^{1}H Nuclear Magnetic Resonance Spectra of Acetals and Thioacetals of 4-Piperidones

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Details of the ^{1}H n.m.r. spectra of some acetals and thioacetals of 4-piperidones are recorded. Protons of the two identical alkoxy- or alkylthio-groups at C-4 of the piperidine ring give rise to two distinct signals and these are interpreted in terms of conformational analysis. Thioacetals of 3-methyl-4-piperidones, in contrast to the acetals, are easily prepared.

DETAILS of the ^{1}H n.m.r. spectra of some 4-piperidone acetals and thioacetals (I) are given in the Table. In all the salts, protons of the two identical groups substituted at C-4 of the piperidine ring give rise to two distinct signals which are separated, in most cases, by 1—3 c./sec. (at 60 Mc./sec.). Signal splitting of this type has been noted in methyl acetals of homocyclic ketones [1] and is the result of (*a*) a difference in chemical shift between the axial and equatorial groups and (*b*)

TABLE

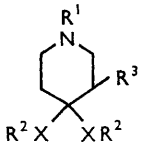
^{1}H N.m.r. characteristics of alkoxy- and alkylthio-groups in acetals and thioacetals of 4-piperidones (I)

						^{1}H N.m.r. signal of XR^2 protons [a]		
	R^1	XR^2	R^3	Form	Solvent	Mid-point signal	Signal separation	Group
a	CH_2Ph	OMe	H	HCl	$CDCl_3$	191·5	1·0	Me [b]
	,,	,,	,,	,,	$CDCl_3$–D_2O	191·5		Me [c]
	,,	,,	,,	Base	CCl_4	186		Me [c]
b	CH_2Ph	OEt	H	HCl	$CDCl_3$	70 (*J* 7) [k]	1·0	CH_2Me [d]
	,,	,,	,,	,,	,,	208 (*J* 7)	3·5	CH_2Me [e]
	,,	,,	,,	,,	$CDCl_3$–H_2O	70 (*J* 7)		CH_2Me [f]
	,,	,,	,,	,,	,,	207·5 (*J* 7)		CH_2Me [g]
c	CH_2Ph	OEt	H	MeI	$CDCl_3$	69 (*J* 6·5)	3·5	CH_2Me [d]
d	$[CH_2]_2Ph$	SEt	H	HCl	$CDCl_3$	75 (*J* 7)	1·0—1·5	CH_2Me [d]
	,,	,,	,,	,,	,,	159 (*J* 7)	2·0	CH_2Me [e]
	,,	,,	,,	,,	$CDCl_3$-py	73·5 (*J* 7)		CH_2Me [f]
e	$(CH_2)_2Ph$	SEt	Me	HCl	$CDCl_3$	74 (*J* 7)	2·0	CH_2Me [d,h]
	,,	,,	,,	,,	,,	159 (*J* 7)	3·5	CH_2Me [e]
	,,	,,	,,	,,	$CDCl_3$-py	73 (*J* 7)	1·0	CH_2Me [d]
	,,	,,	,,	,,	,,	160 (*J* 7)	3·0	CH_2Me [e]
f	$CHMe_2$	SEt	H	HI	$CDCl_3$	74 (*J* 7)	<0·5	CH_2Me [d]
	,,	,,	,,	,,	,,	159 (*J* 7)	0·5	CH_2Me [e]
	,,	,,	,,	Base	,,	66 (*J* 7)		CH_2Me [i,j]

[a] Chemical shifts c./sec. at 60 Mc./sec. [b] Two singlets. [c] One sharp singlet. [d] Two triplets. [e] Two quartets. [f] One triplet [g] One quartet. [h] Overlaps secondary Me signal at 67 c./sec. [i] One triplet. [j] Overlaps isoPr signal at 78 c./sec. [k] *J* refers to coupling constant c./sec.

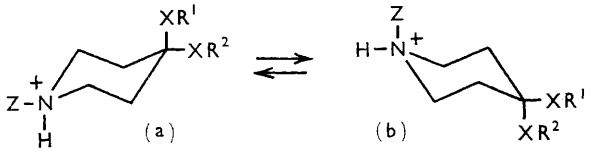
[1] M. Anteunis, *Bull. Soc. chim. belges*, 1964, **73**, 731.

the existence of unequal populations in the equilibrium set up as a result of chair–chair interconversion. In the



(I)

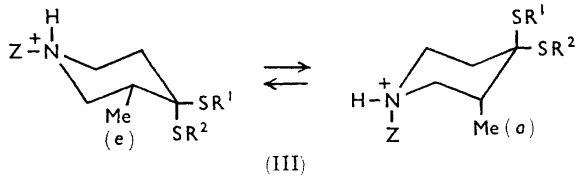
present examples the chair–chair equilibrium (II) exists where (IIa), with the *N*-substituent (Z) equatorial, is the favoured conformer.



(II ; X = O or S)

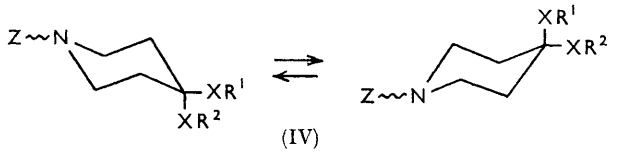
The chemical shifts of R^1 (axial) and R^2 (axial) (assumed identical although this is not strictly the case) are denoted by ν_a, while those of R^1 (equatorial) and R^2 (equatorial) are denoted by ν_e. In the case of rapid interconversion the mean chemical shifts will be $p_a{}^1\nu_a + p_e{}^1\nu_e$ for R^1 and $p_a{}^2\nu_a + p_e{}^2\nu_e$ for R^2 where p refers to the fractional populations of groups R^1 and R^2 in axial and equatorial positions.[2] Thus, if (IIa) predominates the resonance frequency of R^1 will be found near the extreme axial position and that of R^2 near the extreme equatorial position. The greater the preponderance of the favoured conformer, the greater the signal separation.

The signal separation in the 3-methylthioacetal (Ie) is greater than in the analogue which lacks this substituent (Id) because there is a greater population imbalance between the two chair-forms of (Ie) than between the two chair-forms of (Id), and because of the magnetic anisotropy of the 3-methyl group. The equilibrium in (Id) is represented by (II; X = S). In (Ie), however, the equilibrium is given by (III) where one conformer has three groups equatorial and one axial and the other conformer has three groups axial and one equatorial.*



(III)

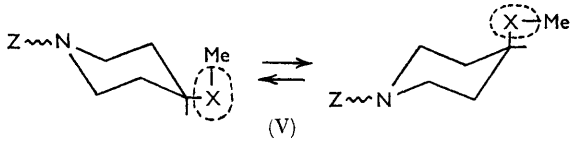
Single, sharp signals are observed in the acetal free-bases (Ia) and (If) where, owing to the rapid inversion of the trivalent nitrogen atom, the populations of the two forms in the chair–chair interconversion equilibrium (IV) are equal.



(IV)

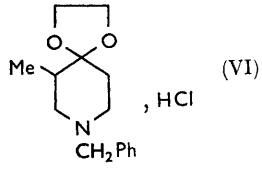
The rate of exchange of the proton at the nitrogen atom in the salts can be increased by adding D_2O or pyridine to the $CDCl_3$ solutions, to a point where signal separation vanishes and single signals are observed (Table 1; (Ia), (Ib), and (Id). 4-Piperidone acetals are weak bases [3] [(Ib), pK_a 7·1] and slow proton exchange probably occurs in $CDCl_3$, catalysed by trace impurities. This process does not occur in the methiodide (Ic), and it is noteworthy that signal separation in this case is greater than in the corresponding hydrochloride (Ib). For the hydrochloride (Ie), signal separation remains upon addition of base since the influence of the 3-methyl group in dictating conformational preference remains although that of the *N*-phenethyl group is removed.

Chemical-shift differences between axial and equatorial alkoxy- and alkylthio-groups are to be expected since their possible rotamers are influenced by markedly different environments (V).



(V)

When rotation about the C(4)–X bond is prevented, as in the dioxalan salt (VI), the signal due to $-CH_2CH_2-$ of the ethylenedioxy-group is a sharp singlet.[4]



(VI)

With an axial ethoxy- or ethylthio-group, the methylene ($X-CH_2CH_3$) protons approach the ring more closely than the methyl ($X-CH_2CH_3$)protons, and thus the signal separations of methylene are greater than those for methyl [Table 1, (Ia), (Ib), (Ia), and (If)].

The ethyl and methyl acetals were prepared by treating the appropriate 4-piperidone in ethanol or methanol with excess of hydrogen chloride and diluting the mixture with ether when the acetal hydrochloride separated in good yield. From 3-methyl-1-phenethyl-4-piperidone, however, only the ketone hydrochloride was isolated.

* It is assumed that (Ie) has the more stable *cis*-*N*-phenethyl/3-methyl configuration. If the configuration were *trans* then both conformers would have two groups equatorial and signal separation would be less. This might constitute a valuable criterion for distinguishing *cis* from *trans* when pairs are available. Further studies on this point are in progress.

[2] 'High-resolution Nuclear Magnetic Resonance,' J. A. Pople, W. G. Scheider, and H. J. Bernstein, McGraw-Hill, London, 1959, p. 221.

[3] H. Birnbaum, Ph.D. Thesis, University of London, 1964.

[4] A. F. Casy and P. Pocha, *J. Chem. Soc.* (*C*), 1967, 979.

Corresponding thioacetals were prepared under similar conditions using ethanethiol; the thioacetal of 3-methyl-1-phenethyl-4-piperidone was isolated in good yield. It has been suggested that the 3-methyl group prevents acetal formation by steric hindrance.[5] The fact that the sulphur analogue is easily made, in spite of sulphur being a larger atom than oxygen, is a good example of the well-known greater stability of thioacetals relative to acetals.

EXPERIMENTAL

Thioacetals.—1-Phenethyl-4-piperidone (5 g.) was dissolved in ethanethiol (10 ml.) and hydrogen chloride was bubbled in for 1 hr. The solid produced was recrystallised from isopropyl alcohol to give the *diethyl thioacetal hydrochloride* (7 g.) m.p. 201—204° (decomp.) (Found: C, 58·5; H, 8·0; N, 4·05; S, 19·0. $C_{17}H_{27}NS_2$,HCl requires C, 59·05; H, 8·1; N, 4·05; S, 18·55. The *diethyl thioacetal hydrochloride* of 3-*methyl*-1-*phenethyl*-4-*piperidone* was similarly prepared; m.p. 152—154° (Found: C, 59·6; H, 8·4; N, 3·7; Cl, 9·6; S, 18·35. $C_{18}H_{29}NS_2$,HCl requires C, 60·1; H, 8·35; Cl, 9·85; N, 3·9; S, 17·8%). The *diethyl thioacetal hydrochloride* of 1-*isopropyl*-4-*piperidone* was extremely hygroscopic. The derived free base, b.p. 109—112° 0·6 m.m. (Found: Equiv. wt. 243. $C_{12}H_{25}NS_2$ requires Equiv. wt. 247); the base gave a *hydriodide*, m.p. 185—186° (Found: C, 39·1; H, 7·3; N, 3·7; S, 17·25) $C_{12}H_{25}NS_2$,HI requires C, 38·4; H, 6·95; N, 3·75; S, 17·05.

Acetals.—The dimethyl acetal hydrochloride of 1-benzyl-4-piperidone, m.p. 175—176° (Found: C, 61·75; H, 8·0; N, 5·2) $C_{14}H_{22}ClNO_2$ requires C, 61·85; H, 8·1; N, 5·15 and the diethyl analogue, m.p. 172—173° (lit., 172—173°) [6] were prepared by treating 1-benzyl-4-piperidone with excess of hydrogen chloride in methanol and ethanol respectively. The quaternary salt m.p. 184—186° [7] was prepared by treating the same piperidone with methyl iodide at the reflux temperature.

The ^{1}H n.m.r. spectra were recorded on a Varian A-60 or Perkin-Elmer R-10 spectrometer with tetramethylsilane as an internal standard; we thank Miss J. Lovenack, School of Pharmacy, University of London and Mr. G. McDonough for recording the spectra.

[8/015 *Received*, *January 4th*, 1968]

[5] A. F. Casy, *Experientia*, 1964, **20**, 437.
[6] P. Brooks and J. Walker, *J. Chem. Soc.*, 1957, 3173.
[7] J. Sugden, Ph.D. Thesis, University of London, 1964.