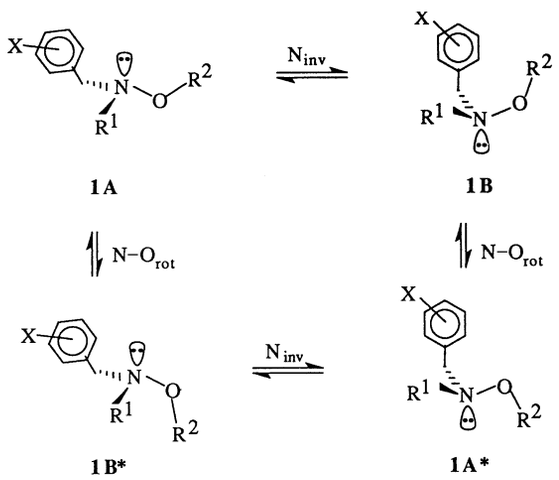
Nitrogen inversion and N–O bond rotation in some hydroxylamine and isoxazolidine derivatives

Azfar Hassan, Mohamed I. M. Wazeer,* Herman P. Perzanowski and Sk. Asrof Ali

Chemistry Department, King Fahd University of Petroleum and Minerals, Dhahran 31261, Saudi Arabia

A series of trisubstituted hydroxylamine derivatives, both cyclic and acyclic, has been prepared. The energy barriers in these hydroxylamines are found to be dominated either by nitrogen inversion or N–O bond rotation depending on the nature of the substituents attached to the nitrogen. In several series of compounds, having $XC_6H_4CH_2$ substituents attached to nitrogen, Hammett free energy correlations are obtained with positive ρ values, indicating increased electron density at the transition state for the inversion process. Isoxazolidines with C(5) ethoxy substituents demonstrate a strong anomeric effect.

In acyclic hydroxylamines **1** the diastereotopic methylene hydrogen resonances appear as an AB quartet in the ^{1}H NMR spectrum at low temperatures. At higher temperature the chiral amine **1A** (the most stable conformer with bonds and lone pairs formally eclipsed) would undergo stereomutation to the enantiomer **1A*** (Scheme 1) and when the rate process becomes



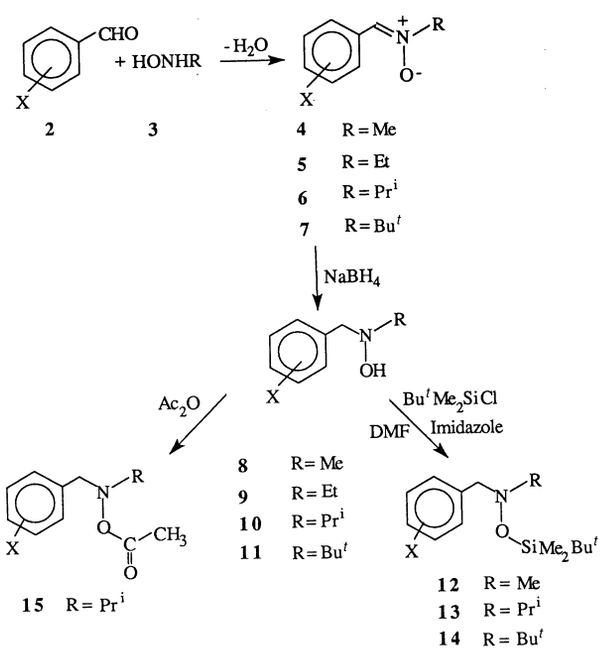
Scheme 1

faster on the NMR timescale the methylene AB quartet coalesces and then appears as a singlet.[1]

Such a stereomutation requires two steps: nitrogen inversion and N–O bond rotation both of which have considerable and comparable energy barriers. As a consequence there has been considerable discussion (and controversy) as to whether nitrogen inversion[2] or N–O rotation[3] or even a complex composite of both (in an energy saving pathway) is the rate-limiting step.[4] While solvent studies provided conflicting conclusions, much experimental evidence points to steric acceleration and deceleration of the rate as an indication of inversion and rotation-controlled rate-limiting processes, respectively. Steric crowding raises the energy of the pyramidal ground state whereas in the planar transition state for the inversion with an expanded CNC angle (120°) such crowding is relieved and as a consequence the energy barrier decreases. Steric crowding on the other hand would normally raise the energy barrier for the rotational process, since the crowding is expected to have a greater impact in raising the energy of the rotational transition state than that of the ground state.[4]

It is well known that electronegative substituents (O, N, halogen) on nitrogen raise the inversion barrier by their σ inductive electron-withdrawing ability and π repulsive character due to lone pairs.[5] Both electronegativity and maximized lone pair repulsion destabilize the planar transition state. The relative contribution of these two effects (which are the origins of the 'hetero effect') still remain a long-standing question which many researchers including theoreticians have been unable to answer.[5a]

In order to study the substituent effects on the inversion and rotational behaviour we have synthesized a variety of hydroxylamine derivatives **8**–**15** and isoxazolidines **17** (Schemes 2 and 3).



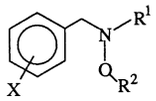
Scheme 2

The lack of N–O bond rotation in the ring skeleton of the five-membered ring in **17** would involve only the inversion process. The presence of an ethoxy group at C(5) in isoxazolidines **17** would also enable us to study the anomeric effect in five-membered ring systems.

Results and discussion

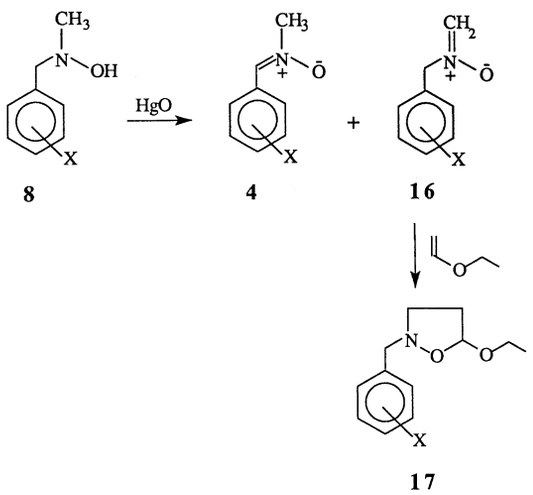
The *N*-oxides **4**–**7** with a variety of alkyl (R) groups and substituents X were prepared by condensation reaction of the

Table 1 Compounds studied and their nitrogen inversion barriers in $CDCl_3$



Compound	X	R^1	R^2	$\Delta\nu_{AB}$[a]/Hz	$\Delta G^{\ddagger}$ (273 K)/kJ mol^{-1}
8a	H	Me	H	—	55.8[b]
12	H	Me	$SiMe_2Bu^t$	70.5 (0 °C)	57.8
9	H	Et	H	41.3 (−30 °C)	55.3
10a	H	Pr^i	H	54.4 (−40 °C)	51.6
13	H	Pr^i	$SiMe_2Bu^t$	19.6 (−30 °C)	59.2
11	H	Bu^t	H	89.9 (−50 °C)	49.2
14	H	Bu^t	$SiMe_2Bu^t$	95.4 (−30 °C)	56.1
8b	*p*-NO_2	Me	H	15.6 (−40 °C)	52.3
8c	*p*-Cl	Me	H	—	—
8d	*p*-OMe	Me	H	—	—
8e	*p*-Me	Me	H	25.3 (−20 °C)	56.6
8f	*p*-NMe_2	Me	H	24.8 (−30 °C)	57.7
8g	*m*-NO_2	Me	H	31.6 (−40 °C)	54.1
8h	*o*-OMe	Me	H	50.3 (−40 °C)	56.2

[a] For the benzylic protons at 200 MHz. [b] Estimated from the Hammett relation.



Scheme 3

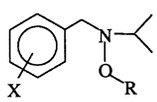
corresponding aromatic aldehydes **2** and hydroxylamines **3**, and on reduction with sodium borohydride afforded the hydroxylamines **8**–**11** required for the study of inversion and rotational energy barriers. A series of *N*-acetoxy derivatives **15a**–**k** were obtained by treating the hydroxylamines with acetic anhydride (Scheme 2).

The hydroxylamines **8a**, **10a** and **11** were silylated with *tert*-butyldimethylchlorosilane in the presence of imidazole to give the compounds **12**–**14**, respectively. The various compounds studied are included in Tables 1–3.

With a series of di- and tri-substituted hydroxylamines in hand we proceeded to study the inversion–rotation process by ^{1}H NMR spectroscopy. At ambient temperature benzylic proton resonances in most of the compounds appeared as broad singlets which on lowering the temperature became AB quartets. The complete band shape analysis yielded the rate constants and the free energy of activation ($\Delta G^{\ddagger}$) calculated using transition state theory: $k = (k_B T/h)e^{-\Delta G^{\ddagger}/RT}$.

The activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated from the plots of ln (k/T) *vs.* $1/T$. It is well known[6] that NMR bandshape fitting frequently gives rather large but mutually compensating systematic errors in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ and as such is not reported here. However, band shape fitting is viewed[6] as a method of getting rather accurate values (probably to within ±0.3 kJ mol^{-1}) for $\Delta G^{\ddagger}$ in the vicinity of the coalescence temperature. (Activation entropies for the hydroxylamines are in the range −4 to −30 J mol^{-1} K^{-1}.) The $\Delta G^{\ddagger}$ values calculated at 0 °C are reported in Tables 1–3.

Table 2 Energy barriers of various *N*-isopropylhydroxylamine derivatives in $CDCl_3$

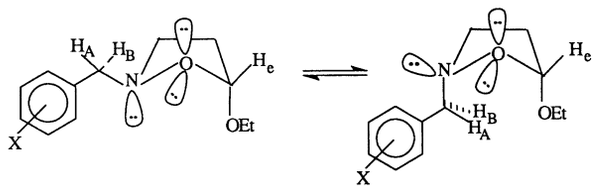


Compound	X	R	$\Delta\nu_{AB}$[a]/Hz	$\Delta G^{\ddagger}$ (273 K)/kJ mol^{-1}
10a	H	H	54.4 (−40 °C)	51.6
15a	H	Ac	54.0 (−40 °C)	50.2[b]
10b	*p*-NO_2	H	44.1 (−50 °C)	49.5
15b	*p*-NO_2	Ac	45.7 (−60 °C)	48.7
10c	*p*-Cl	H	53.2 (−40 °C)	51.0
15c	*p*-Cl	Ac	53.4 (−50 °C)	50.2
10d	*p*-OMe	H	48.6 (−40 °C)	52.0
15d	*p*-OMe	Ac	54.9 (−50 °C)	50.7
10e	*p*-Me	H	46.5 (−40 °C)	51.3
15e	*p*-Me	Ac	53.4 (−45 °C)	50.7
10f	*p*-NMe_2	H	32.0 (−50 °C)	52.1
15f	*p*-NMe_2	Ac	49.7 (−50 °C)	51.2
10g	*m*-NO_2	H	41.8 (−40 °C)	50.4
15g	*m*-NO_2	Ac	44.5 (−50 °C)	49.0
10h	*m*-Br	H	51.3 (−35 °C)	50.7
15h	*m*-Br	Ac	51.6 (−50 °C)	49.9
10i	*p*-Br	H	51.6 (−50 °C)	51.2
15i	*p*-Br	Ac	52.1 (−50 °C)	50.2
10j	2,4,5-$(OMe)_3$	H	97.8 (−40 °C)	54.3
15j	2,4,5-$(OMe)_3$	Ac	44.5 (−54 °C)	53.9
10k	*p*-OH	H	48.7 (−40 °C)	52.2
15k	*p*-OH	Ac	48.9 (−40 °C)	51.9

[a] For the benzylic protons at 200 MHz. [b] From ref. 15.

For the hydroxylamines **8a**, **9**, **10a** and **11** (Table 1) the barriers obtained fit best with the nitrogen inversion as the rate-determining step. Compound **11** with the most crowded *tert*-butyl group has the lowest energy barrier as a consequence of the steric acceleration of the rate inversion. However, increased steric crowding in the silylated derivatives **12**–**14** caused steric deceleration of the rate of inversion in comparison to their corresponding hydroxylamines (*cf.* **10a** and **13**; **11** and **14**). Incorporation of a silyl group increases the barrier by *ca.* 8 kJ mol^{-1} and the barriers observed fit best with the N–O rotation as the rate-limiting process. Involvement of the vacant d orbitals in silicon in bonding with the oxygen lone pair should decrease the barriers for both the inversion and rotational processes insofar as the destabilization of the transition state by

Table 3 Free energy of activation ($\Delta G^{\ddagger}$) for nitrogen inversion (major ⟷ minor) and isomer ratios of **17** in $CDCl_3$



Compound **17**	X	$\Delta G^{\ddagger}$ (273 K)/ kJ mol^{-1}	Major/minor ratio[a]
a	H	59.6	57:43
b	*p*-NO_2	57.4	60:40
c	*p*-Cl	58.8	58:42
d	*p*-OMe	60.4	60:40
e	*p*-CH_3	60.0	59:41
f	*p*-NMe_2	61.6	62:38
g	*m*-NO_2	57.2	63:37
h	*o*-OH	66.3	52:48
i	*o*-OMe	59.4	62:38

[a] At −40 °C.

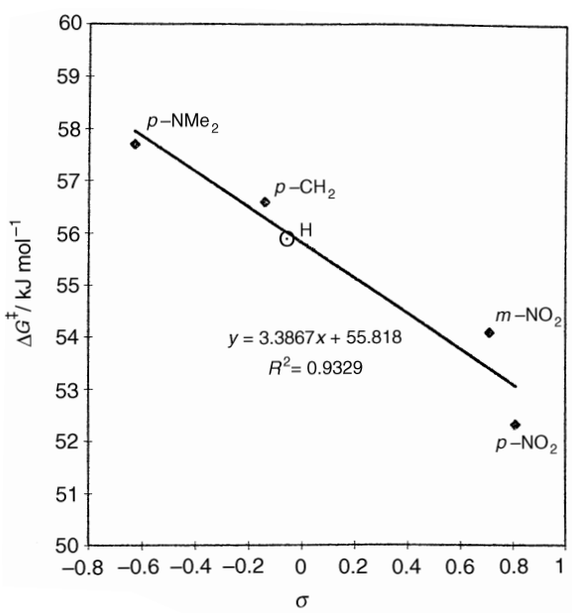


Fig. 1 Hammett plot for the nitrogen inversion barrier in *N*-aryl-*N*-methylhydroxylamines (**8**)

lone pair repulsion is concerned. However, steric encumbrance of the silyl group forces the rotational process to play a dominant part in the overall process. In the series **12**–**14** changing the R group from methyl to isopropyl causes an increase in the energy barrier in line with the rate-limiting rotational process. However, changing to *tert*-butyl groups (compound **14**) makes the barrier lower than the isopropyl **13** or even methyl derivative **12**. Had the energy barrier depended solely on the rate-limiting rotational process, there would have been a steady increase in the barrier in the series **12**–**14**. The results clearly demonstrate the contribution of both inversion and rotation processes to the energy barrier with one of the processes playing the dominant role. The lowest energy pathway leading to inversion follows sequential rotation[7] and inversion processes as predicted by molecular orbital calculations[8] on simpler, related model compounds. However, it is suggested in a recent study[4] that complex composites of the two processes with an energy saving pathway may constitute a single process. It is tempting to contemplate that near or at the transition state for the nitrogen inversion, the rotation around the extended C–N–C bond (with bond angle of 120°) would be easier than when it is pyramidal.

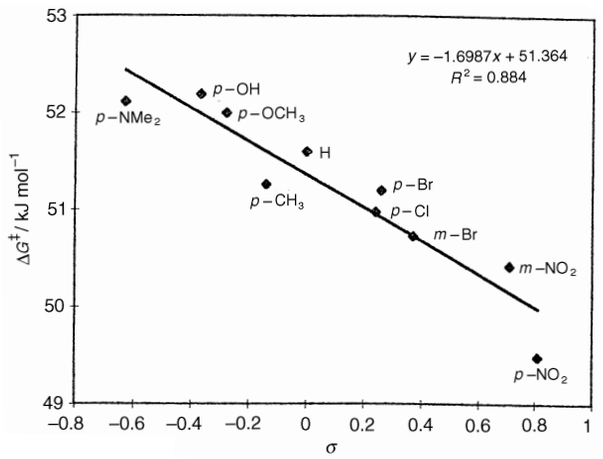


Fig. 2 Hammett plot for the nitrogen inversion barrier in *N*-aryl-*N*-isopropylhydroxylamines (**10**)

In such a complex process, however, the substituent effects will also be complex.

In order to assess the importance of substituents on the nitrogen inversion process we measured the energy barrier for hydroxylamines **8b**, **8e**–**g**, **8i** (Table 1). For compounds with X = H (**8a**), *p*-Cl (**8c**) and *p*-OMe (**8d**) we did not observe the usual AB quartet for the benzyl methylene protons at −40 °C which is well below the coalescence temperature of the other compounds in this series. This could be attributed to accidental rather than real equivalence of the methylene protons. However, at *ca.* −90 °C the methylene proton signals of **8a** did indeed split into an AB quartet (δ_A 3.51 ppm, 1 H, *J* 12.0; δ_B 3.66 ppm, 1 H, *J* 12.0). Increasing the temperature did not broaden the line width as is observed in the usual exchange process; however, the chemical shift difference between the methylene protons decreased and finally became a singlet at *ca.* −40 °C. At −90 °C the separation of the inner peaks was 15.0 Hz. However, at −70, −50 and −40 °C this separation became 4.76, 2.5 and 0 Hz, respectively. A similar observation was made for the *p*-Cl (**8c**) and *p*-OMe (**8d**) derivatives. This is a temperature dependence of chemical shifts rather than an exchange phenomenon.

Using the Hammett plot of free energy of activation against substituent constants,[9] σ, (Fig. 1) and using the free-energy form of the Hammett equation, $\Delta G^{\ddagger} = -2.3\,RT\rho\sigma + \Delta G_o^{\ddagger}$, a value of +0.648 for the reaction constant, ρ, is obtained. The transition state for the inversion process is, thus, richer in electron density and perhaps 'through-space' conjugation with the aromatic ring or the inductive electron withdrawal effect stabilizes the planar transition state.

The free energy of activation for the exchange process in the *N*-hydroxy and *N*-acetoxy compounds in the isopropyl series **10** and **15** are included in Table 2 and the Hammett plots are shown in Figs. 2 and 3. The acetyl derivatives have barriers approximately 1 kJ mol^{-1} lower than their parent hydroxylamines. While the acetoxy group, by virtue of being more electronegative than the OH group, should increase the nitrogen inversion barrier, by depletion of the lone pair density in oxygen by delocalization into the acyl group it actually decreases the activation energy. The two effects contribute to the energy barrier in opposite directions. However, such a small lowering of activation energy, presumably, reflects lesser dominance of nitrogen inversion—an increase in the steric bulk owing to the incorporation of an acyl group moves the process more towards an N–O rotation-controlled process. Positive ρ values of 0.33 (Fig. 2) and 0.35 (Fig. 3) for the hydroxy **10** and acetoxy **16** series, respectively, again demonstrate the increased electron density in the planar transition state.

A series of isoxazolidines with C(5) ethoxy substituent and

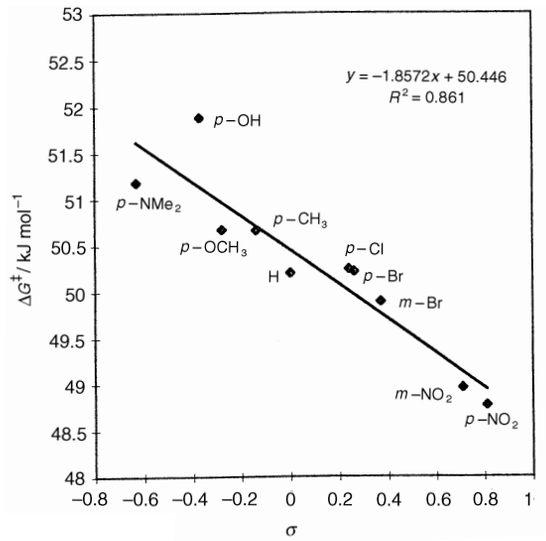


Fig. 3 Hammett plot for the nitrogen inversion barrier in *N*-aryl-*N*-isopropyl-*O*-acetyl hydroxylamines (**15**)

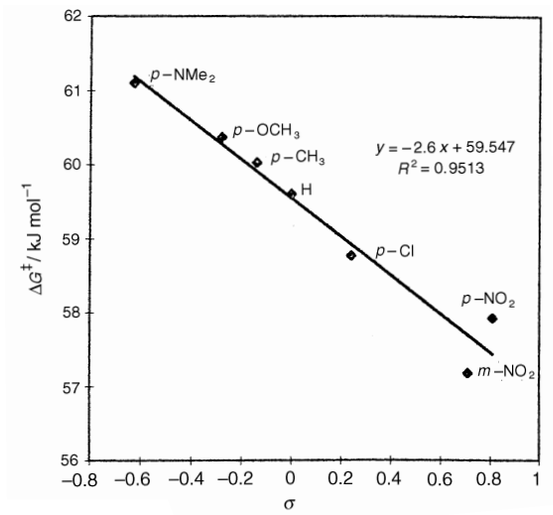


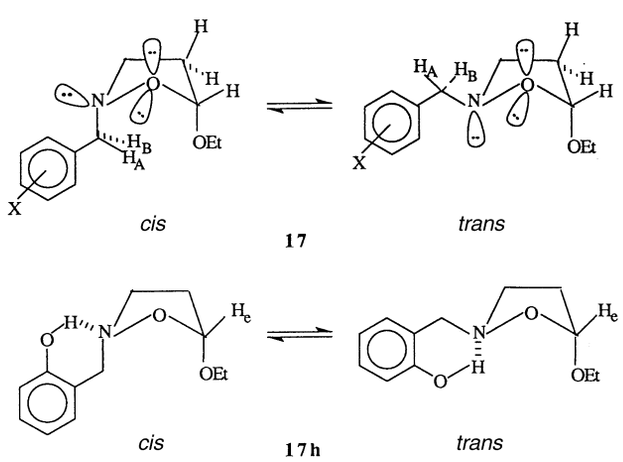
Fig. 4 Hammett plot for the nitrogen inversion barrier in isoxazolidines (**17**)

several *o*-, *m*- and *p*-substituted benzyl groups at nitrogen were prepared as shown in Scheme 3.

The mercury(II) oxide oxidation of the hydroxylamines (**8**) afforded a mixture of **4** and **16**. The monosubstituted **16** is anticipated to be more reactive than **4** towards dienophiles as a result of the steric encumbrance in the disubstituted **4**. The mixture of **4** and **16** on treatment with ethyl vinyl ether at 30 °C gave the cycloadduct **17** regiospecifically. Compound **4** was found to be unreactive under the reaction conditions.

The ^{1}H NMR spectra of all these isoxazolidines show broadened signals as the temperature is lowered below ambient and distinct signals for the *cis* and *trans* isomers are displayed in the spectrum. The population ratios for the major and minor isomers are listed in Table 3. Invariably, the benzylic proton signals (AB or dd) for the major isomers appear upfield in all the derivatives. Further evidence that the major isomer in all these derivatives have the same configuration comes from the signal of the CH_3 protons. In almost all instances the major triplet for the methyl protons appeared upfield. Unfortunately, the signals for the C(5) H_e of the two isomers appeared at the same chemical shifts (*i.e.* chemical shift equivalence) in all the derivatives at *ca.* δ 5.24–5.29 as multiplets (at −40 °C). The linewidths of *ca.* 10–12 Hz at half heights indicate the small coupling constants associated with the pseudo-equatorial orientation of the C(5) proton. Major isomers were assigned the *cis* configuration based on our earlier work.[10] The *cis*-form has the advantage of having the lone pairs of electrons in *gauche* orientation which overcomes the unfavourable steric encumbrance in 1,3-diaxially substituted isoxazolidines. The NMR spectra at +50 °C revealed the signal of the C(5)H as a dd in all compounds (with coupling constant *J ca.* 2.0, *ca.* 5.5) at δ 5.22–5.26. The magnitude of coupling constants are indicative of the pseudo-axial orientation of the C(5) ethoxy group in both the isomers,[11] where the inspection of Drieding models indicate that a dihedral angle of *ca.* 90° is possible between the C(5)H and the *trans* disposed C(4)H. In related isoxazolidines, in the absence of anomeric effect, the axially oriented C(5)H appeared as triplets with large coupling constants ranging from 7–9 Hz.[12] The ratio of the isomers was found to be 60:40 in all cases except for X = *o*-OH (*ca.* 50:50). The Hammett plot for the nitrogen inversion barrier (Table 3) for the isoxazolidines **17** is given in Fig. 4. The N–O bond is locked in the ring skeleton of the five-membered ring, hence the question of rotation around the bond does not arise. It is now purely a matter of nitrogen inversion. Electronegative substituent X accelerates the rate of inversion by stabilizing the transition state which has higher electron density than the ground state as indicated by a ρ value of +0.49. To the best of our knowledge this is the first time the Hammett free energy relationship has been obtained for a purely nitrogen inversion process in isoxazolidines.

In all the isoxazolidines studied a strong anomeric effect is demonstrated since the ^{1}H NMR spectra did not reveal the presence of the isomers with an equatorially orientated C(5) ethoxy substituent. The effect of H-bonding is amply demonstrated in the inversion barrier of the compound **17h** with *o*-hydroxy substituent. The barrier is found to be 7 kJ mol^{-1} higher than the barrier found for the corresponding *o*-methoxy derivative **17i** (Scheme 4). The nitrogen inversion requires prior



Scheme 4

breaking of the H-bond. The H-bonding is demonstrated by the appearance of the proton signal downfield (δ 10.2) as a singlet.

Experimental

Variable temperature ^{1}H NMR spectra were recorded on a Varian XL 200 NMR spectrometer operating at 200.05 MHz in the Fourier transform mode. *J* values are in Hz. Compounds were examined in $CDCl_3$ solutions at 0.15 M concentrations. Temperature control was achieved using the XL-200 temperature controller and calibrated using standard chemical shifts of methanol for low temperatures. The temperatures are accurate to ±1.0 °C.

Simulations of exchange affected NMR spectra of hydroxylamines were carried out using the library program ABSHAPE[13] which calculates the band shapes for the mutually exchanging spin system of AB going to BA. The small tempera-

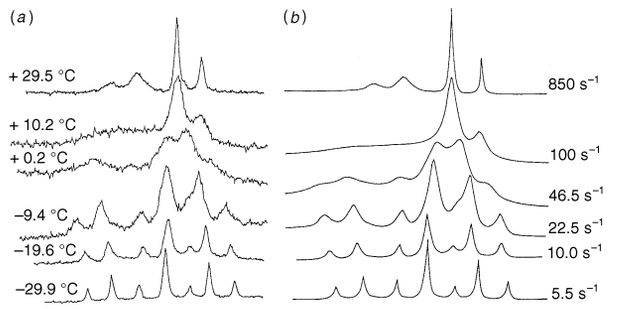


Fig. 5 Experimental and calculated bandshapes of the benzylic protons of **17b** at different temperatures. The temperature and corresponding rate constants for the major ⟶ minor isomerization are indicated on the experimental and calculated spectra respectively.

ture dependence of the chemical shift of the AB systems were taken into account in the simulation of exchange-broadened spectra. The matching of simulated and experimental spectra were carried out by superposition of calculated and experimental spectra by eye. In isoxazolidines, the exchange of benzylic CH_2 protons can be depicted as AB ⟷ A′B′ (exchange between two AB systems with unequal populations). The program ABEX [13] was used to calculate the rate constants. Fig. 5 shows the experimental and the calculated spectra for compound **17b**.

All mps are uncorrected. Elemental analyses were performed on a Fisons Instruments Elemental Analyser 1108. IR spectra were recorded on a Nicolet 5 DXB FTIR. Silica gel chromatographic separations were performed with flash silica gel (Baker Chemicals Co.). Compounds **10a**, **10k**, **15a**, **15k** and **17a** have been reported [10,14] previously.

General procedure for the preparation of the hydroxylamines

To a solution of the hydroxylamine (**3**) (5.0 mmol) in ethanol (10 cm^3) was added the aldehyde (**2**) (5.5 mmol). (While the hydroxylamines were used as their free bases, *N*-methylhydroxylamine was introduced as its hydrochloride and the free base was liberated from its salt by adding 1.1 equiv. of sodium acetate in the reaction mixture.) The reaction mixture was stirred at 50–60 °C for 5 h and TLC (silica, diethyl ether) revealed the complete formation of the *N*-oxides **4**–**7**. To this solution was added $NaBH_4$ (10 mmol) and the mixture was then stirred at 50 °C for 5 h. Further $NaBH_4$ (10 mmol) was added and the reaction mixture was stirred at 20 °C for 24 h to ensure complete reduction of the nitrone (checked by TLC experiment). After removal of the ethanol by a gentle stream of N_2 the reaction mixture was taken up in H_2O (15 cm^3) and extracted with $CHCl_3$ (3 × 25 cm^3). Removal of the solvent followed by passing through a silica column using hexane–diethyl ether mixture (3:1) as eluent afforded the hydroxylamines (**8**–**11**) in 70–85% yield.

***N*-Benzyl-*N*-methylhydroxylamine 8a.** Compound **8a** formed colourless needles, mp 40–41 °C, δ_H(+22 °C) 2.49 (3 H, s), 3.70 (2 H, s), 7.32 (5 H, s), OH proton signal was not observed.

***N*-*p*-Nitrobenzyl-*N*-methylhydroxylamine 8b.** Compound **8b** formed pale-yellow plates, mp 134–136 °C (diethyl ether–hexane) (Found: C, 52.8; H, 5.5; N, 15.6. $C_8H_{10}N_2O_3$ requires C, 52.75; H, 5.53; N, 15.38%); ν_{max}(KBr)/cm^{-1} 3225, 2850, 1514, 1344, 1320, 1109, 1067, 972, 957, 861, 805 and 748; δ_H(+22 °C), 2.62 (3 H, s), 3.84 (2 H, s), 7.52 (2 H, d, *J* 10.0) and 8.23 (2 H, d, *J* 10.0); OH proton signal was not observed.

***N*-*p*-Chlorobenzyl-*N*-methylhydroxylamine 8c.** Compound **8c** formed white needles, mp 88–90 °C (diethyl ether–hexane) (Found: C, 56.2; H, 5.9; N, 8.2. $C_8H_{10}NOCl$ requires C, 55.98; H, 5.87; N, 8.16%); ν_{max}(KBr)/cm^{-1} 3237, 3000, 2900, 1490, 1437, 1362, 1195, 1084, 1016, 969, 849 and 796; δ_H (+20 °C) 2.52 (3 H, s), 3.67 (2 H, s), 7.25 (2 H, d, *J* 8.0), 7.34 (2 H, d, *J* 8.0) and 7.52 (1 H, broad s).

***N*-*p*-Methoxybenzyl-*N*-methylhydroxylamine 8d.** Compound **8d** formed colourless plates, mp 52–54 °C (diethyl ether–hexane) (Found: C, 64.7; H, 7.9; N, 8.5. $C_9H_{13}NO_2$ requires C, 64.66; H, 7.84; N, 8.38%); ν_{max}(KBr)/cm^{-1} 3200, 2950, 2825, 1618, 1520, 1463, 1445, 1362, 1280, 1177, 1040, 960, 855, 802 and 748; δ_H(+22 °C) 2.56 (3 H, s), 3.68 (2 H, s), 3.80 (3 H, s), 6.90 (2 H, d, *J* 10.0) and 7.27 (2 H, d, *J* 10.0); OH proton signal was not observed.

***N*-*p*-Methylbenzyl-*N*-methylhydroxylamine 8e.** Compound **8e** formed white crystals, mp 56–58 °C (diethyl ether–hexane) (Found: C, 71.6; H, 8.7; N, 9.3. $C_9H_{13}NO$ requires C, 71.49; H, 8.66; N, 9.26%); ν_{max}(KBr)/cm^{-1} 3225, 2863, 2825, 1517, 1350, 1144, 1067, 960, 852, 793 and 760; δ_H(+20 °C) 2.30 (3 H, s), 2.60 (3 H, s), 3.70 (2 H, s), 7.15 (2 H, d, *J* 9.0) and 7.22 (2 H, d, *J* 9.0); OH proton signal was not observed.

***N*-*p*-*N*,*N*-Dimethylbenzyl-*N*-methylhydroxylamine 8f.** Compound **8f** formed white crystals, mp 75–77 °C (diethyl ether–hexane) (Found: C, 66.6; H, 9.1; N, 15.65. $C_{10}H_{16}N_2O$ requires C, 66.64; H, 8.95; N, 15.54); ν_{max}(KBr)/cm^{-1} 3250, 3000, 2950, 2850, 1619, 1526, 1365, 1237, 1192, 1073, 972, 924, 808 and 733; δ_H(+20 °C) 2.59 (3 H, s), 2.99 (6 H, s), 3.67 (2 H, s), 6.70 (2 H, d, *J* 9.0) and 7.18 (2 H, d, *J* 9.0); OH proton signal was not observed.

***N*-*m*-Nitrobenzyl-*N*-methylhydroxylamine 8g.** Compound **8g** formed white crystals, mp 88–90 °C (diethyl ether–hexane) (Found: C, 52.8; H, 5.5; N, 15.6. $C_8H_{10}N_2O_3$ requires C, 52.75; H, 5.53; N, 15.38%); ν_{max}(KBr)/cm^{-1} 3150, 2863, 1526, 1347, 1186, 1084, 984, 950, 805, 739 and 694; δ_H(+20 °C) 2.65 (3 H, s), 3.82 (2 H, s), 5.60 (1 H, broad s), 7.5 (1 H, t, *J* 8.5), 7.65 (1 H, d, *J* 8.0), 8.14 (1 H, d, *J* 8.0) and 8.24 (1 H, s).

***N*-*o*-Methoxybenzyl-*N*-methylhydroxylamine 8h.** Compound **8h** formed white crystals, mp 88–90 °C (diethyl ether–hexane) (Found: C, 64.45; H, 7.7; N, 8.3. $C_9H_{13}NO_2$ requires C, 64.66; H, 7.84; N, 8.38%); ν_{max}(KBr)/cm^{-1} 3225, 3000, 2850, 1687, 1428, 1329, 1294, 1186, 939, 811, 712 and 670; δ_H(+20 °C) 2.56 (3 H, s), 3.81 (2 H, s), 3.83 (3 H, s) and 6.86–7.41 (4 H, m, 1 H, hydroxy below).

***N*-Benzyl-*N*-ethylhydroxylamine 9.** Compound **9** was a colourless liquid (Found: C, 71.3; H, 8.8; N, 9.2. $C_9H_{13}NO$ requires C, 71.49; H, 8.67; N, 9.26%); ν_{max}(neat)/cm^{-1} 3222, 3026, 2960, 2829, 1496, 1454, 1341, 1090, 1031, 983, 909, 825, 742 and 700; δ_H(+20 °C) 1.12 (3 H, t, *J* 7.0), 2.80 (2 H, q, *J* 7.0), 3.84 (2 H, s) and 7.45 (5 H, s, 1 H, hydroxy proton underneath); mass spectrum: *m/z* 151 (M^+ 28%).

***N*-*p*-Nitrobenzyl-*N*-isopropylhydroxylamine 10b.** Compound **10b** formed colourless plates, 83–85 °C (diethyl ether–hexane) (Found: C, 57.0; H, 6.9; N, 13.4. $C_{10}H_{14}N_2O_3$ requires C, 57.13; H, 6.71; N, 13.33%); ν_{max}(KBr)/cm^{-1} 3200, 3069, 2971, 2873, 1069, 1529, 1347, 1174, 1117, 1019, 954, 879, 864, 817 and 745; δ_H(+24 °C) 1.08 (6 H, d, *J* 6.0), 3.02 (1 H, hept, *J* 6.0), 3.89 (2 H, s), 4.77 (1 H, s), 7.58 (2 H, d, *J* 9.0) and 8.24 (2 H, d, *J* 9.0).

***N*-*p*-Chlorobenzyl-*N*-isopropylhydroxylamine 10c.** Compound **10c** formed white crystals, mp 72–74 °C (diethyl ether–hexane) (Found: C, 60.1; H, 7.2; N, 7.0. $C_{10}H_{14}NOCl$ requires C, 60.15; H, 7.07; N, 7.01%); ν_{max}(KBr)/cm^{-1} 3212, 2972, 2873, 1493, 1377, 1126, 1094, 1019, 936, 888, 843, 825 and 748; δ_H(+22 °C) 1.13 (6 H, d, *J* 6.0), 2.97 (1 H, hept, *J* 6.0), 3.77 (2 H, s), 5.29 (1 H, broad s) and 7.35 (4 H, s).

***N*-*p*-Methoxybenzyl-*N*-isopropylhydroxylamine 10d.** Compound **10d** formed white crystals, mp 49–51 °C (diethyl ether–hexane) (Found: C, 67.6; H, 8.9; N, 7.15. $C_{11}H_{17}NO_2$ requires C, 67.66; H, 8.78; N, 7.17%); ν_{max}(KBr)/cm^{-1} 3212, 2839, 2835, 2829, 1517, 1371, 1255, 1186, 1040, 930, 799 and 754; δ_H(+20 °C) 1.18 (6 H, d, *J* 7.0), 2.98 (1 H, hept, *J* 7.0), 3.76 (2 H, s), 3.82 (3 H, s), 5.27 (1 H, s), 6.94 (2 H, d, *J* 10.0) and 7.36 (2 H, d, *J* 10.0).

***N*-*p*-Methylbenzyl-*N*-isopropylhydroxylamine 10e.** Compound **10e** formed white plates, mp 79–81 °C (diethyl ether–hexane) (Found: C, 73.8; H, 9.7; N, 7.8. $C_{11}H_{17}NO$ requires C, 73.70; H, 9.56; N, 7.81%); ν_{max}(KBr)/cm^{-1} 3222, 2971, 2002,

1517, 1457, 1362, 1121, 1082, 1028, 933, 882, 843, 817 and 745; δ_H(+23 °C) 1.16 (6 H, d, *J* 7.0), 2.36 (3 H, s), 2.96 (1 H, hept, *J* 7.0), 3.78 (2 H, s), 5.29 (1 H, broad s), 7.18 (2 H, d, *J* 9.0) and 7.30 (2 H, d, *J* 9.0).

***N*-*p*-*N*,*N*-Dimethylbenzyl-*N*-isopropylhydroxylamine 10f.** Compound **10f** formed yellow crystals, mp 66–68 °C (diethyl ether–hexane) (Found: C, 69.1; H, 9.8; N, 13.6. $C_{12}H_{20}N_2O$ requires C, 69.19; H, 9.68; N, 13.45%); ν_{max}(KBr)/cm^{-1} 3200, 2971, 2884, 1624, 1606, 1529, 1448, 1353, 1129, 1064, 951, 882, 846, 820 and 751; δ_H(+24 °C) 1.16 (6 H, d, *J* 6.0), 2.97 (6 H, s and 1 H, hept, *J* 6.0 underneath), 3.74 (2 H, s), 5.98 (1 H, broad s), 6.77 (2 H, d, *J* 8.0) and 7.27 (2 H, d, *J* 8.0).

***N*-*m*-Nitrobenzyl-*N*-isopropylhydroxylamine 10g.** Compound **10g** formed pale-yellow crystals, mp 79–81 °C (diethyl ether–hexane) (Found: C, 57.15; H, 6.8; N, 13.2. $C_{10}H_{14}N_2O_3$ requires C, 57.13; H, 6.71; N, 13.33%); ν_{max}(KBr)/cm^{-1} 3212, 2961, 2917, 1586, 1532, 1371, 1347, 1231, 1177, 1085, 1031, 954, 817 and 796; δ_H(+23 °C) 1.17 (6 H, d, *J* 6.0), 3.02 (1 H, hept, *J* 6.0), 3.87 (2 H, s), 4.80 (1 H, broad s) and 7.46–8.38 (4 H, m).

***N*-*m*-Bromobenzyl-*N*-isopropylhydroxylamine 10h.** Compound **10h** formed white crystals, mp 78–80 °C (diethyl ether–hexane) (Found: C, 49.1; H, 5.9; N, 5.7. $C_{10}H_{14}NOBr$ requires C, 49.20; H, 5.78; N, 5.74%); ν_{max}(KBr)/cm^{-1} 3189, 2971, 2895, 1576, 1478, 1427, 1368, 1177, 1129, 1073, 992, 957, 939, 894, 859, 775, 697 and 673; δ_H(+23 °C) 1.15 (6 H, d, *J* 7.0), 2.95 (1 H, hept, *J* 7.0), 3.73 (2 H, s), 5.08 (1 H, broad s) and 7.13–7.59 (4 H, m).

***N*-*p*-Bromobenzyl-*N*-isopropylhydroxylamine 10i.** Compound **10i** formed white crystals, mp 76–78 °C (diethyl ether–hexane) (Found: C, 49.3; H, 5.8; N, 5.8. $C_{10}H_{14}NOBr$ requires C, 49.20; H, 4.78; N, 5.74%); ν_{max}(KBr)/cm^{-1} 3233, 2960, 2906, 1490, 1368, 1174, 1073, 1016, 957, 807 and 784; δ_H(+24 °C) 1.11 (6 H, d, *J* 6.0), 2.00 (1 H, s), 2.95 (1 H, hept, *J* 6.0), 3.94 (2 H, s), 7.26 (2 H, *J* 10.0) and 7.48 (2 H, d, *J* 10.0).

***N*-2,4,5-Trimethoxybenzyl-*N*-isopropylhydroxylamine 10j.** Compound **10j** formed white crystals, mp 87–89 °C (diethyl ether–hexane) (Found: C, 61.0; H, 8.3; N, 5.5. $C_{13}H_{21}NO_4$ requires C, 61.16; H, 8.29; N, 5.49%); ν_{max}(KBr)/cm^{-1} 3222, 2961, 2851, 1612, 1526, 1469, 1407, 1308, 1216, 1180, 1040, 981, 885, 861, 817 and 754; δ_H(+22 °C) 1.10 (6 H, d, *J* 6.0), 2.82 (6 H, s), 3.76 (2 H, s), 3.80 (3 H, s), 3.85 (3 H, s), 3.89 (3 H, s), 5.89 (1 H, s), 6.58 (1 H, s) and 6.99 (1 H, s).

***N*-Benzyl-*N*-*tert*-butylhydroxylamine 11.** Compound **11** formed white crystals, mp 59–61 °C (diethyl ether–hexane) (Found: C, 73.5; H, 9.80; N, 7.7. $C_{11}H_{17}NO$ requires C, 73.70; H, 9.98; N, 7.81%); ν_{max}(KBr)/cm^{-1} 3400, 2975, 2925, 1362, 1207, 1055, 910, 894, 820, 727 and 697; δ_H(+20 °C) 1.24 (9 H, s), 3.84 (2 H, s) and 7.32–7.52 (5 H, m).

General procedure for the preparation of *tert*-butyldimethylsilyl derivatives

To a solution of imidazole (6.0 mmol) in dry DMF (1.5 cm^3) was added *tert*-butyldimethyl chlorosilane (2.0 mmol) at 0 °C. To this mixture was added the corresponding hydroxylamine (1 mmol). The mixture was stirred at 50 °C for 2 h. The resulting mixture was taken up in diethyl ether (25 cm^3) and washed with H_2O (4 × 25 cm^3). The organic layer was dried (Na_2SO_4), concentrated and the residual liquid was chromatographed using hexane–diethyl ether mixture (90 : 10) as the eluent to give the silyl derivative.

***O*-*tert*-Butyldimethylsilyl-*N*-benzyl-*N*-methylhydroxylamine 12.** Compound **12** was a colourless liquid (Found: C, 67.0; H, 10.2; N, 5.75. $C_{14}H_{25}NOSi$ requires C, 66.88; H, 10.02; N, 5.57%); ν_{max}(neat)/cm^{-1} 2928, 2851, 1255, 1087, 954, 915, 885, 843, 784, 703 and 671; δ_H(+20 °C) −0.10 (3 H, broad s), 0.10 (3 H, broad s), 0.87 (9 H, s), 2.49 (3 H, s), 3.61 (1 H, d, *J* 13.0), 3.96 (1 H, d, *J* 13.0), 7.33 (5 H, m); mass spectrum: *m/z* 251 (M$^+$ 3%).

***O*-*tert*-Butyldimethylsilyl-*N*-benzyl-*N*-isopropylhydroxylamine 13.** Compound **13** was a colourless liquid (Found: C, 68.6; H, 10.6; N, 5.0. $C_{16}H_{29}NOSi$ requires C, 68.76; H, 10.46; N, 5.01%); ν_{max}(neat)/cm^{-1} 2917, 2840, 1464, 1252, 939, 894, 840, 784 and 697; δ_H(+20 °C) −0.10 (6 H, broad), 0.84 (9 H, s), 1.08 (6 H, d, *J* 7.0), 2.99 (1 H, hept, *J* 7.0), 3.78 (2 H, s) and 7.30 (5 H, m); mass spectrum: *m/z* 279 (M$^+$ 16%).

***O*-*tert*-Butyldimethylsilyl-*N*-benzyl-*N*-*tert*-butylhydroxylamine 14.** Compound **14** was a colourless liquid (Found: C, 69.3; H, 10.7; N, 4.75. $C_{17}H_{31}NOSi$ requires C, 69.56; H, 10.65; N, 4.77%); ν_{max}(neat)/cm^{-1} 2954, 2931, 2841, 1359, 1258, 1207, 1025, 986, 867, 837, 808, 786 and 751; δ_H(+20 °C) −0.2 (6 H, broad s), 0.90 (9 H, s), 1.10 (9 H, s), 3.95 (2 H, broad s) and 7.19–7.40 (5 H, m); δ_H(−50 °C) −0.60 (3 H, s), 0.10 (3 H, s), 0.83 (9 H, s), 1.17 (9 H, s), 3.70 (1 H, d, *J* 15.5) and 4.17 (1 H, d, *J* 15.5) and 7.35 (5 H, m); mass spectrum: *m/z* 293 (M$^+$ 30%).

General procedure for the preparation of acetyl derivatives

Acetic anhydride (2.4 mmol) was added to a solution of the *N*-hydroxylamine (2.0 mmol) in CH_2Cl_2 (3 cm^3) at 0 °C and the mixture was stirred at 0 °C for 1 h. TLC (diethyl ether–hexane) was taken to ensure the completion of the reaction. The reaction mixture was taken up in 5% $NaHCO_3$ solution (10 cm^3) and extracted with CH_2Cl_2 (3 × 20 cm^3). The organic layer was dried (Na_2SO_4), filtered and the solvent was removed by a gentle stream of N_2 at 10 °C to give the acetate which was purified by crystallization. However, the acetate liquid compounds were purified by passing through a short column of silica using diethyl ether–hexane as the eluent to give the acetate as colourless liquid. The acetate solution sould not be warmed since heating leads to decomposition. These samples were kept in the freezer to minimize any decomposition.

***O*-Acetyl-*N*-*p*-nitrobenzyl-*N*-isopropylhydroxylamine 15b.** Compound **15b** formed white crystals, mp 41–42 °C (diethyl ether–hexane) (Found: C, 57.2; H, 6.4; N, 11.2. $C_{12}H_{16}N_2O_4$ requires C, 57.13; H, 6.39; N, 11.10%); ν_{max}(KBr)/cm^{-1} 3075, 2975, 1771, 1612, 1526, 1350, 1201, 1118, 1001, 957, 903, 864, 819 and 754; δ_H(+23 °C) 1.22 (6 H, d, *J* 7.0), 1.85 (3 H, s), 3.28 (1 H, hept, *J* 7.0), 4.12 (2 H, s,), 7.64 (2 H, d, *J* 10.0) and 8.24 (2 H, d, *J* 10.0); δ_H(−40 °C) 1.27 (6 H, d, *J* 7.0), 1.8 (3 H, s), 3.33 (1 H, hept, *J* 7.0), 4.09 (1 H, broad), 4.23 (1 H, broad), 7.67 (2 H, d, *J* 10.0) and 8.30 (2 H, d, *J* 10.0).

***O*-Acetyl-*N*-*p*-chlorobenzyl-*N*-isopropylhydroxylamine 15c.** Compound **15c** was a colourless liquid (Found: C, 59.5; H, 6.65; N, 5.8. $C_{12}H_{16}NO_2Cl$ requires C, 59.63; H, 6.67; N, 5.8%); ν_{max}(neat)/cm^{-1} 2972, 1765, 1493, 1385, 1210, 1091, 1016, 1001, 906, 804 and 736; δ_H(+24 °C) 1.20 (6 H, d, *J* 6.0), 1.84 (3 H, s), 3.21 (1 H, hept, *J* 6.0), 3.97 (2 H, s) and 7.35 (4 H, AB, *J* 9.0).

***O*-Acetyl-*N*-*p*-methoxybenzyl-*N*-isopropylhydroxylamine 15d.** Compound **15d** was a colourless liquid (Found: C, 65.6; H, 8.1; N, 5.9. $C_{13}H_{19}NO_3$ requires C, 65.80; H, 8.07; N, 5.9%); ν_{max}(neat)/cm^{-1} 2972, 2829, 1762, 1615, 1517, 1368, 1262, 1207, 1177, 1034, 1001, 908, 825 and 808; δ_H(+18 °C) 1.22 (6 H, d, *J* 6.0), 1.88 (3 H, s), 3.22 (1 H, hept, *J* 6.0), 3.83 (3 H, s), 3.98 (2 H, s), 6.92 (2 H, d, *J* 10.0) and 7.36 (2 H, d, *J* 10.0); mass spectrum: *m/z* (M$^+$ 2%).

***O*-Acetyl-*N*-*p*-methylbenzyl-*N*-isopropylhydroxylamine 15e.** Compound **15e** was a colourless liquid (Found: C, 70.35; H, 8.4; N, 6.4. $C_{13}H_{19}NO_2$ requires C, 70.56; H, 8.65; N, 6.33%); ν_{max}(neat)/cm^{-1} 2971, 1764, 1526, 1368, 1210, 998, 909 and 798; δ_H(+23 °C) 1.27 (6 H, d, *J* 6.0), 1.73 (3 H, s), 2.43 (3 H, s), 3.28 (1 H, hept, *J* 6.0), 4.07 (2 H, s), 7.26 (2 H, d, *J* 9.0) and 7.40 (2 H, d, *J* 9.0).

***O*-Acetyl-*N*-*p*-*N*,*N*-dimethylbenzyl-*N*-isopropylhydroxylamine 15f.** Compound **15f** was a colourless liquid (Found: C, 67.0; H, 8.7; N, 11.2. $C_{14}H_{22}N_2O_2$ requires C, 67.17; H, 8.86; N, 11.19%); ν_{max}(neat)/cm^{-1} 2949, 2775, 1761, 1618, 1526, 1365, 1213, 1165, 1126, 998, 948, 903 and 811; δ_H(+23.5 °C) 1.17 (6 H, d, *J* 6.0), 1.87 (3 H, s), 2.94 (6 H, s), 3.15 (1 H, hept, *J* 6.0), 3.92 (2 H, s), 6.70 (2 H, d, *J* 10.0) and 7.24 (2 H, d, *J* 10.0).

***O*-Acetyl-*N*-*m*-nitrobenzyl-*N*-isopropylhydroxylamine 15g.** Compound **15g** was a colourless liquid (Found: C, 57.0; H, 6.4;

N, 11.1. $C_{12}H_{16}N2O_4$ requires C, 57.13; H, 6.39; N, 11.10%); ν_{max}(neat)/cm^{-1} 2977, 1764, 1532, 1353, 1204, 1094, 998, 897, 810 and 736; δ_H(+20 °C) 1.23 (6 H, d, *J* 6.0), 1.86 (3 H, s), 2.99 (1 H, hept, *J* 6.0), 4.10 (2 H, s) and 7.47–8.35 (4 H, m); δ_H(−50 °C) 1.27 (6 H, broad), 1.92 (3 H, s), 3.33 (1 H, hept, *J* 7.0), 4.01 (1 H, d, *J* 13.0), 4.26 (1 H, d, *J* 13.0) and 7.55–8.39 (4 H, m); mass spectrum: *m/z* 252 (M^+ 5%).

***O*-Acetyl-*N*-*m*-bromobenzyl-*N*-isopropylhydroxylamine 15h.** Compound **15h** was a colourless liquid (Found: C, 50.2; H, 5.6; N, 4.9. $C_{12}H_{16}NO_2Br$ requires C, 50.37; H, 5.64; N, 4.89%); ν_{max}(neat)/cm^{-1} 2972, 2862, 1765, 1571, 1472, 1371, 1204, 1070, 998, 906 and 778; δ_H(+24 °C) 1.22 (6 H, d, *J* 7.0), 1.90 (3 H, s), 3.24 (1 H, hept, *J* 7.0), 3.98 (2 H, s) and 7.17–7.65 (4 H, m).

***O*-Acetyl-*N*-*p*-bromobenzyl-*N*-isopropylhydroxylamine 15i.** Compound **15i** formed colourless crystals, mp 34–36 °C (diethyl ether–hexane) (Found: C, 50.15; H, 5.6; N, 4.9. $C_{12}H_{16}NO_2Br$ requires C, 50.37; H, 5.64; N, 4.89%); ν_{max}(KBr)/cm^{-1} 3000, 1765, 1490, 1368, 1210, 1174, 1070, 1013, 906 and 799; δ_H(+24 °C) 1.20 (6 H, d, *J* 7.0), 1.84 (3 H, s), 3.21 (1 H, hept, *J* 7.0), 3.95 (2 H, s), 7.31 (2 H, d, *J* 10.0) and 7.49 (2 H, d, *J* 10.0).

***O*-Acetyl-*N*-2,4,5-trimethoxybenzyl-*N*-isopropylhydroxylamine 15j.** Compound **15j** formed white crystals, mp 40–41 °C (diethyl ether–hexane) (Found: C, 60.35; H, 7.8; N, 4.7. $C_{15}H_{23}NO_5$ requires C, 60.59; H, 7.80; N, 4.71%); ν_{max}(KBr)/cm^{-1} 2975, 2925, 2825, 1768, 1615, 1517, 1466, 1434, 1311, 1257, 1216, 1129, 1046, 989, 903, 861, 837, 810 and 751; δ_H(+23 °C) 1.21 (6 H, d, *J* 6.0), 1.88 (3 H, s), 3.22 (1 H, hept, *J* 6.0), 3.84 (3 H, s), 3.86 (3 H, s), 3.91 (3 H, s), 4.03 (2 H, s), 6.57 (1 H, s) and 7.26 (1 H, s).

General procedure for the synthesis of isoxazolidines 17

To a solution of the hydroxylamine **8** (3.0 mmol) in CH_2Cl_2 (10 cm^3) at 0 °C was added yellow HgO (2.60 g, 12 mmol). The reaction mixture was stirred at −10 °C until the formation of the *N*-oxide and the disappearance of the hydroxylamine were complete (*ca.* 2 h) as indicated by TLC (silica, diethyl ether). After passing through a bed of $MgSO_4$ and washing the bed with CH_2Cl_2 the resultant solution was concentrated to *ca.* 10 cm^3 and ethyl vinyl ether (3 cm^3) was added to it. After stirring the mixture at 30 °C for 48 h, the solvent and excess alkane were removed and the residual mixture was chromatographed over silica gel using appropriate eluent as detailed below.

2-(*p*-Nitrobenzyl)-5-ethoxyisoxazolidine 17b. Compound **17b** was purified by chromatography using 4:1 hexane–diethyl ether mixture as eluent. Colourless liquid (18% yield); ν_{max}(neat)/cm^{-1} 2971, 2906, 1520, 1350, 1106, 1101, 935 and 745 (Found: C, 57.1; H, 6.3; N, 11.1. $C_{12}H_{16}N_2O_4$ requires C, 57,13; H, 6.39; N, 11.10%); δ_H(−30.0 °C) 1.25 (0.60 × 3 H, t, *J* 7.0), 1.29 (0.40 × 3 H, t, *J* 7.0), 2.22–2.80 (2.60 × 1 H, m), 3.18–3.32 (0.40 × 1 H, m), 3.34–3.60 (2 H, m), 3.77 (1 H, dq, *J* 7.0, *J* 10.0), 4.05 (0.60 × 1 H, d, *J* 15.0), 4.17 (0.40 × 1 H, d, *J* 14.0), 4.25 (0.60 × 1 H, d, *J* 15.0), 4.41 (0.40 × 1 H, d, *J* 14.0), 5.28 (1 H, broad m), 7.69 (2 H, two overlapping doublets, *J* 9.0) and 8.33 (2 H, two overlapping doublets, *J* 9.0); δ_H(+50 °C) 1.22 (3 H, t, *J* 7.0), 2.44 (2 H, m), 3.0 (1 H, m), 3.27 (1 H, m), 3.50 (1 H, dq, *J* 7.0, *J* 10.0), 3.73 (1 H, dq, *J* 7.0, *J* 10.0), 4.07 (1 H, d, *J* 14.0), 4.27 (1 H, d, *J* 14.0), 5.24 (1 H, dd, *J* 2.3, *J* 5.75), 7.66 (2 H, d, *J* 10.0) and 8.27 (2 H, d, *J* 10.0).

2-*p*-(Chlorobenzyl)-5-ethoxyisoxazolidine 17c. Compound **17c** was purified by chromatography using 4:1 hexane–diethyl ether mixture as eluent. Colourless liquid (25% yield); ν_{max}(neat)/cm^{-1} 2977, 2909, 1493, 1103, 1016, 933 and 811 (Found: C, 59.5; H, 6.7; N, 5.8. $C_{12}H_{16}NO_2Cl$ requires C, 59.62; H, 6.67; N, 5.79%); δ_H(−40 °C) 1.24 (0.58 × 3 H, t, *J* 7.0), 1.29 (0.42 × 3 H, t, *J* 7.0), 2.17–2.71 (2.42 × 1 H, m), 3.11 (0.42 × 1 H, app. q, *J* 8.0), 3.41 (2.16 × 1 H, m), 3.81 (1 H, m), 4.02 (0.58 × 2 H, AB, *J* 13.8), 4.05 (0.42 × 1 H, d, *J* 12.5), 4.25 (0.42 × 1 H, d, *J* 12.5), 5.25 (1 H, broad m) and 7.38 (4 H, s); δ_H(+50 °C) 1.19 (3 H, t, *J* 7.0), 2.18–2.56 (2 H, m), 2.91 (1 H, m), 3.17 (1 H, m), 3.48 (1 H, dq, *J* 7.0, *J* 9.5), 3.75 (1 H, dq, *J* 7.0, *J* 9.5), 3.97 (1 H, d, *J* 14.0), 4.10 (1 H, d, *J* 14.0), 5.22 (1 H, dd, *J* 2.0, *J* 5.5) and 7.35 (4 H, m); mass spectrum: *m/z* 243 (M^+ 24).

2-(*p*-Methoxybenzyl)-5-ethoxyisoxazolidine 17d. Compound **17d** was purified by chromatography using 1:1 hexane–diethyl ether mixture as eluent. Colourless liquid (32% yield); ν_{max}(neat)/cm^{-1} 2977, 2909, 1517, 1249, 1103, 1034, 984 and 820 (Found: C, 65.6; H, 8.05; N, 5.9. $C_{13}H_{19}NO_3$ requires C, 65.80; H, 8.07; N, 5.90%); δ_H(−30 °C) 1.24 (0.60 × 3 H, t, *J* 7.0), 1.29 (0.40 × 3 H, t, *J* 7.0), 2.13–2.69 (2.40 × 1 H, m), 3.09 (0.40 × 1 H, app. q, *J* 8.0), 3.21–3.59 (2.20 × 1 H, m), 3.81 (1 H, m), 3.85 (3 H, s), 3.91 (0.60 × 1 H, d, *J* 12.5), 4.01 (0.40 × 1 H, d, *J* 12.5), 4.09 (0.60 × 1 H, d, *J* 12.5), 4.24 (0.40 × 1 H, d, *J* 12.5), 5.25 (1 H, broad m), 6.95 (2 H, m) and 7.37 (2 H, m); δ_H(+50 °C) 1.22 (3 H, t, *J* 7.0), 2.15–2.51 (2 H, m), 2.89 (1 H, m), 3.13 (1 H, m), 3.49 (1 H, dq, *J* 7.0, *J* 10.0), 3.77 (1 H, m), 3.79 (3 H, s), 4.02 (2 H, broad s), 5.22 (1 H, dd, *J* 2.0, *J* 5.5), 6.90 (2 H, d, *J* 10.0) and 7.34 (2 H, d, *J* 10.0); mass spectrum: *m/z* 237 (M^+ 9%).

2-(*p*-Methylbenzyl)-5-ethoxyisoxazolidine 17e. Compound **17e** was purified by chromatography using 4:1 hexane–diethyl ether mixture as eluent. Colourless liquid (33% yield); ν_{max}(neat)/cm^{-1} 2977, 2932, 1517, 1109, 1076, 1004, 935 and 802 (Found: C, 70.6; H, 8.7; N, 6.5. $C_{13}H_{19}NO_2$ requires C, 70.56; H, 8.65; N, 6.33%); δ_H(−40 °C) 1.26 (0.59 × 3 H, t, *J* 7.0), 1.31 (0.41 × 3 H, t, *J* 7.0), 2.12–2.72 (2.41 × 1 H, m), 2.39 (3 H, s), 3.18 (0.41 × 1 H, app. q, *J* 8.0), 3.22–3.58 (2.18 × 1 H, m), 3.86 (1 H, m), 3.94 (0.59 × 1 H, d, *J* 13.5), 4.04 (0.41 × 1 H, d, *J* 12.5), 4.11 (0.59 × 1 H, d, *J* 13.5), 4.26 (0.41 × 1 H, d, *J* 12.5), 5.26 (1 H, broad m), 7.26 (2 H, m) and 7.38 (2 H, m); δ_H(+50 °C) 1.22 (3 H, t, *J* 7.0), 2.16–2.52 (2 H, m), 2.34 (3 H, s), 2.92 (1 H, m), 3.14 (1 H, m), 3.50 (1 H, dq, *J* 7.0, *J* 10.0), 3.80 (1 H, dq, *J* 7.0, *J* 10.0), 4.05 (2 H, broad s), 5.22 (1 H, dd, *J* 2.0, *J* 5.25), 7.16 (2 H, d, *J* 8.0) and 7.32 (2 H, d, *J* 8.0); mass spectrum: *m/z* 221 (M^+ 52).

2-(*p*-*N*,*N*-dimethylbenzyl)-5-ethoxyisoxazolidine 17f. Compound **17f** was purified by chromatography using 4:1 hexane–diethyl ether mixture as eluent. Colourless liquid (37% yield); ν_{max}(neat)/cm^{-1} 2961, 2884, 1615, 1523, 1344, 1105, 1079, 1010, 984, 951 and 808 (Found: C, 67.25; H, 8.8; N, 11.1. $C_{14}H_{22}N_2O_2$ requires C, 67.17; H, 8.86; N, 11.19); δ_H(−40 °C) 1.26 (0.62 × 3 H, t, *J* 7.0), 1.31 (0.38 × 3 H, t, *J* 7.0), 2.12–2.71 (2.38 × 1 H, m), 2.94 (6 H, s), 3.06 (0.38 H, m), 3.27 (1.24 × H, m), 3.47 (1 H, m), 3.90 (1 H, m), 3.79 (0.62 × 1 H, d, *J* 12.5), 3.96 (0.38 × 1 H, d, *J* 12.5), 4.13 (0.62 × 1 H, d, *J* 12.5), 4.25 (0.38 × 1 H, d, *J* 12.5), 5.28 (1 H, broad m), 6.81 (2 H, m) and 7.33 (2 H, m); δ_H(+50 °C) 1.13 (3 H, t, *J* 7.0), 2.12–2.52 (2 H, m), 2.86 (1 H, s), 2.94 (6 H, s), 3.08 (1 H, m), 3.52 (1 H, dq, *J* 7.0, *J* 10.0), 3.84 (1 H, dq, *J* 7.0, *J* 10.0), 4.02 (2 H, broad s), 5.24 (1 H, dd, *J* 2.0, *J* 5.25), 7.11 (2 H, d, *J* 10.0), 7.65 (2 H, d, *J* 10.0).

2-(*m*-Nitrobenzyl)-5-ethoxyisoxazolidine 17g. Compound **17g** was purified by chromatography using 4:1 hexane–diethyl ether mixture as eluent. Colourless liquid (12% yield); ν_{max}(neat)/cm^{-1} 2977, 2909, 1532, 1350, 1103, 1001, 948, 814, 730 and 677 (Found: C, 57.0; H, 6.3; N, 11.2. $C_{12}H_{16}N_2O_4$ requires C, 57.13; H, 6.39; N, 11.10%); δ_H(−40 °C) 1.29 (0.63 × 3 H, t, *J* 7.0), 1.33 (0.37 × 3 H, t, *J* 7.0), 2.23–3.13 (2.37 × 1 H, m), 3.21 (0.37 × 1 H, app. q, *J* 8.0), 3.50 (2.26 × 1 H, m), 3.82 (1 H, m), 4.06 (0.63 × 1 H, d, *J* 15.5), 4.17 (0.37 × 1 H, d, *J* 13.8), 4.27 (0.63 × 1 H, d, *J* 15.5), 4.39 (0.37 × 1 H, d, *J* 13.8), 5.28 (1 H, broad m), 7.63 (1 H, m), 7.86 (1 H, m), 8.27 (1 H, m) and 8.41 (1 H, m); δ_H(+50 °C) 1.21 (3 H, t, *J* 7.0), 2.21–2.63 (2 H, m), 2.98 (1 H, m), 3.27 (1 H, m), 3.50 (1 H, dq, *J* 7.0, *J* 10.0), 3.76 (1 H, dq, *J* 7.0, *J* 10.0), 4.07 (1 H, d, *J* 15.5), 4.27 (1 H, d, *J* 15.5), 5.24 (1 H, dd, *J* 2.20, *J* 5.5), 7.55 (1 H, t, *J* 8.0), 7.81 (1 H, d, *J* 8.0), 8.19 (1 H, d, *J* 8.0) and 8.36 (1 H, s); mass spectrum: *m/z* 252 (M^+ 54%).

2-(*o*-Hydroxybenzyl)-5-ethoxyisoxazolidine 17h. Compound **17h** was purified by chromatography using 4:1 hexane–diethyl ether mixture as eluent. White crystal, mp 47–49 °C (diethyl

ether–hexane) (27% yield); ν_{max}(KBr)/cm^{-1} 2975, 2913, 2875, 1592, 1490, 1266, 1258, 1099, 1076, 1040, 909, 948 and 760 (Found: C, 64.6; H, 7.55; N, 6.3. $C_{12}H_{17}NO_3$ requires C, 64.56; H, 7.67; N, 6.27%); δ_H(−40 °C) 1.25 (0.52 × 3 H, t, *J* 7.0), 1.29 (0.48 × 3 H, t, *J* 7.0), 2.23–2.77 (2.48 × 1 H, m), 3.18 (0.48 × 1 H, app. q, *J* 8.0), 3.31–3.65 (2.04 × 1 H, m), 3.80 (1 H, m), 4.11 (0.52 × 1 H, d, *J* 14.7), 4.29 (0.48 × 1 H, d, *J* 14.2), 4.39 (0.52 × 1 H, d, *J* 14.7), 4.50 (0.48 × 1 H, d, *J* 14.2), 5.29 (1 H, m), 6.96 (2 H, m), 7.10 (1 H, m), 7.31 (1 H, m) and 10.2 (1 H, s); δ_H(+50 °C) 1.23 (3 H, t, *J* 7.0), 2.54 (2 H, m), 2.96–3.60 (3 H, m), 3.76 (1 H, dq, *J* 7.0, *J* 10.0), 4.08–4.56 (2 H, m), 5.26 (1 H, t, *J* 4.0), 6.81–7.15 (3 H, m), 7.26 (1 H, t, *J* 8.0) and 9.84 (1 H, s).

2-(*o*-Methoxybenzyl)-5-ethoxyisoxazolidine 17i. Compound **17i** was purified by chromatography using 4:1 hexane–diethyl ether mixture as eluent. Colourless liquid (26% yield); ν_{max}(neat)/cm^{-1} 2977, 2909, 1496, 1460, 1240, 1106, 1076, 1031, 1001, 945 and 757 (Found: C, 65.8; H, 8.0; N, 5.8. $C_{13}H_{19}NO_3$ requires C, 65.80; H, 8.07; N, 5.90%); δ_H(−40 °C) 1.61 (3 H, d, *J* 7.0), 2.29–2.71 (2 H, m), 2.76 (0.38 × 1 H, q, *J* 8.0), 3.16 (0.38 × 1 H, q, *J* 8.0), 3.29–3.63 (2.24 × 1 H, m), 3.89 (0.62 × 3 H, s), 3.92 (0.38 × 3 H, s), 3.96 (1 H, m), 4.11 (0.62 × 2 H, AB, *J* 15.0), 4.17 (0.38 × 1 H, d, *J* 13.0), 4.32 (0.38 × 1 H, d, *J* 13.0), 5.29 (1 H, broad m), 6.89–7.15 (2 H, m) and 7.29–7.65 (2 H, m); δ_H(+50 °C) 1.22 (3 H, t, *J* 7.0), 2.14–2.56 (2 H, m), 2.96 (1 H, m), 3.19 (1 H, m), 3.50 (1 H, dq, *J* 7.0, *J* 10.0), 3.83 (1 H, dq, *J* 7.0, *J* 10.0), 3.94 (3 H, s), 4.15 (2 H, s), 5.23 (1 H, dd, *J* 2.0, *J* 5.5), 6.90 (1 H, d, *J* 8.0), 6.98 (1 H, t, *J* 8.0), 7.28 (1 H, t, *J* 8.0) and 7.53 (1 H, d, *J* 8.0); mass spectrum: *m/z* 237 (M^+ 35%).

Acknowledgements

Facilities provided by King Fahd University of Petroleum and Minerals are gratefully acknowledged.

References

1 F. G. Riddell, *Tetrahedron*, 1981, **37**, 849.
2 D. L. Griffith and J. D. Roberts, *J. Am. Chem. Soc.*, 1965, **87**, 4089.
3 (*a*) J. R. Fletcher and I. O. Sutherland, *Chem. Commun.*, 1970, 687; (*b*) D. L. Griffith, B. L. Olson and J. D. Roberts, *J. Am. Chem. Soc.*, 1971, **93**, 1648.
4 J. E. Anderson and J. E. T. Corrie, *J. Chem. Soc., Perkin Trans. 2*, 1992, 1027.
5 (*a*) C. L. Perrin, J. D. Thoburn and S. Elsheimer, *J. Org. Chem.*, 1991, **56**, 7034; (*b*) A. D. Walsh, *Discuss. Faraday Soc.*, 1947, **2**, 18; (*c*) H. A. Bent, *Chem. Rev.*, 1961, **61**, 275; (*d*) C. C. Levin, *J. Am. Chem. Soc.*, 1975, **97**, 5649.
6 J. Sandstrom, *Dynamic NMR Spectroscopy*, 1982, Academic Press, London.
7 M. Raban and D. Kost, *Tetrahedron*, 1984, **40**, 3345.
8 F. Bernardi, I. G. Csizmadia, A. Mangini, H. B. Schelgel, M. H. Whangbo and S. Wolfe, *J. Am. Chem. Soc.*, 1975, **97**, 2209.
9 J. March, *Advanced Organic Chemistry*, 3rd edn., John Wiley, New York, 1985, p. 244.
10 Sk. A. Ali, A. Hassan and M. I. M. Wazeer, *Spectrochim. Acta*, 1995, **51A**, 2279.
11 (*a*) P. Deshong, C. M. Dicken, R. R. Staib, A. J. Freyer and S. M. Weinreb, *J. Org. Chem.*, 1982, **47**, 4397; (*b*) A. T. Bottini and J. D. Roberts, *J. Am. Chem. Soc.*, 1958, **80**, 5203; (*c*) E. Juaristi and G. Cuevas, *Recent Studies of the Anomeric Effect*, Tetrahedron Report No. 315; *Tetrahedron*, 1992, **48**, 5019.
12 M. I. M. Wazeer and Sk. A. Ali, *Can. J. Appl. Spect.*, 1995, **40**, 53.
13 The NMR Program Library, Science and Engineering Research Council, 1975, Daresbury, UK.
14 Sk. A. Ali, A. Hassan and M. I. M. Wazeer, *J. Chem. Soc., Perkin Trans. 2*, 1996, 1479.
15 M. I. M. Wazeer, H. A. Muallem, S. Fayyaz and Sk. A. Ali, *Can. J. Appl. Spec.*, 1995, **40**, 27.

Paper 6/04719J
Received 5*th July* 1996
Accepted 9*th October* 1996