The Conformational Analysis of Saturated Heterocycles. Part LXIII.[1] Tetrahydro-1,2-oxazines [2] and Related Acyclic Hydroxylamines

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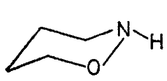
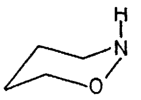
Infrared intensities show that the proton attached to nitrogen in tetrahydro-1,2-oxazine exists predominantly in the equatorial position. For an *N*-methyl group, the equatorial position is favoured by *ca.* 1·9 kcal mol^{-1}, as deduced from electric dipole moments. The conformations of di- and tri-methylhydroxylamines are discussed.

NITROGEN inversion in tetrahydro-2-methyl-1,2-oxazines has been investigated by Riddell *et al.*[3,4] using variable temperature n.m.r. spectroscopy. Only one methyl peak was found even at −100°, indicating either that the intrinsic axial–equatorial chemical shift difference is small, or that one conformation is highly favoured. We have now investigated this conformational equilibrium by dipole moment studies, and have also studied the NH-analogue and the acyclic *NO*-dimethyl- and *NNO*-trimethylhydroxylamines for which no conformational data were available previously.

Conformation of Tetrahydro-1,2-*oxazine*.—This compound was investigated by using the ν_{NH}-overtone technique developed previously.[5,6] Tetrahydro-1,2-oxazine shows a single band in the NH-overtone region at 6497 cm^{-1}. Two criteria were applied to assign the band to the N–H equatorial (1) or axial (2) vibration. The observed separation between the *P* and *R* branches of the band is *ca.* 16 cm^{-1}; the values calculated by the extended [6] Seth-Paul [7] and Badger–Zumwalt [8] methods, respectively, are 18 and 19 cm^{-1} for the N–H equatorial conformer and 24 and 25 cm^{-1} for the N–H axial conformer. The *Q*-branch absorbance calculated for the N–H axial conformer by the method of Gerhard and Dennison,[9] which is strictly applicable only to symmetric tops and therefore used here with caution, is 41%; however, in the observed band the central 8 cm^{-1} comprises only 25% of the total absorbance. Thus both criteria indicate that the observed band is due to the N–H equatorial conformer (1).


(1)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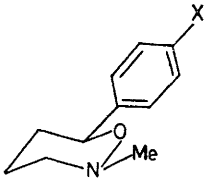
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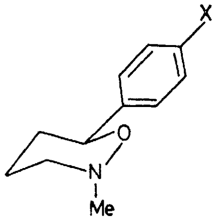
(4) X = Cl


(5) X = H
(6) X = Cl

Conformations of Tetrahydro-2-*methyl*-1,2-*oxazines*.—Recent work in the 5-aryl-1,3-dithian series [10] indicated that a 6-aryl substituent should be a good 'holding'

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[2] Preliminary communication, R. A. Y. Jones, A. R. Katritzky, A. C. Richards, S. Saba, A. J. Sparrow, and D. L. Trepanier, *J.C.S. Chem. Comm.*, 1972, 673.

[3] F. G. Riddell, J. M. Lehn, and J. Wagner, *Chem. Comm.*, 1968, 1403.

[4] F. G. Riddell, D. A. R. Williams, C. Hootelé, and N. Reid, *J. Chem. Soc.* (*B*), 1970, 1739.

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[7] W. A. Seth-Paul, *J. Mol. Structure*, 1969, **3**, 403.

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[9] S. L. Gerhard and D. M. Dennison, *Phys. Rev.*, 1933, **43**, 197.

[10] L. Angiolini, I. D. Blackburne, R. A. Y. Jones, and A. R. Katritzky, *Gazzetta*, in the press.

group. We therefore studied the dipole moments of the 6-aryl-1,2-oxazines (3) $\rightleftharpoons$ (5) and (4) $\rightleftharpoons$ (6).

The geometry of the tetrahydro-1,2-oxazine ring in the chair conformation was elucidated by the computer method previously developed,[11] using bond lengths and bond angles previously selected.[11] No allowance was made for relief of torsional angle strain, as no suitable potential functions are available for torsional strain about an N–O bond; however, the previous work[11] indicated that such refinement should have little effect on the conclusions.

The Cartesian co-ordinates of the atoms thus obtained are used together with the bond and group moments of Table 1. The bond moment of N–O is considered an unknown (x) as is the mole fraction N_e of the N-methyl group equatorial (N_e is assumed to be the same for the p-Cl and the p-H series). Two equations follow, equation (1) for the p-H and equation (2) for the p-Cl series.

TABLE 1

Bond and group moments used for tetrahydro-oxazine calculations

Bond or group	μ/D	Moment derived from	μ/D	Ref.
$C(6)-C_6H_5$	0·62	Phenylcyclohexane	0·62	*a*
$C(6)-C_6H_4Cl$-*p*	2·18	*p*-Chlorophenylcyclohexane	2·18	*a*
$C(6)-O$	1·37	Tetrahydropyran	1·55	*b*
$C(3)-N$	0·74	R_3N	0·77	*c*
$>N(2)-CH_3$	0·80	*N*-Methylpiperidine	0·80	*b*

[a] R. J. Bishop, L. E. Sutton, D. Dineen, R. A. Y. Jones, A. R. Katritzky, and R. J. Wyatt, *J. Chem. Soc.* (*B*), 1967, 493. [b] A. L. McClellan, 'Tables of Experimental Dipole Moments,' W. H. Freeman, San Francisco, 1963. [c] C. W. N. Cumper, *Tetrahedron*, 1969, 3131.

$$(1{\cdot}47)^2 = N_e(-0{\cdot}0002X - 2{\cdot}8892) + 1{\cdot}0002X^2 + 1{\cdot}2514X + 4{\cdot}5421 \qquad (1)$$

$$(2{\cdot}73)^2 = N_e(-0{\cdot}0003X - 2{\cdot}7396) + 1{\cdot}0002X^2 + 4{\cdot}3650X + 8{\cdot}8868 \qquad (2)$$

Solving equations (1) and (2) gives $N_e = 0{\cdot}96$ and x, the bond moment for N–O, as 0·26 D [in the direction $N^{(+)}-O^{(-)}$]. Smyth[12] has estimated this bond moment to be about 0·3 D. The calculated moments of the separate conformers are given in Table 2. The value of ΔG^0_{25} corresponding to $N_e = 0{\cdot}96$ is *ca.* 1·9 kcal mol^{-1}, but we do not claim high accuracy for this value because of the logarithmic relationship of ΔG^0 to N_e.

If we use the value of 0·26 D for the N–O bond moment we can calculate that the dipole moment of tetrahydro-2-methyl-1,2-oxazine in the *eq*-methyl conformation should be 1·13 D. This is in close agreement with the observed value (1·15 D) for tetrahydro-2-t-butyl-1,2-oxazine in which the N-alkyl group is assuredly completely equatorial, and it indicates that the assumptions used in the calculations are not greatly in error. We have attempted to measure the dipole moment of tetrahydro-2-methyl-1,2-oxazine itself, for further confirmation of our conclusions, but we have not yet been able to obtain a sufficiently pure sample.

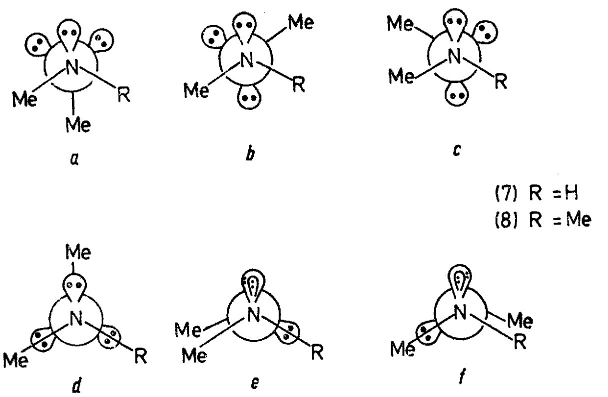
TABLE 2

Observed dipole moments and calculated moments of conformers

Compound	Conformer	μ(calc.)/D	μ(obs.)/D
Tetrahydro-2-methyl-6-phenyl-1,2-oxazine	(3)	1·43	1·47
	(5)	2·22	
6-*p*-Chlorophenyltetrahydro-2-methyl-1,2-oxazine	(4)	2·71	2·73
	(6)	3·18	
NO-Dimethylhydroxylamine	(7*a*)	2·07	0·83
	(7*b*)	1·07	
	(7*c*)	1·07	
	(7*d*)	0·29	
NNO-Trimethylhydroxylamine	(8*a*)	1·81	0·88
	(8*b*, *c*)	0·98	
	(8*d*)	0·45	

Recently, Riddell *et al.*[13] ascertained the molecular geometry of 2-(*p*-carboxybenzyl)tetrahydro-1,2-oxazine by X-ray crystallography. Recalculation of the results on the basis of this geometry gives $N_e = 0{\cdot}92$ and the N–O bond moment as 0·26 D, as previously. This again indicates that the reported calculations are not greatly in error.

Conformations of NO-*Dimethyl- and* NNO-*Trimethylhydroxylamines.*—*NO*-Dimethylhydroxylamine can exist in three staggered conformations (7*a*—*c*) and three eclipsed ones (7*d*—*f*). Conformations *e* and *f* are unlikely to be significantly populated, but *d*, in which the repulsion between the oxygen and nitrogen lone pairs is minimised, may be important. Recent calculations by Fink, Pan, and Allen[14] and by Pedersen and Morokuma[15] suggest that the conformation analogous to *d* is the most stable for hydroxylamine itself, though Gordon and Pople[16] favoured the conformation analogous to *a*. In trimethylhydroxylamine (8) conformers *b* and *c* are of equal energy, being enantiomeric; *e* and *f* are again neglected. Conformers *a* and *c*, respectively, are geometrically analogous to the axial and equatorial conformers of the tetrahydro-oxazines.



(7) R = H
(8) R = Me

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[11] I. D. Blackburne, R. P. Duke, R. A. Y. Jones, A. R. Katritzky, and K. A. F. Record, *J.C.S. Perkin II*, 1973, 332.

[12] C. P. Smyth, *J. Amer. Chem. Soc.*, 1938, **60**, 183.

[13] F. G. Riddell, P. Murray-Rust, and J. Murray-Rust, personal communication.

[14] W. H. Fink, D. C. Pan, and L. C. Allen, *J. Chem. Phys.*, 1967, **47**, 895.

[15] L. Pedersen and K. Morokuma, *J. Chem. Phys.*, 1967, **46**, 3941.

[16] M. S. Gordon and J. A. Pople, *J. Chem. Phys.*, 1968, **49**, 4643.

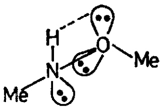
We have measured the electric dipole moments of the two compounds and compared them with values calculated for the separate conformers. In these calculations we have used the Cartesian co-ordinates for hydroxylamine reported by Fink, Pan, and Allen,[14] together with the bond and group moments given in Table **3**. The results of these calculations are given in Table 2. For each compound the observed moment is lower than the values calculated for three of the four conformers (*a*, *b*, and *c*), showing that there must be significant contributions from the conformers *d*. Alternatively there may be a single preferred conformation lying between *d* and *b* or *c*. There is probably little contribution from conformers *a* which have very high dipole moments. If the approximation is made that conformers *a* are absent it can be calculated that *ONN*-trimethylhydroxylamine and *ON*-dimethylhydroxylamines exist to the extent of 25 and 43%, respectively, as conformer *d*. This difference suggests that the attractive force between an oxygen lone pair and NH might be an important factor in stabilising this conformation (9). Such an explanation would accord with the great stability of conformation *d* over *b* or *c* in hydroxylamine itself.

TABLE 3

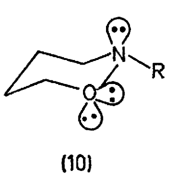
Bond and group moments used for hydroxylamine calculations

Bond or group	μ/D	Derived from	μ/D	Ref.
Dimethyl ether	1·25			*a*
Trimethylamine	0·86			*a*
Dimethylamine	1·18			*a*
C–O	1·11	Dimethyl ether	1·25	*a*
C–N	0·83	Trimethylamine	0·86	*a*
N–O	0·26			

[a] C. W. N. Cumper, *Tetrahedron*, 1969, 3131.



(9)



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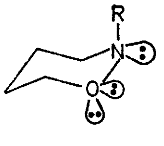

(11)

Conclusions.—We have previously shown that substitution of a heteroatom for C-3 of piperidine increases the proportion of axial-NH [6] and of axial-*N*-alkyl conformers.[17] By contrast, the present results indicate that substitution of an oxygen atom for C-2 in piperidine increases the proportion of equatorial-NH and equatorial-*N*-Me. Qualitatively this may be correlated with the smaller degree of lone pair repulsion in (10) than in (11); we are dealing here with a reverse anomeric effect. These results are in good qualitative agreement with those of MO calculations on the rotamers of unsubstituted hydroxylamine.[14,15] Quantitatively the calculated ΔG^0 values differ from our estimates, but this is hardly surprising on four grounds. (a) The calculated values appear, by comparison with such sparse experimental data as are available (*cf.* ref. 14) to be too high. (b) The present experimental value is not highly precise. (c) The rotational barriers in unsubstituted hydroxylamine include contributions from lone pair interactions with vicinal bonds to hydrogen; alkylated systems are bound to differ. (d) Incorporation of the hydroxylamino-fragment into a ring imposes further restraints on the system. It is relevant that the acyclic systems which we have studied appear to resemble unsubstituted hydroxylamine more closely than do the tetrahydro-oxazines; *i.e.*, in the absence of the restraint imposed by the ring structure, the N–O bond is rotated still further in the direction of minimum lone pair repulsions.

EXPERIMENTAL

Tetrahydro-1,2-oxazine, b.p. 50—51° at 30 mmHg (lit.,[18] 50—51° at 30 mmHg), τ (CCl_4) 4·94 (1H, s), 6·24 (2H, m), 7·00 (2H, m), and 8·35 (4H, m), was liberated from its hydrochloride [19] by treatment until basic with potassium hydroxide followed by extraction with ether. Tetrahydro-2-methyl-6-phenyl-1,2-oxazine, b.p. 66—67° at 0·05 mmHg (lit.,[20] 93° at 0·30 mmHg), τ (CCl_4) 2·80 (5H, s), 5·33 (1H, q, $J_{ax,ax}$ 10, $J_{ax,eq}$ 3 Hz), 7·0—8·5 (6H, m), and 7·47 (3H, s); and 6-*p*-chlorophenyltetrahydro-2-methyl-1,2-oxazine, b.p. 82° at 0·05 mmHg (lit.,[20] 72° at 0·10 mmHg), τ (CCl_4) 2·80 (4H, s), 5·32 (1H, q, $J_{ax,ax}$ 10, $J_{ax,eq}$ 2·7 Hz), 7·1—8·5 (6H, m), and 7·44 (3H, s), were prepared by the method of ref. 20.

2-*Methyl*-2-(*tetrahydro*-1,2-*oxazin*-2-*yl*)*propionitrile*.—This compound was prepared following a method used [21] for making 2-(di-isopropylamino)propionitrile.

Tetrahydro-1,2-oxazine hydrochloride (0·1 mol, 12·5 g) was dissolved in water (30 ml) and saturated aqueous potassium cyanide (0·1 mol, 6·51 g) was added. The solution was then cooled to 0° and acetone (0·1 mol, 5·81 g) was added dropwise. The solution was subsequently stirred at room temperature for 3 h. Two layers appeared; the top layer was separated and the bottom layer was saturated with potassium carbonate and extracted with ether (3 × 20 ml). The ethereal extracts were combined with the upper layer and dried (Na_2SO_4), filtered, and evaporated. The residue was then fractionally distilled. The nitrile was collected as the fraction with b.p. 94—95° at 10 mmHg (6·3 g, 41%); τ (CCl_4) 6·08 (2H, m), 7·08 (2H, m), 7·95—8·70 (4H, m), and 8·57 (6H, s).

Tetrahydro-2-*t*-*butyl*-1,2-*oxazine*.—This was prepared by a method similar to those used for making tri-isopropylamine [21] and 1,2,2-trimethylpiperidine.[22] 2-Methyl-2-(tetrahydro-1,2-oxazin-2-yl)propionitrile (0·04 mol, 6·3 g) in dry ether (50 ml) was added at 0° to methylmagnesium iodide [from methyl iodide (0·12 mol, 17·5 g) and magnesium turnings (3·0 g)] in dry ether (50 ml). The mixture was then heated

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[20] L. D. Quin and G. L. Roof, *J. Org. Chem.*, 1962, **27**, 4451.

[21] F. Kuffner and W. Koechlin, *Monatsh.*, 1962, **93**, 476.

[22] N. J. Leonard and F. P. Hauck, jun., *J. Amer. Chem. Soc.*, 1957, **79**, 5279.

under reflux during 1 h and filtered through sintered glass, and the gummy solid was washed with more ether. Evaporation of the ether left *tetrahydro*-2-*t*-*butyl*-1,2-*oxazine* as a pale yellow liquid, which showed only one peak on g.l.c. After fractional distillation (b.p. 68—69° at 38 mmHg) the yield was 2·93 g (50%). The *picrate* had m.p. 145° (Found: C, 45·2; H, 5·5; N, 14·8. $C_{14}H_{20}N_4O_8$ requires C, 45·2; H, 5·4; N, 15·0%), $\nu_{max.}$ (film) 1365, 1390, and 1225 (Bu^t) cm^{-1}; τ (CCl_4) 5·99—6·18 (2H, m), 7·07—7·45br (2H), 8·05—8·90 (4H, m), and 8·97 (9H, s).

NO-*Dimethyl- and* NNO-*Trimethyl-hydroxylamines*.—These were prepared by literature methods.[23,24] They were dried (BaO) and redistilled immediately before the measurement of their dipole moments.

Physical Measurements.—Dipole moments were measured using the technique of ref. 25; results are recorded in Table 2 and the experimental data are available in Supplementary Publication No. SUP 21069 (4 pp.).*

I.r. spectra were measured as before.[5,6]

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* For details of Supplementary Publications, see *J.C.S. Perkin II*, 1973, Index issue (Notice to Authors No. 7).

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