The Conformational Analysis of Saturated Heterocycles. Part 72.[1] Tetrahydro-1,3,4-oxadiazines

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Variable-temperature proton n.m.r. spectroscopy has been used to study the inversion barriers and conformations of 3,4-dialkyltetrahydro-1,3,4-oxadiazines. The predominant conformer of 3,4-dimethyltetrahydro-1,3,4-oxadiazine was found to be 3*ax*, 4*eq*.

RECENTLY the conformational equilibria of hexahydropyridazines [2-5] and hexahydro-1,2,4,5-tetrazines [6] have been investigated. To help our understanding of these equilibria, we have turned our attention to related systems. The present paper records the preparation and study by variable temperature proton n.m.r. of a series of tetrahydro-1,3,4-oxadiazines.

Preparation of Compounds (*Scheme* 1).—Non-tautomeric tetrahydro-1,3,4-oxadiazines have not previously been reported, although numerous analogues are known

[1] Part 71, W. L. F. Armarego, R. A. Y. Jones, A. R. Katritzky, D. M. Read, and R. Scattergood, *Austral. J. Chem.*, 1975, **28**, 2323.

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

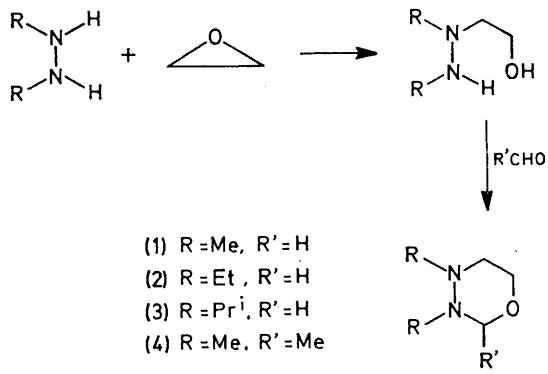
[3] J. E. Anderson, *J. Amer. Chem. Soc.*, 1969, **91**, 6374.

[4] S. F. Nelsen and G. R. Weisman, *J. Amer. Chem. Soc.*, 1974, **96**, 7111.

[5] S. F. Nelsen and J. M. Buschek, *J. Amer. Chem. Soc.*, 1974, **96**, 6987.

[6] 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.

in which ring–chain tautomerism is possible.[7,8] The present compounds were prepared as shown in Scheme 1;



SCHEME 1

ring opening of oxiran by 1,2-dialkylhydrazines yielded the corresponding hydrazinoethanols, and subsequent ring closure with formaldehyde or acetaldehyde afforded the products (1)—(4).

EXPERIMENTAL

^{1}H N.m.r. spectra were measured at the University of East Anglia on a Varian HA-100 MHz and at the Harwell National Laboratory on a Varian HR-220 MHz spectrometer. Temperatures (stable to within ±2 K) were measured with a standard methanol sample [9] down to 183 K. Below 183 K, a platinum resistance thermometer was used. Solvents used were CF_2Cl_2 and $CDCl_3$–$CFCl_3$ (1 : 1). Chemical shifts are measured from Me_4Si as an internal standard and are accurate to within ±0.01 p.p.m. Analytical g.l.c. was performed on a Perkin-Elmer F11 gas chromatograph (Carbowax 20 M on Chromosorb W). Low resolution mass spectra were determined on a Perkin-Elmer–Hitachi R.M.U. spectrometer.

1-(β-*Hydroxyethyl*)-1,2-*dimethylhydrazine*.— Ethylene oxide (3.6 g, 0.08 mol) in methanol (10 cm^3) was added slowly to 1,2-dimethylhydrazine [10] (5.0 g, 0.08 mol) in methanol (20 cm^3) at 0 °C. After the addition was complete, stirring was continued for 24 h at 20 °C. The methanol was removed *in vacuo* and the product fractionated to afford 1-(β-*hydroxyethyl*)-1,2-*dimethylhydrazine* (3.25 g, 38%) as an oil, b.p. 80 °C at 26 mmHg, homogeneous by g.l.c., δ ($CDCl_3$) 2.49 (3 H, s), 2.53 (3 H, s), 2.66 (2 H, t), 3.72 (2 H, t), and 4.06br (2 H, s).

1,2-Diethylhydrazine [11] similarly gave 1,2-*diethyl*-1-(β-*hydroxyethyl*)*hydrazine* (1.7 g, 16%) as an oil, b.p. 85 °C at 20 mmHg, δ ($CDCl_3$) 1.08 (6 H, t), 2.70 (6 H, m), and 3.76 (4 H, m).

1,2-Di-isopropylhydrazine [11] gave 1-(β-*hydroxyethyl*)-1,2-*di-isopropylhydrazine* (3.0 g, 62%) as an oil, b.p. 84 °C at 12 mmHg, δ ($CDCl_3$) 1.04 (12 H, 2 d), 2.61 (2 H, t), 3.04 (2 H, m), and 3.72 (4 H, m).

Tetrahydro-3,4-*dimethyl*-1,3,4-*oxadiazine*.—1-(β-Hydroxyethyl)-1,2-dimethylhydrazine (4.16 g, 0.04 mol), paraformaldehyde (1.3 g, 0.04 mol), and sodium-dried benzene (30 cm^3) were subjected to azeotropic distillation for 2 h in a Dean–Stark apparatus. Fractional distillation gave the *oxadiazine* (3.4 g, 73%), b.p. 119 °C, as an oil, homogeneous by g.l.c., characterised by its n.m.r. spectrum; *m/e* 116 (M^+) and 101 (M − Me).

The following were prepared similarly: 3,4-*diethyltetrahydro*-1,3,4-*oxadiazine* (1.0 g, 54%), oil, b.p. 70 °C at 17 mmHg (Found: N, 19.2. $C_7H_{16}N_2O$ requires N, 19.4%); *m/e* 144 (M^+); *tetrahydro*-3,4-*di-isopropyl*-1,3,4-*oxadiazine* (0.9 g, 36%), oil, b.p. 93 °C at 20 mmHg [*picrate*, yellow powder, m.p. 112 °C (Found: N, 17.4. $C_{16}H_{23}N_5O_9$ requires N, 16.3%)].

Tetrahydro-2,3,4-*trimethyl*-1,3,4-*oxadiazine*.— Acetaldehyde (0.44 g, 0.01 mol) was added dropwise to 1-(β-hydroxyethyl)-1,2-dimethylhydrazine (0.94 g, 0.01 mol) at 0 °C. After 2 h, KOH pellets were added. The organic layer was distilled to give the *oxadiazine* (0.34 g, 26%), b.p. 81 °C at 15 mmHg, as a liquid, homogeneous by g.l.c. (Found: N, 21.6. $C_6H_{14}N_2O$ requires N, 21.5%); *m/e* 130 (M^+).

DISCUSSION

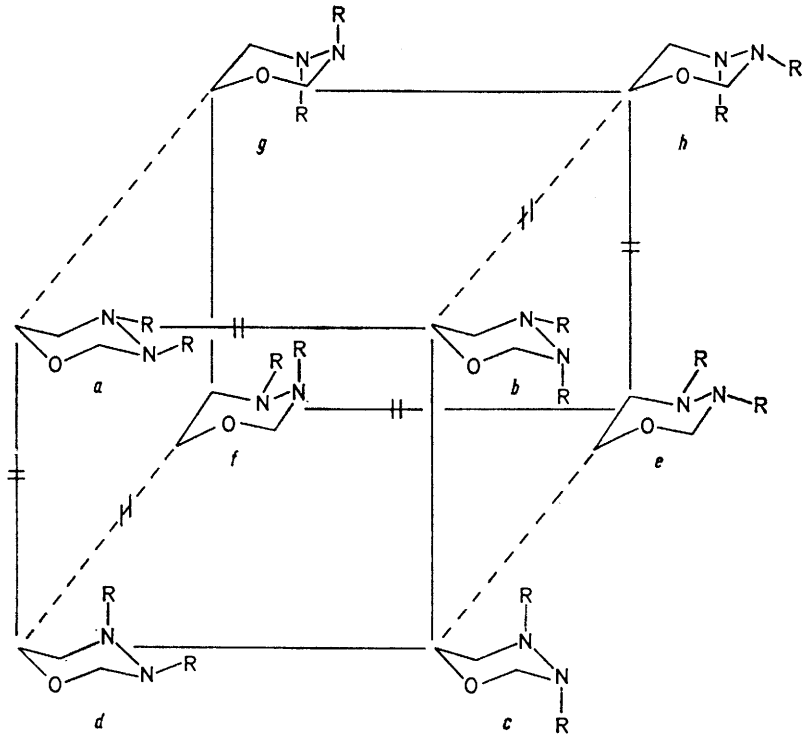
3,4-Dialkyltetrahydro-1,3,4-oxadiazines can exist in eight possible ring conformations (Scheme 2), four of which are mirror images of the others (*ae*, *bf*, *cg*, *dh*). The conformers can interconvert by two distinct conformational processes, ring inversion and pyramidal nitrogen inversion; these inversions can be further subdivided into those which involve the eclipsing of adjacent groups in the transition state (' passing inversions '), and those which do not (' non-passing inversions '). At room temperature all processes are expected to be rapid on the n.m.r. time scale.

Theoretical Considerations.—The *N*-methyl group in 1-methylpiperidine exists preferentially in the equatorial conformation with a bias greater than previously thought: the older value of $\Delta G°$ (from dipole moments) of 0.6 kcal mol^{-1} (ref. 12) has more recently been raised to *ca.* 1.5 (ref. 13) or 2.7 kcal mol^{-1} (ref. 14). An oxygen atom β to the *N*-methyl group however favours the equatorial orientation of *N*-methyl marginally, *e.g.* tetrahydro-3-methyl-1,3-oxazine,[15] $\Delta G°_{298}$ *ca.* 0.16 kcal mol^{-1}, which can be explained in terms of reduced 1,3 CH_3 : H interactions and a 1,3 anomeric effect. Nelsen *et al.* have recently [4,5] shown that 1,2-dimethylhexahydropyridazine exists predominantly as the diequatorial conformer; by comparison in tetrahydro-3,4-dimethyl-1,3,4-oxadiazine the introduction of the β-oxygen atom should increase the amount of 3-*N*-methyl (*ax*) and for this compound the 3-*N*-methyl (*ax*),4-*N*-methyl (*eq*) conformer should be the most favoured. We would further expect that the N-inversion barriers should be *ca.* 12.4 kcal mol^{-1} for a

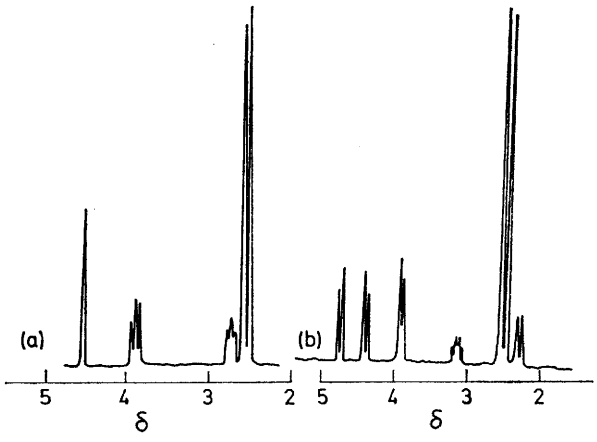
[7] L. C. Dorman, *J. Org. Chem.*, 1967, **32**, 255.
[8] A. A. Potekhin and E. A. Bogan'kova, *Khim. geterotsikl. Soedinenii*, 1973, 1461 (*Chem. Abs.*, 1974, **80**, 70785*k*), and previous parts in the series.
[9] A. L. Van Geet, *Analyt. Chem.*, 1970, **42**, 679.
[10] G. Rosen and F. D. Popp, *J. Heterocyclic Chem.*, 1969, **6**, 9.
[11] R. Renaud and L. C. Leitch, *Canad. J. Chem.*, 1954, **32**, 545.
[12] 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.
[13] E. L. Eliel and F. W. Vierhapper, *J. Amer. Chem. Soc.*, 1975, **97**, 2424.
[14] P. J. Crowley, M. J. T. Robinson, and M. G. Ward, *J.C.S. Chem. Comm.*, 1974, 825.
[15] I. J. Ferguson, A. R. Katritzky, and D. M. Read, *J.C.S. Chem. Comm.*, 1975, 255.

' passing inversion ' and 8.4 kcal mol^{-1} for a ' non-passing inversion '.[15] The nitrogen atoms undergoing inversion possess different molecular environments (one β the other γ to oxygen) but the differential effect of this on the barriers is expected to be small.[15]

Tetrahydro-3,4-dimethyl-1,3,4-oxadiazine (1).—The first-order spectrum of the oxadiazine (1) at 307 K allows assignment of all peaks (Table 1). In particular the single line for the 2-protons and two singlets for the *N*-methyl groups are in accord with rapid ring and nitrogen inversion (Figure). On lowering the temperature the passing ring inversions should be slowed first; however since all distinguishable conformers are still interconvertible *via* alternative processes no consequential changes occur in the spectrum. The first observable spectral change is the separation of the C(2)H_2 singlet into an AB quartet below 256 K; at 153 K the coupling constant is 10.5 Hz and the separation 0.342 p.p.m. This change is attributed to the slowing of ' non-passing ' ring inversion,



SCHEME 2 Conformations of the oxadiazines (1)—(3); conformations interconvertible by ring inversion are connected by dotted lines; *N*-alkyl inversions are connected by solid lines; barred interconversions involve eclipsing of alkyl groups in the transition state



N.m.r. spectra of tetrahydro-3,4-dimethyl-1,3,4-oxadiazine at (a) 307 K and (b) 193 K

$\Delta G^{\ddagger}_{c}$ 12.6 kcal mol^{-1} (*cf.* Table 2). At still lower temperatures, a further change is the appearance of two minor singlets (T_c 247 K) upfield of the two principal *N*-methyl singlets, which have become well resolved by 196 K. The appearance of these two minor signals results from the slowing of ' passing ' nitrogen inversions, $\Delta G^{\ddagger}_{c}$ 12.3 kcal mol^{-1}, and these signals are assigned to the diequatorial conformer *a* (the other ring proton signals of this conformer were not observed owing to either coincidence or lack of magnitude). No distinction is possible between the 3-*N*-methyl ' passing ' inversion and the 4-*N*-methyl ' passing ' inversions, as observable change in the spectrum results only when *both* are slowed.

Direct area measurements at 153 K give $K = 0.22$ with *a* being the minor component and hence $\Delta G^{\circ}_{153} = 0.461$ kcal mol^{-1}. No further spectral changes are observed on lowering the temperature to 123 K. Since the population of the diaxial conformer *c* is likely to be negligible, and conformers *b* and *d* are unlikely to give rise to the same chemical shifts, we conclude that conformer *b* is the principally populated form, with conformer *a* the minor component.

Tetrahydro-2,3,4-trimethyl-1,3,4-oxadiazine (4).—Ring

inversions are not important here since the ring conformations with 2-*C*-methyl equatorial should greatly predominate. Thus only *N*-inversions could cause significant spectral changes. In fact, the spectrum at 307 K (Table 1) showed no significant changes on lowering the temperature to 123 K; the two *N*-methyl groups remained singlets and the 2-proton signal remained a single AB quartet. The introduction of equatorial 2-*C*-methyl in conjunction with β-oxygen and an α-*N*-methyl group diminishes the stability of the 3-*N*-methyl (*eq*) group to the extent that only the conformer *b*, *i.e.* 3-*N*-methyl (*ax*),4-*N*-methyl (*eq*), can be detected.

TABLE 1

Room temperature ^{1}H n.m.r. spectra [a] (δ values) measured at 100 MHz

Compd.	$C(2)H_2$ or $HC(2)CH_3$	$C(5)H_2$	$C(6)H_2$	3-*N*-Alkyl	4-*N*-Alkyl
(1)	4.45 (s)	2.68 (t)	3.83 (t)	2.51 (s)	2.46 (s)
(2)	4.43 (s)	2.76 (m)	3.77 (t)	1.06 (t), 2.76 (m)	1.06 (t), 2.76 (m)
(3)	4.54 (s)	3.18 (t)	3.70 (t)	1.10 (d), 3.39 (m)	1.03 (d), 3.39 (m)
(4)	1.24 (d), 4.74 (q)	3.01 (m)	3.86 (m)	2.52 (s)	2.35 (s)

[a] In 1 : 1 $CDCl_3$–$CFCl_3$ at 307 K.

TABLE 2

Coalescence temperatures (T_c) and free energies of activation ($\Delta G^{\ddagger}_c$)

Compd.	Signal	T_c/K	$\Delta G^{\ddagger}_c$/kcal mol^{-1}
(1)	$C(2)H_2$	256	12.6 ± 0.2
	$N{\cdot}CH_3$	247	12.3 ± 0.2
(2)	$C(2)H_2$	255	12.7 ± 0.2
(3)	$C(2)H_2$	256	12.7 ± 0.2

3,4-Diethyltetrahydro-1,3,4-oxadiazine (2).—The spectrum at 307 K (Table 1) changed significantly on lowering the temperature; the $C(2)H_2$ singlet separated into an AB quartet below 255 K which was well resolved by 208 K (Table 3). The ring 5- and 6-protons also exhibited a more complex pattern. These spectral changes are the result of the slowing of ' non-passing ' ring inversion, $\Delta G^{\ddagger}_c$ 12.7 kcal mol^{-1}. No further spectral changes, with the exception of line broadening, were observed on lowering the temperature to 123 K.

The spectral behaviour of the di-isopropyl analogue (3) was similar to that of the oxadiazine (2); the $C(2)H_2$ singlet separated into an AB quartet below 256 K, again assigned to the slowing of ' non-passing ' ring inversion.

The spectral results for compounds (2) and (3) are inconclusive but it appears that both exist in a single conformer in which the 3-*N*-alkyl group is axial and the 4-*N*-alkyl group equatorial, by analogy with pyridazines.[16] A comparison of activation energy values of ' non-passing ' ring inversions and ' passing ' nitrogen inversions in Table 2 shows them to be of the expected order.

TABLE 3

^{1}H N.m.r. spectra at low temperature (δ values) measured at 100 MHz [a]

Compd.	*T*/K	$C(2)H_2$	$C(5)H_2$	$C(6)H_2$	3-*N*-Alkyl	4-*N*-Alkyl
(1)	153	4.30 (q, Δν 34.2 Hz, *J* 10.5 Hz) [b]	2.99 (m)	3.71br (d)	240 (s), 2.16 (s) [c]	2.32 (s), 2.05 (s) [c]
(2)	208	4.54 (q, Δν 15.6 Hz, *J* 10.7 Hz)	2.79 (m)	3.84 (m)	112 (t), 2.79 (m)	1.12 (t), 2.79 (m)
(3)	192	4.58 (q, Δν 19.6 Hz, *J* 11.9 Hz)	3.30 (m)	3.52 (d) [d]	1.04 (d), 3.34 (m)	1.04 (d), 3.34 (m)

[a] In CF_2Cl_2. [b] Δν = relative chemical shift. [c] Minor peaks. [d] Tentative assignment.

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[16] S. F. Nelsen and G. R. Weisman, *J. Amer. Chem. Soc.*, 1976, **98**, 1842.

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