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THE CONFORMATIONAL ANALYSIS OF TETRAHYDRO-1,4,2-DIOXAZINES

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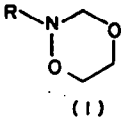
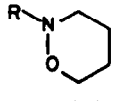
Abstract—A conformational study of some tetrahydro-1,4,2-dioxazines by use of ^1H and ^{13}C NMR spectroscopy is reported. The conformational characteristics of this ring are compared to those of the related systems, tetrahydro-1,2- and 1,3-oxazine. A study of model compounds allows the assignment of ring and nitrogen inversion processes in the variable temperature NMR spectra. Ring inversion is found to be a lower energy process than nitrogen inversion. The barriers to these processes are measured in several derivatives and the implications of the results for studies of nitrogen inversion in other 6-membered rings are pointed out. The conformational free energy differences of N-Me and N-Et groups are measured and discussed. It is somewhat easier to put an N-Et group axial than N-Me (*ca.* 0.25 kcal mole^{-1}). It also appears than an Et group at C-6 goes axial more readily than does a Me.

"The introduction of heteroatoms into a cyclohexane ring as in piperidine or pyran raises conformational problems of considerable interest and sophistication" wrote Barton in 1969.[1] Since then the interest in heterocyclic conformational analysis has grown considerably, and rings containing one and two heteroatoms have been extensively studied and are now relatively well understood. A general conclusion to be drawn from this work is that the more heteroatoms there are in a ring the more interesting and sophisticated do the problems become. Rings containing three or more heteroatoms have however received little attention. Amongst these is the tetrahydro-1,4,2-dioxazine ring (1) which contains fragments from the tetrahydro-1,2-oxazine (2) and tetrahydro-1,3-oxazine (3) rings. The conformational behaviour of the dioxazine ring should be composed of aspects of the behaviour of the 1,2- and 1,3-oxazine rings and should form an interesting test of the ways in which differing conformational tendencies can be fused together. The tetrahydro-1,2-oxazines[2-5] and the tetrahydro-1,3-oxazines[6-10] have been studied by several groups and their conformational analysis is sufficiently well understood for a comparison with the 1,4,2-dioxazine series to be attempted.



(1)



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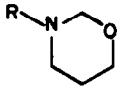


(3)

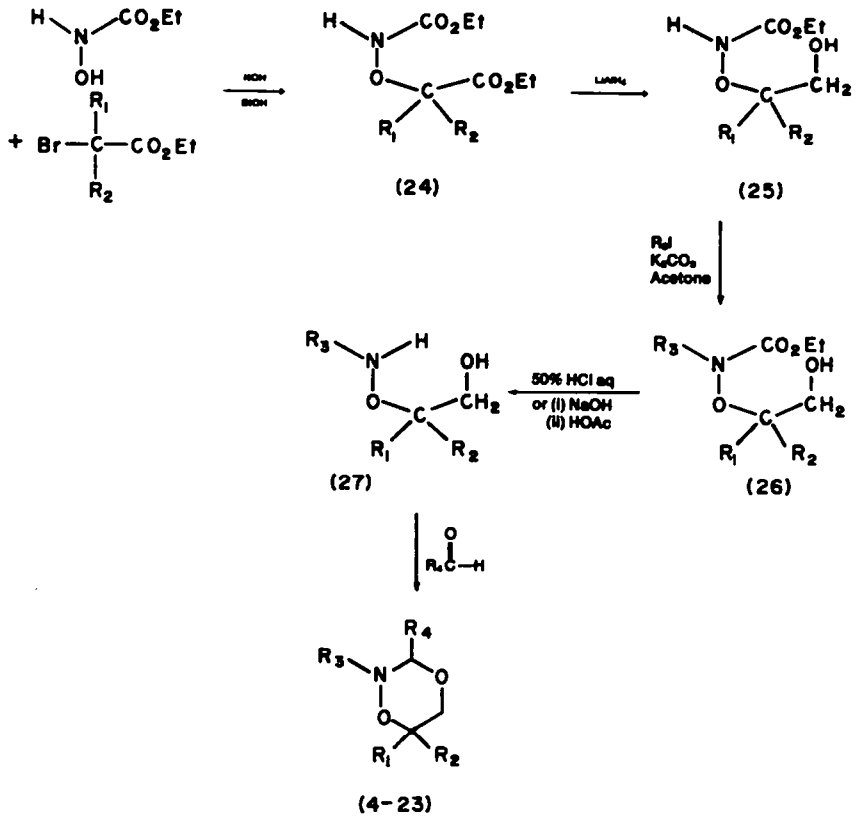
Tetrahydro-1,4,2-dioxazines have previously been studied by Katritzky *et al.* (KCO).[11,12] They reported that these compounds show evidence of the slowing of two conformational processes in their low temperature NMR spectra, and measured two activation energies, 10.2 and 11.7 kcal mole^{-1}. Although they correctly ascribed the processes as being due to ring and nitrogen inversion they had no evidence to distinguish between these processes. In a subsequent communication[13] they assigned the lower energy barrier to nitrogen inversion. We shall demonstrate in this paper that it is the higher energy process that arises from nitrogen inversion. This point is crucial to the current controversy over the magnitudes of nitrogen inversion barriers in 6-membered rings because in the empirical scheme proposed by KCO several of the conclusions are critically dependent on this value. Moreover in our linear regression analysis† of factors affecting nitrogen inversion barriers[14] we implicitly accepted this assignment of barriers with consequences on the values of the parameters found.

In order to carry out a more thorough investigation of the tetrahydro-1,4,2-dioxazine ring we have prepared a number of derivatives (4–23) carrying Me, Et, i-Pr and Bz groups on nitrogen, H or p nitrophenyl at C-3, and H, Me, Et or Ph at C-6.

The syntheses were all accomplished by the same general route (Scheme 1). Reaction of N-hydroxyurethane with an α bromoester in ethanolic sodium or potassium hydroxide solution leads to the esters (24). These compounds may be reduced selectively by lithium aluminium hydride at *ca.* 0° to the hydroxy compounds (25). The urethane remains untouched during this reaction presumably because loss of the relatively acidic amide hydrogen forms a protective anion in this region of the molecule. Alkylation under standard conditions leads to the derivatives (26) which can be hydrolysed and decarboxylated to the hydroxylaminoalcohols (27) either by refluxing with concentrated hydrochloric acid (R_1=H, Me,Et R_2=H) or by basic hydrolysis with aqueous methanolic sodium hydroxide (R_1R_2=Me, R_1=Ph R_2=H, R_1=MeR_2=Et). In the latter cases acid hydrolysis caused decomposition presumably since more stable carbonium ions are available. The amino-alcohols (27) condense with aldehydes when heated under reflux in benzene to form the 1,4,2-dioxazines. These reactions generally proceeded without an acid catalyst but sometimes a trace of toluene-*p*-sulphonic acid was required. Physical data for the intermediates and products are reported in Tables 1 and 2.

The ^1H spectra of 4, 5 and 6 at ambient temperature

†Multiple linear regression analysis is the most suitable technique to use in a case of this sort where more linear simultaneous equations are available than there are unknowns. In any event it is superior to the "*ad hoc*" method employed by KCO.



Scheme 1. Synthesis of tetrahydro-1,4,2-dioxazines.

Table 1.

Compound Number	R_1	R_2	R_3	R_4	*m.p./b.p.*	Formula	*m/e* calc	*m/e* obs	error in *m/e* (ppm)
5	H	H	Et	H		$C_5H_{11}NO_2$	117.0790	117.0796	5.1
6	H	H	i-Pr	H	130–135°/45 mm	$C_6H_{13}NO_2$	131.0946	131.0935	−8.4
7	H	H	Me	pNO_2Ph	92–92.5°	$C_{10}H_{12}N_2O_4$	224.0797	224.0793	−1.8
8	H	H	Et	pNO_2Ph	124–125°	$C_{11}H_{14}N_2O_4$	238.0954	238.0957	1.3
9	H	H	i-Pr	pNO_2Ph	109–110°	$C_{12}H_{16}N_2O_4$	252.1111	252.1111	0.0
10	Me	H	Me	H	55–60°/50 mm	$C_5H_{11}NO_2$	117.0790	117.0779	−9.4
11	Me	H	Et	H	70°/5 mm	$C_6H_{13}NO_2$	131.0947	131.0944	−1.5
12	Me	H	Bz	H	86°/2 mm	$C_{11}H_{13}NO_2$	193.1103	193.1106	1.6
13	Me	H	Me	pNO_2Ph	96–97°	$C_{11}H_{14}N_2O_4$	238.0954	238.0945	−3.8
14	Me	H	Et	pNO_2Ph	128–129°	$C_{12}H_{16}N_2O_4$	252.1110	252.1102	−3.2
15	Et	H	Me	H	60–65°/6 mm	$C_6H_{13}NO_2$	131.0947	131.0947	0.0
16	Et	H	Me	pNO_2Ph	94–95°	$C_{12}H_{16}N_2O_4$	252.1110	252.1109	−0.4
17	Me	Me	Me	H	100°/70 mm	$C_6H_{13}NO_2$	131.0947	131.0947	0.0
18	Me	Me	i-Pr	H	95°/50 mm	$C_8H_{17}NO_2$	159.1259	159.1245	−8.8
19	Me	Me	Me	pNO_2Ph	111–112°	$C_{12}H_{16}N_2O_4$	252.1111	252.1114	1.2
20	Me	Me	iPr	pNO_2Ph	127–128°	$C_{14}H_{20}N_2O_4$	280.1423	280.1411	−4.3
21	Ph	H	Me	H	130°/14 mm	$C_{10}H_{13}NO_2$	179.0947	179.0964	9.5
22	Ph	H	Me	pNO_2Ph	151–152°	$C_{16}H_{16}N_2O_4$	300.1111	300.1133	7.3
23	Me	Et	Me	H	110°/45 mm	$C_7H_{15}NO_2$	145.1103	145.1107	2.8

are consistent with rapid ring and nitrogen inversion displaying sir ets for the C-3 hydrogens, AA'BB' multiplets for he C-5,6 hydrogens and the expected patterns for the N-alkyl substituents. Analysis of the AA'BB' pattern in these compounds gives $J\,cis = \frac{1}{2}(Jea + Jae) = 3.1$ Hz and $J\,trans = \frac{1}{2}(Jee + Jaa) = 6.1$ Hz. These values agree very well with the more limited data available from the anancomeric derivatives (7–23). Using Lambert's R value[15,16] we obtain $R = J\,trans/J\,cis = 1.97$, indicative of an almost "perfect" chair conformation. Buy's equation[17] allows calculation of an internal ring torsion angle of 56.5 ± 2° about the C-5 to C-6 bond. This is in keeping with the internal ring torsion angles of most bonds in saturated six-membered rings. Torsion angles in the closely related tetrahydro-1,2-oxazines (2) have been measured.[2] Whilst the torsion angles in the alicyclic portion of the ring, C_3–C_6, are "normal" and in the region of 53–58°, the torsion angle about the N–O bond is

Table 2. Physical data on intermediates

	R_1	R_2	R_3	b.p.°/pressure (mm)
24	H	H		116–120/1.5
	Me	H		118–120/2
	Et	H		97–103/0.2
	Ph	H		145–150/1
	Me	Me		102/0.7
				96/0.5
	Me	Et		97–100/0.1
25	H	H		104–106/0.15
	Me	H		116–120/2
				107/1
	Et	H		100–105/0.25
	Ph	H		130–135/0.05
	Me	Me		102–103/0.25
	Me	Et		85/1
26	H	H	Me	77–84/0.8
				90/2
	H	H	Et	82–84/0.6
	H	H	i-Pr	100–105/0.15
	Me	H	Me	70/0.05
	Me	H	Et	85–94/0.6
	Me	H	Bz	120/0.05
	Et	H	Me	85/1
	Ph	H	Me	120/0.2
	Me	Me	Me	72–75/0.35
	Me	Me	i-Pr	55/0.075
				105–110/9
	Me	Et	Me	80–85/0.6

found to be 67°. This behaviour, which should also be found in the 1,4,2-dioxazine, arises from the torsional potential about N–O bonds, which is different in form (twofold barrier) and magnitude (*ca.* 10 kcal mole^{-1}) from those found about C–C or C-heteroatom bonds (threefold barrier generally <4 kcal mole). The dihedral angle in the 1,2-oxazine corresponding to the one we have measured in the dioxazine is found to be $56.2 \pm 0.4°$.

The ^{1}H and ^{13}C spectra of the compounds (4–23) are temperature dependent showing effects due to both ring and nitrogen inversion (Tables 3 and 4). Coalescences are observed in the temperature range -30 to $-70°$ and in general resonances due to two conformations differing in energy by *ca.* 1 kcal mole^{-1} are visible at the low temperature limit of our runs (*ca.* $-90°$). In order to interpret the spectral changes it is important to know which are the preferred conformations of this system and to identify the major and minor conformers observed in the low temperature spectra.

The conformations of the closely related tetrahydro-1,3-oxazines (3) have been investigated by Riddell and Lehn.[6,7] From studies of model compounds it was deduced that the geminal coupling constant at C-2 was a good indicator of the conformation at the N atom. This coupling was found to be 7.5 Hz when the N-alkyl group was equatorial and 10.5 Hz when axial.[7] Whilst these values are not expected to be exactly the same in the 1,4,2-dioxazine series, especially because of the greater electronegativity of the oxygen at position 1, and the greater torsion angle about the NO bond altering the relationship of the pair of electrons on nitrogen to the C(3) methylene group, they can serve as indicators. At the low temperature limit for compounds **10** and **11** major and minor doublets for the lowfield C(3) hydrogens are observed with couplings of 8.3 ± 0.2 and 11.2 ± 0.4 Hz respectively. By analogy with the tetrahydro-1,3-oxazines these couplings are best ascribed to the N-alkyl equatorial (major) and N-alkyl axial (minor) conformations respectively. The ambient temperature coupling *ca.* 8.5 Hz is therefore associated with a predominantly equatorial N-alkyl group (Table 3). In addition there is an extremely large chemical shift change of the C-2 hydrogen in the 2-*p*-nitrophenyltetrahydro-1,3-oxazines, on changing the orientation of the N substituent, of up to 1.41 ppm. This indicates that in the 2-*p*-nitrophenyl tetrahydro-1,4,2-dioxazines, the major conformer, with its C-3 hydrogen 1.12 ppm to high field of that of the minor conformer, contains an equatorial N-alkyl group whilst the minor conformer has an axial N-alkyl group. ^{13}C spectra also shed light on this problem (Table 4). At low temperatures peaks from the minor conformers are clearly visible in compounds 4 and 10. It is possible to use chemical shift additivity rules to make predictions as to the expected difference between the shifts of ring atoms in conformations containing axial and equatorial Me groups.[18,19] The relative positions of the observed peaks fit very well for conformations containing equatorial (major) and axial (minor) N-Me groups. We thus conclude that the major conformations have equatorial N-alkyl groups and the minor conformations have axial N-alkyl groups. Other conformations, if frozen out, are not visible in our low temperature spectra.

In the dynamic NMR experiment for exchange between two sites A and B the rate constant measured, k_{obs}, is the sum of the forward and reverse rate constants ($k_f + k_r$). If A and B are equally populated $k_f = k_r = k_{obs/2}$. If however the populations differ by a factor of (say) ten or more then $k_r \gg k_f$ and $k_r = k_{obs}$ and the observed rate constant is the greater of k_f and k_r. The observed free energy of activation at coalescence therefore corresponds to the change least stable conformer→transition state. In order to make the free energy of activation correspond to the change more stable conformer→transition state the free energy difference between the conformers must be added to the observed barrier. This point is of direct relevance in the 1,4,2-dioxazines where all barriers are most sensibly related to the change equatorial N-Me→transition state.†

The spectral changes in 4 as the temperature is varied have been reported by KCO.[11,12] Briefly, but using our data, the methylene group at C-3 splits into an AB quartet at $T_c = -39° \pm 3°$ ($\Delta G_c^{\ddagger} = 11.37 \pm 0.2$ kcal mole^{-1}) and the N-methyl group at lower temperatures splits into an unequal doublet with maximum broadening at $-61 \pm 3°$ ($\Delta G_c^{\ddagger} = 9.95 \pm 0.2$ kcal mole^{-1}).[20] The free energy difference at $-80°$ is 0.93 ± 0.05 kcal mole^{-1} giving a barrier eq N-Me→transition state of 10.88 ± 0.2 kcal mole^{-1}.

The conformational route maps for ring and nitrogen inversion in the dioxazines are shown in Schemes 2 and 3. In Scheme 2 slowing of either N_1 or R_1 would cause the ring hydrogens at C-2 to split into an AB quartet, whilst slowing of both N_1 and R_1 is required to split the N-Me peak in the ^{1}H spectrum or any of the carbon resonances in the ^{13}C spectrum. Although barriers to both processes have been measured it is not possible to assign their origin.

Scheme 3 depicts the conformational route map for molecules containing a 6-alkyl group. There can be no

†In the light of the above discussion the barriers to the lower energy process reported in Refs. 11, 12 presumably correspond to the change axial N-Me→transition state.

Table 3. ^{1}H NMR data†

Compound	T°	Chemical shifts (δ scale) C_3H	C_5H	C_6H	others	Coupling constants (Hz) J_{33}	J_{55}	J_{56}	other
4	+33.5	4.29		3.72 3.99	NMe 2.58	—		A_2B_2 system	
	−85	4.53 4.03	—	—	ax NMe 2.95 eq NMe 2.55	−8.5		$\begin{cases} J\ cis\ 3.1 \\ J\ trans\ 6.1 \end{cases}$	
5	+33.5	4.32		3.75 3.95	Et $\begin{cases} 2.75 \\ 1.15 \end{cases}$	—		A_2B_2 system $\begin{cases} J\ cis\ 3.1 \\ J\ trans\ 6.1 \end{cases}$	
	−78	4.60 4.09	—	—	—	−8.5		A_2B_2 system $\begin{cases} J\ cis\ 3.1 \\ J\ trans\ 6.1 \end{cases}$	
6	+33.5	4.46		3.72 3.96	i-Pr $\begin{cases} 3.08 \\ 1.12 \end{cases}$	—			
	−85	4.87 4.08				−8.5			
7	+33.5	4.97	—	—	NMe 2.33				
	−75	6.06(ax Me) 4.92(eq Me)	—	—	NMe $\begin{cases} \text{ax } 2.50 \\ \text{eq } 2.35 \end{cases}$				
8	+33.5	5.10	—	—	Et $\begin{cases} 2.49 \\ 1.05 \end{cases}$				
	−74	6.06(ax Et) 4.97(eq Et)	—	—	—				
9	+33.5	5.29	—	—	i-Pr $\begin{cases} 2.69 \\ 1.06 \end{cases}$				
10‡	+33.5	4.38 4.00	3.76(eq) 3.19(ax)	4.19	NMe 2.58 CMe 1.04	−8.9	−11.15	+10.10 +2.65	J_6Me 6.44
	−85	4.58 3.96 } Me eq 4.85 Me ax	—	—	NMe $\begin{cases} \text{ax } 2.99 \\ \text{eq } 2.62 \end{cases}$	−8.3(Me eq) −11.3(Me ax)			
11	+33.5	4.43 4.08	3.75(eq) 3.17(ax)	4.15		−8.9			
	−84	4.57 3.85 } Me eq 4.84 Me ax	—	—	—	−8.3(Me eq) −11.2(Me ax)			
13	+33.5	4.86	3.95(eq) 3.43(ax)	4.37	NMe 2.32 CMe 1.13				
	−70	5.90(ax Me) 4.77(eq Me)			NMe $\begin{cases} \text{ax } 2.51 \\ \text{eq } 2.37 \end{cases}$				
14	+33.5	5.00	3.96(eq) 3.44(ax)	4.31	—				
	−80	5.97(ax Me) 4.91(eq Me)	—	—	—				

15	+33.5	4.40 4.04	*ca.*3.81(eq) 3.21(ax)	*ca.*4.00	NMe 3.59	−8.9		
	−75	4.57 3.93	—	—	NMe{ax 2.97 eq 2.61	−8.5(Me eq)		
16	+33.5	4.83	*ca.*3.95 eq 3.42 ax	*ca.*4.10	NMe 2.30			
	−75	5.93(ax Me) 4.80(eq Me)						
17	+33.5	4.10	3.38	—	NMe 2.45 CMe 1.27			
	−75	4.57 3.85	3.62 3.34	—	CMe{1.51 1.14	−8.3	−11	
18	+33.5	4.23	3.33		C_6Me 1.20 i-Pr{2.75 1.04			
19	+33.5	4.60	3.48 3.70		NMe 2.22			
					CMe{ax 1.61 eq 1.15	—	−11	
20	+33.5	5.06	—	—	CMe{ax 1.53 eq1.10			
					i-Pr{2.50 1.01 0.94			
21	+33.5	4.48 4.17	3.90(eq) 3.50(ax)	5.10	NMe 2.66	−9.0	−11.4	10.2 3.0
	−75	4.60 4.08	3.95(eq) 3.57(ax)	5.10	NMe{ax 3.07 eq 2.66	−8.7	*ca.* −11.0	*ca.*11.0 *ca.*2.5
22	+33.5	5.02	4.12(eq) 3.89(ax)	5.28	NMe 2.41			
	−78	6.14(ax Me) 5.01(eq Me)						
23	+33.5	4.12 3.96	3.40 3.30	—	NMe 2.40 CMe 1.12	−8.5	−11.0	
					CEt{CH_2:1.96, 1.40 CH_3 0.88			
	−75	4.50 3.80	3.58 3.30		NMe 2.48	−8.5	−11.5	
					CMe{ax 1.43 eq 1.01			

†Values determined for *ca.* 10% w/v solutions in $CDCl_3$.
‡Values from a LAOCN3 fit of observed spectrum.

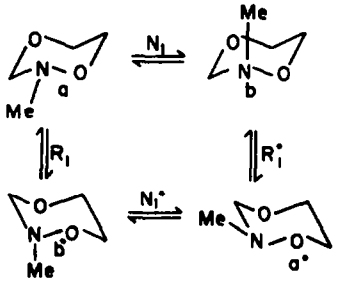
Table 4. ^{13}C Chemical shifts†

Compound	Temp	C_3	C_5	C_6	NMe	CMe
4	+25	87.43	64.82	66.87	39.78	-
4 major conformation	−95	87.10	63.76	67.82	39.88	-
4 minor conformation	−95	82.75	?	57.43	35.93	-
10	+25	86.49	70.34	70.91	39.80	15.16
10 major conformation	−80	86.70	69.60	72.73	40.19	15.00
10 minor conformation	−80	82.15	70.47	61.25	37.42	?

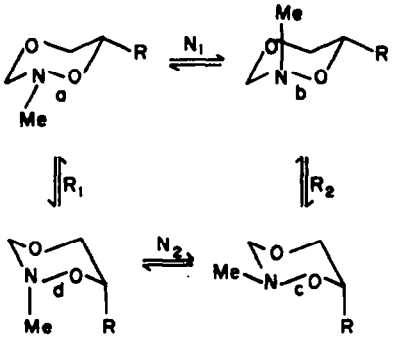
Expected changes on moving an N-Me from equatorial to axial are: C3 *ca.* −4, C5 *ca.* 0, C6 *ca.* −6, N-Me *ca.* 0 ppm. On moving a C6 from eq to axial the changes for 10 would be: C3 *ca.* 0, C5 ca. −4, C6 *ca.* 0, CMe *ca.* −4 ppm. Clearly the former provision fits the data better. Data taken from the most appropriate entries in Tables 5 and 6 (Ref. 18).

? resonance not ascribable (either hidden or not observed).

†Values ±0.05 ppm for *ca.* 20% w/v solutions in $CDCl_3$ measured downfield from TMS.



Scheme 2. Conformational route map for 2-methyltetrahydro-1,4,2-dioxazine.



Scheme 3. Conformational route map for 2-methyl-6-alkyltetrahydro-1,4,2-dioxazines.

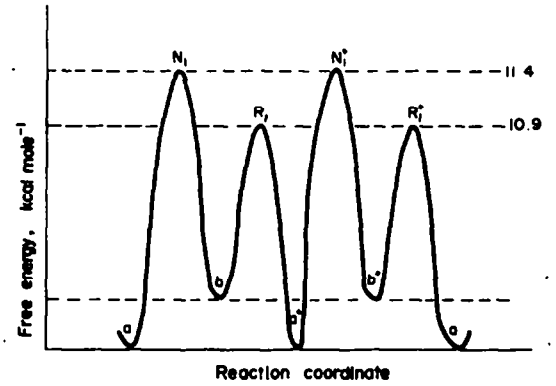


Fig. 1. Free energy changes associated with ring and nitrogen inversion in 2-methyltetrahydro-1,4,2-dioxazine, corresponding to Scheme 2.

doubt from our previous assignments that the major conformation is (a) and that the minor conformation is (b). Slowing of any one of the four different processes in Scheme 3 will lead to no spectral changes as all conformers may still interconvert rapidly. Two processes are required to be slow for the observed change which separates (a) and (b) to be explained. The only compatible pairs of slow rates are N_1R_1, N_1R_2 and N_1N_2. In all cases N_1 plus one other process must be slow on the NMR time scale if (a) and (b) are to be observed separately at low temperature. The value for the barrier a→b (corrected as described above) is measured to be 11.49 ± 0.2 kcal mole^{-1} for 10 and 11.55 ± 0.2 kcal mole^{-1} for 11. *The barrier to process* N_1 *must therefore be at least* 11.5 *kcal mole*$^{-1}$. These values are so close to the barrier observed for the higher energy process in 4 as to imply a common origin.

Figure 1 shows schematically the energy barrier changes around the ring and nitrogen inversion route map presented in Scheme 2. In this graph, following the argument above, N_1 is shown as the larger barrier and R_1 as the smaller.

There is no steric or electronic reason to expect that in Scheme 3 the energy change from (a) to the transition state N_1 should differ much from the energy change (c)→transition state N_2. Since (c) is known to be higher in energy than (a) the transition state N_2 should therefore be higher than N_1. The energy changes for ring and nitrogen inversion in 10 and 11 are shown schematically in Fig. 2. The first process to be frozen out involves passage over the barrier N_2. This is not observable by NMR spectroscopy because all conformations continue to interconvert via the lower barriers R_1, R_2 and N_1. The next process to be frozen out is N_1, which separates (a and d) from (b and c). The rate constant observed from the coalescence measurements corresponds to (b)→N_1, therefore the observed barrier and the free energy difference between (a) and (b) must be added to measure the barrier height relative to (a). Freezing out of the ring inversions (a)→(d) and (b)→(c) will give rise to no spectral changes because of the low amounts of (d) and (c) present.

Examination of the process observed in the trimethyl derivative (17) also leads to a similar conclusion regarding the relative magnitudes of ring and nitrogen inversion barriers. Geminal substitution is known to raise barriers to ring inversion in heterocyclic compounds by 0.4–1.0 kcal mole^{-1},[21,22] but would be expected to have little effect upon nitrogen inversion. The barrier observed in 17 averaged from the three separate coalescences is

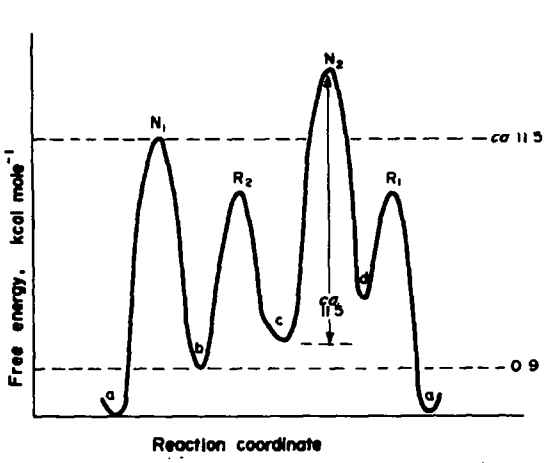


Fig. 2. Free energy changes associated with ring and nitrogen inversions in 2-methyl-6-alkyltetrahydro-1,4,2-dioxazines, corresponding to Scheme 3.

11.15 kcal mole^{-1}. If the 11.37 kcal mole^{-1} barrier in 1 were due to ring inversion the observed barrier in 17 should be substantially greater than that observed. This evidence therefore also points to the 11.37 kcal mole^{-1} process arising from nitrogen inversion.

These results lead us inescapably to the conclusion that the barrier to N-Me *inversion in the tetrahydro-1,4,2-dioxazines is* 11.4 ± 0.2 *kcal mole*$^{-1}$ *and that the barrier to ring inversion is somewhat less than this, ca.* 10.9 ± 0.2 *kcal mole*$^{-1}$.

In their empirical scheme for the prediction of nitrogen inversion barriers in 6-membered rings KCO took the value 10.2 kcal mole^{-1} as the barrier to nitrogen inversion in 4.[13] As we have demonstrated above this figure probably represents the ring inversion barrier of the axial N-methyl conformation. If the correct barrier for nitrogen inversion, *ca.* 11.4 kcal mole^{-1}, is inserted into a linear regression analysis of the data presented in Ref. 14 the overall fit is improved considerably from that found earlier, some of the parameters are altered, but the overall general conclusions are unchanged. The barrier in N-methyl-piperidine is found to be *ca.* 8.85 kcal mole^{-1}. This is 0.78 kcal mole^{-1} less than calculated previously,[14] and closer to the suggested barrier of Kessler and Liebfritz (7.8–8.0 kcal mole^{-1}),[23] but substantially greater than that of KCO (6.4 kcal mole^{-1}).[13] However, the fact that merely altering one piece of data can alter the calculated parameter for N-Me inversion by so much suggests, as one might expect, that the parameters obtained from these analyses are very heavily dependent on the input data, and therefore should not be relied on too heavily for making predictions. Furthermore, there is evidence in this paper to suggest that linear additivity which is the basis for the schemes proposed in Refs. 13 and 14, does not hold for the barriers to nitrogen inversion in the dioxazines. The effect of introducing a 3-*p*-nitrophenyl is to raise the barrier to nitrogen inversion of a Me group by *ca.* 0.6 kcal mole^{-1}. The same structural change has no effect on the inversion barrier of an N-Et group. Linear additivity clearly does not hold in these cases (Table 5).

The data obtained in this work allow estimates to be made of the values of the axial-equatorial free energy differences of N-alkyl groups in the 1,4,2-dioxazine ring. It is now widely believed that the free energy difference in N-Me piperidine is *ca.* 2.7 kcal mole^{-1}.[20,24,25] By contrast the axial and equatorial conformations of N-methyltetrahydro-1,3-oxazine are almost equally populated ($\Delta G = 0.0 \pm 0.35$ kcal mole^{-1}).[6,7] This lowering of the free energy difference by some 2.7 kcal mole^{-1} arises from two effects: firstly replacement of a methylene group by oxygen reduces the non bonded interactions of the axial N-Me group and secondly, an "anomeric effect",[26] be it electronic or dipolar in nature, lowers the energy of the N-methyl axial conformation.[6,7] KCO have claimed that the free energy difference in N-methyl-tetrahydro-1,2-oxazine is 1.9 kcal mole^{-1},[5] although as we shall see this estimate is probably too low.

Table 6 presents the free energy differences obtained by ourselves and KCO. Extracting weighted average values from this table gives free energy differences of Me, 0.93 ± 0.05, Et, 0.72 kcal mole^{-1} in the absence of 3-*p*-nitrophenyl, and Me 1.17 ± 0.1, Et 0.89 ± 0.1 kcal mole^{-1} with a 3-*p*-nitrophenyl group present. Several features worthy of comment stand out. It is easier (*ca.* 0.25 kcal mole^{-1}) to put an Et group axial than a methyl. A similar, but smaller effect has been observed before in

Table 5. Rate data for ring and nitrogen inversion from coalescence measurements

Compound	Resonance observed	Process assigned	Tc†	$\Delta G_c^{\ddagger}$ ± 0.2 kcal mole^{-1}‡
4	C_3H	NMe inv.	−39 ± 3	11.37
	NMe	ring inv.	−61 ± 3	10.88
10	NMe	NMe inv.	−48 ± 4	11.49
15	NMe	NMe inv.	−49 ± 3	11.55
21	NMe	NMe inv.	−49 ± 2	11.38
5	C_3H	NEt inv.	−48 ± 3	11.01
6	C_3H	NiPr inv?	*ca.* −60	*ca.* 10.2
7	C_3H	NMe inv.	−31 ± 2°	12.04
13	C_3H	NMe inv.	−31 ± 3°	12.22
16	C_3H	NMe inv.	−29 ± 4°	12.20
22	C_3H	NMe inv.	−35 ± 3	11.78
8	C_3H	NEt inv.	−47 ± 3	11.10
14	C_3H	NEt inv.	−51 ± 3	10.85
17	C_3H	NMe inv.	−40 ± 2	11.18 } average
	C_5H	NMe inv.	−48 ± 2	11.06 } 11.15
	C_6Me	NMe inv.	−46 ± 2	11.21 } ± 0.1

†Coalescence temperature or temperature of maximum broadening (ref 20).
‡Corrected for equatorial conformation → transition state.

Table 6. Conformational free energy differences on nitrogen

Compound	N substituent	ΔG° kcal mole^{-1}	T°C	Ref.
4	Me	0.93 ± 0.05	−80	
		1.03	−82	11
10	Me	1.01 ± 0.05	−75	
		0.85 ± 0.1	−81	^{13}C spectra This work
15	Me	0.96 ± 0.05	−75	
21	Me	0.84 ± 0.05	−78	
7	Me	1.12 ± 0.1	−75	
13	Me	1.30 ± 0.1	−70	
16	Me	1.20 ± 0.1	−75	
22	Me	1.05 ± 0.1	−78	
5	Et	0.72	−82	11
8	Et	0.92 ± 0.1	−76	
14	Et	0.85 ± 0.1	−80	

Best fit values NMe in absence of 3-pNO_2Ph 0.93 ± 0.05 NEt in absence of 3-pNO_2Ph 0.72 NMe with 3-pNO_2Ph 1.17 ± 0.1 NEt with 3-pNO_2Ph 0.89 ± 0.1. All values from ^{1}H spectra in this work unless otherwise indicated.

the 5-alkyl-1,3-dioxane series.[27,28] In the presence of a 2-*p*-nitrophenyl group it is slightly more difficult (*ca.* 0.2 kcal mole^{-1}) to put an N-alkyl group axial. This effect probably arises from slightly different gauche torsional interactions about the N-C(3) bond in the axial and equatorial conformations. Also the orientation of the *p*-nitrophenyl to the dioxazine ring will vary with the axial or equatorial nature of the N-substituent.

If we accept, as suggested earlier, that there is a lowering of the energy of the axial conformation of *ca.* 2.7 kcal mole due to the presence of O(4), we can predict that the free energy difference in N-methyltetrahydro-1,2-oxazine should be *ca.* 2.7 + 1.0 = *ca.* 3.7 kcal mole^{-1}. This is roughly twice the value suggested by KCO from dipole moment studies.[5]

The low temperature spectrum of compound 23 allows a qualitative estimate to be made of the relative ease of putting Me groups axial in the 6-position. Tl lower field C6 Me was of somewhat lower intensity than the higher field Me. In the 1,3-dioxan series axial Me groups at C5 (analogous to C6 in the dioxazines) resonate at lower field than equatorial Me groups. It follows therefore that more Me's are equatorial than axial, and that it is therefore slightly easier to put an Et group axial in this position.

Therefore it appears that at both positions 2 and 6 in the ring it is easier by a small margin to put an Et group axial than a Me. Both positions on the ring have O atoms in α and β positions. The αO atoms will lower the vicinal interactions in one of the set of (three) axial Et conformations, lowering the total energy of the set and reducing the axial equatorial free energy difference of an ethyl group.

EXPERIMENTAL

Preparation of diesters (24) as illustrated by the preparation of diester (24; R_1=Me, R_2=R_3=H) from N-hydroxyurethane and ethyl 2-bromopropionate.

A soln of N-hydroxyurethane (52.5 g; 0.5 mol) in abs EtOH (50 ml) was added to a well stirred soln of KOH (28 g; 0.5 mol) in abs EtOH (25 ml). To the resultant soln was added a soln of ethyl 2-bromopropionate (90 g; 0.5 mol) in abs EtOH (100 ml); and the soln was heated under reflux for 3 hr. The cooled soln was decanted from the ppt of KBr which was washed with EtOH (2 × 50 ml). The mixture and extracts were combined and solvent was removed by rotary evaporation to leave a pale yellow oil. This oil was washed with water (50 ml) and the aqueous washings extracted with ether (50 ml). The combined organic fractions were dried (Na_2SO_4) and solvent evaporated. Distillation afforded the diester as a colurless oil, b.p. 118–120°(73 g, 71%).

Reduction of di-esters. Reduction of the di-esters (24) with LAH to give the alcohols (25) as illustrated by the reduction of 24 (R_1=ME, R_2=R_3=H) to the corresponding alcohol.

A soln of 24 (R_1=Me, R_2=R_3=H) (73 g; 0.395 mol), in anhyd ether (150 ml) was added slowly to a stirred cooled suspension of LAH (26.4 g; 0.695 g) in anhyd ether (800 ml). Addition was controlled so as to maintain the mixture at below 5°. After stirring for 5 hr, solid CO_2 (100 g) and then water (48 ml) were added and the mixture stirred until the separated solids were completely white (2 hr). The ethereal layer was decanted and the residue washed with ether (3 × 300 ml). The combined organic fractions were evaporated and distilled. The alcohol boiled at 116–20°/2mm (31 g, 48%).

N-alkylation. The alcohols 25 were converted to their corresponding N-alkyl derivatives (26) by treatment with alkyl halides and K_2CO_3 in anhyd acetone. Alkylation with MeI generally required under 24 hr reflux, with EtI and i-PrI correspondingly longer periods (up to 1 week) were required. A typical alkylation is the conversion of the alcohol (25; R_1=Me, R_2=R_3=H) into the corresponding N-Et compound (26; R_1=Me, R_2=Hm R_3=Et).

A mixture of 25 (R_1=Me, R_2=R_3=H: 10 g), anhyd K_2CO_3 (50 g), EtI (50 g) and dry acetone (150 ml) was heated under reflux for 48 hr. The hot suspension was filtered and the solid residue washed with warm dry acetone (2 × 100 ml). The combined organic fractions were evaporated and the residual yellow oil distilled. N-carbethoxy-N-ethyl-2-(aminohydroxy)-propan-1-ol boiled at 85–94°/0.6 mm (8.5 g, 73%).

Decarbethoxylation. The procedure first adopted for decarbethoxylation involved acid hydrolysis and decarboxylation in one step, and is exemplified by the transformation of 26 (R_1=Me, R_2=H, R_3=Et) to 27 (R_1=Me, R_2=H, R_3=Et).

Procedure A. A suspension of 26 (R_1=Me, R_2=H, R_3=Et: 8.5 g) in water (20 ml) and HCl (20 ml: *d*.1.16) was heated under reflux until evolution of CO_2 had ceased (5 hr). The cooled, orange, soln was washed with ether (50 ml) and evaporated *in vacuo*. The residual dark oil was dissolved in water (10 ml) and made basic by addition of NaOH pellets. The free amine was extracted into ether (3 × 10 ml). The combined extracts were dried (Na_2SO_4) and evaporated cautiously to give 27 (R_1=Me, R_2=H R_3=Et) as a brown free-flowing liquid, yield 4.8 g (91%).

With urethanoalcohols in which R_1=Ph or R_1=R_2=alkyl, procedure A gave intractable tars. With these compounds, decarbethoxylation was accomplished by the procedure exemplified below for conversion of 26 (R_1=Me, R_2=Et, R_3=Me) into 27 (R_1=Me, R_2=Et, R_3=Me).

Procedure B. A mixture of 26 (R_1=Me, R_2=Et, R_3=Me: 4 g) and

NaOH (1.5 g) in water (30 ml) containing sufficient MeOH to ensure soln, was heated under reflux for 1 hr, treated with AcOH until the pH was just below 6, then heated under reflux for a further 30 min. The soln was rotary evaporated and the crude amine liberated as in procedure A, yield 1.9 g (73%).

These aminoalcohols were not further purified but used in their crude states in the cyclisation steps.

Cyclisation reactions. The amino alcohols (**27**) were cyclised to give the corresponding tetrahydro-1.4.2-dioxazines by condensation with paraformaldehyde or *p*-nitrobenzaldehyde in benzene. In some cases (R_1=R_2=Alkyl, or R_1=Ph) reaction was very slow unless a catalytic amount of toluene-*p*-sulphonic acid was added.

(A) *With formaldehyde.* A soln of **27** (R_1=R_2=R_3=Me; 900 mg) in dry benzene containing paraformaldehyde (350 mg) and toluene-*p*-sulphonic acid (5 mg) was heated under reflux using a Dean–Stark water trap. When the condensate was homogeneous the mixture was cooled and the excess paraformaldehyde removed by filtration. The benzene was removed by slow distillation on a Vigreux column and the residue distilled under reduced pressure. 2,6,6-trimethyl-tetrahydro-1,4,2-dioxazine boiled at 100°/70 mm, yield 760 mg (77%).

(B) *With p-nitrobenzaldehyde.* A soln of **27** (R_1=R_2=R_3=Me; 300 mg), *p*-nitrobenzaldehyde (375 mg) and toluene-*p*-sulphonic acid (5 mg) was heated under reflux as in section A above. The orange crystalline mass obtained on removal of solvent was recrystallized from light-petrol and ether to give the dioxazine as slightly yellow prisms: m.p. 111–112°; yield 550 mg (86%).

NMR spectra. ^{1}H NMR spectra were recorded on *ca.* 10% w/v solns in $CDCl_3$ on a Perkin Elmer R32 (90 MHz) instrument. Low temperature limit spectra (−80 to −90°) are of supercooled solutions. Calibration over the entire temp range showed dial settings of temps to be accurate to within 1.5° and reproducible to ±0.5°. ^{13}C spectra were recorded on *ca.* 20% w/v solns in $CDCl_3$ on a Varian XL100 spectrometer in Edinburgh University. Relative amounts of conformations were determined by planimetry of the low temperature ^{1}H spectra (most cases), or by cutting and weighing of stout card (16 and 22).

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