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THE NMR SPECTRA AND CONFORMATIONS OF SOME TETRAHYDRO-1,3-OXAZINES

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Abstract—The conformations assigned to 5-nitro-5-methyl-tetrahydro-1,3-oxazines on the basis of dipole moment data are consistent with the geminal coupling constants. The NMR spectra of 6-mono, and 6,6-disubstituted tetrahydro-1,3-oxazines is discussed in relation to the preferred conformations of these compounds and long range coupling in tetrahydro-1,3-oxazines is described.

DIPOLE moment data on 5-nitro-5-methyl-tetrahydro-1,3-oxazines (I) led Urbanski[1,2] to assign conformation II with an axial N–R group to I (R = Me, and R = Et) and conformation III with an equatorial N–R group to I (R = cyclohexyl and R = tBu). NMR spectra of I (R = Me, Et, and tBu) were quoted[2] in support of the conclusions based on the dipole moment data. The NMR arguments were based on differences in chemical shift between the axial and equatorial protons of the C_2, C_4 and C_6 methylene groups, but assignment of conformations on the basis of chemical shifts alone is open to objection since work by Booth[3] has shown the sensitivity of chemical shifts of N—CH_2 protons in piperidine derivatives to the nature of the substituent on the nitrogen atom. A related example[4] is the variation of the chemical shift difference between the N—CH_2—N methylene protons in hexahydropyrimidines with the N-alkyl substituent.

As a continuation of our work on geminal coupling constants[5,6] the NMR spectra of I (R = Me, Et, tBu) studied by Urbanski[2] together with the spectra of I (R = nPr, iPr, cyclohexyl), not previously reported, were measured as dilute solutions in carbon tetrachloride (Table 1). The chemical shifts of I (R = Me, Et, tBu) agreed with those observed by Urbanski, but on studying the extended series of compounds the regularities in the values of δ_{ae} on which the conformational assignments were based appear to be somewhat tenuous, particularly in the case of the C_4 methylene protons. This was felt to be especially so since the NMR spectra of I were found to vary with the concentration of the solution (Table 2).

The factors affecting geminal coupling constants are now generally explicable on the basis of the molecular orbital treatment given by Pople and Bothner-By.[7] Thus the presence of an axial nitro group in all the compounds of type I should produce an algebraic decrease in the value of J_{gem} for the C_4 and C_6 methylene protons.* These coupling constants will be sensitive to the orientation of the lone pairs of electrons on the heteroatoms with the adjacent C—H bonds: theory predicts no effect on the value of J_{gem} if one of the hydrogens in —CH_2—X—R (X = O, N) lies in the C—X—R plane as it does in the case of C_2—H_e and C_4—H_e in conformation II. On the other

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* J_{gem} is assumed negative throughout the compounds discussed here.

Table 1. NMR spectra (ca. 5% w/v CCl_4 solution) of 5-Nitro-5-methyl-tetrahydro-1,3-oxazines (I)

Compound	Chemical shifts (τ)			*H*			Coupling constants (c/s)				
	H_{2e}	H_{2a}	H_{6e}	H_{6a}	H_{4e}	H_{4a}	J_{2e2a}	J_{6e6a}	J_{4e4a}	J_{4e6e}	J_{2e4e}
I, R = Me	5·92	6·04	5·59	6·43	6·53	7·23	−8·6	−12	−13	2	1·1
I, R = Et	5·81	5·97	5·56	6·44	6·41	7·18	−9	−12	−13·2	2	1·2
I, R = n-Pr	5·82	5·98	5·56	6·44	6·40	7·19	−8·8	−12	−13·4	2	1·2
I, R = i-Pr	5·75	5·95	5·64	6·47	6·46	7·25	−8	−12	−12·4	2	1·2
I, R = Cyclohexyl	5·72	5·90	5·67	6·46	6·45	7·18	−8·2	−12	−12·4	1·6	1·6
I, R = t-Bu	5·65	5·97	5·68	6·52	6·42	7·30	−7·7	−12	−12	1·6	1·6

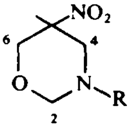
The long range couplings were all readily obtained by first order analysis of the spectra but were confirmed in many cases by spin-decoupling techniques on a Varian A-60 spectrometer.

Table 2. NMR Spectra (ca. 20% w/v) of 5-Nitro-5-methyl-tetrahydro-1,3-oxazines (I)

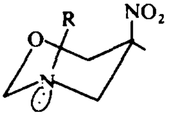
Compound	Solvent	Chemical shifts (τ)						Coupling constants (c/s)				
		H_{2e}	H_{2a}	H_{6e}	H_{6a}	H_{4e}	H_{4a}	J_{2e2a}	J_{6e6a}	J_{4e4a}	J_{4e6e}	J_{2e4e}
I, R = Me	CCl_4	5·89	6·19	5·53	6·54	6·45	7·36	−8·4	−12·4	−13	2·2	1·6
I, R = Et	CCl_4	5·79	6·03	5·52	6·49	6·35	7·26	−9	−12·4	−13·3	2·2	1·4
	$CDCl_3$	5·62	6·07	5·37	6·45	6·21	7·32	−8·7	−12·8	−13·4	2·4	1·6
I, R = n-Pr	CCl_4	5·80	6·01	5·55	6·47	6·40	7·23	−8·9	−12·3	−13·2	2	1·4
I, R = i-Pr	$CDCl_3$	5·59	6·0	5·42	6·50	6·27	7·34	−8·1	−12·7	−12·6	2·5	1·7
I, R = Cyclohexyl	$CDCl_3$	5·56	5·94	5·45	6·5	6·24	7·27	−8·2	−12·7	−12·6	2·3	1·5
	CCl_4	5·65	5·96	5·58	6·52	6·35	7·26	−8·2	−12·5	−12·5	2·0	1·5
I, R = t-Bu	CCl_4	5·59	6·05	5·62	6·58	6·35	7·37	−8	−12·2	−12	1·8	1·8

hand, when an adjacent C—H is parallel to a lone pair of electrons as in III (C_2—H_a and C_4—H_a) an increase in J_{gem} is expected.[6,8] A study of J_{gem} for the C_2, C_4 and C_6 methylene protons in I should therefore provide a more reliable guide to conformation than chemical shift data.

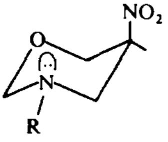
J_{gem} for the C_6-methylene protons is -12 c/s for all the compounds studied. The high dipole moments[2] appear to indicate a predominence of conformations (II and III) with an axial nitro group in all the compounds. Since in both conformations II and III the orientation of the lone pairs of electrons on oxygen with the C_6 methylene group is the same no change in J_{gem} with conformation is expected. This also confirms the assignment of the signals giving rise to the quartet ($J = -12$ c/s) to the C_6 methylene protons. J_{4e4a} varies from -13 to $-13{\cdot}4$ c/s for I(R = Me, Et, nPr) and from -12 to $-12{\cdot}4$ c/s for I(R = iPr, cyclohexyl, tBu) and in the light of the discussion above this leads us to assign conformation II to the compounds showing the more negative values of J_{gem} and conformation III to those compounds with the more positive J_{gem}. A similar division of the compounds into two groups can be made on the basis of J_{2a2e}, J_{gem} being more positive for I(R = iPr, cyclohexyl, tBu) than for the remaining three compounds. Thus from a study of their NMR spectra, compounds I (R = Me, Et, nPr) must exist predominantly in conformation II, and I (R = iPr, cyclohexyl, tBu) predominantly in conformation III. The small variations in J_{4a4e} and J_{2a2e} may be due to the differing electron releasing properties of the alkyl groups, but a certain proportion of II in equilibrium with III and vice versa due to nitrogen inversion as well as the presence of the conformations with equatorial nitro groups cannot be ruled out. Urbanski[2] reported a J_{2a2e} of -9 c/s for all the compounds I (R = Me, Et, tBu).



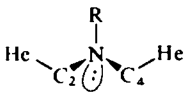
I



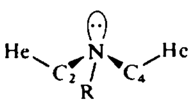
II



III

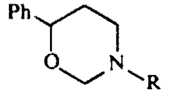


IIa



IIIa

Compounds I all show long range coupling between the equatorial protons. $|J_{4e6e}|$ is large, $|J_{2e4e}|$ varies from 1·1 to 1·6 c/s but surprisingly $|J_{2e6e}|$ is only about 0·2 c/s whereas in 1,3-dioxans $|J_{2e6e}|$ is ca. 1·5 c/s. Although in 1,3-dioxans $|J_{2e}J_{4a}|$ for example is observable[9] these types of couplings are small, and large values of ^4J all seem to require a planar zig-zag arrangements of atoms. A large value of 2–2·5 c/s for $|J_{4e6e}|$ has been observed[10,11] in 1,3-dioxans and in commenting upon this Anderson[10] has suggested that the high ^4J-values are due to the electronegative effect of the oxygen atom. Studying the values of ^4J in Table 1 and being mindful of the effect of lone pair orbital overlap on geminal[7] and on vicinal coupling constants[12] it is tempting to postulate a similar effect on ^4J. For example J_{2e4e} is numerically greater for I (R = tBu) in which the nitrogen lone pair is axial with respect to the four bond coupled C—H protons (IIIa) than for I (R = Me) in which the stereochemistry is as depicted in IIa. An opposite effect is observed in the case of the couplings between H_{4e} and H_{6e}. In order to investigate further these long range couplings, the methiodide of I (R = Et) was prepared. The NMR spectrum was observed in mixtures of formic acid and water of various proportions in order to reduce the number of overlapping signals arising when other solvents were used. The following coupling constants were obtained: $J_{2a2e} = -9{\cdot}2$ to $-9{\cdot}4$ c/s, $J_{4a4e} = -13{\cdot}8$ c/s, $|J_{2e4e}| = |J_{4e6e}| = 2$ c/s. Thus, removal of the lone pair of electrons on the N atom results in only a slight numerical increase in J_{2e4e}.



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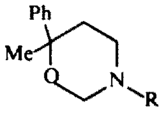

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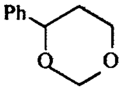

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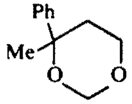
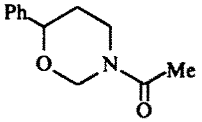
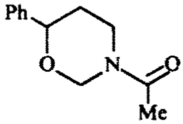


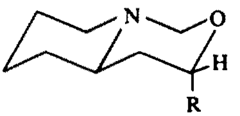
VII



IVa



IVb



VIII

The 6-monosubstituted tetrahydro-1,3-oxazines (IV, R = Me, CH_2Ph) showed J_{2a2e} values of $-9{\cdot}2$ and $-9{\cdot}7$ c/s respectively compared with the J_{2a2e} of -9 c/s observed for I (R = Et). The signals arising from the C_6 proton in compounds IV were partially obscured by the C_2 methylene signals but by varying the solvent it was shown beyond doubt that in IV (R = Me) $J_{6a5a} = 10{\cdot}6$–11 c/s and $J_{6a5e} = 3$ c/s. These compare extremely well with the values observed[13] for 4-phenyl-1,3-dioxan ($J_{4a5a} = 10{\cdot}4$, $J_{4a5e} = 3{\cdot}2$ c/s) for which a chair conformation is accepted. Thus compounds IV must exist essentially in a chair conformation with the R-group axially orientated, the more negative value of J_{2a2e} possibly arising from a small increase in the O—CH_2—N angle.[5] In IV (R = H), J_{2a2e} is $-10{\cdot}5$ c/s, too negative a value to have arisen from angle changes, but is most likely due to changes in electron density in the N—CH_2—O bonds in going from R = alkyl to R = H. In this connection Riddell[4] has quoted unpublished observations of Lehn which show a different electron distribution in ammonia and in trimethylamine between the nitrogen lone pair of electrons and the N—R bonds.

In Table 3, it can be seen that, for a particular substituent R, J_{2a2e} becomes more negative, and signals arising from H_{2e} and H_{2a} move to higher field on going from IV to V. Since in all the compounds in Table 3 the low field signals of the C_2 methylene quartet show additional coupling the weight of evidence suggests these to have arisen from the C_{2e} protons. Application of Booth's[14] correlations for chemical shifts in cyclohexanes to IV and V would lead us to expect a deshielding of the C_{2a} proton if a chair conformation with an axially situated Me is considered for V. The fact that this is not observed, together with the more negative J_{2a2e} for V, might suggest a non-chair conformation for V were it not for the recent papers[15–17] concerned with the conformation and NMR spectrum of 4-methyl-4-t-butyl-1,3-dioxan. Here the NMR evidence did originally seem to suggest a twisted boat conformation[15] but it is now generally agreed[16, 17] that this compound exists in a chair conformation and that an axial C_4-phenyl group let alone an axial C_4-Me group should not introduce sufficient strain into 1,3-dioxan to seriously distort the chair conformation.[17] In order to examine these seemingly anomalous chemical shift changes on going from IV to V 4-phenyl-1,3-dioxan (VI) and 4-phenyl-4-methyl-1,3-dioxan (VII) were compared. In carbon tetrachloride solution 4-phenyl-1,3-dioxan showed chemical shifts of 4·92 and 5·31 τ respectively for the H_{2e} and H_{2a} protons, whereas these protons in 4-phenyl-4-methyl-1,3-dioxan absorbed at 5·25 and 5·40 τ. Thus both C_2-protons are shielded by replacing the axial C_4 hydrogen by an axial Me group. In VI and VII respectively the low field signals of the C_2 methylene quartet showed evidence of long range coupling whereas the high field signals were sharp. This rules out the possibility of a reversal of chemical shifts (i.e. H_{2a} appearing at a lower

TABLE 3. NMR SPECTRA OF 6-SUBSTITUTED TETRAHYDRO-1,3-OXAZINES (IV AND V)

Compound	Solvent	Chemical shifts (τ)		Coupling constants (c/s)	
		H_{2e}	H_{2a}	J_{2e2a}	J_{2e4e}
IV, R = Me	CD_3CN	5·57	5·87	−9·2	a
IV, R = Me	Pyridine	5·43	5·81	−9·4	1
	Benzene	5·54	5·92	−9·2	1
	Furan	5·51	5·89	−9·4	1
V, R = Me	CH_3CN	5·85	6·01	−9·6	0·9
IV, R = Benzyl	CD_3CN	5·54	5·70	−9·7	a
V, R = Benzyl	CH_3CN	5·75	5·91	−10	0·9
V, R = Allyl	CD_3CN	5·75	5·91	−10	1·0
V, R = i-Pr	CD_3CN	5·78	5·94	−9·8	1
IV, R = H	CD_3CN	5·40	5·70	−10·5	1
V, R = H	CD_3CN	5·65	5·85	−10·7	a
IV, R = Acetyl	CD_3CN	4·02	5·26	−10	2·1
		4·60	5·58	−10·8	2·4
	DMSO 140°C	4·41	5·43	−10·3	2·0
V, R = Acetyl	CD_3CN	4·67	5·57	−10	1·2
		5·00	5·4	−11·4	1·9
	DMSO 80°C	4·87	5·37	−11	1·5

a = H_{2e} signals broad.

field than H_{2e} in VII) since although non-planar W long range couplings are now well recognized,[9] the largest long range couplings seem still to require this stereochemistry. Thus the chemical shift data observed for IV and V do not necessarily indicate serious deviations from chair geometry. It has recently been found[18] that relative to VIII (R = H) the axial N—CH—O proton in VIII (R = Me) is deshielded and so in this case Booth's cyclohexane chemical shift correlations apply. VIII is more likely to have a chair conformation for the tetrahydrooxazine ring than V because of the fusion to another 6-membered ring, so perhaps small deviations from chair geometry, particularly in heterocyclic systems, are sufficient to make arguments based on chemical shift data uncertain.

The NMR spectra of IV and V (R = Ac) at room temperature were a superposition of the NMR spectra of two rotational isomers (i.e. IVa and IVb). The two pairs of doublets arising from the C_2 methylene protons in V (R = Ac) coalesced at about 60° and gave rise to a single sharp pair of doublets at temperatures above 80°. Because of the larger differences in chemical shifts coalescence occurred at a rather higher temperature in the case of IV (R = Ac). In the N-acetyl compounds deviations from chair geometry are now certain to be observed because of flattening around the nitrogen atom. The massive shielding of the H_{2e} proton of $+0{\cdot}65$ on going from IV (R = Ac) to V (R = Ac) (considering one rotational isomer) can give rise to no other interpretation but that V (R = Ac) exists in some twist boat conformation with the amide carbonyl sufficiently removed from H_{2e} so as to be unable to deshield this proton.

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