The Conformational Analysis of Saturated Heterocycles. Part LXV.[1] Low Temperature Nuclear Magnetic Resonance Studies on 2-Methyl-, 2-Ethyl-, and 2,3,3-Trimethyl-2,3,5,6-tetrahydro-1,4,2-dioxazines [2]

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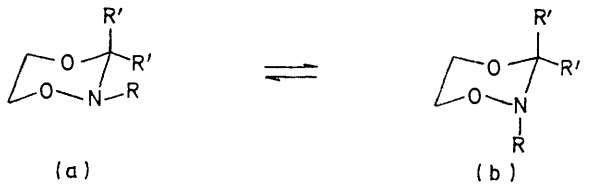
The *N*-alkyl equatorial conformers of 2-methyl-, 2-ethyl-, and 2,3,3-trimethyl-2,3,5,6-tetrahydro-1,4,2-dioxazines predominate, with ΔG°_{191} values of 1·03, 0·72, and 0·61 kcal mol^{-1}, respectively.

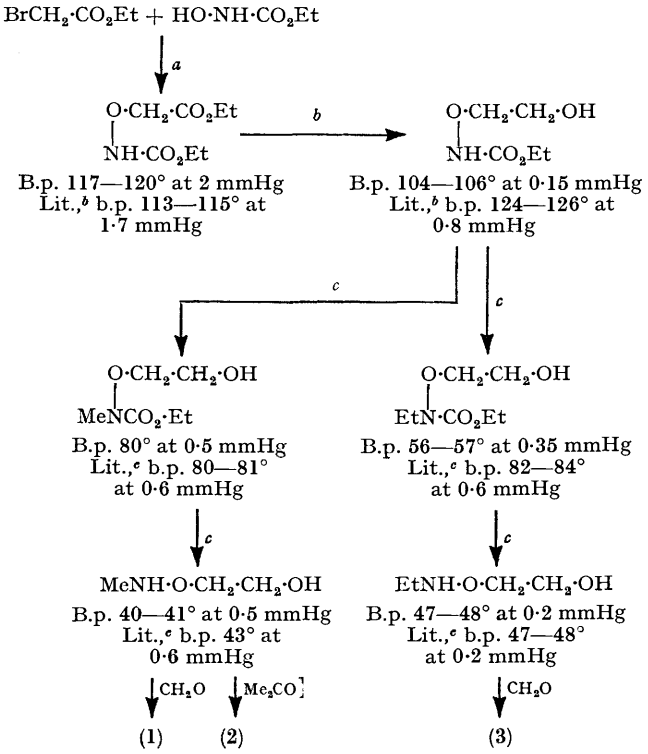
WE have previously shown that in *N*-alkylpiperidines containing a further heteroatom at the 3-position, such as tetrahydro-1,3-oxazines,[3a] the conformational equilibrium favours the *N*-alkyl axial conformer relative to the position with simple piperidines, and that conversely in analogues containing a heteroatom at the 2-position, such as tetrahydro-1,2-oxazines,[3b] the *N*-alkyl equatorial conformer is strongly favoured. We have suggested that this behaviour is the consequence of interactions between the lone pair of the additional heteroatom and the lone pair and/or alkyl group on nitrogen. We now report a study of the conformational behaviour of the 1,4,2-dioxazines (1)—(3) in which both 1,2- and 1,3-heteroatom interactions are present.



(a) (b)

(1) R = Me, R′ = H (2) R = R′ = Me (3) R = Et, R′ = H

Preparation of Compounds (*Scheme* 1).—2,3,5,6-Tetrahydro-1,4,2-dioxazines have not been reported previously, although 5,6-dihydro-1,4,2-dioxazines [4] and their 5- [5] and 6-oxo- [6] and 5,6-dioxo-derivatives [7] have been made. The present compounds were prepared by the reaction of an *N*-alkyl-*O*-(2-hydroxyethyl)-hydroxylamine with acetone or formaldehyde. Attempts to prepare an *N*-unsubstituted product failed; treatment of *O*-(2-hydroxyethyl)hydroxylamine itself with formaldehyde gave only the corresponding oxime.



SCHEME 1

Preparation of compounds

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[2] R. A. Y. Jones, A. R. Katritzky, A. R. Martin, and S. Saba, *J.C.S. Chem. Comm.*, 1973, 908.

[3] (*a*) R. A. Y. Jones, A. R. Katritzky, and D. L. Trepanier, *J. Chem. Soc.* (*B*), 1971, 1300; 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; (*b*) R. A. Y. Jones, A. R. Katritzky, S. Saba, and A. J. Sparrow, *J.C.S. Perkin II*, 1974, 1554.

[4] J. E. Johnson, J. R. Springfield, J. S. Hwang, L. J. Hayes, W. C. Cunningham, and D. L. McClaugherty, *J. Org. Chem.*, 1971, **36**, 284.

[5] D. McHale, *J. Chem. Soc.* (*C*), 1967, 1178.

[6] A. I. Artemenko, *Trudy Khar'kov. Med. Inst.*, No. 67, 1966, 15 (*Chem. Abs.*, 1968, **68**, 78,262*k*).

[7] E. H. Burk, jun., and D. D. Carlos, Fr.P. 1,543,701/1968 (*Chem. Abs.*, 1970, **72**, 21,506*w*).

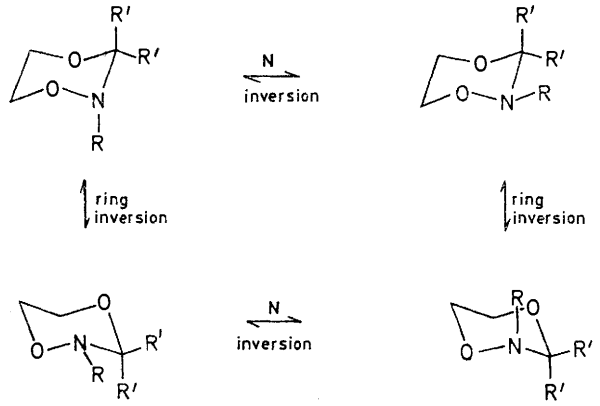
DISCUSSION

Conformational Equilibria.—The low temperature spectra of the *N*-methyl compounds (1) and (2) show separate signals for the two conformers (a) and (b). (Non-chair conformations are assumed absent.) The relative proportions were measured by planimetry (100 MHz) and by electronic integration (220 MHz); the results from two methods are in good agreement. The errors quoted in Table 2 are based on the 220 MHz data, assumed accurate to ±1%. Assignment of the signals to the two conformers was based on the assumption that the *gem*-dimethyl groups of compound (2) would destabilise the *N*-alkyl equatorial conformer (a) relative to the unsubstituted compound (1) because of the unfavourable *gauche*-butane interactions. The results show that in both (1) and (2) the *N*-alkyl equatorial conformer is preferred. The conformational free energy difference for 2,3,5,6-tetrahydro-2-methyl-1,4,2-dioxazine (1) (1·03 kcal mol^{-1}) is, as expected, between the values for tetrahydro-3-methyl-1,3-oxazine [3a] (0·18 kcal mol^{-1}) and tetrahydro-2-methyl-1,2-oxazine [3b] (1·9 kcal mol^{-1}). (The latter two values were obtained at 298 K, but as $\Delta S°$ is likely to be close to zero in these systems the effect of temperature on $\Delta G°$ will be small.)

The low temperature spectrum of the *N*-ethyl compound (3) shows separate AB quartets for the NCH_2O protons of the two conformers (a) and (b) [although the axial proton signal of (b) is buried under signals for the major conformer] and separate signals for the ethyl methylene resonances. An increase in the proportion of *N*-alkyl axial conformer ($\Delta G°$ 0·72 kcal mol^{-1}) was observed as the *N*-alkyl group is changed from methyl to ethyl. This result can be explained in terms of two factors: first, the presence of the adjacent oxygen atom removes one *gauche*-butane interaction, permitting the *N*-ethyl axial system to exist as a low energy rotamer; and secondly, the presence of 1- and 4-oxygen atoms permits sufficient ring distortion to allow a large axial *N*-substituent to avoid the remaining unfavourable 1,3-diaxial interaction.[8]

An interesting solvent effect was observed for the ethyl methylene group of (3) at −80°; whereas a quartet (deceptively simple spectrum) was observed in $CDCl_3$–$CFCl_3$, the expected quartet of quartets arising from magnetic nonequivalence of the methylene protons was observed in $(CD_3)_2CO$. Decoupling at the methyl resonance gave the expected AB quartet for the methylene system.

Inversion Processes.—Two distinct conformational processes can occur in these compounds, namely ring inversion and pyramidal nitrogen inversion (Scheme 2). We have studied these using the two *N*-methyl compounds (1) and (2). If both inversion processes are fast on the n.m.r. timescale the signals from the *N*-methyl protons and those from the groups R′ (H or Me) at the 3-position will each appear as singlets. If one of the two processes is slow and the other fast the *N*-methyl group will still be rapidly alternating between axial and equatorial positions and its signal will remain a singlet, but the groups R′ will become anisochronous and their signals will appear as an AB quartet (R′ = H) or as a doublet (R′ = Me). Finally, if both processes are slow the *N*-methyl signal will separate into two singlets and that of the groups R′ into two AB quartets (R′ = H) or two doublets (R′ = Me).



SCHEME 2

These two distinct stages of coalescence can be observed for both compounds (Table 1). The higher energy barrier has $\Delta G_c^{\ddagger}$ 11·7 kcal mol^{-1} in each case; the lower has $\Delta G_c^{\ddagger}$ 10·2 kcal mol^{-1} in compound (1) and 11·0 kcal mol^{-1} in the *gem*-dimethyl compound (2). The coalescence processes are not simple; even the high temperature one with the R′ signal changing from a singlet to an AB quartet or to two equal singlets is actually a four-site exchange rather than a two-site. Consequently the precise significance of the calculated $\Delta G_c^{\ddagger}$ values in relation to the ground state energies of conformers (a) and (b) is not clear. Moreover, we have no evidence which enables us to distinguish between the two conformational processes (nitrogen and ring inversion). What is clear is that they are distinct, not synchronous.

TABLE 1

N.m.r. coalescence data for 2,3,5,6-tetrahydro-1,4,2-dioxazines (1) and (2) [a]

Compound	Signals observed	$\Delta\nu_{ax,eq}$/Hz	T_c/K	$\Delta G_c^{\ddagger}$ [b] / kcal mol^{-1}
(1)	3-H	52·2	240·5 ± 3	11·7 ± 0·2
	2-Me	43	209 ± 3	10·2 ± 0·2
(2)	3-Me	14·8	228·5 ± 3	11·7 ± 0·2
	2-Me	39	224 ± 3	11·0 ± 0·3

[a] Measured in $CFCl_3$–$CDCl_3$ (1 : 1) at 100 MHz. [b] Calculated following the method of L. Angiolini, R. P. Duke, R. A. Y. Jones, and A. R. Katritzky, *J.C.S. Perkin II*, 1972, 674.

EXPERIMENTAL

References for the preparation of intermediates are given in Scheme 1.

N.m.r. Spectra.—These were measured in Norwich on a Varian HA 100 MHz spectrometer and at the Harwell National Laboratory on a Varian HR 220 MHz spectrometer. Temperatures (stable to ±1°) were measured

[8] R. P. Duke, R. A. Y. Jones, A. R. Katritzky, R. Scattergood, and F. G. Riddell, *J.C.S. Perkin II*, 1973, 2109.

with a standard methanol sample. The solvent in each case was $CDCl_3$–$CFCl_3$ (1 : 1). Chemical shifts, measured from an Me_4Si internal standard, are accurate to ±0·01 p.p.m. Results are recorded in Table 2.

TABLE 2

Low temperature n.m.r. and conformational equilibria for 2,3,5,6-tetrahydro-1,4,2-dioxazines (1)—(3)

Compound and conformation	Chemical shifts (δ) [a] R′	R	Relative intensities [b]	K [c]	$\Delta G°_{191}$ / kcal mol^{-1}
(1a)	3·94, 4·45 [d]	2·50	94·6, 93·8	15	1·03 ± 0·05
(1b)	—, 4·97 [e]	2·93	5·4, 6·2		
(2a)	1·46, 1·35	2·51	84·5, 83·4	5	0·61 ± 0·04
(2b)	1·73, 1·29	2·89	15·5, 16·6		
(3a)	4·10, 4·60 [f]	2·66, 1·22	87·9 [j]	6·7	0·72 ± 0·04
	3·89, 4·57 [g]	2·53, 1·06			
(3b)	—, 5·02 [h]	2·85, —	13·1		
	—, 4·81 [i]	—, —			

[a] At 191 K in $CDCl_3$–$CFCl_3$ (1 : 1); data from 220 MHz spectra. [b] First value obtained by planimetry of 100 MHz spectra; second value by electronic integration of 220 MHz spectra. [c] Conformational equilibrium constant, [(a)]/[(b)], from 220 MHz data. [d] ^2J 9·2 Hz. [e] ^2J 10·2 Hz; one signal lost under peaks from major conformer. [f] ^2J 8·8 Hz obtained in $CDCl_3$–$CFCl_3$ (1 : 1). [g] ^2J 8·6 Hz obtained in $(CD_3)_3CO$. [h] ^2J 10·1 Hz obtained in $CDCl_3$–$CFCl_3$ (1 : 1); one signal lost under peaks from major conformer. [i] ^2J 10·0 Hz; one signal lost under peaks of major conformer. [j] Obtained by cutting out and weighing the peaks in the 220 MHz spectra.

2,3,5,6-*Tetrahydro*-2-*methyl*-1,4,2-*dioxazine* (1).—*N*-Methyl-*O*-(2-hydroxyethyl)hydroxylamine (9·1 g) and paraformaldehyde (3·0 g) were heated under reflux in benzene (100 ml) for 4 h with continuous removal (Dean–Stark apparatus) of the water formed. The residue was twice fractionated to give the *dioxazine* (3·5 g, 34%) as an oil, b.p. 128—129° at 760 mmHg (Found: C, 47·0; H, 8·5; N, 13·6. $C_4H_9NO_2$ requires C, 46·6; H, 8·8; N, 13·5%); τ (CCl_4) 5·87 (2H, s), 6·00—6·05 (4H, m), and 7·55 (3H, s).

2-*Ethyl*-2,3,5,6-*tetrahydro*-1,4,2-*dioxazine* (3) was prepared as above from *N*-ethyl-*O*-(2-hydroxyethyl)hydroxylamine (10·5 g) and paraformaldehyde (3·0 g). The *product* (4·0 g, 34%), an oil, had b.p. 140—141° at 760 mmHg (Found: C, 51·3; H, 9·4; N, 12·1. $C_5H_{11}NO_2$ requires C, 51·3; H, 9·5; N, 12·0%); τ (CCl_4) 5·82 (2H, s), 6·00—6·05 (4H, m), 7·20—7·6 (2H, q), and 8·70—9·55 (3H, t).

2,3,5,6-*Tetrahydro*-2,3,3-*trimethyl*-1,4,2-*dioxazine* (2).—*N*-Methyl-*O*-(2-hydroxyethyl)hydroxylamine (3·6 g) and acetone (2·3 g) in benzene (40 ml) similarly gave the *dioxazine* (2) (1·3 g, 26%), b.p. 60—61° at 25—26 mmHg (Found: C, 54·2; H, 9·5; N, 10·6. $C_6H_{13}NO_2$ requires C, 54·9; H, 10·0; N, 10·7%); τ (CCl_4) 6·00—6·40 (4H, m), 7·48 (3H, s), and 8·68 (6H, s).

Formaldehyde O-(2-*Hydroxyethyl*)*oxime*.—*O*-(2-Hydroxyethyl)hydroxylamine (7·7 g) and paraformaldehyde (3·0 g) were heated under reflux (Dean–Stark tube) for 4 h. Distillation gave the product (3·8 g, 43%) as an oil, b.p. 72—74° at 29—30 mmHg; τ (CCl_4) 2·70—3·70 (2H, q), 5·80—6·00 (2H, m), 6·20—6·40 (2H, m), and 7·12 (1H, s). The *hydrochloride* crystallised from absolute ethanol as needles, m.p. 83° (Found: C, 28·4; H, 6·5; N, 11·0. $C_3H_8ClNO_2$ requires C, 28·7; H, 6·4; N, 11·2%).

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