Conformational Analysis of Saturated Heterocycles. Part 85.[1] Perhydrodipyrido[1,2-b;1',2'-e]-1,4,2,5-dioxadiazine

By Alan R. Katritzky,* Ranjan Patel, and Shahrokh Saba, School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ

Richard L. Harlow and Stanley H. Simonsen, Department of Chemistry, University of Texas at Austin, Austin, Texas 78712, U.S.A.

The title compound is shown to be the trans-isomer which exists both in the crystal (X-ray) and in solution (n.m.r.) in the tetraequatorial conformation.

PERHYDRODIPYRIDO[1,2-b;1',2'-e]-1,4,2,5-DIOXADIAZINE (1) † was prepared by Thesing and Mayer [2] and again by Colonna and De Martino [3] by oxidation of 1-hydroxypiperidine. Neither group discussed its configuration or conformation, but Nonnenmacher et al.[4] studied the symmetric dimethoxy-analogue (2) and

assigned it the trans-configuration (2b) with a cis–cis ring fusion [cf. (II)] considered more probable.

As monocyclic 1,4,2,5-dioxadiazines are unknown (although other more complex polycyclic derivatives have been reported [5]) and as our attempts to prepare them failed,[6] we have studied the tricycle (1).

Configuration and Solid State Conformation.—X-Ray

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† Crystallographic numbering system (see Figure 1) used throughout.

[1] Part 84, V. J. Baker, I. J. Ferguson, A. R. Katritzky, R. Patel, and S. Rahimi-Rastgoo, *J.C.S. Perkin II*, 1978, 377.

[2] J. Thesing and H. Mayer, *Chem. Ber.*, 1956, 89, 2159.

[3] M. Colonna and U. De Martino, *Gazzetta*, 1963, 93, 1183.

[4] G. Eikelmann, W. Heimberger, G. Nonnenmacher, and W. M. Weigert, *Annalen*, 1972, 759, 183.

[5] H. Gnichtel, W. Griebenow, and W. Löwe, *Chem. Ber.*, 1972, 105, 1865; H. Gnichtel and K. Hirte, *ibid.*, 1975, 108, 3387.

[6] For full details see R. Patel, Ph.D. Thesis, University of East Anglia, 1977.

diffraction shows that (1) possesses the *trans*-configuration (1b) and in the crystal exists in the *eeee* conformation (I), rather than the alternatives (II)—(IV).

unusually short intermolecular contacts were noted. The central ring is puckered (ϕ 67°) possibly due to repulsion between *gauche* nitrogen atoms.
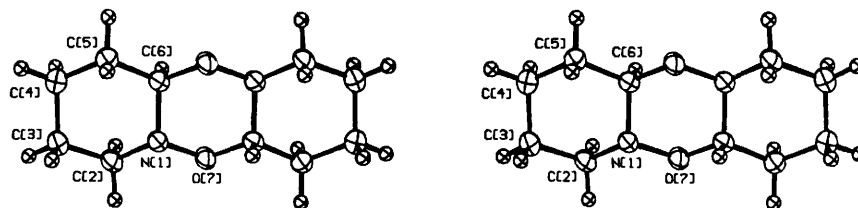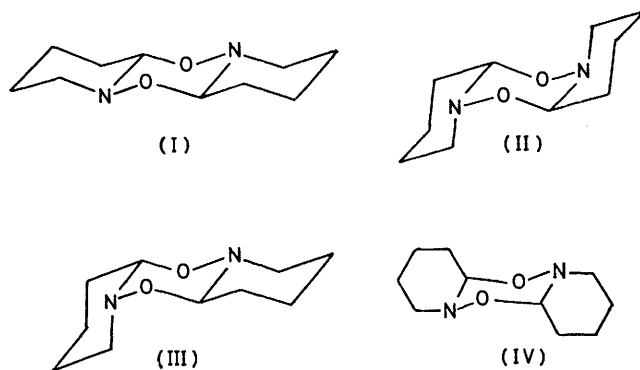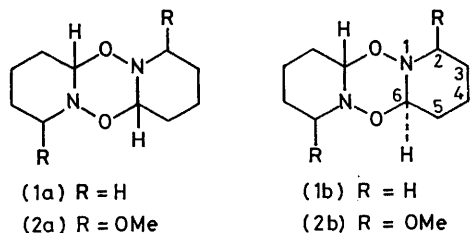

FIGURE 1 Molecular conformation and crystallographic atom-numbering scheme. Each hydrogen atom is numbered in accord with the carbon atom to which it is bonded

Figure 1 is a stereodrawing of the molecule, the centre of which is coincident with a crystallographic inversion

(1a) R = H
(2a) R = OMe
(1b) R = H
(2b) R = OMe

(I) (II)

(III) (IV)

centre. The details of the molecular geometry are given in Figure 2 and Table 1. The bond distances, bond

TABLE 1

Torsion angles (°) for perhydrodipyrido[1,2-*b*;1',2'-*e*]-1,4,2,5-dioxadiazine (1)

N(1)–C(2)–C(3)–C(4)	58.0	C(3)–C(2)–N(1)–C(6)	−64.2
N(1)–C(6)–C(5)–C(4)	−58.5	C(3)–C(2)–N(1)–O(7)	−177.1
N(1)–C(6)–O(7)'–N(1)'	66.7	C(3)–C(4)–C(5)–C(6)	53.2
N(1)–O(7)–C(6)'–C(5)'	175.5	C(4)–C(5)–C(6)–O(7)'	−175.8
C(2)–N(1)–C(6)–C(5)	64.8	C(5)–C(6)–N(1)–O(7)	176.6
C(2)–N(1)–C(6)–O(7)'	−177.6	C(6)–N(1)–O(7)–C(6)'	65.2
C(2)–N(1)–O(7)–C(6)'	−178.6	O(7)–N(1)–C(6)–O(7)'	−65.8
C(2)–C(3)–C(4)–C(5)	−53.0		

angles, and torsion angles associated with the N–O bond are consistent with previously reported values.[7] No

[7] F. G. Riddell, P. Murray-Rust, and J. Murray-Rust, *Tetrahedron*, 1974, **30**, 1087; J. Murray-Rust and P. Murray-Rust, *Acta Cryst.*, 1975, **31B**, 589.

N.m.r. Spectra.—The ^{1}H spectrum is uninformative: at 20 °C it shows peaks for the O–CH–N protons at

TABLE 2

^{13}C N.m.r. data [25.0 MHz] for perhydrodipyrido[1,2-*b*;-1',2'-*e*]-1,4,2,5-dioxadiazine (1)

	C-2	C-3	C-4	C-5	C-6
Un-	52.6	24.5	22.4	28.8	95.9
decoupled	(t, J_{CH}	(t, J_{CH}	(t, J_{CH}	(t, J_{CH}	(d, J_{CH}
(δ)	146.0)	127.1)	130.0)	130.5)	152.2)
Decoupled	52.6	24.6	22.4	28.9	95.8
(δ)					
+30 °C					
−120 °C	52.7	24.3	22.2	28.6	96.2
t_c (°C)	8 [b]		3		10
Δv (p.p.m.)					5.2
$\Delta \omega_{\frac{1}{2}}$ (Hz) [a]	3.6 [c]		1.4 [b]		11.4
P (%)					8.8
$\Delta G^{\ddagger}_c$ ±0.4					12.7
ΔG°_c ±0.2					1.31

[a] Corrected for natural linewidth ($\Delta \omega_{\frac{1}{2}}$ 1.95 Hz). [b] It was difficult to assess Δv. [c] Population of minor conformer.

δ 4.35, for N–CH$_2$ protons at 3.25 and 2.60, and a complex multiplet for the C–CH$_2$–CH$_2$–CH$_2$–C at 1.6. Little change is observed on lowering the temperature.

The ^{13}C n.m.r. spectrum at +30 °C (Table 2) showed five signals which immediately suggests the *trans*-configuration (1b) [the *cis*-configuration (1a) should

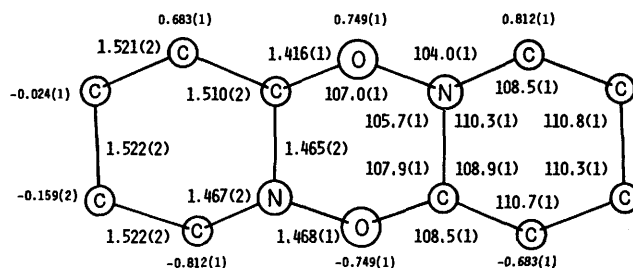FIGURE 2 Bond distances (Å) and angles (°) for the non-hydrogen atoms. The small numbers are deviations from the N-1, N-1', C-6, C-6' plane. The C–H distances ranged from 0.96 to 1.01 Å and averaged 0.99 Å. The interatomic angles involving the hydrogen atoms ranged from 106 to 113° and averaged 110°

show ten distinct signals]. The assignment to C-6 (Table 2) follows from the undecoupled spectrum: the C–H couplings are normal. The other peaks are assigned

on relative chemical shift grounds: C-2, α to N possesses the lowest shift and C-4 the highest. The shift of C-3 is slightly higher than that of C-5. On lowering the

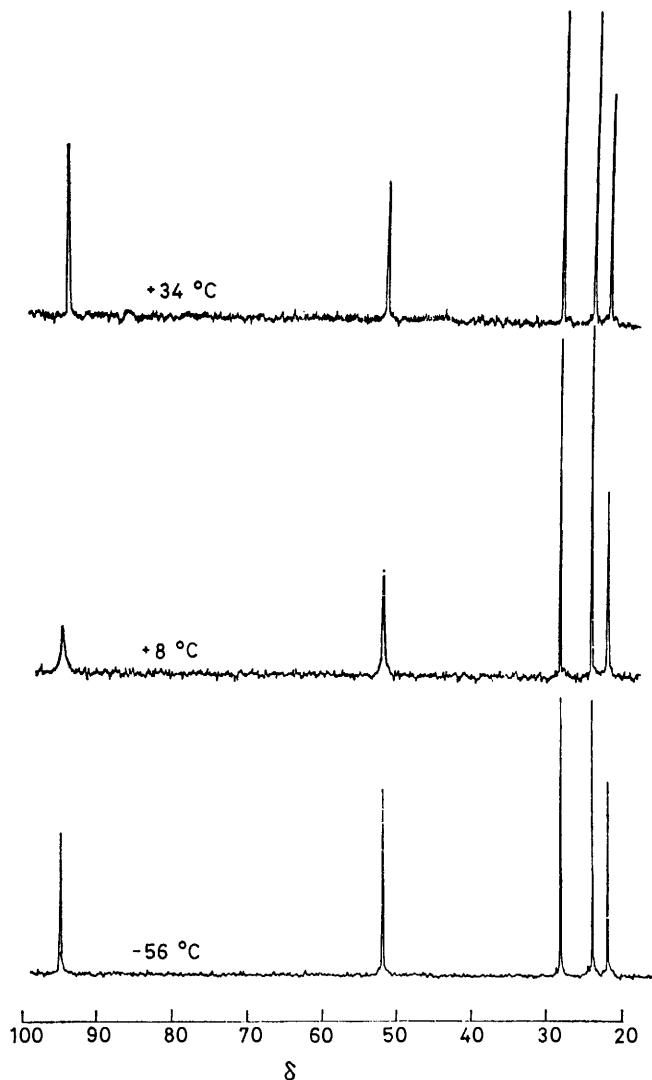FIGURE 3 ^{13}C n.m.r. spectrum [25 MHz; (CD$_3$)$_2$CO] of per-hydrodipyrido[1,2-b;1',2'-e]-1,4,2,5-dioxadiazine (1). Sweep width, 3 kHz; data points, 8192

temperature to 8 °C, the spectrum (solvent deuterio-acetone) shows considerable broadening of the C-6, -2, and -4 signals (Figure 3). When the temperature is further lowered, these signals sharpen and remain sharp down to —80 °C. No signals for minor conformations are seen: hence a single symmetric conformation is strongly preferred. The broad signals at 8 °C also sharpen when the solution is heated to +35 °C: thus a dynamic effect occurs at ambient temperatures.

Equilibration between (I) and (III) and between (II) and (III) would be expected to cause broadening of the

[8] F. A. L. Anet, I. Yavari, I. J. Ferguson, A. R. Katritzky, M. Moreno-Mañas, and M. J. T. Robinson, *J.C.S. Chem. Comm.*, 1976, 399.

[9] E. L. Eliel and F. W. Vierhapper, *J. Amer. Chem. Soc.*, 1975, **97**, 2424.

C-2, -4, and -6 signals, whereas equilibration between (IV) and (III) should cause broadening of C-3 and -5. The observed broadenings thus provide good evidence for the predominance of (I) or (II) with a little (III). Maximum broadenings at half height ($\Delta\omega_{\frac{1}{2}}$) and the temperatures for maximum broadenings are recorded in Table 2. These quantities are related to $\Delta G^{\ddagger}$ and ΔG° by equations (1) and (2).[8] However, for their calculation Δv, the chemical shift difference between the two

$$\Delta w_{\frac{1}{2}} = P\Delta v \qquad (1)$$

$$k_c = 2\pi\Delta v = (k_B T_c/h) \exp(-\Delta G^{\ddagger}_c/RT_c) \qquad (2)$$

carbon environments must be known. For C-6, we have estimated $\Delta v = 5$ p.p.m., as the effect is similar to those found by Eliel and Vierhapper [9] for the γ-effect and we have found Δv ca. 5 p.p.m. for the chemical shift difference between C-3 of (3) and (4).[10] Hence we deduce $\Delta G^{\ddagger}_{281}$ 12.7 ± 0.4 (minor to major) and ΔG°_{281} 1.3 ± 0.2 kcal mol^{-1} (errors cover the range 4—6 p.p.m. for Δv).

To distinguish between the possible predominance of (I) or (II) in solution, i.r. evidence was sought. Conformer (I) has two C–H bonds adjacent, axial and anti-periplanar to each axial nitrogen lone pair whereas (II) has only one such interaction. Therefore (I) should show Bohlmann bands (ν ca. 2 800 cm^{-1}) in the i.r.[11] but not (II). Two Bohlmann bands (2 610 and 2 700 cm^{-1}) observed hence strongly indicate that (I) is the predominant conformation; it is of interest that the tricyclic tetrazine (5) also exists predominantly in the tetraequatorial conformation shown.[12]

Dipole Moment.—The relatively high dipole moment found for (1a) in benzene (0.75 ± 0.02 D) (Table 3)

TABLE 3

Dipole moment measurements for perhydrodipyrido-[1,2-b;1',2'-e]-1,4,2,5-dioxadiazine (1)

(a) Dielectric constants and specific volumes

$10^6 w_2$	$10^6(\varepsilon_{12} - \varepsilon_1)$	$10^6(v_1 - v_{12})$
2 845	998	755
4 971	1 706	1 297
5 545	1 843	1 450
6 558	2 503	

(b) Electric dipole moment

$d\varepsilon/dw_2$	$-dv/dw_2$	$T^P_{2\infty}$	E^P	μD
0.32 ± 0.02	0.257 ± 0.002	64.44	53.1	0.75 ± 0.02

could be taken to indicate the presence of ca. 35% of the non-symmetrical conformation (III): however, we believe that this is merely another illustration of the danger of using dipole moments for quantitative conformational analysis. The n.m.r. method indicates merely ca. 10% of (III) at 25 °C.

Crystal Data.—C$_{10}$H$_{16}$N$_2$O$_2$, M 196.14. Monoclinic, space group $P2_1/c$, $Z = 2$. At —35 °C, $a = 5.369$ 9(7),

[10] A. R. Katritzky and R. Patel, *Heterocycles*, 1978, **9**, 263; A. R. Katritzky and R. C. Patel, in preparation.

[11] F. Bohlmann, *Chem. Ber.*, 1958, **91**, 2157; W. E. Rosen, *Tetrahedron Letters*, 1961, 481.

[12] V. J. Baker, A. R. Katritzky, J.-P. Majoral, A. R. Martin, and J. M. Sullivan, *J. Amer. Chem. Soc.*, 1976, **98**, 5748.

$b = 6.640\ 8(7)$, $c = 14.559(1)$ Å, $\beta = 96.51(1)°$, $V = 515.8$ Å^3, $D_c = 1.263$ g cm^{-3}. Mo-K_α radiation, $\lambda = 0.710\ 69$ Å, $\mu = 0.96$ cm^{-1}.

Colourless plates of perhydrodipyrido[1,2-b;1',2'-e]-1,4,2,5-dioxadiazine were grown by slow evaporation of

(3)   (4)

(5)
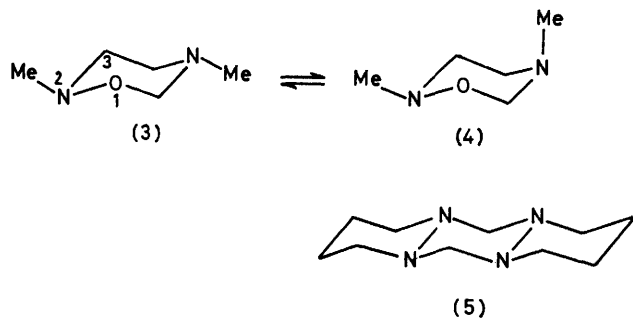
an n-hexane solution and generally exhibited the {100}, {011}, and {001} forms. Cleavage of one crystal parallel to the (100) and (011) faces produced a fragment with dimensions of 0.53 × 0.50 mm perpendicular to these faces and 0.19 mm perpendicular to the (001) face. This fragment was mounted on a Syntex P2$_1$ diffractometer (Mo-K_α radiation) equipped with a low-temperature apparatus which cooled the crystal to -35 °C. The unit-cell dimensions were refined by the least-squares method using the Bragg angles of 45 carefully centred reflections.

Intensity data for 1 505 unique reflections ($4° < 2\theta < 60°$) were collected by the ω-scan technique. Scans of 1.0° were used with scan rates which ranged from 2.0 to 5.0° min^{-1} depending upon the number of counts accumulated in a rapid preliminary scan. Backgrounds were measured at both ends of the scan with ω displaced 1.0° from the K_α peak. The intensities of four standard reflections were monitored after every 96 reflections; only statistical variations were noted. The intensities were corrected for Lorentz and polarization effects but not for absorption.

Solution and Refinement.—The structure was solved by direct methods (MULTAN). Refinement of the structure by the full-matrix least-squares method was carried out using only those 1 193 reflections for which $I > 2\sigma(I)$. A difference map was used to locate the hydrogen atoms. Refinement of all positional and thermal (anisotropic for the non-hydrogen atoms and isotropic for the hydrogen atoms) parameters converged at a conventional R of 0.048. The parameter shifts in the final cycle of refinement were all $<0.01\sigma$. The largest positive peaks in the final difference Fourier map corresponded to the bonding electron-density between the non-hydrogen atoms; the largest peak was located between C-5 and -6 and had a magnitude of 0.24 e Å^{-3}. The refined positional and thermal parameters are given

† Structure amplitudes ($\times 10$) for (1) are given in Supplementary Publication No. SUP 22293 (8 pp.). For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1977, Index issue.

in Table 4. The computational and mathematical details are noted elsewhere.†,[13]

TABLE 4

Final atomic coordinates and thermal parameters for perhydrodipyrido[1,2-b;1',2'-e]-1,4,2,5-dioxadiazine (1)

(a) Atomic co-ordinates for the non-hydrogen atoms

Atom	x	y	z
N(1)	0.070 0(2)	0.195 7(1)	0.022 11(7)
C(2)	0.277 8(3)	0.340 2(2)	0.032 43(9)
C(3)	0.295 2(3)	0.430 0(2)	0.129 06(9)
C(4)	0.333 2(3)	0.265 7(2)	0.202 17(9)
C(5)	0.132 6(3)	0.104 4(2)	0.184 03(8)
C(6)	0.122 3(2)	0.027 0(2)	0.086 22(8)
O(7)	0.078 5(2)	0.111 3(1)	-0.070 66(5)

(b) Anisotropic thermal parameters ($\times 10^4$) for the non-hydrogen atoms in the form $\exp[-2\pi^2(U_{11}h^2a^{*2} + \ldots + 2U_{23}klb^*c^*)]$

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	382(6)	235(5)	264(5)	$-27(4)$	35(4)	$-5(4)$
C(2)	426(7)	277(6)	330(7)	$-93(6)$	47(6)	14(5)
C(3)	465(8)	289(7)	361(7)	$-73(6)$	11(6)	$-28(5)$
C(4)	397(8)	351(7)	318(6)	$-33(6)$	$-8(5)$	$-25(6)$
C(5)	399(7)	316(7)	272(6)	$-30(6)$	36(5)	4(5)
C(6)	317(6)	234(6)	286(6)	$-16(5)$	36(5)	14(4)
O(7)	420(5)	291(5)	258(4)	$-96(4)$	72(3)	$-8(3)$

(c) Positional and thermal parameters for the hydrogen atoms

Atom	x	y	z	U_{iso}
H(2) ^{a}	0.241(3)	0.443(2)	$-0.014(1)$	0.032(4)
H(2) ^{b}	0.439(2)	0.270(2)	0.021(1)	0.033(4)
H(3) ^{a}	0.137(3)	0.504(2)	0.140(1)	0.038(4)
H(3) ^{b}	0.432(3)	0.525(2)	0.136(1)	0.035(4)
H(4) ^{a}	0.500(3)	0.209(2)	0.198(1)	0.042(4)
H(4) ^{b}	0.335(3)	0.322(2)	0.265(1)	0.032(4)
H(5) ^{a}	$-0.028(3)$	0.159(2)	0.192(1)	0.036(4)
H(5) ^{b}	0.170(3)	$-0.013(2)$	0.227(1)	0.038(4)
H(6)	0.283(3)	$-0.039(2)$	0.073(1)	0.029(3)

EXPERIMENTAL

[13]C N.m.r. spectra were recorded on a JEOL FX-100 pulsed Fourier transform n.m.r. spectrometer with an internal deuterium lock [(CD$_3$)$_2$CO]. The spectra were run on samples contained in 10 mm diameter tubes, with Me$_4$Si (2%) as internal standard. Temperatures were checked by calibration of the dial to a copper–constantan thermocouple. [1]H N.m.r. spectra were measured on a Varian HA-100 spectrometer in CDCl$_3$–CFCl$_3$ (1 : 1). Temperatures (± 2 K) were measured with a standard methanol sample [14] above 183 K. Dipole moment measurements were measured in benzene at 25 °C by the standard technique.[15]

Perhydropyrido[1,2-b;1',2'-e]-1,4,2,5-*dioxadiazine* (1).—This compound was prepared by the method of Thesing and Mayer,[2] m.p. 126 °C (lit.,[2] 126—127 °C).

[13] R. L. Harlow and S. H. Simonsen, *Acta Cryst.*, 1976, **32B**, 466.
[14] A. L. Van Geet, *Analyt. Chem.*, 1970, **42**, 679.
[15] R. A. Y. Jones, A. R. Katritzky, P. G. Lehman, K. A. F. Record, and B. B. Shapiro, *J. Chem. Soc.* (*B*), 1971, 1302.