Preparation and Conformational Analysis of 2,3,3-Trimethyl- and 2-Methyl-tetrahydro-1,4,2-dioxazine

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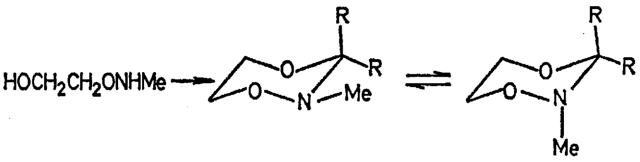
Summary The title compounds exist preferentially with *N*-methyl equatorial to the extent of ΔG°_{191} of 0·61 and 1·05 kcal mol^{-1}, respectively.

Tetrahydro-1,4,2-dioxazines have not previously been described: we now find that such compounds [(**2**) and (**3**)] are readily prepared by reaction of the disubstituted hydroxylamine (**1**)[1] with formaldehyde and with acetone.

Low temperature n.m.r. spectra show separate signals for the two conformers (**a**) and (**b**) of both (**2**) and (**3**). The relative proportions were measured by planimetry (100 MHz) and by electronic integration (220 MHz); the two methods are in good agreement. Assignment of the signals to the two conformers was based on the assumption that the *gem*-dimethyl groups in the 3-position of compound (**3**) would destabilise the *N*-equatorial conformer (**a**) relative to the 3-unsubstituted compound (**2**) because of the unfavourable *gauche*-butane interactions. The results (see Table) show that in both compounds the *N*-equatorial conformer is preferred.



(1) (a) (b)

(2) R = H
(3) R = Me

The conformational free-energy difference for tetrahydro-2-methyl-1,4,2-dioxazine (2) (1·05 kcal mol^{-1}) is about midway between the values for 3-methyltetrahydro-1,3-oxazine[2] (0·18 kcal mol^{-1}) and 2-methyltetrahydro-1,2-oxazine[3] (*ca.* 2 kcal mol^{-1}). The latter two values were obtained at 298 K, but as ΔS° is likely to be close to zero in these systems the effect of temperature on ΔG° will be small. The present result hence supports the previous conclusions, obtained from dipole moment evidence, that the conformational equilibrium of an *N*-methyl group in piperidine is displaced towards the equatorial position by substitution of an α-ring CH$_2$ by oxygen, and towards the axial position by the substitution of a β-ring CH$_2$ by oxygen. The contrast between the position of the *N*-methyl equilibrium for the tetrahydro-1,4,2-dioxazine

TABLE

Low temperature n.m.r. data and conformational equilibria for tetrahydrodioxazines [(**2**) and (**3**)]

Compound and conformation	Chemical shifts (δ)[a]		Relative intensities[b]	K[c]	ΔG°_{191} (kJ mol^{-1})
	R	NMe			
(**2a**)	3·94, 4.45[d]	2·50	95, 94	15	4·39 ± 0·21
(**2b**)	—, 4·97[e]	2·93	5·4, 6·2		
(**3a**)	1·46, 1·35	2·51	84, 83	5	2·55 ± 0·17
(**3b**)	1·73, 1·29	2·89	16, 17		

[a] At 191 K. Data from 220 MHz spectra. [b] Of NMe peaks of conformers (**a**) and (**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] $^2J = 9{\cdot}2$ Hz. [e] $^2J = 10{\cdot}2$ Hz; one signal lost under peaks from major conformer.

system now reported, where the *N*-methyl group goes axial with little difficulty, and the tetrahydro-1,2-oxazine ring where the energy difference is considerably higher, as shown qualitatively by Riddell and co-workers[4] and quantitatively by our own work,[3] is significant.

The observation of two conformations in the tetrahydro-1,4,2-dioxazine system shows that both nitrogen inversion and ring inversion are slow on the n.m.r. time-scale. We have not yet studied detailed rates, but for the *gem*-dimethyl derivative the *gem*-dimethyl groups show magnetic non-equivalence at 214 K while the *N*-methyl group remains a singlet. This demonstrates that one process is slowed before the other.

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