The Conformational Analysis of Saturated Heterocycles. Part LXX.[1] Nitrogen Inversions in 1,3,4-Oxadiazolidines

By **Victor J. Baker, Alan R. Katritzky,* and Jean-Pierre Majoral,** School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ

Free energies of activation for inversion at nitrogen in *NN'*-disubstituted 1,3,4-oxadiazolidines depend markedly on the bulk of the substituents demonstrating that the steric strain of substituents eclipsed in the transition state is a dominant effect in the nitrogen inversions of substituted hydrazines.

WE have recently demonstrated [2] that the kinetic processes in saturated and partially saturated pyridazines are due to three types of barrier (a) ' high ' energy barriers of $\geqslant$12 kcal mol^{-1} for inversion of saturated six-membered rings and ' passing ' nitrogen inversions, (b) ' medium ' energy barriers of 10—11 kcal mol^{-1} for ' non-passing ' nitrogen inversions, and (c) ' low ' energy barriers of $\leqslant$8 kcal mol^{-1} for the inversions of unsaturated six-membered rings. The concept of ' passing ' [*e.g.* (2) $\rightleftharpoons$ (3)] and ' non-passing ' [*e.g.* (2) $\rightleftharpoons$ (1)] nitrogen inversions, differentiated by the necessity for substituents to become eclipsed during the inversion, was also shown to explain the kinetic processes of acyclic hydrazines [2] and of hexahydro-1,2,4,5-tetrazines.[3]

Our work in the hydropyridazine series [2] was concerned with *N*-methyl substituents. We wished to study the effect of the size of the nitrogen substituents P and R on passing inversions of type (2) $\rightleftharpoons$ (3), particularly in view of complications encountered [4] in more complex hexahydrotetrazines. We have accordingly prepared

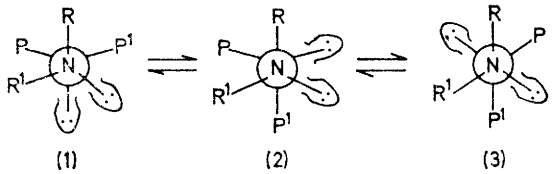
[1] Part LXIX, A. R. Katritzky and M. Moreno-Mañas, submitted to *Anales de Quím.*

[2] R. A. Y. Jones, A. R. Katritzky, K. A. F. Record, and R. Scattergood, *J.C.S. Perkin II*, 1974, 406.

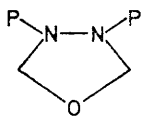
[3] R. A. Y. Jones, A. R. Katritzky, A. R. Martin, D. L. Ostercamp, A. C. Richards, and J. M. Sullivan, *J.C.S. Perkin II*, 1974, 948.

[4] J.-P. Majoral and V. J. Baker, unpublished work.

the 1,3,4-oxadiazolidines (4)—(7) by the reaction of the corresponding *NN'*-disubstituted hydrazines with formaldehyde. Ring inversions in saturated five-membered rings are fast on the n.m.r. time-scale, and thus kinetic processes are unambiguously due to nitrogen inversion.



(1) (2) (3)

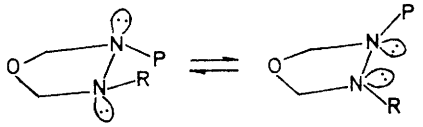


(4) P = R = Me
(5) P = R = Pr^i
(6) P = Me; R = Pr^i
(7) P = R = CH_2Ph

1,3,4-Oxadiazolidine represents a saturated five-membered ring system on which little has been published.[5,6] These compounds are formed to a greater or lesser extent in the condensation between the appropriate hydrazine and formaldehyde.[5,6] In every case, the corresponding hexahydrotetrazine is also formed;[7] hydrazines substituted with larger groups seem to give larger proportions of the five-membered ring relative to the six-membered. Various conditions are available for the condensation, *e.g.* aqueous solution and formaldehyde gas with benzene as solvent, but synthetic results are rather variable.

DISCUSSION

Except for the di-isopropyl derivative (5) all the compounds showed room temperature spectra expected for fast inversion, in particular singlets for the CH_2 protons [two singlets in the case of (6)]. Lowering the temperature resulted in each case in the broadening of the CH_2 signals and eventual formation of an AB system. The di-isopropyl compound (5) displayed the AB system at room temperature, but on raising the temperature this coalesced to a singlet (Table).



(a) (8) (b)

These spectral changes are consistent with the slowing of the inversion processes (8a) ⇌ (8b).[8] As this inversion is slowed, the geminal protons or methyl groups of the C-2(5) methylene, benzylic methylene, or isopropyl groups become anisochronous but the *N*-methyl groups do not: the observed spectra (Table) are in complete agreement with these predictions.

N.m.r. spectral data at 100 MHz for 3,4-disubstituted 1,3,4-oxadiazolidines in $CDCl_3$–$CFCl_3$ solution [a]

Compound	(4)	(5)	(6)		(7)
N-Substituent(s)	Me	Pr^i	Me	Pr^i	CH_2Ph
Above coalescence					
T/°C	34	120	34		34
CH_2 singlets	4.27	4.27	4.19, 4.40		4.39
N-Subst. CH_3 or CH_2	2.44	1.03	2.48, 1.05		3.76
N-Subst. CH		2.67	2.65		
N-Subst. *J*(CH/CH_3)(Hz)		6.2	6.2		
Below coalescence					
T/°C	−80	34	−80		−80
CH_2 A	4.25	4.48	4.31, 4.52		4.40
CH_2 B	4.31	4.20	4.23, 4.45		4.50
CH_2 *J*(Hz)	5	5.5	4.75, 5.05		4.2
N-Subst. CH_3 or CH_2	2.52	1.10	2.53, 1.16		3.88
N-Subst. CH_3 or CH_2		1.03	1.05		3.66
N-Subst. CH		2.68	2.65		
N-Subst. *J*(Hz)		6.2	6.2		12.2
Coalescence data					
T/K	212	384	283,[b] 265		235
$\Delta G^{\ddagger}$/kcal mol^{-1}	10.6	19.4	14.6,[b] 13.6		12.0

[a] δ Values from Me_4Si. [b] Coalescence temperature difficult to define, hence $\Delta G^{\ddagger}$ considered less reliable than the value of 13.6 kcal mol^{-1}.

The $\Delta G^{\ddagger}$ values for the inversion processes were obtained from the coalescence temperatures using the Eyring equation [equation (1)].[9] This equation was applied to data obtained from the ring methylene protons; for the other diastereotopic protons, as *e.g.* for the isopropyl methyl protons in (5), the coalescences were not as clear cut as for the ring methylene AB quartets and were therefore not examined.

$$\Delta G^{\ddagger} = 4.57T_c\left[9.97 + \log \frac{T_c}{(\Delta\nu_{AB}^2 + 6J_{AB}^2)^{\frac{1}{2}}}\right] \quad (1)$$

This work demonstrates the marked influence of steric size of substituents on nitrogen inversion rates and

[5] G. Zinner, W. Kliegel, W. Ritter, and H. Böhlke, *Chem. Ber.*, 1966, **99**, 1678.
[6] S. F. Nelsen and P. J. Hintz, *J. Amer. Chem. Soc.*, 1972, **94**, 3138.
[7] (*a*) E. Schmitz, *Annalen*, 1960, **635**, 73; (*b*) G. Zinner and W. Kilwing, *Arch. Pharm.*, 1973, **306**, 134.
[8] J. Elguero, C. Marzin, and D. Tizané, *Org. Magnetic Resonance*, 1969, **1**, 249.
[9] J. M. Lehn and J. Wagner, *Tetrahedron*, 1970, **26**, 4227.

strongly supports the previous conclusion [2] which distinguished between 'passing' and 'non passing' nitrogen inversions in six-membered rings and acyclic compounds.

EXPERIMENTAL

NN'-*Dimethyloxadiazolidine* (4).—*NN'*-Dimethylhydrazine dihydrochloride (1 g, 7.6 mmol) was added with stirring to 7.5N-sodium hydroxide (2 ml) under nitrogen followed by 40% formaldehyde (0.89 ml, 11 mmol H_2CO) again dropwise and with stirring at 20°. After 3 h the mixture was ether-extracted (2 × 5 ml). The dried (K_2CO_3) extracts were filtered and evaporated to give a colourless *oil* which was chromatographed over alumina and distilled, b.p. 53—58° at 15 mmHg (0.16 g, 20.6%) (Found: C, 48.1; H, 9.35; N, 27.4. $C_4H_{10}N_2O$ requires C, 47.0; H, 9.9; N, 27.6%).

NN'-*Di-isopropyloxadiazolidine* (5).—*NN'*-Di-isopropylhydrazine [10] (10.0 g, 86.3 mmol) was treated as for the dimethyl analogue above. The oxadiazolidine distilled as an oil, b.p. 72° at 17 mmHg (lit.,[5] 64—65° at 13 mmHg) (9.6 g, 70%) (Found: C, 60.4; H, 10.8; N, 17.9. Calc. for $C_8H_{18}N_2O$: C, 60.7; H, 11.4; N, 17.7%). The high boiling fractions contained tetraisopropylhexahydrotetrazine, m.p. 57—58° (lit.,[7a] 57—58°).

N-*Methyl*-N'-*isopropylhydrazine*.—This was prepared by a method similar to that of Spialter *et al.*,[11] but starting from methylhydrazine rather than formylhydrazine. The product had b.p. 102—103° at 760 mmHg (lit.,[11] 99—100° at 740 mmHg).

N-*Methyl*-N'-*isopropyloxadiazolidine* (6).—*N*-Methyl-*N'*-isopropylhydrazine (9.68 g, 110 mmol) was treated as above to give the *oxadiazolidine* as an oil, b.p. 40—42° at 17 mmHg (5.0 g, 35%) (Found: C, 55.1; H, 10.7; N, 21.2. $C_6H_{14}N_2O$ requires C, 55.3; H, 10.9; N, 21.5%). Higher boiling fractions were mixtures of dimethyl-di-isopropylhexahydrotetrazines.[4]

NN'-*Dibenzyloxadiazolidine* (7) *and* NN'-*Dibenzylperhydrodipyridazino*[1,2-a:1',2'-d]-s-*tetrazine*.[4]—To 1,2,3,6-tetrahydropyridazine (6.2 g, 74 mmol) obtained by hydrolysis of diethyl 1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate [12] was added *NN'*-dibenzylhydrazine (10.6 g, 52.5 mmol) and formaldehyde solution (15 ml, 185 mmol H_2CO), followed by stirring for 10 h at 25°. Water and unchanged formaldehyde were removed *in vacuo* and the residue taken up in chloroform (100 ml), filtered through anhydrous potassium carbonate, evaporated, and allowed to stand. Crystals of *NN'*-dibenzylperhydrodipyridazino[1,2-*a*:1',2'-*d*]-*s*-tetrazine appeared and were collected, leaving an oil which was distilled yielding the *oxadiazolidine* as an oil, b.p. 120° at 12 mmHg (Found: C, 75.1; H, 7.05; N, 10.6. $C_{16}H_{18}N_2O$ requires C, 75.6; H, 7.15; N, 11.0%).

Physical Measurements.—These were obtained on a Varian HA-100 n.m.r. spectrometer, including a V-4343 variable temperature unit. Temperatures were determined by the use of methanol shifts and the linear Varian chart. Chemical shift data were obtained from 100 Hz sweeps of the appropriate region. Coalescences were obtained by successive 1 000 Hz sweep examinations of the appropriate region at 1° temperature intervals.

We thank the S.R.C. for a postgraduate studentship to V. J. B. and Professor S. F. Nelsen for helpful correspondence regarding this work. Similar conclusions regarding these processes were reached independently in his laboratory and are referred to in our joint preliminary communication.[13]

[4/2659 *Received*, 20*th December*, 1974]

[10] R. Renaud and L. C. Leitch, *Canad. J. Chem.*, 1954, **32**, 545.
[11] L. Spialter, D. H. O'Brien, G. L. Untereiner, and W. A. Rush, *J. Org. Chem.*, 1965, **30**, 3278.
[12] E. W. Bittner and J. T. Gerig, *J. Amer. Chem. Soc.*, 1972, **94**, 913.
[13] V. J. Baker, A. R. Katritzky, J.-P. Majoral, S. F. Nelsen, and P. J. Hintz, *J.C.S. Chem. Comm.*, 1974, 823.