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PMR STUDIES OF THE REACTION BETWEEN METHIODIDES OF SUBSTITUTED 4-PIPERIDONES AND PRIMARY BASES

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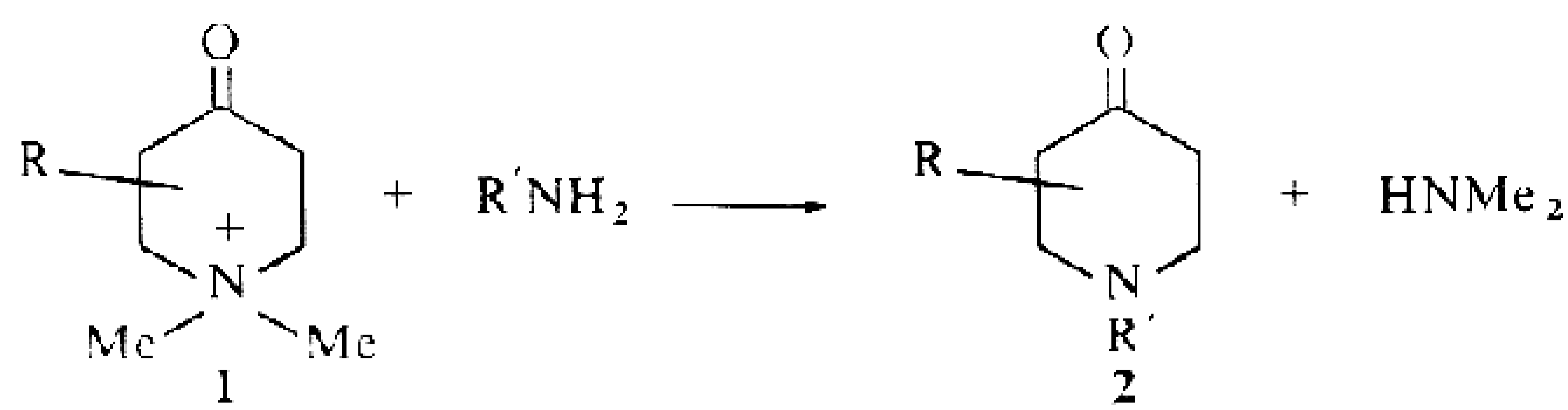
Abstract—Exchange reactions between the methiodides of 1,3-di (and 1,2,5-tri) methyl-4-piperidone and isopropylamine, s-butylamine or t-butylamine give the corresponding N-substituted piperidones. In the case of 2,5-dimethyl derivatives, PMR analyses establish that the major products of exchange retain the *trans* configuration of the precursor methiodide, and also that the 1-isopropyl and 1-s-Bu derivatives have a preferred chair conformation. PMR characteristics of the *trans* 1-t-butyl analogue show this to have a skew-boat conformation. Stereo-chemical preferences are interpreted in terms of avoidance of interactions between the 1- and 2-substituents of the piperidone ring. The PMR spectra in deuterium oxide (D_2O) of salts of all 4-piperidones reported, save the 1-t-butyl-2,5-dimethyl derivative, demonstrate extensive addition of D_2O to the CO group. A proposed mechanism for the exchange reaction is supported by the isolation of acyclic diaminoketones as by products.

N-SUBSTITUTED-4-PIPERIDONES (2) are conveniently prepared from corresponding N-Me analogues by an exchange reaction between the N,N-dimethyl quaternary salt (1) and a primary base.[1] The 1-methyl-4-piperidones themselves are usually



readily obtained by the Dieckmann cyclization of bis (β-carbalkoxyethyl) methylamines but yields are often unsatisfactory when this route is applied to analogues carrying larger N-substituents.[2,3] We now report a PMR study of the products of exchange between the methiodides of 1,3-dimethyl-(3) and 1,2,5-trimethyl-4-piperidone (4), and certain branched chain primary amines, in extension of previous work.[4]

Reaction between the methiodide of (3a) and isopropylamine or t-butylamine in

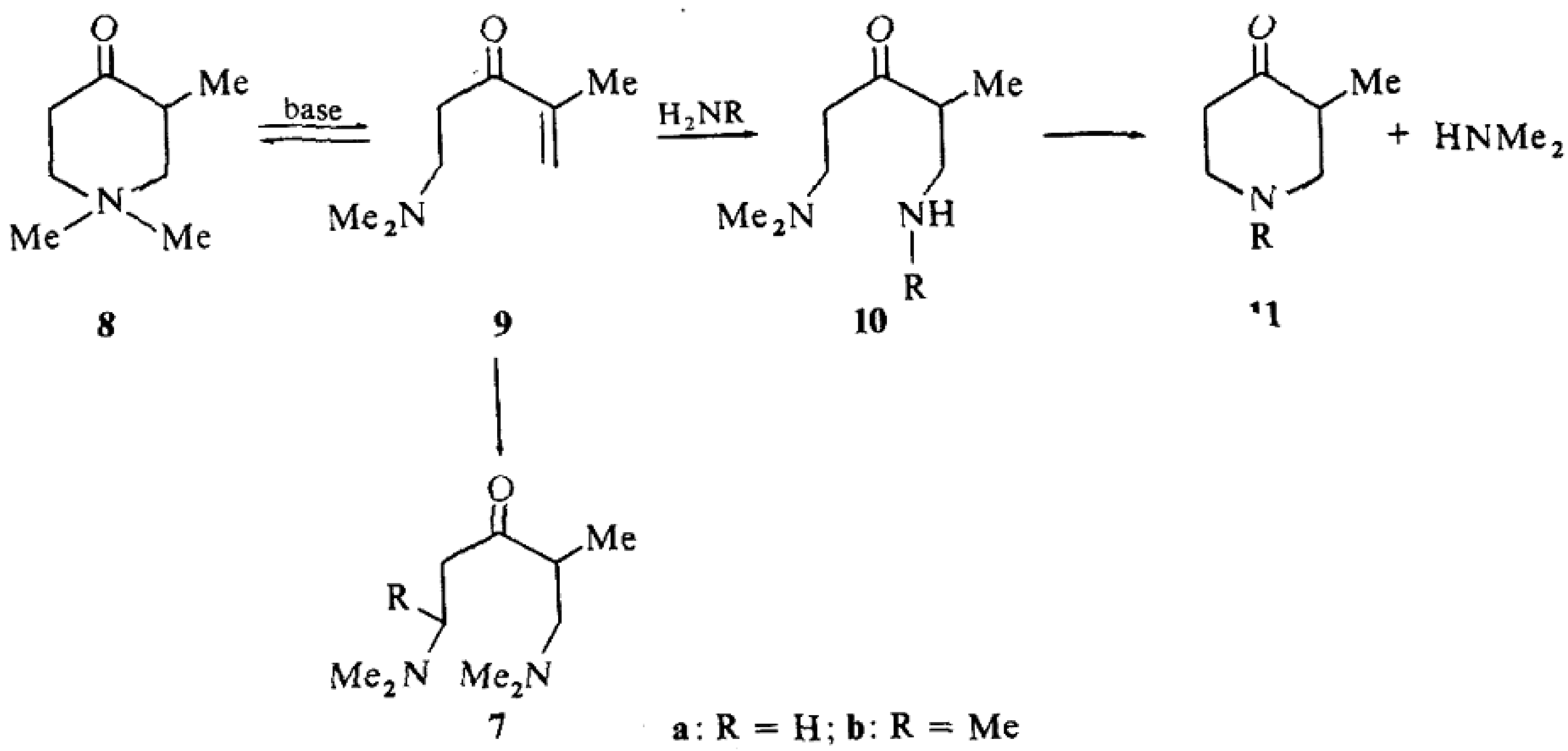
a: R = Me; b: R = isoPr; c: R = t-Bu; d: R = s-Bu; e: R = CH_2Ph; f: R = $(CH_2)_2Ph$; g: R = C_6H_{11}

the presence of a critical amount of water (Experimental) gave the corresponding N-substituted piperidones **3b** and **3c** respectively.

An equilibrium between free ketone (**5**) and 4,4-dideuteroxy (**6**) species arose when the hydrochlorides **3b** and **3c** were dissolved in D_2O as was apparent from the duplication of 3-Me and N-substituent signals in the PMR spectrum of the solution.

5 **6**

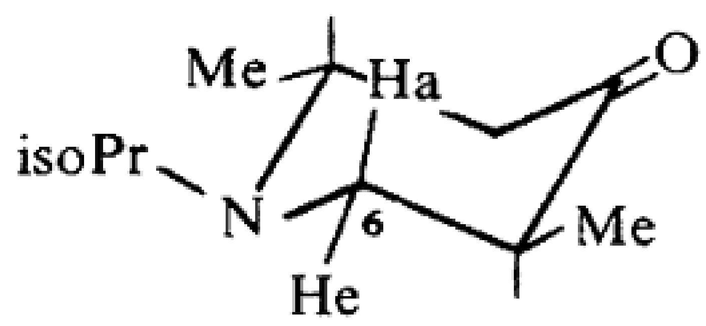
Signal assignments (Table 2) were made on the basis of previous studies of the reaction between salts of 4-piperidones and D_2O. The same by product was isolated from both exchange reactions and it was assigned the structure **7a** on the evidence of its forming a dihydrochloride and of its PMR spectrum displaying a 12-proton N-Me signal.



a: R = H; **b**: R = Me

The formation of the acyclic derivative (**7a**) supports the sequence (**8**) through (**11**) as a likely mechanism for the exchange process[1] since it could arise by conjugate addition of displaced dimethylamine to the intermediate (**9**).

Reaction of the methiodide of *trans*-1,2,5-trimethyl-4-piperidone[4] with isopropylamine gave the analogue **4b**. The 100 MHz PMR spectrum of the base derived from a recrystallized hydrochloride of the product showed it to be the pure *trans* isomer. Details of the analysis are as follows. The C-Me region was composed of four doublets due to the 2-, 5- and non-equivalent N-isopropyl secondary Me groups. When the lowest field signal of the spectrum (a septet at δ 3·23 due to the isopropyl-methine proton) was irradiated the doublets at δ 1·19 and 0·86 collapsed; hence these are due to the $HCMe_2$ groups (irradiation of either of these signals collapsed the methine septet to a quartet). Of the remaining doublets, that a higher field (δ 0·98) appeared as a singlet in the deuterated ketone (**4b**, α-protons replaced by D) and is therefore assigned to 5-Me, thus the lower field doublet (δ 1·15) arises from 2-Me. The 2- and 5-Me chemical shifts correspond closely with those of the same groups of the *trans*-N-methylpiperidone **4a**. A quartet near δ 3·0 (*J* 11·5 and 5·5 Hz) and a triplet near



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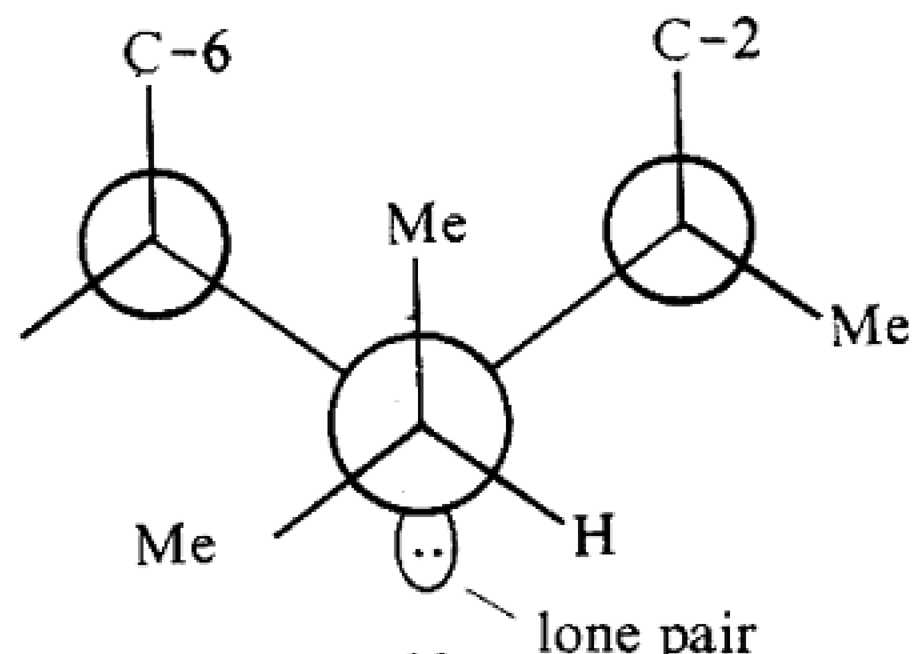
δ 2·0 (J 11·5 Hz) assigned to equatorial and axial protons at C-6 respectively (**12**) were also present in the spectrum of **4b**, these signals likewise being diagnostic of the *trans*-piperidone **4a**.[4] Both methine signals appeared as doublets (J 12 Hz) in the spectrum of the deuterated ketone, and that at higher field (the broader of the two due to significant coupling with the axial C-5 D atom)[3,4] collapsed to a singlet when the lower field signal was irradiated. The spectrum of the total product of the exchange reaction (distilled) closely resembled that of the pure *trans* base, hence this compound is the major stereoisomer formed in the exchange reaction. Analysis of its PMR spectrum supports the chair form (**12**) as its preferred conformation.

The large difference in chemical shift (Δ = 0·33 ppm) between the isopropyl Me groups is in contrast with the chemical shift identity of the same group in the 3-methyl-4-piperidone **3b**, and indicates that the preferred orientation of the N-substituent with respect to the piperidine ring is (**13**).* In this conformation (which



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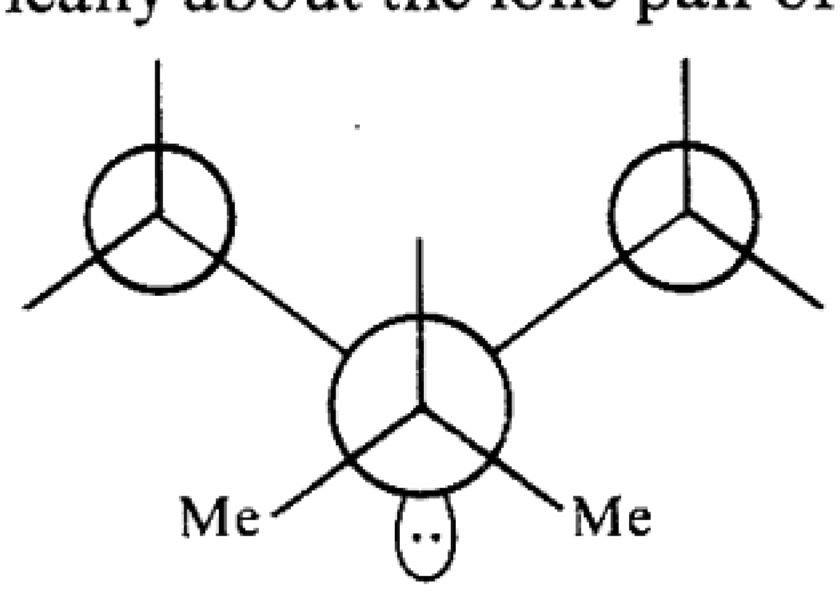
avoids Me/Me interactions involving the equatorial substituent at C-2), the two isopropyl Me groups differ in their magnetic environment, one being *gauche* and the other *trans* to the nitrogen lone pair. The conformation (**14**), in which the isopropyl methyls are disposed symmetrically about the lone pair orbital, is likely to be favoured



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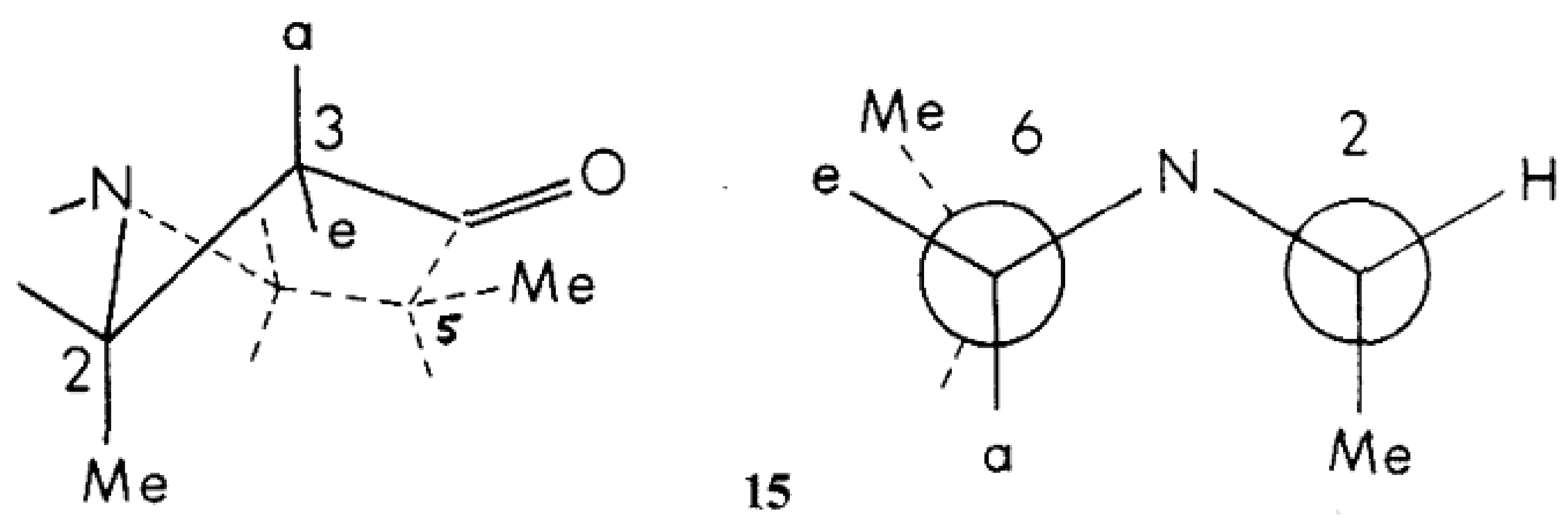
for the analogous 3-methyl-4-piperidone (**3b**); in support the $HCMe_2$ resonance of this compound appears as a single doublet. The spectra of both hydrochloride and methiodide salts of **4b** in D_2O provided evidence of partial formation of the corresponding 4,4-dideuteroxy species (Table 2).[5]

An exchange reaction between the methiodide of *trans*-**4a** and t-butylamine gave a binary mixture of bases. One component was the acyclic derivative (**7b**), analogous to

* In all Newman projections the central atom represents carbon of the 1-substituent directly linked to ring nitrogen which is eclipsed; upper atoms are C-6 and C-2 of the piperidone ring.

the by product (**7a**) encountered in exchange reactions of the quaternary salt (**8**), and its isolation further corroborates the proposed mechanism.[1] The second component was the N-t-butylpiperidone (**4c**). The ring proton region of the 100 MHz PMR spectrum of this ketone was particularly well resolved (Fig 1) and differed distinctly from those seen in the spectra of other 2,5-dimethyl-4-piperidones reported here and previously;[4] the analysis described below establishes that the N-t-Bu derivative has a *trans* configuration and exists in a preferred skew boat conformation (**15**) with a pseudo-axial 2-Me substituent. The Me resonance region was composed of a singlet at δ 1·15 due to the t-Bu protons, and doublets at δ 1·15 (J 7·0 Hz) and 1·06 (J 6·8 Hz) due to the 2- and 5-Me groups. Each line of the higher field doublet showed a small splitting (0·6 Hz) due to long-range coupling. The lower field doublet appeared as a singlet in the spectrum of the deuterated ketone and is therefore assigned to 5-Me; hence (from the spin-decoupling experiments, see Fig 1) the one-proton signal D



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arises from the C-5 methine proton. Similarly, the higher field doublet (unchanged after deuteration) is assigned to 2-Me and the lowest field signal A to the 2-methine proton. Since A and E are coupled, the latter is one of the 3-methylene protons; a quartet (J 15 and 6·5 Hz) in the C multiplet exhibits the same geminal coupling as signal E and is therefore assigned to the other C-3 proton. By elimination, the second quartet of the C group (J 11·5 and 7 Hz) and the B quartet (J 11·5 and 4·25 Hz) are due to the C-6 methylene protons. Double resonance experiments further establish that the 3-methylene signal of the C group is long-range coupled to 2-Me (J 0·6 Hz), while the 6-methylene signal of the same multiplet is weakly coupled to the C-2 methine signal ($J \sim 1$ Hz). The 3-methylene proton signal E displays three splittings (J 15, 2·5 and 1 Hz) and is probably long-range coupled to the C-5 methine (the two signals were too close to allow a successful spin-decoupling experiment).

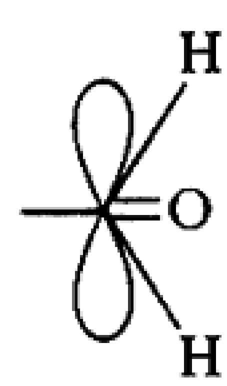
The PMR parameters of **4c** are summarized in Table 1. The absence of vicinal J values in the *trans* diaxial range, the abnormally high J_{gem} value of the 3-methylene protons, and the long-range couplings are accounted for in terms of the *trans* skew-boat conformation (**15**) as follows: (1) the protons H-6(e) and H-2, and H-3(e) and H-5 lie close to a mean plane connected by a W pathway, while the C-2 Me group and C-3 methylene proton H-3(a) have a near-1,2 diaxial relationship; all these orientations are conducive to long-range couplings,[6, 7] and account for experimental findings in this respect (*a* and *e* represent pseudo rather than true axial and equatorial orientations). (2) In **15** the two C-3 methylene protons lie on the same side of the p-orbital of the carbonyl function (**16**); this type of orientation leads to a numerical enhancement of the geminal coupling value[8, 9] and is consistent with the J_{gem} value (15 Hz) observed for the C-3 protons. Assignment of H-3(a) to a quartet in the C group and H-3(e) to signal E (Fig 1) follows from the long-range coupling data and from

TABLE 1. PMR CHARACTERISTICS OF RING PROTONS OF 1-t-BUTYL-2,5-DIMETHYL-4-PIPERIDONE IN $CDCl_3$ (1st ORDER TREATMENT OF 100 MHz SPECTRUM)

Proton	Location in Figure	Resonance Position[a]	Description	*J* values (Hz)[d] Geminal	Vicinal
2-Methine	A	3·62	multiplet	—	6·8[b], 6·5 and 2·5
3-Methylene (high field)	E	2·04	quartet of doublets	15·0	2·5
3-Methylene (low field)	C	2·76	doublet of doublets (plus long-range)	15·0	6·5
5-Methine	D	2·45	multiplet	—	7·0[c] 7·0; 4·25
6-Methylene (high field)	C	2·74	doublet of doublets (plus long-range)	11·5	7·0
6-Methylene (low field)	B	3·06	doublet of doublets	11·5	4·25

[a] in ppm (δ) from TMS
[b] coupling to 2-Me
[c] coupling to 5-Me
[d] all signals except B displayed long-range coupling ($J \sim 1$ Hz)

predictions based on the differential shielding influence of 2-Me upon these protons. By analogy with Booth's findings for cyclohexane derivatives,[10] 2-Me should deshield H-3(a) and shield H-3(e), a conclusion which accounts for the higher field position of



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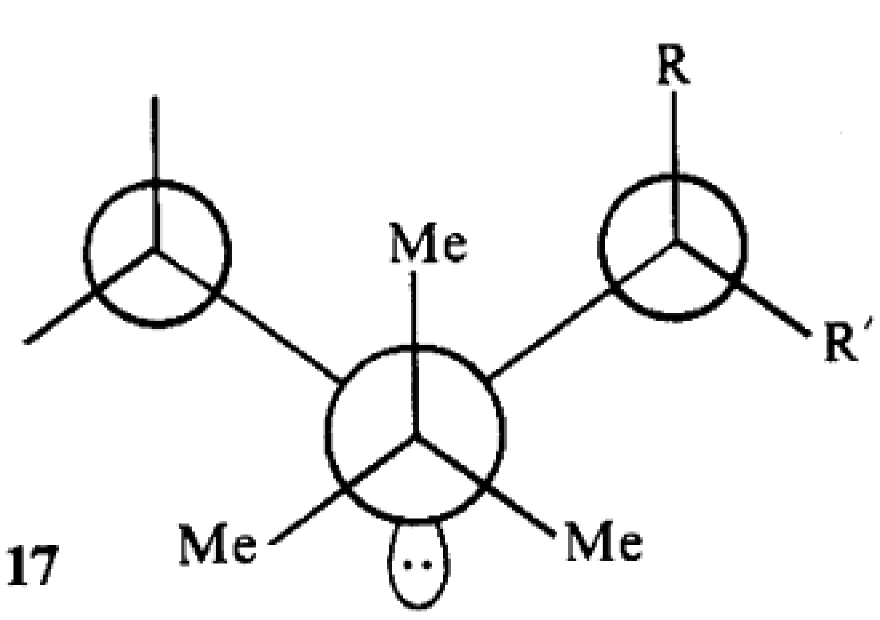
the latter proton. Similarly the quartet in the C group which is long-range coupled to the C-2 proton (W-planar pathway) is assigned to H-6(e) in **15**, and signal B to H-6(a); the 5-Me group is *cis* to H-6(e) and should shield this proton more than H-6(a),[10] in agreement with the assignment of H-6(e) to higher field.

Both the *cis* and *trans* 4-piperidones **4c** entail interactions between the N-substituent and 2-Me when in chair conformations (see **17**). The two (*gauche*) substituents are



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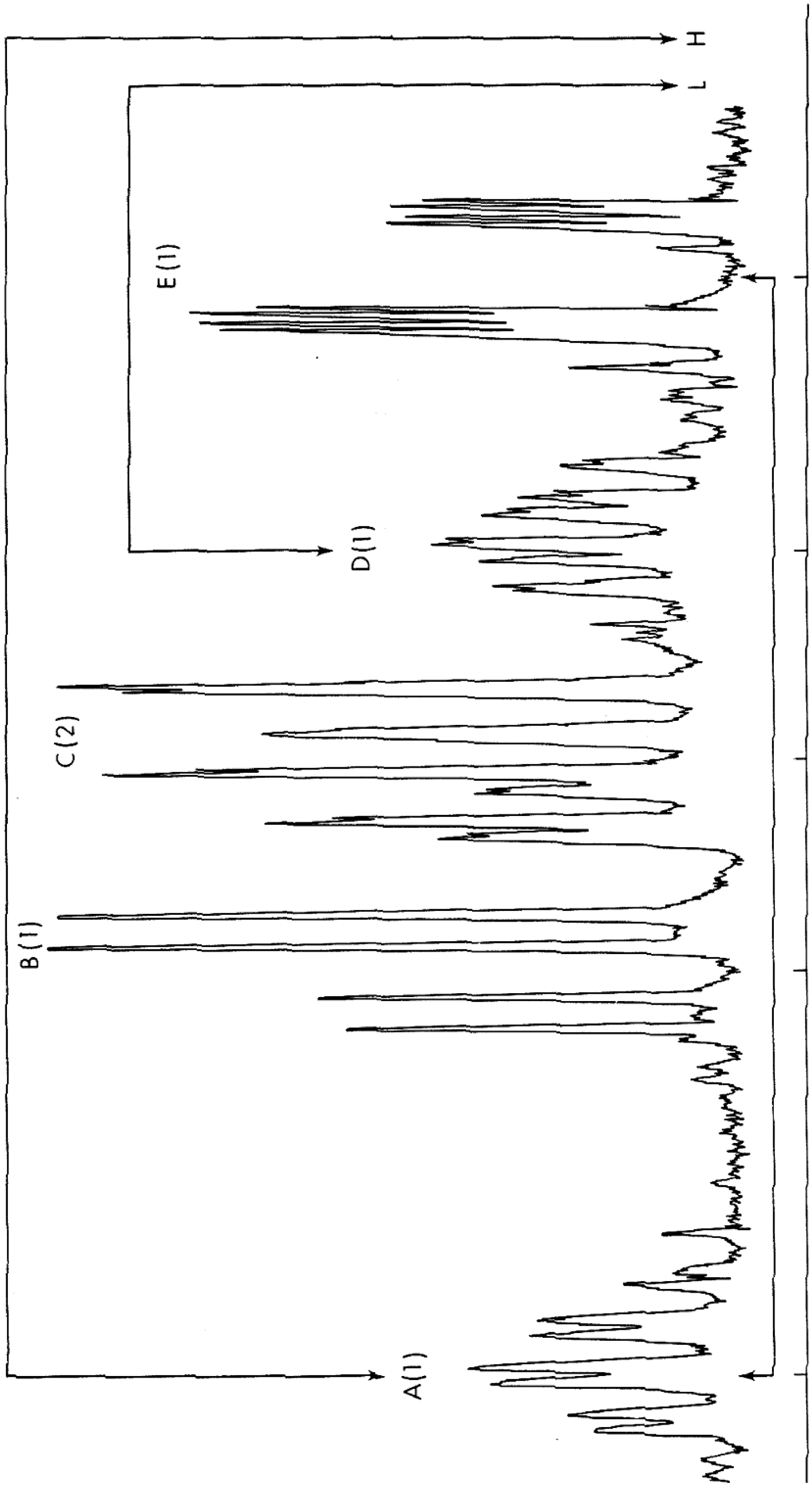
trans: R = H, R′ = Me
cis: R = H, R′ = Me *or* R = Me, R′ = H

able to move further apart in the skew-boat **15** with 2-Me pseudo axial (evidence of models), and avoidance of an interaction between the two may be the chief factor governing the conformational preference of this 4-piperidone. The destabilization of chair conformations of cyclohexanone derivatives by *gauche* t-Bu/OR interactions represents a similar example.[11] *cis*-Skew-boat geometry for **4c**, unlikely on the grounds

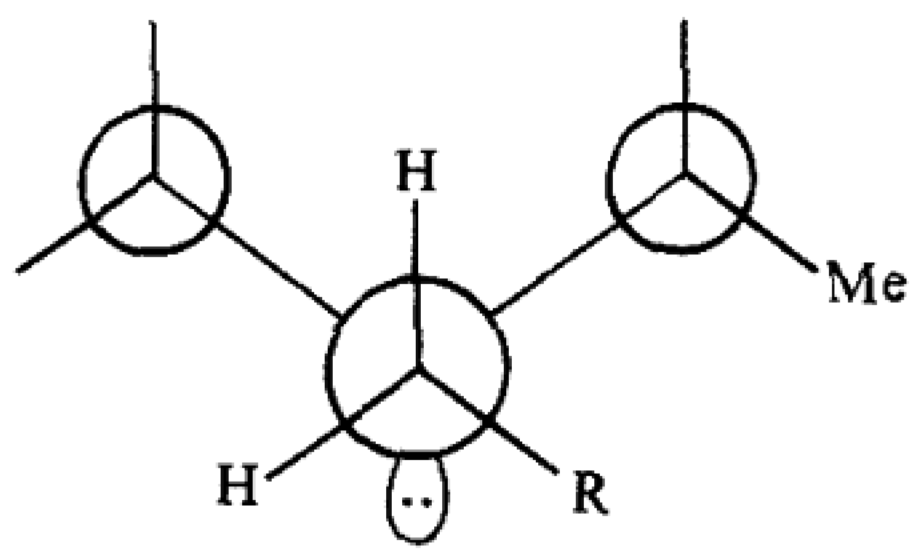


Part of the 100 MHz spectrum of 1-*t*-butyl-2,5-dimethyl-4-piperidone in $CDCl_3$, sweep width 250 Hz. L and H denote the lower and higher *s*-methyl doublets respectively. The integral *of each group is given in parenthesis after its* letter of identification. Arrows indicate some of the spin systems established by decoupling experiments.

of a 2-Me/5-Me or 2-Me/t-Bu interaction, cannot be accommodated by the PMR data. The spectrum of the hydrochloride of **4c** in D_2O showed sharp 2-, 5- and t-Bu signals that were not in duplicate, and hence gave no evidence of the existence of a 4-piperidone-4,4-dideuteroxide equilibrium (cf **5** and **6**). This result is in contrast with spectral data upon all other piperidone salts reported here and previously,[4, 5] and shows that **4c** is unique amongst the series. Addition of D_2O to the carbonyl group of **15** (protonated and solvated) is presumably unfavoured because it must raise 1,2 and 1,4 (bowsprit-flagpole) non-bonded interactions; addition, followed by reversion to a chair would re-introduce a *gauche* 2-Me/t-Bu interaction.

Finally the 4-piperidone **4d**, obtained by exchange between **4a** methiodide and 2-butylamine was examined. The PMR spectrum of the base derived from a re-crystallized hydrochloride was difficult to resolve, a multiplet formed from three overlapping doublets and one triplet appearing, for example, near δ 1·0. The components of this band were further apart in the spectrum of the hydrochloride in $CDCl_3$ but the rest of the spectrum remained poorly resolved. The overall spectral appearance, however, closely resembled spectra of *trans*-**4a** and *trans*-**4b**, and, in particular, doublets assigned to 2-Me, 5-Me, and an isopropyl Me (lower field) of the reference spectra were duplicated at almost the same resonance positions in that of the N-2-Bu analogue. On these grounds the major product of this last exchange reaction is assigned a *trans* configuration. The CO group of the hydrochloride **4d** almost certainly adds D_2O since its spectrum in this solvent was characteristically more complex and closely resembled those of **4a** and **4b** salts in D_2O.

These results, together with previous studies of the N-benzyl (**4e**), N-phenethyl (**4f**), and N-cyclohexyl (**4g**) analogues[4] show that exchange reactions between *trans*-**4a** methiodide and primary bases proceed largely with retention of configuration to yield the thermodynamically more stable product (as is clear from equilibration experiments upon **4a**,[4] **4c**, and **4e**).[4] Substantial amounts (~40%) of the *cis* isomer were only encountered when benzylamine was the exchanging base and this result has been accounted for in terms of the bulkyl phenyl substituent raising the energy of one of the *trans* conformers (**18**, R = Ph). *Gauche* interactions involving phenethyl



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and cyclohexyl groups are likely to be less severe; these groups are large but their bulk is not so directly in the vicinity of the 2-Me group as is that of phenyl, cf. **19**. A *gauche* interaction also obtains in the isopropyl case **4b**; here, however, a conformation **13** is favoured (PMR evidence) of a type that the benzyl analogue is unlikely to adopt. Similar considerations apply to the N-2-Bu derivative. In the t-Bu example **4c**, relief of interactions between the N-substituent and the piperidone moiety (see **17**) require a change in conformation, rather than configuration.

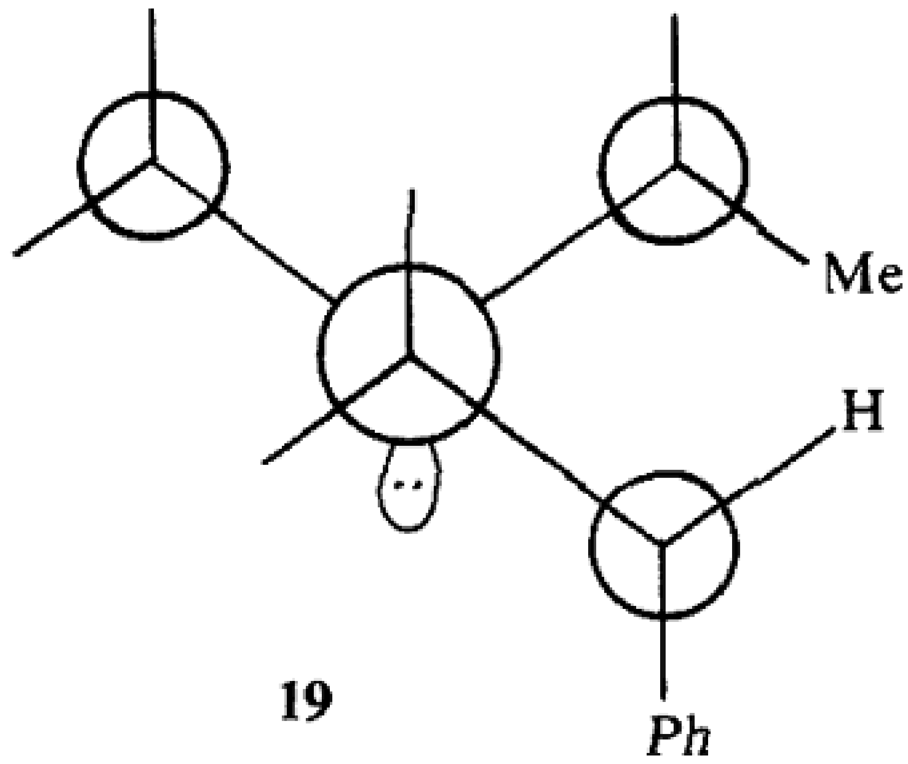

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TABLE 2. PMR CHARACTERISTICS OF SOME TRANS 2,5-DIMETHYL-4-PIPERIDONE SALTS

No.	Structure	Form	Solvent	Signal	Chemical shift[a] Free ketone	Dideuteroxy form[b]
1	**3b**	HCl	$CDCl_3$	3-Me[c]	1·08	—
				NCHMe$_2$[c]	1·50	—
	3b	HCl	D_2O	3-Me	1·08 (minor)	0·99 (major)
				NCHMe$_2$	1·38 (minor)	1·33 (major)
				α-ring protons	within 2·6–3·8 band	2·1[d]
2	**3c**	HCl	$CDCl_3$	3-Me	1·08	—
				N-t-Bu[e]	1·58	—
	3c	HCl	D_2O	3-Me	1·08 (minor)	0·98 (major)
				N-t-Bu	1·42 (minor)	1·48 (major)
				α-ring protons	within 2·6–3·9 band	2·15[d]
3	**4b**	HCl	$CDCl_3$	5-Me[c]	1·08	—
				2-Me[c]	1·58	—
				NCHMe$_2$[c]	1·30, 1·65	
	4b	HCl	D_2O	5-Me	1·08 (minor)	0·98 (major)
				2-Me, NCHMe$_2$	multiplet, 1·18–1·60, composed of at least 4 overlapping doublets	
				α-ring protons	within 2·5–4·2 band	2·15[d]
4	**4b**	MeI	DMSO-d_6	5-Me	1·00	—
				2-Me, NCHMe$_{-2}$	3 overlapping doublets between 1·15 and 1·6	
				N-Me[e]	3·27	—
	4b	MeI	D_2O	5-Me	1·08 (major)	0·98 (minor)
				2-Me, NCHMe$_{-2}$	multiplet, 1·2–1·7, composed of at least *3 overlapping doublets*	
				N-Me	3·23 (major)	3·00 (minor)
				α-ring protons	within 2·6–4·5 band	2·1[d]
5	**4c**	HCl	DMSO-d_6	5-Me	1·05	—
				2-Me	1·38	—
				t-Bu[e]	1·45	—

	4c	HCl	D_2O	5-Me	1·13	—
				2-Me	1·43	—
				t-Bu	1·48	—
6	**4c**[f]	MeI	DMSO-d_6	5-Me	1·08	—
				2-Me	1·35	—
				t-Bu	1·43	—
	4c	MeI	D_2O	5-Me	1·15	—
				2-Me	1·45	—
				t-Bu	1·50	—
				N-Me	3·18	—

[a] Chemical shifts in ppm (δ) from TMS in $CDCl_3$ or DMSO-d_6, and from DSS in D_2O.
[b] Assignments based on previous studied. (refs. 4 and 5)
[c] Doublet (s), *J* 6–7 Hz.
[d] Centre of multiplet
[e] Singlet.
[f] The 2-Me and t-Bu PMR signals of the spectrum of **4c** methiodide showed no evidence of ^{14}NCCH spin–spin coupling, anticipated to be of the order of about 2 Hz;[12] in the spectrum of **4b** methiodide, overlap of the 2-Me and isopropyl Me signals prevented the detection or otherwise of ^{14}NCCH coupling. The magnitude of coupling of this type in piperidine quaternary salts appears very sensitive to the overall symmetry of the molecule; this point will be discussed elsewhere.

EXPERIMENTAL

General method for the preparation of 1-*substituted* 3-(*and* 2,5-*di*-)*methyl*-4-*piperidones*

The methiodide of **3a** or **4a** (0·1 mole), a primary base (0·1 mole) and water (0·55 mole) were combined to give a clear soln (in some cases the mixture required warming to achieve complete miscibility); when the product was left overnight at room temp, an oil separated which was isolated by extraction with ether and distilled. In experiments using benzylamine and phenethylamine as the exchanging bases, intractable resins formed in the absence of water, while starting materials were recovered when twice the usual proportion of water was employed. Specific cases follow.

1-*Isopropyl*-3-*methyl*-4-*piperidone* (**3b**). The base (5 g), b.p. 48°/3 mm, derived from a mixture of **3a** methiodide (9 g), isopropylamine (8 ml) and water (4·5 ml) was acidified with ethanolic HCl when **3b** *hydrochloride* (2·5 g), m.p. 175–177° from EtOH–ether, separated (Found: C, 56·2: H, 9·3. $C_9H_{18}ClNO$ requires: C. 56·4; H, 9·5%); PMR, Table 2, No. 1. The *acyclic diaminoketone* **7a** *dihydrochloride*, m.p. 188–190° from EtOH–ether (Found: C, 46·2; H, 9·35. $C_{10}H_{24}Cl_2ON_2$ requires: C, 46·3; H, 9·3%) separated from the mother liquors; PMR: NMe δ 2·9 (singlet, HCl in D_2O), 2·2 and 2·23 (singlets, base in $CDCl_3$), integral 12.

1-t-*Butyl*-3-*methyl*-4-*piperidone* (**3c**). The base (3 g), b.p. 52–54°/2·5 mm, derived from a mixture of **3a** methiodide (6·5 g), t-butylamine (6 ml), and water (3 ml) was acidified as usual when **7a** dihydrochloride (0·8 g), m.p. and mixed m.p. 188–190° separated. **3c** Hydrochloride (1·3 g), m.p. 191–193° (reported[1] 180–182°) (Found: C, 58·1; H, 9·9. Calc for $C_{10}H_{20}ClNO$: C, 58·4; H, 9·9%) was obtained from the mother liquors (PMR, Table 2, No. 2).

2,5-*Dimethyl*-1-*isopropyl*-4-*piperidone* (**4b**). The base derived from a mixture of **4a** methiodide (28·3 g), isopropylamine (8 ml) and water (10 ml) distilled at 48–50°/2 mm to give **4b** (10 g) (Found: C, 70·6; H, 11·2. $C_{10}H_{19}NO$ requires: C, 70·9; H, 11·3%). It formed a *hydrochloride*, m.p. 165–167° from EtOH–ether (Found: C, 58·5; H, 9·9. $C_{10}H_{20}ClNO$ requires: C, 58·4; H, 9·8%), and a *methiodide*, m.p. 165–167°, from MeOH–ether (Found: C, 42·3; H, 7·05. $C_{11}H_{22}INO$ requires: C, 42·4; H, 7·1%); PMR, Table 2, No. 3 and 4.

1-t-*Butyl*-2,5-*dimethyl*-4-*piperidone* (**4c**). The base derived from a mixture of **4a** methiodide (28·3 g), t-butylamine (20 ml) and water (12 ml) distilled at 64–66°/0·1 mm to give a mixture (10 g) of **4c** and **7b**.

Fractional crystallization of the base hydrochlorides from EtOH–ether gave **4c** *hydrochloride* (5 g) as a hemihydrate, m.p. 178–180° (Found: C, 57·5; H, 9·8. $C_{11}H_{22}ClNO . 0{\cdot}5\ H_2O$ requires: C, 57·75; H, 10·1%: ν_{max} 3350 cm^{-1} (H_2O), PMR, Table 2, No. 5. The derived base formed a *methiodide*, m.p. 203–205° (Found: C, 44·3; H, 7·4. $C_{12}H_{24}INO$ requires: C, 44·3; H, 7·2%; PMR, Table 2, No. 6. The *acyclic diaminoketone* **7b** *dihydrochloride* (3·5 g), m.p. 150–152° (Found: C, 45·0; H, 9·8. $C_{11}H_{26}Cl_2N_2O \cdot H_2O$ requires: C, 45·35; H, 9·7%; ν_{max} 3350 cm^{-1} (H_2O), separated from mother liquors as a hydrate; PMR: s-Me δ 1·33 (d J 7 Hz, 6 protons), N-Me δ 2·9 (s, 12 protons). The base **7b** distilled at 52°/0·1 mm (Found: C, 66·4; H, 11·9; N, 14·3. $C_{11}H_{24}N_2O$ requires: C, 66·0; H, 12·1; N, 14·0%).

1-s-Butyl-2,5-dimethyl-4-piperidone (**4d**). The base obtained from a mixture of **4a** methiodide (28·4 g), s-butylamine (10·6 ml) and water (10 ml) was distilled to give **4d** (10 g), b.p. 74–76°/0·1 mm (Found: C, 72·4; H, 11·55; N, 8·0. $C_{11}H_{21}NO$ requires: C, 72·1; H, 11·5; N, 7·6%). It formed a *hydrochloride*, m.p. 148–150° from EtOH–ether (Found: C, 59·8; H, 9·8. $C_{11}H_{22}ClNO$ requires: C, 60·1; H, 10·1%).

The PMR spectra were recorded on Varian A-60D and HA-100 spectrometers at normal operating temps. Chemical shifts were recorded relative to DSS in D_2O and TMS in other solvents. IR spectral data refer to Nujol mulls.

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