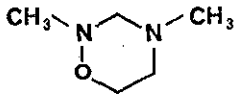
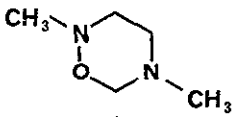
THE SYNTHESIS AND CONFORMATIONAL ANALYSIS OF TETRAHYDRO-1,2,4- AND 1,2,5-OXADIAZINES

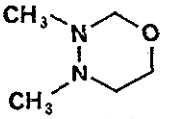
Frank G. Riddell and Eric S. Turner
Department of Chemistry, The University, Stirling, Scotland

Derivatives of tetrahydro-1,2,4-oxadiazine and tetrahydro-1,2,5-oxadiazine have been prepared. Both systems show coalescences in their nmr spectra corresponding to either ring inversion or 2-N-methyl inversion.

We have previously reported on the synthesis and conformational analysis of six-membered cyclic derivatives of hydroxylamine.[1-7] We now report the synthesis and preliminary conformational results for two further six-membered ring derivatives of hydroxylamine, tetrahydro-1,2,4-oxadiazine (1) and tetrahydro-1,2,5-oxadiazine (2).


(1)

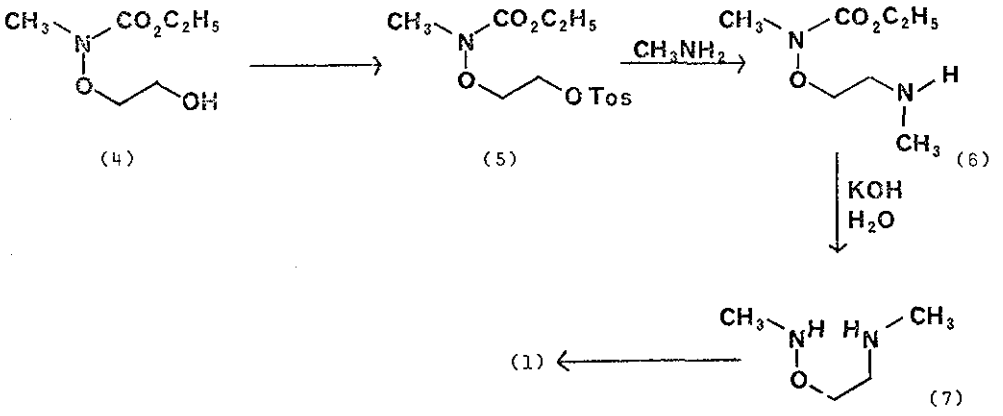

(2)


(3)

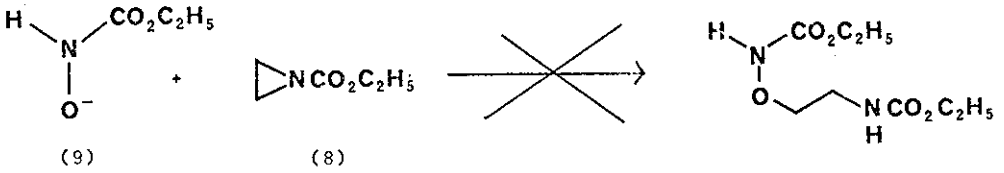
These two rings represent the remaining unknown oxadiazines containing two contiguous heteroatoms, tetrahydro-1,3,4-oxadiazine (3), having been reported recently.[8,9]

The synthesis of N,N'-dimethyltetrahydro-1,2,4-oxadiazine (1) is straightforward. The tosylate (5) of the hydroxylamino alcohol (4) is stirred at room temperature with an aqueous solution of methylamine to give (6). Hydrolysis of (6) with aqueous base leads to the amino hydroxylamine (7).

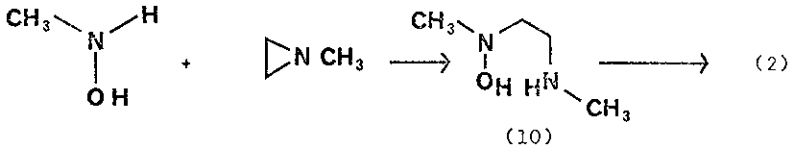
which readily cyclises with paraformaldehyde to give the oxadiazine (1).



Attempts to enter this series by ring opening of N-carbethoxyaziridine (8) with the anion of N-hydroxyurethane (9) failed. Our studies show that this reaction most probably proceeds by attack of the nucleophile on the carbethoxy group, ring opening proceeding at a much slower rate.



The N,N'-dimethyl-1,2,5-oxadiazine (2) can be prepared by ring opening of N-methylaziridine by N-methylhydroxylamine in the presence of a trace of ammonium chloride to give the amino hydroxylamine (10). The latter compound readily cyclises with paraformaldehyde to give N,N'-dimethyltetrahydro-1,2,5-oxadiazine (2).



(10)

Compound (1) displays a temperature dependent ^{1}H nmr spectrum consistent with the slowing down of either ring or 2-N-methyl inversion. The methylene group at C-3, a singlet at ambient temperatures, broadens as the temperature is lowered and splits into an AB quartet. The barrier is found to be 12.7±0.2 kcal mole^{-1} in $CDCl_3$ and 13.2±0.2 kcal mole in D_2O. We cannot at present decide between the two alternative explanations of the origin of the barrier. We do however note that if the barrier arises from slowing of nitrogen inversion the β-nitrogen atom (at position 4) is reducing the barrier found in N-methyltetrahydro-1,2-oxazine[1] by ca 1.0 kcal mole^{-1} in line with our expectations.[6,10] The coupling constant in the low temperature C-3H spectrum (9.5Hz) points to the molecule existing in a mixture of 4-methyl axial and 4-methyl equatorial conformations, after comparison with model compounds.[11]

The ^{1}H spectrum of compound (2) in $CDCl_3$ shows some evidence of a coalescence phenomenon at ca +10°. However the very small, and highly temperature variable chemical shift difference at C-6 precluded an accurate measurement of a free energy of activation.* In toluene d8 the chemical shift difference of the C-6 hydrogens is sufficiently large to enable an activation energy of 14.6±0.2 kcal mole^{-1} to be measured. This barrier increases to 15.2 ±0.2 kcal mole^{-1} in D_2O solution. Again we are unable at present to distinguish between ring and nitrogen inversion, but note that this would be an exceptionally large barrier for a ring inversion process in a simple

*We thank Professor Katritzky and Dr Ranjan Patel for prior communication of their results on this system. In our opinion there is probably a substantial systematic error in their reported $\Delta G_c^{\ddagger}$ of 13.7 kcal mole^{-1} because of factors mentioned above. Error limits of ±1 kcal mole^{-1} would seem appropriate to us. See accompanying communication.

sterically unhindered system.[12] We are therefore currently of the opinion that the barrier arises from nitrogen inversion. Comparison of the coupling constant between the C-6 hydrogens (ca 9.5Hz) with that of known models[13] suggests that the compound exists as a mixture of the N-5 methyl equatorial and axial conformations.

Table

Compound	Solvent	T_c°	$\Delta\nu^*$(Hz)	J(Hz)	$\Delta G_c^{\ddagger}$ kcal mole^{-1}
1	$CDCl_3$	-8 ± 3	76.6	9.5	12.7 ± 0.2
1	D_2O	$+1\pm3$	ca 72†	9.5	13.2 ± 0.3
1	CD_3OD	0 ± 3	87	9.5	13.1 ± 0.2
2	Toluened8	$+22\pm2$	30.5	9.4	14.6 ± 0.2
2	D_2O	$+28\pm2$	8.8	9.8	15.2 ± 0.2

Spectra were obtained on a Perkin Elmer R32 instrument operating at 90 MHz.

* Based on extrapolation to Tc from several slow exchange limit spectra.

† This value is an estimate based on the -10° spectrum, which was the lowest temperature attainable before the sample froze. Variations of up to 10 Hz on this value do not greatly affect $\Delta G_c^{\ddagger}$.

References

1. F G Riddell, J M Lehn and J Wagner, Chem.Comm., 1968, 1403.
2. F G Riddell and D A R Williams, Tetrahedron, 1974, 30, 1083.
3. F G Riddell, P Murray-Rust and J Murray-Rust, Tetrahedron, 1974, 30, 1087.
4. F G Riddell and D A R Williams, Tetrahedron, 1974, 30, 1097.
5. F G Riddell, Tetrahedron, 1975, 31, 523.
6. F G Riddell and H Labaziewicz, Chem.Comm., 1975, 766.
7. H Labaziewicz, F G Riddell and B G Sayer, JCS Perkin II, 1977, 619.
8. I J Ferguson, A R Katritzky and D M Read, JCS Perkin II, 1976, 1861.
9. F G Riddell and A J Kidd, JCS Perkin II, 1977, 1816.
10. F G Riddell and J E Anderson, JCS Perkin II, 1977, 588.
11. F G Riddell and D A R Williams, Tetrahedron Letters, 1971, 2073.
12. J E Anderson, Fortschritte der Chemischen Forschung, 1974, 45, 140.
13. F G Riddell and J M Lehn, J.Chem.Soc.(B), 1968, 1224.

Received, 13th December, 1977