difference is understandable in terms of configuration **6** since an axial deuterium atom at C-5 would be expected to couple more strongly with the axial than the equatorial C-6 proton.[7]

(b) The doublet at δ0·98 collapses to a singlet after deuteration and is therefore assigned to 5-methyl adjacent to the carbonyl group. Its equatorial orientation follows from ring proton assignments already made and from the fact that its chemical shift is close to that of methyl in the analogs **8** of known preferred conformation.



(8)

(a) R = Me, δ0·97
(b) R = CH_2CH CH_2, δ0·98
(c) R = CH_2Ph, δ0·94
(solvent $CDCl_3$)

(c) The doublet at δ1·14 remains after D/H exchange and is assigned to the C-2 methyl group. Its equatorial orientation follows from its chemical shift identity with the analogs **9**, and the fact (revealed by its appearance, Fig. 1) that it is virtually

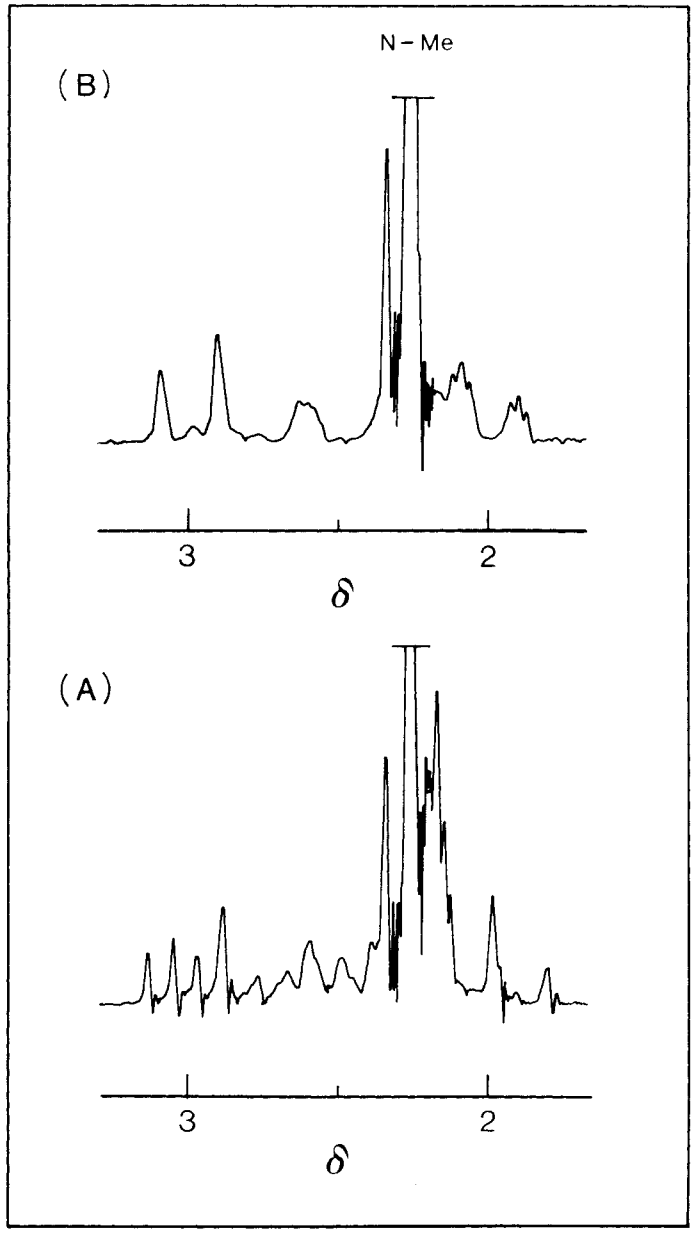
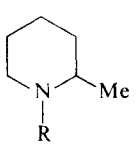


FIG. 2. Part of the 60 MHz PMR spectra of 1,2,5-trimethyl-4-piperidone in CCl_4, (A) before, and (B) after, treatment with sodium-D_2O.

coupled to the C-3 protons.[8] Virtual coupling in the system **10** is most likely when a large α/β vicinal coupling is involved, as provided by the C-2 and C-3 axial protons in configuration **6**. After deuterium exchange, this coupling is removed and the 2-methyl signal appears, significantly, as a clear doublet.

The lack of a pure sample of the *cis* isomer of **4a** prevented analysis of its PMR



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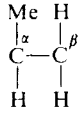
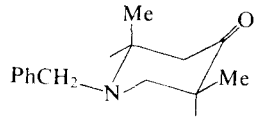


(10)

(a) R = Me, δ1·07

(b) R = CH_2Ph, δ1·13
(solvent $CDCl_3$)

characteristics, but evidence about the conformation of the *cis* ketones **4** was obtained by study of the corresponding *N*-benzyl derivatives **4b**. The PMR spectrum of the base derived from a recrystallized hydrochloride of the *N*-benzyl piperidone mixture showed it to be the pure *trans* isomer. Thus, the *C*-methyl resonance region showed two clear doublets, one at δ1·27 (2-Me) and the other at δ0·90 (5-Me) while a quartet near δ3 (J 5·5 and 11 Hz) due to the equatorial C-6 proton and a triplet at δ2 (J 11 Hz, axial C-6 proton) were also present. The lower field position of the 2-methyl signal, compared with the corresponding signal of *trans* **4a** must be due to the deshielding influence of the benzyl substituent because 2-methyl chemical shifts in the analogs **9a** and **9b** differed in the same way. The change in shielding of the 2-methine (axial) proton which follows replacement of *N*-methyl by *N*-benzyl is probably responsible for the absence of virtual coupling effects in the 2-methyl signal. The methylene signal of the benzyl group forms an AB quartet (δ3·24 and 4·09, J 13·5 Hz) almost identical with that seen in the spectrum of 1-benzyl-2-methylpiperidine.[9] This is typical of a methylene group in an asymmetric environment. Two additional secondary methyl doublets (at δ0·93 and 0·98) are clearly apparent in the spectrum of the *cis-trans* mixture **4b**; the higher field signal is assigned to the *cis* 5-methyl group (it collapsed to a singlet after D/H exchange), and the lower field doublet (unchanged after exchange) to the 2-methyl group. It was anticipated that the benzyl methylene signal of the *cis* isomer would be a quartet (as in the *trans* spectrum) since the environment of this group is asymmetric in either isomer. Its appearance as a singlet at δ3.68 was surprising. There is evidence, however, that chemical shift differences between methylene protons in 1-benzyl-2-methylpiperidines only arise when the methyl substituent is equatorial.[10]* Hence the singlet nature of the *cis* *N*-CH_2Ph signal indicates that the 2-methyl group is axial in the preferred *cis* **4b** conformation **11**. Secondary methyl chemical shift data support this conformation,

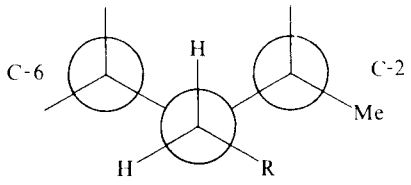


(11)

because the *cis* 5-methyl value is close to that of the 5-methyl (equatorial) in the *trans* isomer while the *cis* 2-methyl signal is upfield from the *trans* 2-methyl resonance. This is in accord with the greater deshielding of equatorial 2-methyl groups by the nitrogen lone-pair (unpublished results). The *cis* and *trans* 2- and 5-methyl chemical shifts of the *N*-methyl analog **4a** are similarly related. The clear separation of *cis*

* A. F. Casy and M. M. A. Hassan, unpublished results.

and *trans* N-CH_2Ph signals in the mixture **4b** allow their separate integration and from these measurements the *trans*:*cis* ratio is 16:13. This ratio was little changed after treatment of the mixture in carbon tetrachloride with Na-H_2O and therefore approximates the equilibrium composition. The ratio in the case of the N-methyl mixture **4a** cannot be determined by integration because of signal overlap but it is evident from the weak intensity of the *cis* 2- and 5-methyl signals that a far higher proportion of *trans* isomer is present in this case. An explanation for the differing proportions of isomeric ketones in equilibrated mixtures of **4a** and **4b** may lie in the fact that the conformer **12** is less favoured in the benzyl derivative (**12**, R = Ph) than in the 1-methyl ketone (**12**, R = H) with the result that a higher proportion of the *cis* ketone (axial 2-methyl) is formed in the former case.



(12)

Newman diagram of C-2-N(CH_2Ph)-C-6 fragment of **4b**; nitrogen is eclipsed by central, benzylic, carbon atom.

The solid bases obtained from the exchange reactions between **4a** methiodide and β-phenethylamine or cyclohexylamine proved to be the pure *trans* ketones from the 2- and 5-methyl and 6-methylene signals of their PMR spectra (details in Experimental). No *cis* isomers were detected in the reaction mother liquors.

Deuteration and hydration studies

This section extends previous studies on 1,3-disubstituted-4-piperidones.[4] The α-protons of the 1,2,5-trimethyl-4-piperidone mixture **4a** exchange for deuterium when the ketone is dissolved in heavy water as seen by changes in the 5-methyl and ring proton signals. After two hours a singlet is apparent between the *trans* 5-methyl doublet peaks while after eighteen hours, singlets due to both *cis* and *trans* 5-methyl are clear and their intensities exceed those of the corresponding doublets.

The rate of D/H exchange in the disubstituted ketone **8a** is faster than that of its trimethyl analog **4a** (in the former case the singlet was the major 3-methyl PMR signal after 1·5 hours)[4] and the rate difference is probably due to the ketone **4a** being the weaker base (a 2-methyl group has a small base weakening influence in piperidine derivatives).[11] From the relative peak heights of the *cis* and *trans* N-methyl signals, the proportion of *cis* isomer **4a** was higher in the ketone stored for eighteen hours in D_2O at room temperature than in the product obtained after its treatment in carbon tetrachloride with Na-D_2O (H_2O) at the reflux temperature.

The PMR spectrum of the recrystallized hydrochloride salt of **4a** in $CDCl_3$ or DMSO-d_6 was consistent with its being the pure *trans* isomer (Table, Nos. 1 and 2); two secondary methyl doublets were present and the protonation shifts in $CDCl_3$, 0·45 ppm for the lower (2-Me) and 0·12 ppm for the higher field (5-Me) signals, were

TABLE. PMR CHARACTERISTICS OF *trans* 1,2,5-TRIMETHYL-4-PIPERIDONE DERIVATIVES

No.	Structure	Form	Solvent	Signal	Chemical Shift (ppm)[a] Free Ketone	Dideuteroxy or acetal form
1.	(**4a**)	HCl	$CDCl_3$	2-Me[b]	1·6	—
				5-Me	1·08	—
				N-Me[c]	2·95	
2.	(**4a**)	HCl	DMSO-d_6	2-Me	1·39	—
				5-Me	0·94	—
				N-Me	2·83	—
3.	(**4a**)	HCl	D_2O	2-Me	1·56	1·46
				5-Me	1·13	1·06
				N-Me	3·08	2·97
				α-ring protons	within 2·7 to 4·1 band	2·2[d]
4.	(**14**)	HCl	$CDCl_3$	2-Me	—	1·5
				5-Me	—	0·91
				N-Me	—	2·87
				α-ring protons	—	2·0[d]
			D_2O	2-Me	—	1·43
				5-Me	—	0·97
				N-Me	—	2·93
				α-ring protons	—	2·0[d]
5.	(**4a**)	MeI	DMSO-d_6	2-Me	1·37	—
				5-Me	0·94	—
				N-Me[e]	3·27, 3·30	—
6.	(**4a**)	MeI	D_2O	2-Me[f]	1·55	1·42
				5-Me	1·14	1·04
				N-Me[g]	3·37	3·09, 3·23
				α-ring protons	within 2·8 to 4·4 band	2·2[d]
7.	(**14**)	MeI	D_2O	2-Me[h]	—	1·37
				5-Me	—	0·9
				N-Me[e]	—	3·0, 3·12
				α-ring protons	—	2·0[d]

[a] Spectra recorded with a Varian A-60D spectrometer with TMS as standard, internal in $CDCl_3$ and DMSO-d_6, external in D_2O.

[b] 2-Me and 5-Me signals are doublets (J 6 to 7 Hz).

[c] Broad singlet or doublet (J 5 Hz) due to $^{\oplus}$NH coupling; narrow singlet when D_2O present.

[d] Centre of multiplet.

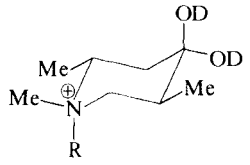
[e] Singlet(s).

[f] Shows fine structure, see Fig. 3.

[g] Singlets at δ3·09 and 3·23 of same area and less intense than singlet at δ3·37.

[h] Shows fine structure similar to 2-Me signal No. 6.

close to those in 1,2-dimethyl-piperidine (0·45 ppm) and **8b** (0·13 ppm), models for equatorial 2- and 5-methyl groups respectively (**8a** hydrochloride could not serve because it is insoluble in $CDCl_3$). Protonated epimers, as seen for 1,2-dimethyl-piperidine hydrochloride[12] were not apparent in the spectrum of the salt of **4a** probably because formation of the minor isomer requires a conformation with two axial methyl groups. In D_2O, however, the *N*-methyl, 2- and 5-methyl signals were duplicated showing that a high proportion (judged to be about fifty per cent from relative signal intensities) of the 4,4-dideuteroxy form **13a** is present in solution (Table, No. 3). In accord with previous work,[4] the higher field members of the three pairs of signals are assigned to the dideuteroxy derivative **13a**, and the multiplet



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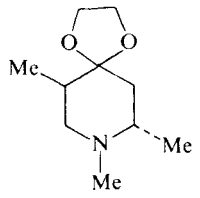


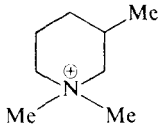
(14)

(a) R = H

(b) R = Me

centred near δ2·2 to the α-methylene protons of the same species; the model ketal **14** provided chemical shift data which corroborated these assignments (Table, No. 4).

The spectrum of **4a** methiodide in DMSO-d_6 (Table, No. 5) was consistent with it being the pure *trans* isomer. The chemical shifts of its 2- and 5-methyl signals are close to those of corresponding signals in the spectra of the model compounds **8a** methiodide (3-Me, δ0·95) and 1,2-dimethylpiperidine methiodide (2-Me, δ1·28) in the same solvent. The 2-methyl signal of **4a** methiodide was broader than that of 5-methyl probably due to ^{14}NCCH coupling.[13] Fine structure in this signal is more pronounced in the presence of benzene and in D_2O (Fig. 3). The **4a** methiodide spectrum showed two distinct *N*-methyl signals, these being at higher field and closer together than those of *N*-methyl signals due to the methiodide of the 1,3-dimethyl analog **8a**. The extra 2-methyl group of **4a** methiodide will shield both *N*-methyl groups as judged by data on the methiodides of 1,3- and 1,2-dimethyl-piperidine (**15** and **16**) (in the 1,3-derivative the *C*-methyl group has a negligible



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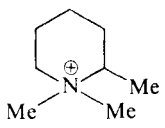

(16)

e-*N*Me	δ3·27	δ3·15	Δ0·12 ppm
a-*N*Me	δ3·18	δ2·94	Δ0·24 ppm

($\Delta = \nu_{NMe}$ **15** $- \nu_{NMe}$ **16**)

influence on resonances of the *N*-methyl groups but anchors the conformation). The former's influence on the axial group chemical shift is greater by a factor of two

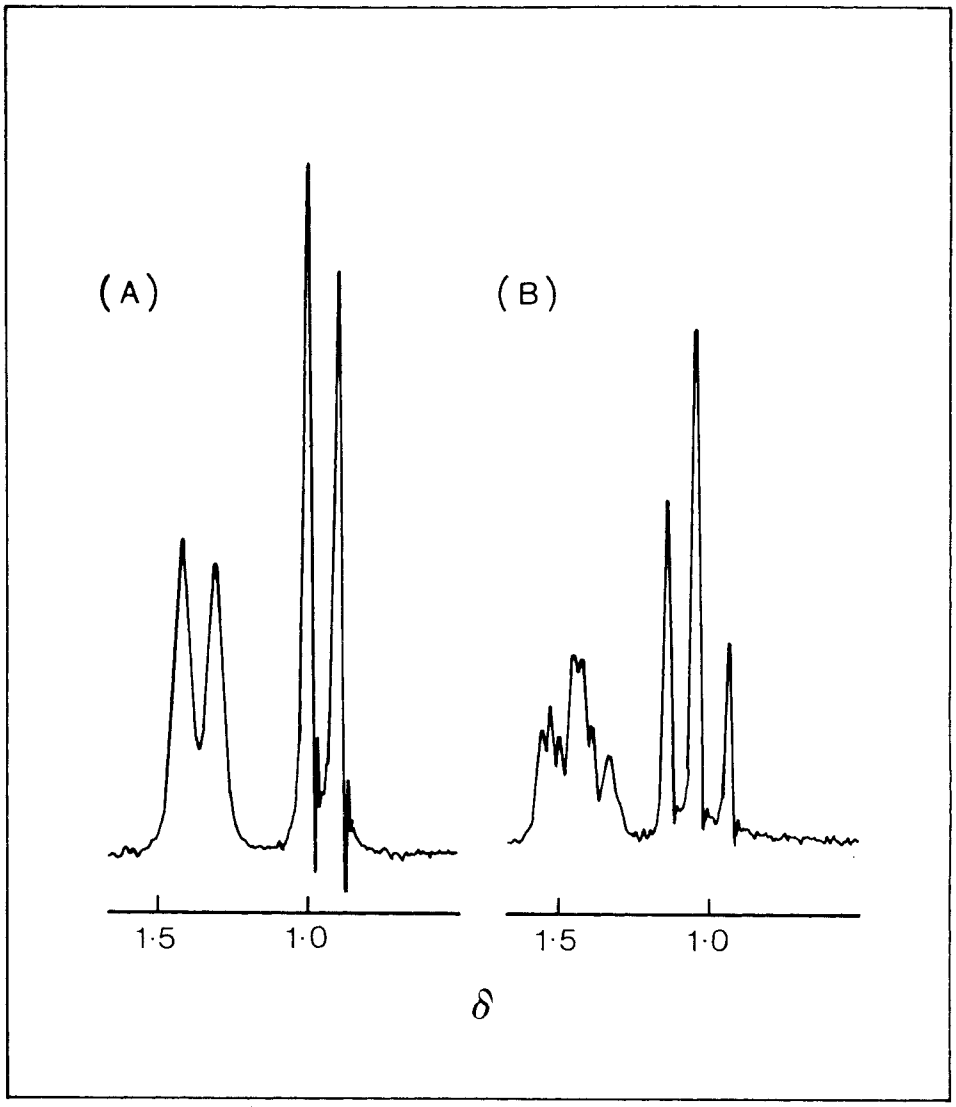

FIG. 3. 2- and 5-methyl PMR signals of *trans* 1,2,5-trimethyl-4-piperidone methiodide; (A) in DMSO-d_6; (B) in D_2O. In (B) signals due to the 4,4-dideuteroxy derivative are also present.

(solvent, DMSO-d_6). In these comparisons, the lower field *N*-methyl signals are assigned to equatorial groups.[14] Assuming, similarly, that the lower field *N*-methyl signal of the ketone **4a** methiodide is due to the equatorial group, insertion of a 2-methyl group into the molecule should *increase* the separation of the *N*-methyl signals since the axial group will be more shielded as a result of this structural change. A *decrease* in chemical shift separation between these signals is, in fact, observed, however. This result must mean that the relative field positions of the *N*-methyl signals in methiodides of the 4-piperidones **4a** and **8a** are the reverse of those in

substituted piperidine salts lacking a trigonal atom;* on these grounds, the greater deshielding of axial than equatorial *N*-methyl by 2-methyl will then result in the *N*-methyl signals being closer together.

Addition of D_2O to the carbonyl group of **4a** methiodide clearly occurs in D_2O because its spectrum in this solvent shows duplicate *N*-, 2- and 5-methyl signals plus an α-proton multiplet near δ2·2 which is upfield from the main ring proton signal (Table, No. 6). The 2- and 5-methyl signals form triplets composed of overlapping doublets, with the former signal showing the additional fine structure referred to already (Fig. 3). The lower field, more intense, singlet of the *N*-methyl signal is assigned to the ketone component of the equilibrium mixture, and the higher field pair of singlets (of equal intensities) to the 4,4-dideuteroxy species **13b**. The peak height of the lower field *N*-methyl signal increases at the expense of the higher field resonances when the temperature is raised; this result, from previous work,[4] corroborates these assignments. In the methiodide of the 1,3-dimethylketone **8a**, the *N*-methyl signal in D_2O is a doublet and its singlet nature in the 2,5-dimethyl analog is consistent with the differential screening influence of the additional 2-methyl substituent (Δ values of 0·23 ppm for axial and 0·12 ppm for equatorial *N*-methyl, *assuming the e-group at higher field*, cause the two *N*-methyl signals to coincide). The doublet nature of the *N*-methyl signal of the 2,5-dimethyldideuteroxy derivative **13b** (the signal of the analog lacking 2-methyl is a singlet) is accounted for in the same way. Observation of D_2O addition to the methiodide **4a** is not complicated by D/H exchange because the latter process is very slow at room temperature.

Confirmatory chemical shift data relative to the dideuteroxy derivative **13b** was obtained from spectra of the methiodide of the acetal **14** (Table, No. 7). The *N*-methyl signal was two singlets and not one as in the 1,3-dimethyl analog[4] as might have been anticipated from the preceding results.

CONCLUSION

This PMR analysis of 2,5-dimethyl-4-piperidones establishes that the major component of the mixture **4a**, derived from the *bis*-α,β-unsaturated ketone **3**, has a *trans* 2-Me/5-Me configuration. The products of exchange between **4a** methiodide and cyclohexylamine or β-phenethylamine are largely (if not exclusively) the *trans* piperidones; the *trans* ketone also preponderates when the exchanging base is benzylamine but the proportion of *cis* isomer (~45%) is higher than in any other of the mixtures examined.

Both the D/H exchange of α-protons in 1,2,5-trimethyl-4-piperidone base, and the addition of D_2O to the carbonyl group of hydrochloride and methiodide salts of *trans*-**4a** occur readily as is also the case with 1,3-dimethyl-4-piperidone base and salts. The extra 5-methyl substituent slows the D/H exchange rate (relative to that

* This point is being further studied. On the basis of the model Apsimon and others,[15] an axial *N*-methyl group should be deshielded and an equatorial group probably shielded by the carbonyl group in a 4-piperidone. The trideuteromethylation technique for assigning *N*-methyl signals in the quaternization of cyclic bases[14] was not conclusive in respect of the ketone **8a** since the reaction showed no pronounced stereospecificity.[4] It was significant, however, that the higher field *N*-methyl signal of the total product of alkylation of **8a** with CD_3I had a distinctly greater peak height than the signal at lower field, and could therefore be assigned most probably to the equatorial group.

of **8a**) but has no significant influence upon the extent of formation of the 4,4-dideuteroxide.

EXPERIMENTAL

The PMR spectra were recorded on a Varian A-60D spectrometer at the normal operating temperature unless otherwise stated. Chemical shifts were recorded relative to sodium 2,2-dimethyl-2-silapentane-5-sulfonate in D_2O and water, and tetramethylsilane in all other solvents. The abbreviations d (doublet) and t (triplet) are used in presenting the PMR data.

Source of compounds: a commercial sample of 1,2,5-trimethyl-4-piperidone (**4a**) was generously supplied by Dr N. S. Prostakov. This was converted to the *N*-substituted analogs **4b, c** and **d** by exchange reactions between **4a** methiodide and the appropriate primary amine.[5] Hydrochloride and methiodide salts of the piperidone bases were obtained by reported methods.[4]

The following derivatives were prepared (salts crystallized from ethanol-ether unless otherwise stated). **4a** *hydrochloride* m.p. 189 to 190° (Found: C, 54·01; H, 8·85. $C_8H_{16}ClNO$ requires: C, 54·1; H, 9·01%) **4a** *methiodide*, m.p. 210° (Found: C, 38·34; H, 6·55. $C_9H_{18}INO$ requires: C, 38·2; H, 6·36%); the *acetal* **14** *hydrochloride*, m.p. 149 to 151° (Found: C, 54·49; H, 9·06. $C_{10}H_{20}ClNO_2$ requires: C, 54·2; H, 9·03%) obtained from **4a**, ethylene glycol and *p*-toluene sulfonic acid in benzene;[4] the *acetal* **14** *methiodide*, m p. 239 to 240° (Found: C, 40·38; H, 6·71. $C_{11}H_{22}INO_2$ requires: C, 40·4; H, 6·73%) D/H *Exchange*:[7] A mixture of **4a** (0·1 g), carbon tetrachloride (1 ml), sodium (23 mg) and D_2O (0·5 ml) was shaken for 24 hrs. The organic layer was separated and the procedure repeated with fresh sodium —D_2O, and the carbon tetrachloride used for the PMR analysis.

1-*Substituted*-2,5-*dimethyl*-4-*piperidones*. A mixture of **4a** methiodide (56·6 g), *β*-phenethylamine (24·2 g), and water (24 ml) was stirred at room temperature for 1 hr. and then extracted with ether. The solid residue (45 g) from the ether extract was recrystallized from ethyl acetate to give the 1-(2-*phenylethyl*)-4-*piperidone* **4c**, m.p. 79 to 81° (Found: C, 77·42; H, 9·12. $C_{15}H_{21}NO$ requires: C, 77·9; H, 9·09%) PMR characteristics in $CDCl_3$: δ3·23 (centre of quartet J 4·5 and 10 Hz, 6-*e*-methylene proton), 1·17 (d, J 6 Hz, 2-Me), 1·02 (d, J 6·5 Hz, 5-Me). It gave a *hydrochloride*, m.p. 160 to 162° (Found: C, 67·12; H, 7·94. $C_{15}H_{22}ClNO$ requires: C, 67·3; H, 8·22%) and a *methiodide*, m.p. 165 to 167° (Found: C, 51·30; H, 6·64. $C_{16}H_{24}INO$ requires: C, 51·3; H, 6·43%). The 1-benzyl-4-piperidone **4b**, from **4a** methiodide (56·6 g), benzylamine (21·4 g) and water (20 ml), was obtained as a *cis-trans* mixture, b.p. 100 to 102°/0·08 mm. It formed a *hydrochloride*, m.p. 170 to 172° (Found: C, 65·96; H, 8·07. $C_{14}H_{20}ClNO$ requires: C, 66·3; H, 7·89%). The 1-cyclohexyl-4-piperidone **4d**, from **4a** methiodide (28·4 g), cyclohexylamine (9 g), and water (10 ml), was obtained as a base (12·5 g), m.p. 74 to 76° from ethanol-water (Found: C, 74·40; H, 11·13; N, 6·85. $C_{13}H_{23}NO$ requires: C, 74·6; H, 11·08; N, 6·70%), PMR characteristics in $CDCl_3$: δ3·17 (centre of quartet J 4·5 and 10·5 Hz, 6-*e*-methylene proton), 2·09 (t, J 10·5, 6-*a*-methylene proton), 1·15 (d, J 6 Hz, 2-Me), 0·98 (d, J 6·5 Hz, 5-Me). It formed a *hydrochloride*, m.p. 187 to 189° (Found: C, 63·31; H, 9·80. $C_{13}H_{24}ClNO$ requires: C, 63·5; H, 9·77%), and a *methiodide*, m.p. 180 to 182° (Found: C, 45·92; H, 7·43. $C_{14}H_{26}INO\,H_2O$ requires: C, 45·5; H, 7·59%) ν_{max} 3350 cm^{-1} (H_2O).

1,2-Dimethylpiperidine formed a *methiodide*, m.p. 315 to 317° (Found: C, 37·48; H, 7·14. $C_8H_{18}IN$ requires: C, 37·7; H, 7·06%) and the 1,3-dimethyl isomer a *methiodide*, m.p. 115 to 117° (Found: C, 38·11; H, 7·10%). The spectra of **4b, 4c** and **4d** and the methiodide of **4a** are shown in Spec. No. 0188–0191.

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