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1,2-OXAZINE CHEMISTRY—IV

THE CONFORMATIONAL EQUILIBRIA IN 2,5- AND 2,4-DIMETHYLTETRAHYDRO-1,2-OXAZINES

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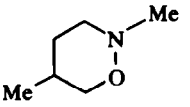
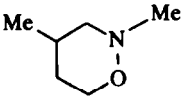
Abstract—The synthesis of 2,5-dimethyltetrahydro-1,2-oxazine via 5-methyldihydro-1,2-oxazine and the preparation of a pure sample of 2,4-dimethyltetrahydro-1,2-oxazine are reported. For the 2,5-dimethyl derivative low temperature (−40° to −45°) ^{1}H NMR measurements show signals from the *trans* (95%) and *cis* (5%) conformations. From this result it follows that an axial 5-Me group in a tetrahydro-1,2-oxazine ring is 5·7 ± 0·4 kJ mole^{-1} less stable than when equatorial. Low temperature measurements on the 2,4-dimethyl derivative fail to show any sign of the conformation with an axial Me group. These results in conjunction with earlier relative free energy difference measurements, give the following conformational free energy differences for Me groups on ring C atoms; C(4) 7·1 ± 1·0; C(3) 7·9 ± 0·8; C(6) 10·1 ± 1·6 kJ mole^{-1}.

In our previous papers in this series we have described investigations into the synthesis[1], structure[2] and conformational properties[3] of tetrahydro-1,2-oxazines. The X-ray crystallographic investigation[2] gave details of the geometry of this ring system showing the ring to adopt a chair conformation that is appreciably more puckered than cyclohexane. NMR measurements on appropriate derivatives at low temperatures, when nitrogen inversion is known to be slow on the NMR time scale,[4] enabled us to deduce the relative free energy differences of Me groups on the four ring C atoms.[3] It was apparent from this work that position 5 in the ring should have the least hindered axial Me group. However, we were at that time only able to obtain 2,5-dimethyltetrahydro-1,2-oxazine as the minor component in a mixture with its 2,4-dimethyl isomer. We were however, able to estimate that there should be less than 5% of the less favoured conformation present at −35°. We now report the synthesis and low temperature spectra of pure samples of 2,5-dimethyltetrahydro-1,2-oxazine (**1**), and 2,4-dimethyltetrahydro-1,2-oxazine (**2**).

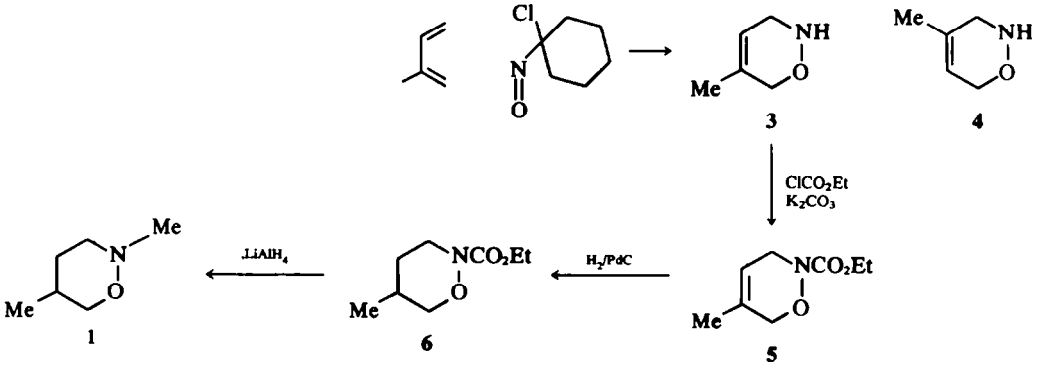


1



2

Since our previous synthetic route,[1] involving reaction of a 1,4-dibromide with N-hydroxyurethane had given a mixture of the 4- and 5-Me isomers, we turned our attention to the Diels Alder entry into this series.[5] Reaction of isoprene with 1-chloro-1-nitrosocyclohexane gives a mixture of 5-Me (80%) and 4-Me (20%) dihydro-1,2-oxazines as their hydrochlorides (**3** and **4**). Recrystallisation of this mixture from isopropanol gave the hydrochloride of **3** free from that of **4**. Conversion of **3** to its N-carbethoxy derivative **5**, catalytic hydrogenation of the double bond giving **6**, and finally LAH reduction gave the desired 2,5-dimethyl oxazine free from its constitutional isomer (Scheme 1).



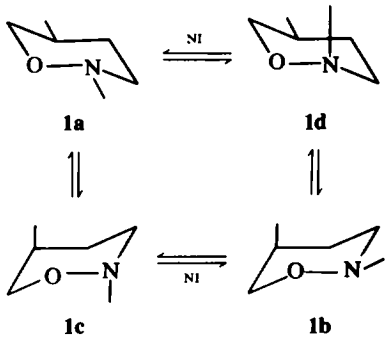
SCHEME 1

Although the structure of the major dihydro-oxazine obtained from isoprene was unknown for some years, Leonard *et al.*, converted it into the *cis* zeatin **7** of known constitution thus demonstrating the structure of **3**.[6] Although the synthesis of 2,5-dimethyltetrahydro-1,2-oxazine **1** further confirms this structure it may also be deduced from ^{1}H NMR decoupling experiments. The spectrum of the free base shows the expected resonances (Table 1) consistent with either **3** or **4**. There is evidence of considerable fine structure in all the resonances, but analysis is impossible due to the complex nature of the spin system and the small size of the coupling constants. With irradiation at the Me frequency the CH_2N resonance becomes a well defined doublet of triplets with splittings of *ca* 3·5 Hz (doublet) and *ca* 2·2 Hz (triplet). The 3·5 Hz coupling which can only be with the olefinic hydrogen, is only compatible with CH_2N next to the olefinic hydrogen i.e. **3** not **4**. The value of this coupling is very similar to that found in cyclohexene and similar systems (3·1 to 4·1 Hz).[7] Further decoupling experiments reveal an allylic coupling CH_2O to olefinic H of 1·6 Hz and a Me to olefinic H coupling also of 1·6 Hz. These values agree with those for similar systems.[7,8]

The structure of 2,5-dimethyltetrahydro-1,2-oxazine follows from its ^{1}H NMR spectra at 90 and 220 MHz. The resonance due to the CH_2O group shows a geminal splitting of 10·8 ± 0·3 Hz. The lowfield, equatorial, portion has additional gauche vicinal and long range couplings of < 4 Hz, whilst the highfield, axial, part has a larger trans vicinal splitting of *ca* 10·7 Hz. Clearly this resonance is consistent with a largely equatorial 5-Me group. Decoupling the C(4 and 5) hydrogens reduces the CH_2O resonance to a simple AB quartet. The CH_2N resonance, which surrounds the N-Me peak is slightly more complex. The geminal coupling is 11·2 ± 0·3 Hz with two additional splittings of *ca* 4 Hz (twice gauche vicinal) on the lowfield portion and 12·3 and *ca* 3 Hz (*trans* and *gauche* vicinal) on the highfield, axial, hydrogen. Again decoupling of the C(4 and 5) hydrogens reduces this resonance to a quartet.

The 2,4-dimethyl derivative **2** was obtained by the previously described route[1] which gives a mixture of **1** and **2** in which the latter predominates. Conversion of the mixed oxazines to the hydrochlorides and recrystallisation from isopropanol gave the hydrochloride of **2** which was converted to the free base by standard procedures.

The structure of the 2,4-dimethyltetrahydro-1,2-oxazine follows from its ^{1}H NMR spectra at 90 and 220 MHz. The lowfield (equatorial) C(3) hydrogen shows a 10·9 Hz geminal coupling and a 3·1 Hz vicinal coupling whilst the highfield (axial) C(3) hydrogen shows the 10·9 Hz geminal coupling and a 10·5 Hz vicinal coupling. This clearly shows the C(4) Me group to be equatorial.



SCHEME 2

The conformational inversion scheme in 2,5-dimethyltetrahydro-1,2-oxazine is shown in Scheme 2. Our reasons for believing those conformations with axial N-Me groups (**1c, d**) to be present in negligible amounts have been outlined before.[3] The conformational equilibrium in this compound is therefore between **1a** and **1b**.

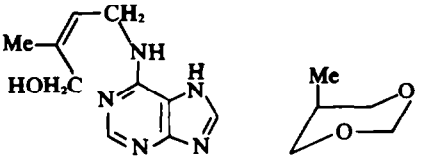
For solutions in CD_2Cl_2 and pyridine d_5, as the temperature is lowered the signal of the C-Me group in **1** undergoes changes consistent with a coalescence phenomenon. A small doublet separates from the main peak and sharpens by − 40°, where planimetry shows it to be 4·5 ± 1% of the total Me intensity in pyridine solution, and 5·5 ± 1% at − 45° in CD_2Cl_2 solution. We believe this small doublet to be due to the *cis* conformation with C(5)-Me axial for three main reasons. Firstly, it arises from a coalescence phenomenon involving broadening and subsequent sharpening of peaks as the temperature is lowered. Secondly, the coupling constant for the minor doublet 7·4 ± 0·3 Hz is greater than that of the equatorial Me 6·5 ± 0·3 Hz as would be expected for an axial Me group.[9] Moreover, both doublets collapse to singlets with decoupling of the C(4, 5) hydrogens. Finally, in the 1,3-dioxan series 5-axial Me groups are deshielded relative to 5-equatorial groups due to the proximity of the

Table 1. NMR spectral data on τ scale for *ca* 10% w/v solutions unless otherwise stated

Compound	Solvent	Temp.°	NCH_3	C(3)H	C(4)H	C(5)H	C(6)H	C(5)Me
1	*CD_2Cl_2	+23°	7·46	7·10, 7·52	8·26, 8·53	8·35	6·18, 6·55	9·16
	CD_2Cl_2	−40°	—	—	—		—	8·89, 9·15
1	Pyridine d_5	+33·5°	7·44	7·15, 7·50	8·2 to 8·8		6·15, 6·45	9·28
	Pyridine d_5	−40°						8·99, 9·34
2	*CD_2Cl_2	+20°	7·45	7·09, 7·89	8·05	8·41, 8·80	6·10	9·08
3	$CDCl_3$	+33·5°	—	6·45	4·35	—	5·82	8·30
5	$CDCl_3$	+33·5°	—	5·92	4·45	—	5·80	8·35
6	CCl_4	+33·5°	—	6·7	7·8 to 8·5		6·1	9·1

*Values from 220 MHz spectra

ring O atoms **8**. A similar deshielding is expected, and found, for our minor doublet.



7 **8**

From the results in CD_2Cl_2 and pyridine solutions we estimate there to be $5 \pm 1\%$ of **1b** present at $-40°$, therefore the axial equatorial free energy difference of a 5-Me group is $5{\cdot}7 \pm 0{\cdot}4$ kJ mole^{-1} at $-40°$. This value enables the relative values for the free energy differences of the other ring Me groups in tetrahydro-1,2-oxazines reported previously[3] to be put on an absolute scale: C(4) $7{\cdot}1 \pm 1{\cdot}0$; C(3) $7{\cdot}9 \pm 0{\cdot}8$ and C(6) $10{\cdot}1 \pm 1{\cdot}6$ kJ mole^{-1}.

We now turned our attention to the 4-Me derivative for which 3% or less of the axial C-Me conformation would be expected. Neither at 90 MHz or 220 MHz and $-40°$ could any trace of a second conformation be identified. This is either due to accidental equivalence of the C(4)-Me and N-Me signals in both conformations, even 220 MHz, or to a very low amount of the minor conformation. We regard the first possibility as the most likely explanation. As the temperature is lowered there is a discernable broadening followed by sharpening of the C-Me doublet, although it is less marked than in **1**. Moreover, there is no reason to expect a separation either of the N-Me signals, which remain a singlet at $-45°$ in **1**, or of the C-Me doublet because a nitrogen long pair has a less marked deshielding effect on a syn axial Me group than does an O atom.

EXPERIMENTAL

NMR spectra were recorded on a Perkin Elmer R32 spectrometer operating at 90 MHz, a Perkin Elmer R10 spectrometer at 60 MHz and a Varian HR 220 spectrometer at 220 MHz. We thank the S.R.C. for the spectra run at 220 MHz.

2,5-Dimethyltetrahydro-1,2-oxazine. The hydrochloride of **3**[5] (1·35 g) in EtOH (50 ml) was left overnight with anhyd K_2CO_3 (3·0 g) and ethylchloroformate (1·3 g). The mixture was heated under reflux for 1 hr the following morning, allowed to cool, filtered and distilled, yield 760 mg (**5**) (44%) BP 60–64° at 3 mm.

The dihydro-oxazine (**5**) was hydrogenated over 5% Pd C in MeOH at atmospheric pressure and room temp. When 1 mole of H_2 had been taken up the solution was filtered and the MeOH removed on a rotary evaporator.

LAH reduction of **6** under the standard conditions described earlier[1] yielded **1** b.p. 119–120°/760 mm. Picrate m.p. 109–112, $C_{12}H_{16}N_4O_8$ requires: C, 41·68; H, 4·68; N, 16·27; Found C, 42·04; H, 4·86; N, 16·29%.

2,4 - Dimethyltetrahydro - 1,2 - oxazine. The mixture of 2,4- and 2,5 - dimethyltetrahydro - 1,2 - oxazines prepared as described earlier[1] was treated with excess conc HCl. The excess acid was removed in a rotary evaporator to leave the mixed solid hydrochlorides. Recrystallisation from isopropanol gave the hydrochloride of **2** contaminated by *ca* 5% of the hydrochloride of **1**. Treatment of the hydrochloride with cold 50% NaOH aq released the free base which was separated from the aqueous layer and distilled, b.p. 119–120°/760 mm. Picrate, m.p. 110–113°, $C_{12}H_{16}N_4O_8$ requires: C, 41·86; H, 4·68; N, 16·27; Found C, 41·70; H, 4·50; N, 16·31%.

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