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

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Abstract—The synthesis and variable temperature ^1H and ^{13}C NMR spectra of three tetrahydro-1,2,4-oxadiazines are reported. The N(4)-Me inversion barriers are 6.8–7.0 (ax→ts) and 7.4–7.9 kcal mol^{-1} (eq→ts) with $\Delta G°$ 0.6–0.9 kcal mol^{-1}. The N(2)-Me inversion barriers are 10.4–11.4 (ax→ts) and 11.6–13.1 kcal mol^{-1} (eq→ts) with $\Delta G°$ 1.2–1.7 kcal mol^{-1}. The barrier to ring inversion is *ca.* 12.7 kcal mol^{-1}. "R value" analysis shows the ring to have a 56.5 ± 2° dihedral angle about the C(5)–(6) bond, indicative of the expected chair conformation.

The conformational analysis of molecules capable of undergoing any one of several different conformational changes presents a fascinating and complex problem. Such a system is the tetrahydro - 1,2,4 - oxadiazine ring (1), whose synthesis two of us have reported recently.[1] This ring may undergo any one of three different conformational processes, *viz.* ring inversion, or inversion at either of the two different N centres. Of added interest is the study of the positions of the conformational equilibria associated with substituents on both N atoms. Thus we are searching for three activation energies and two free energy differences in our conformational analysis of 1. We now believe that we have evaluated all five parameters for the dimethyl derivative (1a).

The differentiation between ring and N inversion in this and related heterocyclic systems is a matter of some current concern. That the assignation of processes observed in NMR spectral experiments to their origins is not always easy, is illustrated by the conflicting literature on the hexahydropyridazines (2)[2–5] and the hexahydro - 1,2,4,5 - tetrazines[6–8] before the problems in each system were solved.[5,8]

Of enormous use in solving conformational problems of this sort are the equations for the dynamic interpretation of NMR line broadening phenomena developed by Anet, and first used in conjunction with one of our research groups to establish $\Delta G°$ and $\Delta G^{\neq}$ for N inversion in a hindered piperidine.[9] In this paper we make use of these equations to derive free energies of activation and free energy differences from the broadening of ^{13}C spectral lines. Since the Anet equations give the rate constant, and hence the activation energy for the process least stable conformation→transition state we shall report $\Delta G°$ and $\Delta G^{\neq}$ (minor→ts) and correct the $\Delta G^{\neq}$ value by adding $\Delta G°$ to give the activation energy for ground state conformation→transition state. All N inversion barriers quoted in this paper are therefore designated (eq→ts) or (ax→ts) to avoid confusion and we recommend that other workers follow this practice.

Systems closely related to tetrahydro - 1,2,4 - oxadiazine that have been studied include the tetrahydro - 1,2 - oxazine ring (4),[10–15] the 1,3-diazine ring (5)[16–20] and the tetrahydro - 1,4,2 - dioxazine ring (3).[21–24] Results on 2 - methyltetrahydro - 1,4,2 - dioxazine indicate a ring inversion barrier of 10.9 kcal mole^{-1} and a N inversion barrier (eq→ts) of 11.4 kcal mole^{-1}.[24] The two processes were clearly distinguishable in the ^1H NMR spectra by their differing coalescences. Changing from the 1,4,2-dioxazines (3) to the 1,2,4-oxadiazines (1) involves replacement of O(4) by an N-Me group. This change is expected to raise the barrier to ring inversion by over 1 kcal mole^{-1}.[25] The (eq→ts) barrier to N inversion at N(2) is also expected to be higher in 1 than in 3, because β-nitrogen and β-oxygen substituents *lower* the eq→ts barrier[26] (they *raise* the ax→ts barrier[27]), but the effect of N(4) should be less than that of O(4).[23] Thus we expect the barriers to ring and N(2) inversion to be greater in the oxadiazines (1) than in the dioxazines (3), but for a quantitative evaluation of effects it is essential to distinguish between them.

The synthesis of the tetrahydro - 1,2,4 - oxadiazines is outlined in Scheme 1. The tosylates (7) of the hydroxylaminoalcohols (6)[24] were stirred at room temperature with aqueous methylamine. With short reaction times the amines (8) could be isolated. With longer reaction times or more vigorous conditions the ureas (9) were formed. Hydrolysis and decarboxylation of 8 gave rise to 10 which could be condensed with formaldehyde or paranitrobenzaldehyde to give derivatives of 1. It was however simpler to allow the urea (9) to form and then to reduce it with LAH to the oxadiazine derivatives (1, R_3 = H).

The tetrahydro - 1,2,4 - oxadiazines show the expected ambient temperature ^1H spectra, consistent with rapid inversion of ring and N atoms (Table 1). The C(5,6) region shows an approximate A_2X_2 spectrum with two five line resonances. Analysis gives J_{cis} = 3.23 Hz and J_{trans} = 6.41 Hz from which R = 1.98 and the internal ring dihedral angle = 56.5 ± 2°[28,29] identical to that found in the dioxazines[24] and in keeping with the internal torsion

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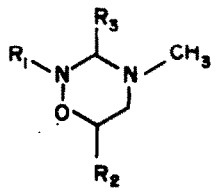

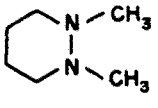

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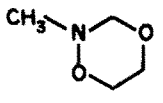
1a: $R_1 = CH_3$, $R_2 = H$, $R_3 = H$
1b: $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = H$
1c: $R_1 = iPr$, $R_2 = H$, $R_3 = H$



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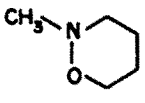

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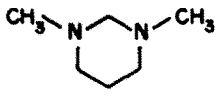

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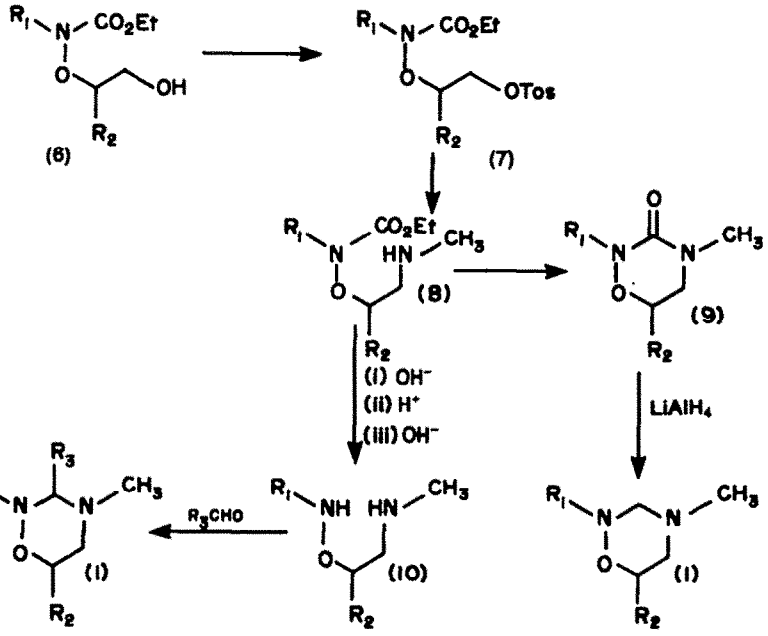


Scheme 1.

angles in most normal chair conformations of saturated 6-membered rings.

The conformational route map for N,N' - dimethyltetrahydro - 1,2,4 - oxadiazine (**1a**) is shown in Scheme 2. Vertical directions indicate ring inversion, horizontal directions indicate N inversions. It is expected that the most rapid processes will be inversions of N(4).[20]

The ^1H spectra of **1a** in $CDCl_3$ show a coalescence phenomenon involving the C(3) hydrogens (singlet → AB quartet) at $-8 \pm 3°$ ($\Delta G_c^{\ddagger}$ 12.7 ± 0.2 kcal mole^{-1}). The ^{13}C spectra show two broadening and resharpening phenomena at *ca.* −20° and *ca.* −112°.

Assignment of the ^{13}C proton noise decoupled spectrum of **1a** which consists of five resonances (Table 2), follows from an off resonance decoupled spectrum to distinguish between Me's and methylenes. The methylene carbon resonances were identified from their chemical shifts, and the Me's from their broadening phenomena. The low temperature effect (*ca.* −112°) involves the C(6) and one of the Me signals. It is known that N-inversion in 1,3 - dimethyl - 1,3 - diazane (**5**) becomes slow in the same temperature range (*ca.*−120°) separating the major (diequatorial) conformation from the minor (axial-equatorial) conformation.[20] Thus the low temperature effect in **1a** refers to slowing of the N(4) inversion process, leads to an assignment of the 4-Me resonance, and refers to separation of the 2e4e and 2e4a conformations. The higher temperature process involves the broadening and resharpening of the C(6) and the other N-Me signal at *ca.* −20°. This process is thus compatible with the slowing of any combination of processes in Scheme 2 that would isolate the 2e4e conformation from the 2a4e conformation.

Using chemical shift data derived from the low temperature spectra of **5**[20] and the Anet equations[9] these dynamic phenomena may be quantitatively studied

Table 1. ^{1}H NMR results for *ca.* 10% w/v solutions in $CDCl_3$

Compound	T°	Chemical Shifts (δ scale)					Coupling Constants (Hz)
		C3H	C5H	C6H	4 Me	Other	
1a R_1=CH_3,R_2=H,R_3=H	+35	3.26	2.49	3.96	2.31	2Me 2.55	Jcis 56 = 3.23 J trans 56 = 6.41
	-50	3.73 2.85					J33' = 9.5
1b R_1=CH_3,R_2=CH_3,R_3=H	+35	eq 3.83 ax 2.82	eq 2.72 ax 2.72	4.12	2.31	2Me 2.56 6Me 1.10	J33' 9.5, J3e5e 1.4, J5e5a 11.2, J5e6e 2.5 J5a6a 10.0, J6aMe 6.2
1c R_1=iPr,R_2=H,R_3=H	+35	3.34	2.46	3.94	2.29	iPr doublet 1.08 septet 2.89	Jcis 56 = 3.23, Jtrans 56 = 6.41
	-70	eq 3.90 ax 2.87					J33' = 9.5
1d R_1=CH_3,R_2=H,R_3 =pNO_2Ph	35°	3.55	eq ca 2.91 ax ca 2.50	eq ca 3.96 ax ca 4.35	1.95	2Me 2.24	
1e R_1=CH_3,R_2=CH_3,R_3 =pNO_2Ph	35°	3.47	eq ca 2.93 ax ca 2.10	4.32	1.92	2Me 2.2 6Me 1.17	J55 11.2, J5a6a 10.2, J5e6a 2.4

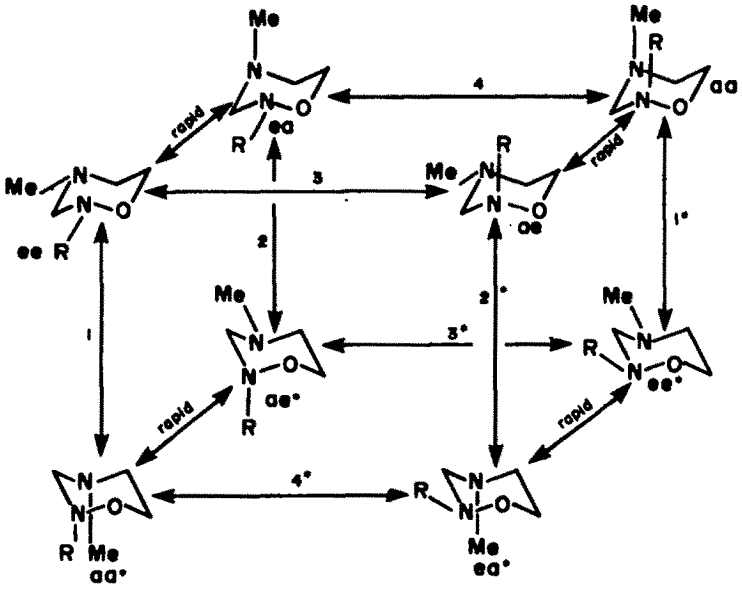
Table 2. Proton noise decoupled ^{13}C NMR shifts at high and low temperatures in the tetrahydro-1,2,4-oxadiazines*

	Compound							
	1a[a]			1b[b]			1c[b]	
Signals	+12°C	-50°C	-132°C	+10°C	-50°C	-144°C	+31°C	-62°C
N(2)-C	43.3	43.5	43.2	43.2	43.2	43.4	C 54.4	54.9
							$C-\underline{C}H_3$ 19.5	(19.7 (19.5
C(3)	81.4	81.2	80.9	80.5	80.3	80.0	76.3	76.6
N(4)-C	42.5	42.6	42.9	42.4	42.4	42.7	45.5	42.7
C(5)	54.0	53.8	53.7	60.8	60.3	60.2	54.4	54.2
C(6)	67.4	67.6	67.9	71.5	71.9	72.8	67.2	67.5
C(6)-C	-	-	-	17.8	17.7	17.8	-	-

a Solvent: CF_2Cl_2/acetone-d_6;

b Solvent Acetone-d_6: A spectral width of 4005 Hz and 16384 data points were used (digital resolution = 0.24Hz).

* All shifts in ppm downfield from TMS.



Scheme 2.

(Table 3). For the first broadening effect $\Delta G^\circ = 1.6$ kcal mole^{-1} in favour of 2e4e and $\Delta G^{\neq}$ 11.3 kcal mole^{-1} for the N(2) inversion (ax→ts). Hence $\Delta G^{\neq}$ (eq→ts) is 12.9 kcal mole^{-1}, a value very similar to that obtained from the ^1H spectra. The second broadening effect gives $\Delta G^\circ = 0.9$ kcal mole^{-1} in favour of 2e4e and $\Delta G^{\neq}$ 7.0 kcal mole^{-1} for the N(4) inversion (ax→ts), and hence $\Delta G_e^{\neq}$ (eq→ts) is 7.9 kcal mole^{-1}. There is excellent agreement between the last set of results and those recently obtained for 5 by the Norwich group.[20]

An analysis of the possible combinations of slow processes and their compatibility with the observed spectral changes is given in Table 4. It can be seen that the sole necessary criterion for observation of the -20° ^{13}C phenomenon is that processes 1, 2, 3 and 4 in Scheme 2 be slow. Other combinations could account for the ^1H result. Indeed any combination of three slow processes is a sufficient condition for the ^1H observation. The ^1H and ^{13}C observations must therefore arise from different combinations of processes. If we now undertake the not unreasonable speculation that transition states 4 and 2, referred in energy to 2e4e, will be higher than their analogues 3 and 1, because they "start" from higher energy conformations that are in rapid equilibrium with the ground state, we may deduce that the processes 4 and 2 will be "frozen out" before processes 3 and 1. Our

Table 3. Broadening data[a] from the ^{13}C DNMR of the tetrahydro-1,2,4-oxadiazines

Compound	1a[b]		1b					1c			
Parameter	C(6)		C(6)	N(2)–C	C(5)	C(3)	C(6)	N(2)–C	$N(2)-OCH_3$	C(3)	
t_c (°C)	-20	-112	-17	-116	-17	-121	-123	-39	-41	-46	-46
$\Delta w_{\frac{1}{2}}$ (H_z)	5.5	7.7	4.9	17.1	1.2	9.8	7.3	9.6	-g	-h	4.5
$\Delta\nu$(ppm)[c]	5.7	5.7	5.7	5.7	3.6	3.0	3.0	5.7	3.6	0.2	3.0
Pop (%)[d]	4	5.4	3.4	12.0	4.0	13.0	10.0	6.7	-	-	6.0
ΔG^0(±0.1 kcal mol^{-1})[e]	1.6	0.9	1.7	0.6	1.6	0.57	0.66	1.22	-	-	1.24
$\Delta G_c^{\ddagger}$(±0.2 kcal mol^{-1})[f]	11.3	7.0	11.4	6.9	11.7	6.82	6.72	10.4	-	-	10.4

a Using Anet equations (ref 9)

b Signals N(2)–C (t_c = -25°C) and N(4)–C (t_c=-116°C) also show broadening but overlap with each other precluded accurate assessment of $\Delta w_{\frac{1}{2}}$

c Obtained from low temperature 'frozen' spectrum of 1,3-dimethyl-1,3-diazane (ref 20)

d First coalescence, population of minor form ae: second coalescence, population of minor form ea: major form is ee

e First coalescence, in favour of ee+ea: second in favour of ea

f First coalescence, $\Delta G_c^{\ddagger}$ in direction ae to TS; second coalescence, $\Delta G_c^{\ddagger}$ in direction ea to TS.

g Overlap with C(5) shift precludes accurate assessment of $\Delta w_{\frac{1}{2}}$

h Total coalescence into two equal signals.

Table 4. Compatibility of combinations of "slow" processes in Scheme 2 with experimental observations

Combination	^1H compatibility	^{13}C compatibility
1,2	✓	x
1,3	x	x
1,4	x	x
2,3	x	x
2,4	x	x
3,4	✓	x
1,2,3	✓	x
1,2,4	✓	x
1,3,4	✓	x
2,3,4	✓	x
1,2,3,4	✓	✓

✓ = compatible x = incompatible

observations therefore refer to 3 and 1 but we cannot assign them to the ^1H and ^{13}C processes on the basis of our results. However, since the ^1H and ^{13}C barriers are identical within experimental error we can say that barriers 3 and 1 are both *ca.* 12.7–12.9 kcal mole^{-1}. Therefore ring inversion in **1a** has a similar barrier to N(2) inversion.

To confirm this conclusion we synthesised 2,4,6 - trimethyltetrahydro - 1,2,4 - oxadiazine (**1b**). In this compound there are negligible changes in the ^1H spectrum on cooling. The ^{13}C spectra however again show two broadening and resharpening phenomena at temperatures almost identical to those observed before (*ca.* −17° and *ca.* −120°). The ^{13}C spectrum of **1b** was easily assigned by analogy with that of **1a**. The low temperature process ($\Delta G° = 0.6$; $\Delta G^{\neq} = 6.8$ kcal mole^{-1} (ax → ts) hence $\Delta G^{\neq}$ in the direction eq → ts = 7.4 kcal mole^{-1}) is associated with broadening of the N(4) Me and C(6) signals and clearly arises from inversion of the N(4) centre. The higher energy process ($\Delta G° = 1.7$; $\Delta G^{\neq}$ 11.4 kcal mole^{-1} (ax → ts) hence $\Delta G^{\neq}$ eq → ts = 13.1 kcal mole^{-1}) from broadening of the N(2) Me and C(6) signals, clearly arises from slowing of all modes of interconversion between 2e4e and 2a4e.

The conformational route map for this compound is shown in Scheme 3. If we accept the reasonable assumption that the activation energies in the lower half of the cube, related in energy to ee, will be higher than the related processes in the upper half of the cube, it is readily shown that the *ca.* 13.1 kcal mole process arises from inversion of the N(2) centre (eq → ts).

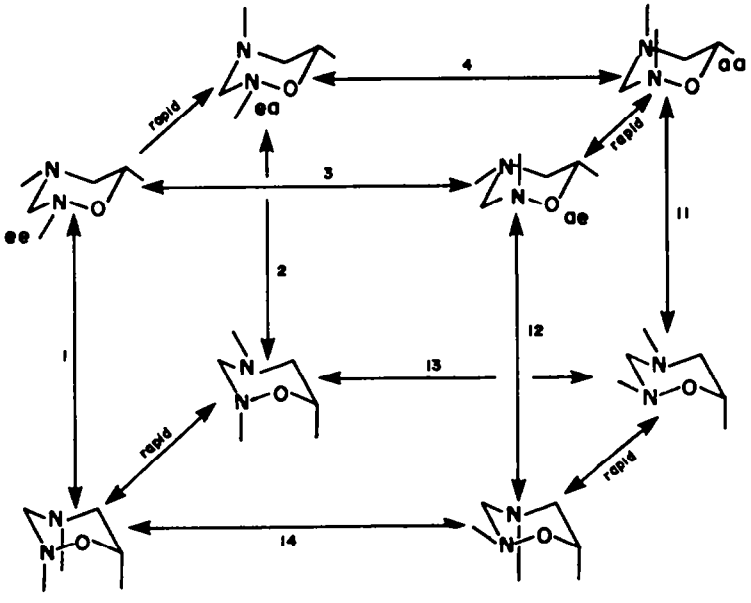
The ^1H spectra of the 2-isopropyl derivative (**1c**) in $CDCl_3$ shows a coalescence involving the C(3) hydrogens (singlet → AB quartet) at −15 ± 5° ($\Delta G_c^{\neq}$ 12.3 ± 0.3 kcal mole^{-1}).

The room temperature proton noise decoupled ^{13}C NMR spectrum in acetone d6 consists of 5 signals, the off resonance splitting of which shows that N(2)–Ç and Ç(5) have coincident chemical shifts at high temperature (+31°). As the temperature is lowered, signals due to the Ç(6), N(2)–Ç, N(2)–C(ÇH_3)$_2$ and Ç(3) carbon atoms broaden in the region of −30° to −45°, the maximum broadening being observed for Ç(6)—the carbon γ to N(2)–C(CH_3)$_2$. Using Anet's equations, $\Delta G_c^{\neq}$ = 10.4 ± 0.2 kcal mol^{-1} (ax → ts) and ΔG_c° = 1.2 ± 0.1 kcal mol^{-1} (in favour of ee), hence $\Delta G_c^{\neq}$ eq → ts = 11.6 kcal mole^{-1}.

Comparing ΔG_c° for **1a** and **1c** (1.6 and 1.2 kcal mole^{-1}

Table 5. Physical and analytical data on products

Compound	R_1	R_2	R_3	MP or BP	m/e required	m/e found
1a	Me	H	H	140–145°/760mm	116.0949	116.0948
1b	Me	Me	H	145–150°/760mm	130.1107	130.1109
1c	iPr	H	H	176–178/760mm	144.1263	144.1283
1d	Me	H	pNO_2Ph	118–119°	237.1113	237.1112
1e	Me	Me	pNO_2Ph	131–133°	251.1271	251.1276
9	iPr	H	-	100–105/8mm	158.1056	158.1066



Scheme 3.

respectively), it appears that it is easier to place an N-isopropyl group axial than an N-Me group. This surprising effect has been observed previously for the N-Et substituent in 2-ethyl-1,4,2-oxadiazine[9] when compared to 2-methyl-1,4,2-oxadiazine.

It is quite reasonable that the ^1H and ^{13}C $\Delta G_c^{\neq}$ measurements should be different. As is shown in Table 4 at least one more process is required to be slow for the ^{13}C observation to be possible than for the ^1H observation. Changing from N-Me to N-i-Pr is expected to lower the free energy of activation for ring inversion by *ca.* 0.4 kcal mole^{-1} (i.e. 12.3 kcal mole^{-1})[30] whilst lowering the N inversion barrier probably by a greater amount.[26] Thus in compound 1c *ca.* 12.3 kcal mole^{-1} probably corresponds to ring inversion and *ca.* 11.6 kcal mole^{-1} probably corresponds to N inversion (eq → ts).

The activation parameters for N inversion in tetrahydro - 1,2 - oxazine have been studied in some detail by Riddell *et al.*[10-15] The free energy of activation (eq → ts) is now known to be *ca.* 14.4 kcal mole^{-1}. The conformational free energy difference of an N-Me group has been estimated as *ca.* 3.7 kcal mole^{-1}[24] leading to an estimate of the free energy of activation in the reverse direction (ax → ts) of 10.7 kcal mole^{-1}. When these results are correlated with the results in this paper for the oxadiazines and those found earlier for the dioxazines[9] the effect of β-heteroatoms on N inversion of equatorial substituents are clearly demonstrated to depend on whether we consider the eq → ts or ax → ts half barriers. A full discussion will be given later,[27] but both β-oxygen and β-nitrogen lower the eq → ts barrier (by *ca.* 3.0 and *ca.* 1.5 kcal mole^{-1} m respectively)† whereas β-nitrogen raises the ax → ts barrier by 0.6 kcal mole^{-1}.

EXPERIMENTAL

Hydroxylaminoalcohols (6). The preparation of these compounds followed established literature routes.[24]

Representative syntheses of other compounds are outlined below.

N,N' - *Dimethyl* - O - (1 - *aminoprop* - 2 - *yl*) - *hydroxylamine.* (10, R_1 = Me, R_2 = Me). A suspension of crude tosylate 7 (R_1 = Me, R_2 = Me; 7 g) obtained by treatment of 6 with *p*-toluene sulphonyl chloride in pyridine, in aqueous methylamine (40%; 30 ml) was stirred at ambient temp. for 1.5 hr. The resulting homogeneous soln was evaporated under reduced pressure and the residue was heated under reflux with 30% NaOH aq (40 ml) and sufficient EtOH to ensure soln, for 45 min. The soln was cooled, acidified with HCl (*d* 1.16) and heated under reflux for 30 min to ensure complete decarboxylation. The residue obtained after evaporating the soln to dryness was dissolved in water (3 ml) and extracted with CH_2Cl_2 (4 × 30 ml). The combined extracts were dried (K_2CO_3) and distilled to give 10 (R_1 = Me, R_2 = Me; 1.7 g) b.p. 60–65°/1 mm.

N,N' - *Dimethyl* - O - (2 - *aminoethyl*) - *hydroxylamine* (10 - R_1 = Me, R_2 = H). Treatment of 7 (R_1 = Me, R_2 = Me) as above gave 10 (R_1 = Me, R_2 = H) b.p. 80°/4 mm. If the reaction was conducted at 80° for 1 hr the acidification step resulted in no evolution of CO_2 and the urea 9 (R_1 = Me, R_2 = H) was isolated; ν_{max}^{film} 1650 cm^{-1}; b.p. 100–110°/3.5 mm.

2 - *Isopropyl* - 4 - *methyl* - 3 - *oxotetrahydro* - 1,2,4 - *oxadiazine* (9; R_1 = i-Pr, R_2 = H). The crude 7 (R_1 = i-Pr, R_2 = H; 14.2 g) was treated with aqueous methylamine (60 ml) at ambient temp. for 2 hr and then treated consecutively with base and acid as described above. Very little CO_2 was evolved. Work up as above gave the urea 9 (R_1 = i-Pr, R_2 = H; 4.8 g) b.p. 100–105°/8 mm. ν_{max}^{film} 1650 cm^{-1}.

2 - *Isopropyl* - 4 - *methyltetrahydro* - 1,2,4 - *oxadiazine* (9; R_1 = iPr, R_2 = H). A soln of the urea 9 (R_1 = iPr, R_2 = H; 1 g) in anhydrous ether (10 ml) was added dropwise over a period of 5 min to a stirred suspension of LAH (180 mg) in anhyd ether (15 ml). After stirring for 1 hr the suspension was treated with 50% NaOHaq until the inorganic solids precipitated out. The clear ether layer was decanted and the residual solids washed with ether (2 × 50 ml). The combined ethereal layers were evaporated and distilled to give 1 (R_1 = i-Pr, R_2 = H; 550 mg) b.p. 110°/760 mm.

Condensations of diamines with aldehydes. 10 → 1 were carried out according to literature precedent.[32]

NMR spectra. ^1H spectra were recorded on a Perkin–Elmer R32 (90 MHz) instrument in Stirling, using *ca.* 10% w/v solns. Temps are accurate to ±1.5° and reproducible to ±0.5°. ^{13}C spectra were recorded on a Jeol FX-100 spectrometer in Norwich on *ca.* 20% w/v solns. Spectra were normally run using an internal ^2H lock and employing a sweep width of 3005 Hz giving a digital resolution of 0.375 Hz. Temperatures are accurate to ±2°, and the temp. control units were checked with a copper constantan thermocouple inserted in a standard 10 mm Jeol FX-100 NMR tube.

†Two of us (FGR and EST) consider that this result together with the barrier-raising effect of the same heteroatoms in the α-position[26] provide a clear experimental demonstration of "charge alternation" brought about by electronegative substituents of the first row of the periodic table first predicted by MO calculations.[31]

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