SYNTHESIS AND CONFORMATIONAL ANALYSIS OF TETRAHYDRO-1,2,5-OXADIAZINES[1]

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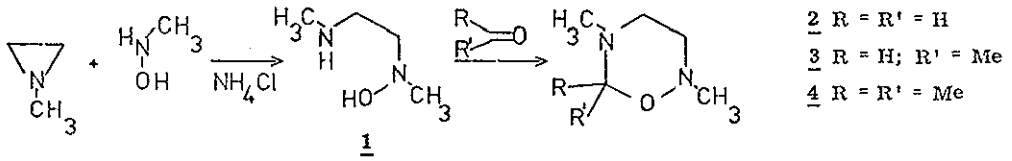
Tetrahydro-1,2,5-oxadiazines are prepared for the first time. They show two coalescence processes in the n. m. r. spectra, corresponding to (a) ring reversal or 2-NMe inversion and (b) 5-NMe inversion.

The saturated 1,2,5-oxadiazine ring system has not previously been reported: we have prepared several examples by the apparently general method of Scheme 1. The compounds are colourless oils, which can be purified by distillation and are stable for several weeks at ambient temperatures: the tetrahydro-1,2,5-oxadiazines (2, 3, 4) were characterised by microanalysis, proton and carbon-13 n. m. r. and their structures confirmed by their respective mass spectral fragmentation pattern.



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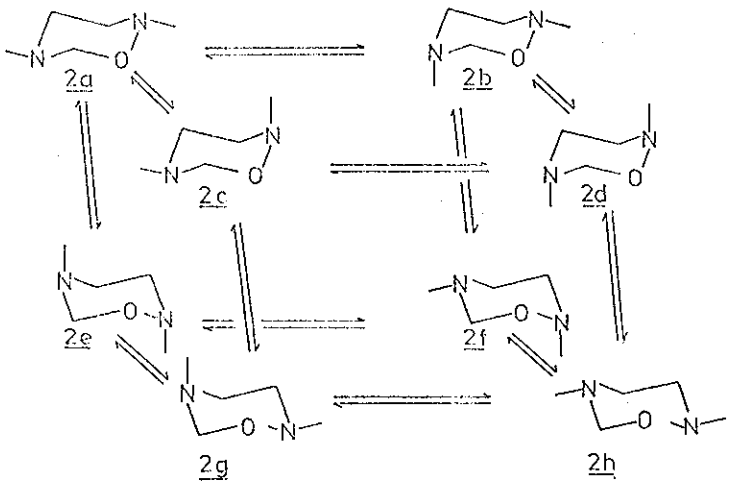
2 R = R' = H
3 R = H; R' = Me
4 R = R' = Me

SCHEME 1

Conformational Equilibria. Of the potential energy barriers in these compounds, those for ring reversal and the 2-NMe inversion should be considerably higher than that for the 5-NMe inversion on the basis of previous evidence from the tetrahydro-3-methyl-1,3-oxazine[2] and tetrahydro-2-methyl-1,2-oxazine[3] systems. Similarly we expect all the 2-NMe axial conformers (cf. 2c, 2d, 2e, 2f) to be sparsely populated,[4] whereas appreciable amounts of the 2-NMe equatorial 5-NMe axial conformers (2b, 2g) should coexist with the 2-NMe-5-NMe diequatorial forms (2a, 2h).

In the symmetrically substituted compounds 2 and 4 slowing of either 2-NMe inversion or ring reversal will prevent interconversion of the pairs (2a, 2b) with (2g, 2h). Such slowing should therefore be accompanied by changes in the proton n. m. r. spectrum of the ring methylene groups, the hydrogen atoms of which become non-equivalent. Changes in the ^{13}C spectrum of 2 will become apparent only when additionally the 5-NMe inversion separating 2a ⇌ 2b is slowed, whereas for 4 the gem-dimethyl signals alone will be differentiated by slowing the higher energy barriers.



SCHEME 2. CONFORMATIONAL CUBE FOR 2

Tetrahydro-2,5-dimethyl-1,2,5-oxadiazine (2). As expected, the proton spectral changes (see Table 1) near 0° indicate a high barrier of 13.7 ± 0.3 kcal mole^{-1}: this barrier must be either 2-NMe inversion or ring-reversal, whichever process is of the higher energy. The ^{13}C spectral coalescence near -110° (Table 2a) indicates 7.7 ± 0.2 kcal mole^{-1} for the barrier for the 5-NMe inversion process. Gated decoupling and integration give ΔG°_{147} 0.31 ± 0.05 kcal mole^{-1} in favour of 2a,2h, the minor forms being 2b,2g (see Table 2a for assignments).

Tetrahydro-2,5,6,6-tetramethyl-1,2,5-oxadiazine (4). The proton nmr spectral changes (Table 1) here give ca. 13.9 ± 0.4 kcal mole^{-1} for the higher energy process. In this case the high energy barrier may be checked from the ^{13}C spectrum (Table 2b): 13.7 ± 0.3 kcal mole^{-1} is found in good agreement with the ^{1}H results. Again the process slowed could be either ring reversal or 2-NMe inversion.

A second dynamic process is observed around -100°, yielding a barrier of 7.7 ± 0.2 kcal mole^{-1} (Table 2b). The concentration of the minor conformer is too small to be integrated accurately but application of Anet's equations[5] yields a barrier of 7.3 ± 0.1 kcal mole^{-1} for the minor ⟶ major conformation and ΔG°_{c} = 0.55 ± 0.05 kcal mole^{-1}. The major form is assigned the 5-NMe axial conformation upon consideration of C(3) shifts in conformers 2b and 4b (δ 57.0 and 57.7, respectively).

Conformational Conclusions. The novel tetrahydro-1,2,5-oxadiazines (2,3,4) all show high energy processes of ca. 13.7 kcal mole^{-1}, the assignment of which to ring or N(2)-inversion is not unequivocal: cf. 'passing' ring and N-inversions ($\Delta G^{\ddagger}_{c}$ > 12 kcal mole^{-1}) in hexahydro-1,2-dimethylpyridazines.[6]

The lower energy processes ($\Delta G_c^{\ddagger}$ = 7.5 to 8.2 kcal mole^{-1}) observed for 2, 3 and 4 are assigned to N(5)-inversion and compare well with N-inversion activation barriers in tetrahydro-1, 3-oxazines.[2]

Table 1: Proton n. m. r. (100 MHz) data for some novel tetrahydro-1, 2, 5-oxadiazines (in $CDCl_3$)[a]

Cpd	Signal	δ at 31 °C	δ at -50 °C	t_c (°C)	$\Delta\nu$ (Hz)	J (Hz)	$\Delta G_c^{\ddagger}$[b] (kcal mole^{-1})
2	N-CH_2-O	4.32	4.39, 4.26	0	13.0	10.2	13.7 ± 0.3[c]
4	C-CH_3	1.03	1.09, 0.98	-5	11.0	-	13.9 ± 0.4

[a] δ ppm downfield from Me_4Si. [b] Eyring equation, (f=1)[7]. [c] This value is unreliable because of the rapidly changing and small chemical shift difference. Dr. F. G. Riddell (Univ. of Stirling, Scotland) kindly informs us that he finds values of 14.6 ± 0.2 kcal mole^{-1} and 15.2 ± 0.2 kcal mole^{-1} for this barrier in toluene and D_2O respectively in which solvents this chemical shift difference although highly temperature variable is sufficiently large to give reliable values (see accompanying communication).

Table 2a: ^{13}C N. m. r. (25.05 MHz) data[a] for tetrahydro-2, 5-dimethyl-1, 2, 5-oxadiazine

Carbon site	Chemical shift (δ) at 40 °C[b, c]	Chemical shift (δ) at -136 °C[d] 2a, 2h[e]	Chemical shift (δ) at -136 °C[d] 2b, 2g	t_c (°C)	$\Delta\nu$ (ppm)	$\Delta G_c^{\ddagger}$[f] (kcal mole^{-1})
N(2)-C	47.0 (q)	46.6	46.9	-127	0.2	-
C-3	54.6 (t)	51.9	57.0	-106	5.2	7.69
C-4	52.4 (t)	50.3	53.4	-110	3.1	7.69
N(5)-C	39.6 (q)	38.9	39.8	-119	1.0	7.58
C-6	87.9 (t)	86.6	87.9	-114	1.3	7.74

Table 2b: ^{13}C N.m.r. (25.05) MHz data[a] for tetrahydro-2,5,6,6-hexamethyl-1,2,5-oxadiazine

Carbon site	Chemical shift (δ) at 40 °C[b,c]	-39 °C	-136 °C		t_c (°C)		$\Delta\nu$		$\Delta G_c^{\ddagger}$[f]	
			2b, 2g[e]	2a, 2h	g	h	g	h	g	h
N(2)-C	47.0 (q)	46.9	46.7	46.7	-	-	-	-	-	-
C(3)	57.1 (t)	56.9	57.7	50.2	-	-103	-	7.5	-	7.71
C(4)	50.1 (t)	49.8	48.9	48.9	-	-	-	-	-	-
N(5)-C	38.4 (q)	38.4	38.8	36.3	-	-111	-	2.5	-	7.69
C(6)	90.8 (s)	90.6	90.6	90.6	-	-	-	-	-	-
C(6)-C	22.1 (q)	27.0(eq)	26.5	26.5	25	-	10.0	-	13.7	-
		16.9(ax)	14.7	25.1	-	-103		10.3	-	7.60

[a] Solvent: CF_2Cl_2/acetone-d_6. [b] From off-resonance decoupling. [c] Solvent: $CDCl_3$. [d] Assignments with reference to ^{13}C dnmr spectra of tetrahydro-3-methyl-1,3-oxazine (V.J. Baker, I.J. Ferguson, A.R. Katritzky, and F.M.S. Brito-Palma, J. Chem. Soc. (Perkin II), to be published).[7] [e] Major conformer. [f] Eyring equation. [g] First coalescence at ca. +25 °C. [h] Second dynamic phenomenon at ca. -100 °C.

REFERENCES

1 Part 88 in the series 'The Conformational Analysis of Saturated Heterocycles.' Part 87, V.J. Baker, I.J. Ferguson, A.R. Katritzky, and R.C. Patel, submitted to J. Chem. Soc. (Perkin II).

2 I.J. Ferguson, A.R. Katritzky, and D.M. Read, Chem. Comm., 1975, 255; I.J. Ferguson, A.R. Katritzky, and D.M. Read, J. Chem. Soc. (Perkin II), 1977, 818.

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

4 R.A.Y. Jones, A.R. Katritzky, S. Saba, and A.J. Sparrow, J. Chem. Soc. (Perkin II), 1974, 1554.

5 F.A.L. Anet, I. Yavari, I.J. Ferguson, A.R. Katritzky, M. Moreno-Mañas, and M.J.T. Robinson, Chem. Comm., 1976, 399.

6 S F. Nelsen and G R. Weisman, J. Am. Chem. Soc., 1976, 98, 3281.

7 H.S. Gutowsky and C.H. Holm, J. Chem. Phys., 1956, 25, 1228.

Received, 13th December, 1977