Conformational Analysis of Saturated Heterocycles. Part 78.[1] Passing Pyramidal Nitrogen Inversions in Some Perhydro-1,3-oxazines and -1,3-Diazines

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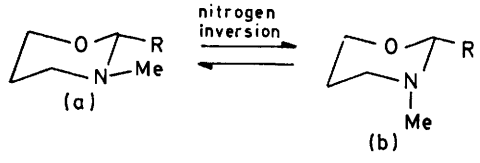
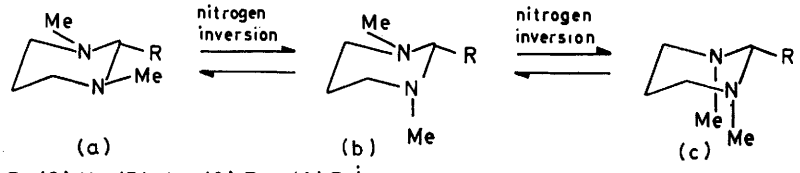
Variable temperature proton n.m.r. studies allowed the direct observation of pyramidal nitrogen inversion hindered by an adjacent equatorial alkyl group in some 2-alkyl-3-methylperhydro-1,3-oxazines and 2-alkyl-1,3-dimethylperhydro-1,3-diazines. The axial–equatorial free energy differences for the *N*-methyl groups and the conformer populations have been measured.

It has previously been shown [2-5] that the free energy of activation for *N*-methyl inversion in saturated five- and six-membered rings can be raised, in comparison to *N*-methyl inversion free of all rate-retarding factors, when an adjacent equatorial *C*-methyl group is present: in the transition state the two methyl groups are eclipsed and the resulting steric interactions have to be overcome to effect the inversion. Adjacent *N*-methyl groups act similarly, but for these electronic interactions also intervene. The present paper examines the effects of varying the size of the 2-alkyl equatorial group, in consistent series of perhydro-1,3-oxazine and -1,3-diazine derivatives, on (*a*) the free energy barrier of pyramidal nitrogen inversion and (*b*) the conformational equilibrium.

The perhydro-1,3-oxazine and -1,3-diazine systems were selected since these analogues of piperidine in which the ring CH_2 has been replaced by O or NR would be expected to show significant populations of both *N*-methyl axial and *N*-methyl equatorial conformers as well as free energy barriers of sufficient magnitude to be detected by dynamic n.m.r. Furthermore, apart from the parent compounds 3-methylperhydro-1,3-oxazine (1) and 1,3-dimethylperhydro-1,3-diazine (6), ring inversion should not be an important process as the ring conformations having the 2-*C*-alkyl group equatorial are expected to predominate greatly.[6] Thus only conformers (1a and b) of the perhydro-1,3-oxazines and the conformers (6a and b) of the perhydro-1,3-diazines need be considered.



R=(1) H; (2) Me; (3) Et; (4) Pr^i; (5) Bu^t



R=(6) H; (7) Me; (8) Et; (9) Pr^i

Preparation of Compounds (Table 1).—The 3-methylperhydro-1,3-oxazines (1)—(5) were obtained from 3-methylaminopropan-1-ol [7] (see Scheme) and the corresponding aldehyde. The 1,3-dimethylperhydro-1,3-diazines (6)—(9) were prepared in a similar manner

TABLE 1

Preparative details

Compound [a]	Method [b]	Yield (%)	B.p. (°C) [mmHg]
(1)	A	72	124 [760] [c]
(2)	B	59	120 [760] [d]
(3) [e]	B	45	48 [15]
(4) [f]	B	41	56 [15]
(5)	B	36	126 [18]
(6)	A	65	40 [22]
(7)	B	58	70 [38]
(8)	B	40	78 [31]
(9)	B	39	92 [33]

[a] Characterised on the basis of spectral data. [b] See Experimental section. [c] Lit.,[7] 125 [760]. [d] Lit.,[8] 97 [700]. [e] Found: N, 11.1. $C_7H_{15}NO$ requires N, 10.9%. [f] Found: C, 66.9; H, 12.1; N, 10.0. $C_8H_{17}NO$ requires C, 67.1; H, 12.0; N, 9.8%.

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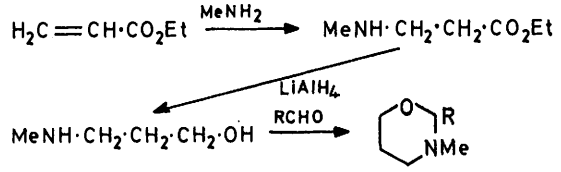
by the condensation of 1,3-bismethylaminopropane and the appropriate aldehyde.



SCHEME

EXPERIMENTAL

Spectra.—Proton n.m.r. spectra were measured with a Varian HA-100 spectrometer. Temperatures (stable to within ±2 K) were measured with reference to a standard methanol sample [8] down to 183 K. Below 183 K a platinum resistance thermometer was used. Solvents used were CF_2Cl_2, $H_2C{:}CHCl$, and $CDCl_3$. Chemical shifts were measured from internal Me_4Si and are accurate to within ±0.01 p.p.m. Low resolution mass spectra were determined with a Perkin-Elmer–Hitachi RMU spectrometer.

Dipole Moments.—Dipole moments were calculated [9] by the method of Halverstadt and Kumler as described previously [9] from measurements in cyclohexane solution at 298 K. The electronic polarisation was summed from bond electronic polarisabilities;[10] no allowance was made for atomic polarisation.

Predicted dipole moments were calculated from the energy minimised ' geometry [11] evaluated for the perhydro-1,3-oxazine and -1,3-diazine systems. The results are given in Table 2 and additional data are given in Supplementary Publication No. SUP 21954 (3 pp.).*

TABLE 2

Calculated conformational equilibria from dipole moment measurements

Compound	μ_{obs}/D	Predicted μ/D: all-*eq*	Predicted μ/D: mono-*ax*	Calculated % *ax* [a] or % *ax,eq* [b]	ΔG^0_{298}/kcal mol^{-1}
(1)	1.58	1.86	1.06	42	−0.20 [c]
(3)	1.48	1.86	1.06	54	0.10
(4)	1.48	1.86	1.06	54	0.10
(6)	1.28	1.54	0.88	45	0.54 [c]
(7)	1.09	1.54	0.88	74	0.62
(8)	1.12	1.54	0.88	70	0.50
(9)	1.13	1.54	0.88	69	0.46

[a] For perhydro-1,3-oxazine. [b] For perhydro-1,3-diazines. [c] Previously measured.

2-Alkyl-3-methylperhydro-1,3-oxazines and 2-Alkyl-1,3-dimethylperhydro-1,3-diazines (*Table* 1).—*Method A.* 3-Methylaminopropan-1-ol (0.1 mol) or 1,3-bismethylaminopropane (0.1 mol) with the corresponding aldehyde (0.1 mol) and benzene (100 ml) were heated under reflux for 4 h with continuous removal of the water formed. Removal of benzene and fractional distillation afforded the cyclic compounds.

Method B. Typically the aldehyde † (0.1 mol) was added dropwise with stirring to 3-methylaminopropan-1-ol (0.1 mol) or 1,3-bismethylaminopropane (0.1 mol) at 273 K. After the addition the mixture was stirred for a further 2 h at 298 K. Potassium hydroxide pellets were then added and the organic layer was separated. Distillation gave the cyclic products.

Analytical data proved difficult to obtain but all compounds were homogeneous by g.l.c. and were uniquely characterised by their n.m.r. spectra.

* For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1975, Index issue. Items less than 10 pp. are supplied as full-size copies.

† With acetaldehyde, diethyl ether was employed as solvent and magnesium sulphate was used to remove the water formed.

RESULTS AND DISCUSSION

The proton n.m.r. spectral data at 307 K (Table 3) for the perhydro-oxazines (1)—(5) indicate fast nitrogen inversion; the *N*-methyl signal appears as a sharp singlet. Compound (1) is also undergoing rapid ring inversion (the 2-H_2 signal is observed as a singlet). Below 193 K ring inversion is slowed and the 2-H_2 signal appears as a quartet. Nitrogen inversion in this series is slowed only in the range 120—140 K (Table 4). The *N*-methyl protons then give rise to two separate signals corresponding to the conformers (1a and b). Direct area measurement of the peaks at 128 K gave the proportions of conformers present as 35% axial, 65% equatorial; the upfield signal was assigned to the *N*-methyl protons in an axial environment. When the populations of the conformers are corrected to room temperature (Table 5) they are in good agreement with the results obtained from dipole moment measurements (Table 2). The

TABLE 3

Proton n.m.r. spectra at 307 K (δ values; 100 MHz) [a] of some perhydro-1,3-oxazines and -1,3-diazines

Compound	N·C*H*$_3$	C(2)H*R*
(1)	2.48 (s)	5.79 (s)
(2) [b]	2.25 (s)	1.22, 1.28 (d)
(3) [b]	2.30 (s)	0.92 (t)
(4) [b]	2.29 (s)	0.91 (q)
(5)	2.40 (s)	0.93 (s)
(6)	2.13 (s)	2.9 (s)
(7)	2.07 (s)	1.08, 1.14 (d)
(8)	2.16 (s)	0.84 (t, CH_2·*C*H$_3$)
(9)	2.41 (s)	0.89 (s), 0.97 (s)

[a] In CF_2Cl_2. [b] In $CDCl_3$.

TABLE 4

Low temperature proton n.m.r. spectra (δ values; 100 MHz) of some perhydro-1,3-oxazines and -1,3-diazines [a]

Compound	*T*/K	N·C*H*$_3$
(1)	128	2.48 (s), 2.02 (s)
(2) [b]	133	2.33 (s), 2.08 (s)
(3)	130	2.07 (s), 2.24 (s)
(4)	133	2.09 (s), 2.26 (s)
(5)	126	2.29 (s)
(6)	123	2.03 (s)
(7)	139	2.25 (s), 1.96 (s)
(8)	130	2.17 (s), 2.00 (s)
(9)	124	2.29 (s), 2.00 (s)

[a] In CF_2Cl_2. [b] In $CH_2{:}CHCl$.

[8] A. L. Van Geet, *Analyt. Chem.*, 1970, **42**, 679.
[9] J.-L. Imbach, R. A. Y. Jones, A. R. Katritzky, and R. J. Wyatt, *J. Chem. Soc.* (*B*), 1967, 499.
[10] R. J. W. Le Fèvre and K. D. Steel, *Chem. and Ind.*, 1961, 670.
[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.

proton n.m.r. spectra of compounds (2)—(5) showed a similar slowing of nitrogen inversion at low temperatures (Table 4). An increase in the proportion of the *N*-methyl axial conformer was observed in the 2-*C*-alkyl series Me, Et, Pr^i, Bu^t (Table 5). This result can best be explained in terms of the increase in steric bulk of the *C*-alkyl (*eq*) group disfavouring the *N*-methyl (*eq*) environment. The expected large increase in ground-state free energy is relieved to some extent by an increase

TABLE 5

Coalescence temperatures (T_c), free energies of activation ($\Delta G^{\ddagger}_c$) [a] for nitrogen inversion, and percentage populations of conformers

Compound	T_c/K	$\Delta G^{\ddagger}_c$/kcal mol^{-1}	% NMe axial [b] (T/K)	ΔG^0_{298} [c]
(1)	142	6.8	35 (128), 43 (298)	−0.16
(2)	155	7.6	45 (127), 48 (298)	−0.05
(3)	150	7.4	61 (130), 55 (298)	0.11
(4)	155	7.6	74 (133), 61 (298)	0.27
(5)			*ca.* 100 (130), *ca.* 100 (298)	
(6)		≤6.7 [d]		
(7)	163	8.0	91 (139), 81 (298)	0.85
(8)	153	7.6	74 (130), 70 (298)	0.50
(9)	138	6.7	73 (124), 69 (298)	0.48

[a] Error ±0.2 kcal mol^{-1}. [b] Based on peak area measurements determined in CF_2Cl_2 at low temperature with the values extrapolated to 298 K. [c] Positive sign indicates that alkyl axial is favoured. [d] Estimated.

in the axial preference of the *N*-methyl group. The predictable increase in the barrier for nitrogen inversion is observed going from C(2)H_2 to C(2)H-alkyl (Table 5). That the barrier subsequently remains essentially the same for alkyl = Me, Et, and Pr^i implies that the ground-state energies of the molecules are changed by approximately the same extent as the transition states.

In the perhydro-1,3-diazines (6)—(9) ring inversion and nitrogen inversion are possible but again ring inversion should not be an important process except in the case of the parent compound (6). The proton n.m.r. spectra at 307 K show only one *N*-methyl singlet, reflecting the symmetric nature of these compounds. On lowering the temperature, ring inversion in the parent compound (6) is slowed (the 2-H_2 singlet separates to a quartet by 193 K): however, nitrogen inversion cannot be slowed even at 123 K. Assuming a chemical shift of 10 Hz * places an upper barrier limit of $\Delta G^{\ddagger}$ = 6.7 kcal mol^{-1} at 132 K. It is important to note that variation in the free activation energy within a series such as the perhydro-1,3-diazines can be a consequence not only of changes in the transition state energies but also of the ground state energies, or both. The perhydro-1,3-diazines (7)—(9) did exhibit slowing of nitrogen inversion at low temperatures, and the free energies of activation and free energy differences were determined in the usual manner with allowance being made for an entropy contribution due to symmetry (Table 5). The expected trend of an increase, due to steric interaction and buttressing, in the barrier height initially observed on going from the parent perhydro-1,3-diazine (6) to the 2-methylperhydro-1,3-diazine (7) is in fact reversed with the higher alkyl homologues (8) and (9) since the ground state is presumably destabilised to a greater extent than the transition state. The partial relief of the increase in the ground state free energy which is observed in the perhydro-oxazine series by the *N*-methyl group adopting with an increasing preference an axial environment is not possible in the perhydro-1,3-diazine series as the resulting 1,3-*NN'*-dimethyl axial interactions (2c) would be highly unfavourable.

The conformer population of the parent 1,3-dimethylperhydro-1,3-diazine, which has been measured by dipole moments [12] and deduced from chemical shift data,[13] is known to be *ca.* 55% *eq,eq*. The introduction of the 2-methyl substituent increased the percentage of axial,-equatorial conformer (2b) to 81% as expected, as this conformer relieves the steric interactions to some degree. The exact conformer populations of the ethyl- and isopropylperhydro-1,3-diazines (8) and (9) were difficult to ascertain owing to line broadening and overlap of signals, but both exhibited a marked increase in the amount of the axial,equatorial conformer (2b) in comparison with the parent perhydro-1,3-diazine (6).

To confirm the observed conformer population preferences of the perhydro-1,3-oxazines and -1,3-diazines we carried out a dipole moment investigation of some of these compounds. In the dipole moment calculations the C–NR–C moment is assumed to be as in the corresponding piperidines. The C–O–C moment is taken to be 1.26 D from the 3-t-butylperhydro-1,3-oxazine, which exists in the all *N*-alkyl equatorial conformation (different from that found for tetrahydropyran, but then this also differs from that of diethyl ether). The two moments in the perhydro-1,3-oxazine are calculated [11] to act at 52° 53′ in the *N*-methyl equatorial conformation (1a) and 123° 38′ in the *N*-methyl axial conformer (1b) and in the perhydro-1,3-diazines in the *N*-methyl diequatorial conformer (6a) at 3° 34′ and 110° 14′ in the axial,equatorial conformer (6b). The results shown in Table 2 are in general agreement with those extrapolated from the low temperature n.m.r. measurements.

In conclusion, the perhydro-1,3-oxazines show a clear trend in the increase of *N*-methyl axial population with increase in the steric bulk of the 2-alkyl equatorial substituent. The trend in the perhydro-1,3-diazine series is more complex but the introduction of 2-alkyl equatorial substituents creates a decided preference for the axial,equatorial conformer (2b).

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* We take 10 Hz to set an upper limit on the possible $\Delta G^{\ddagger}$ value (which is not particularly sensitive to $\Delta\nu$) at the lowest measured temperature. For the other perhydro-1,3-diazines values range from 17 to 29 Hz.

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