Tetrahedron Vol. 46, No. 20, pp. 7247-7262, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

ALKOXYNITRENIUM ION CYCLISATIONS: EVIDENCE FOR DIFFERENT MECHANISMS IN THE FORMATION OF BENZOXAZINES AND BENZOXAZEPINES.

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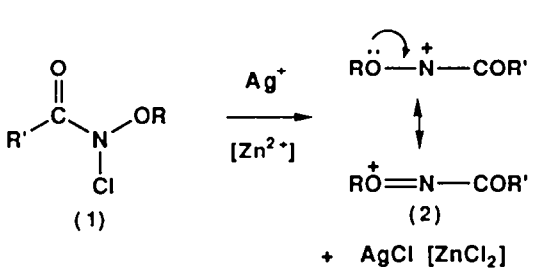
(*Received in UK* 29 *June* 1990)

Deuterium labelling experiments and n.m.r.studies indicate that cyclisations of N-acyl-N-(2-phenylethyloxy)nitrenium ions occur via direct attack at the *ortho* position to give 3,4-dihydro-1*H*-2,1-benzoxazines. In contrast N-acyl-N-(3-phenylpropyloxy)nitrenium ions cyclise to 1,3,4,5-tetrahydro-2,1-benzoxazepines through *ipso* attack followed by 1,2-carbon migration. In both cases hydrogen circumambulation occurs in the sigma complex before aromatisation.

Introduction.

N-alkoxy-N-acylnitrenium ions (2) can be generated by the treatment of N-chloro-N-alkoxyamides (1) with Lewis acids due to the intrinsic stabilization of the electron deficient nitrogen by the neighbouring oxygen lone pair. [1,2,3,4]



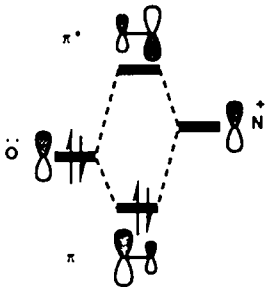
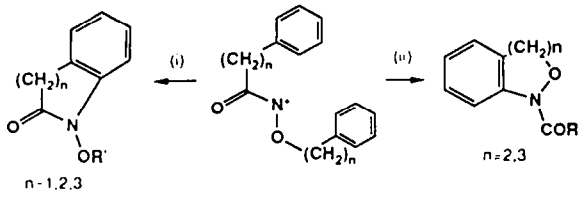


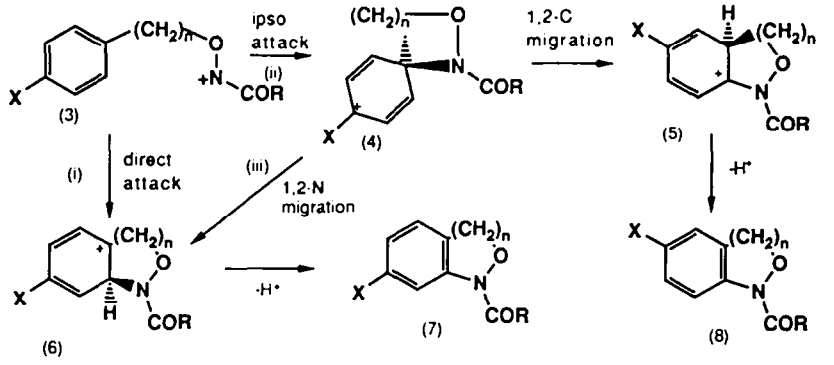
Figure 1.

We have recently reported calculations at the MNDO and *ab initio* levels which demonstrate the efficacy of this mesomeric stabilization and that derived from other heteroatom lone pairs as well as a phenyl substituent. [5] Notably, π-overlap between the vacant $2p_z$ orbital on nitrogen and the filled $2p_z$ orbital on the heteroatom leads to a substantial π bond character between nitrogen and the heteroatom (π bond-orders in excess of 0.9) (Figure 1). This double bond character has been invoked in explaining the different modes of reaction in intramolecular cyclization of N-alkoxy-N-acylnitrenium ions onto aromatic rings. [2] N-alkoxylactam formation by attack onto the acyl side-chain is



Scheme 1

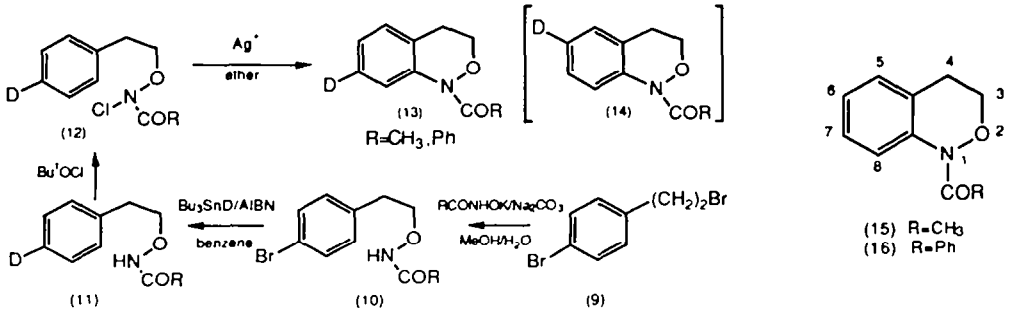
facilitated by the exocyclic nature of this NO π-bond and γ,δ as well as ε lactam formation is possible (Scheme1,i). [2,3,6] Cyclization onto the alkoxy side-chain can result in benzoxazine and benzoxazepine but not benzoxazole formation (Scheme 1,ii). [1,2] In these cyclisations, we have proposed that since the π-bond is endocyclic in the transition state there is a consequent increase in strain and five-membered ring formation is more difficult. In addition the mechanisms by which unsubstituted 2,1-benzoxazepine and 2,1-benzoxazine are formed are fundamentally different. The former are formed predominantly by *ipso* attack followed by carbon migration (Scheme2,ii,n=3) while the latter occur by direct *ortho* attack (Scheme 2,i,n=2). [2] These conclusions were drawn from labelling experiments which are the subject of this communication.



Scheme 2

Results and discussion.

The mechanism of benzoxazine formation was established from cyclization of deuterated N-chloro-2-phenylethylhydroxamates (12). Incorporation of deuterium at the *p*-position of (11) was effected by radical chain substitution of a *p*-bromo substituent in (10) [7] which in turn was synthesised by condensation of 2-(4-bromophenyl)ethyl bromide (9) and the appropriate potassium hydroxamate (Scheme 3). [8] Direct attack onto the *ortho* position (Scheme2, i,n=2) would be indicated by formation of (13). *ipso* attack followed by carbon migration (Scheme2,ii,n=2) would lead to (14) as major product.



Scheme 3

The position of deuterium in the final product was determined by ^{1}H and ^{13}C nmr spectroscopy which necessitated complete assignment of the proton and carbon resonances in the parent compounds (15) and (16). The four spin aromatic region of N-acetyl 1*H*-3,4-dihydro-2,1-benzoxazine (15) (Figure2a) was characterised by a low-field doublet (δ7.93) which could either be H_5 or H_8. The other terminus of the four-spin system was a doublet centred on δ7.18. $^{1}J_{CH}$ correlated spectroscopy was used to label resonances due to C_5 or C_8 as those at δ121.0 and δ128.8. The resonance at δ128.8 was unequivocally assigned to C_5 from $^{2,3}J_{CH}$ correlated spectroscopy which displayed strong correlations between the benzylic protons (δ3.03) and methine carbon at δ128.8, quaternaries at δ123.1 and δ136.4 as well as the methylene carbon C_3 (Figure 3a). The final assignments shown in (Figure3b) were established by other long range heteronuclear correlations and COSY 45. The deshielding of H_8 can be attributed to its proximity to the acetyl oxygen. X-ray data shows that slight puckering of the oxazine ring places the acetyl group slightly below the benzoxazine plane with the carbonyl oxygen orientated towards rather than away from H_8 (Figure 3c). [9] AM1 calculations predict a similar conformation to be that of minimum energy. [10]

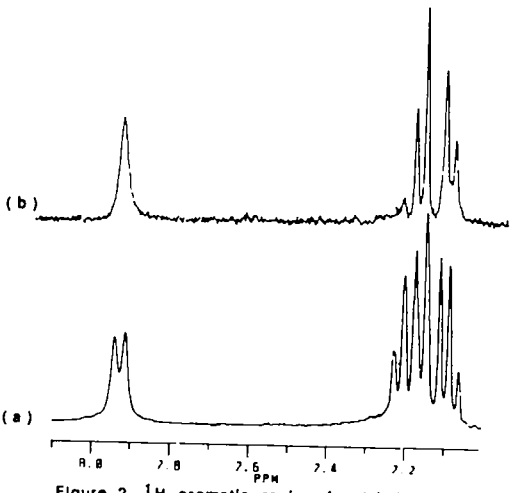
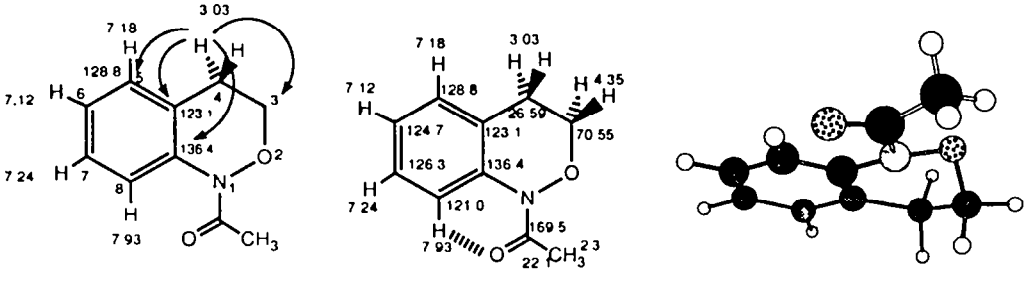


Figure 2. ^{1}H aromatic region for (a) (15) and (b) (13,R=CH_3) at 298K in $CDCl_3$.



(a) (b) (c)

Figure 3

The deuterated benzoxazine which was isolated by chromatography from cyclization of (12,R=CH_3) with silver tetrafluoroborate in anhydrous ether was (13,R=CH_3). The proton nmr spectrum (Figure 2b) clearly shows the absence of proton H_7 together with removal of an *ortho* coupling from both H_8 (δ7.93) and H_6 (δ7.12). The resonance due to C_7 at δ126.3 was attenuated in the normal ^{13}C proton decoupled spectrum and both $^{13}C_6$ and $^{13}C_8$ experienced upfield β-isotope shifts of 112 and 97ppb respectively, consistent with the presence of one deuterated isomer (*vide infra*).

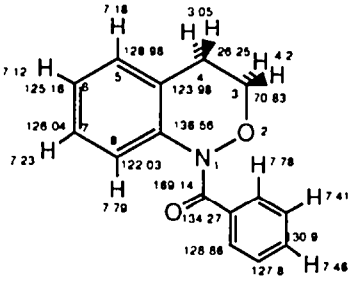


Figure 4

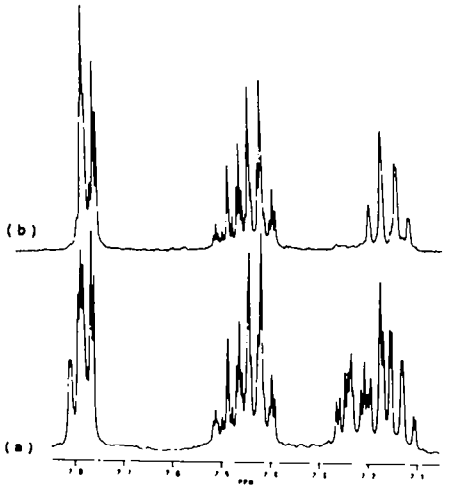
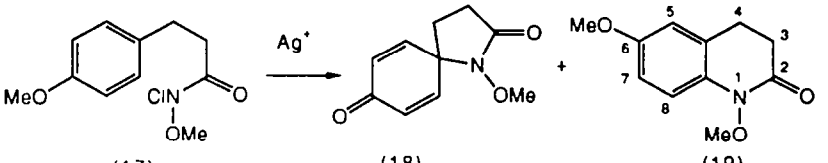


Figure 5. ^1H aromatic region for (a) (16) and (b) (13,R=Ph) at 298K in $CDCl_3$.

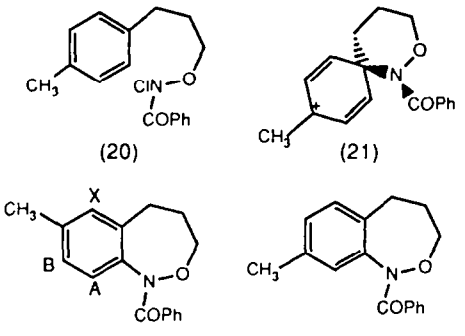
The ^1H and ^{13}C assignments for N-benzoyl 1*H* -3,4 dihydro-2,1- benzoxazine (16), determined by similar methods, are depicted in Figure 4. The proton H_8 resonates as a doublet (δ7.79) which is superimposed on the multiplet of the *ortho* protons on the benzoyl ring. (Figure 5a). H_7,H_5 and H_6 resonate as a finely coupled triplet, doublet and triplet centred at δ7.23, δ7.18 and δ7.12 respectively. Like the acetyl compound, the deuterated analogue of (15), (13,R=Ph) showed an absence of the proton H_7 and collapse of H_8 and H_6 to a singlet and doublet respectively (Figure 5b). In addition, the ^{13}C resonance at δ126.0 was attenuated in the ^{13}C spectrum while $^{13}C_6$ and $^{13}C_8$ each experienced upfield β-isotope shifts of 105ppb.

These results are indicative of direct cyclisation onto the *ortho* position. An alternative pathway via spirane carbocation intermediate (4) (Scheme 2, n=2) followed by **nitrogen** migration (Scheme 2,iii,n=2) is unlikely on two accounts. Firstly, this would lead to the least stable carbocation (6) while **carbon** migration gives a cation adjacent to the nitrogen atom with effective lone pair stabilisation (5). AM1 calculations predict similar activation energies for both processes however. [10] Secondly, carbon migration is the preferred mode of rearrangement of such cation intermediates as evidenced by the formation of benzoxazepines (*vide infra)* and cyclisation of N-chloro-O-methyl-3-(4-methoxyphenyl)-propanohydroxamate (17) which gives a mixture of spirodienone (18, 9%) and N-methoxy-6-methoxy-1*H*-3,4-dihydro-2-quinolone (19, 13%) instead of the 7-methoxy derivative. (19) clearly arises by a 1,2-carbon migration. [2]



(17) (18) (19)

Early indications that benzoxazepine formation proceeds through a 2-oxo-1-azaspiro-[6,6]-undecadienyl cationic intermediate (4) (Scheme 2, n=3) followed by a 1,2-carbon migration were found in the cyclisation of N-chloro-O-[3-(4-methylphenyl)propyl] benzohydroxamate (20) with silver tetrafluoroborate in ether which gave a 17% conversion to N-benzoyl-7-methyl-1,3,4,5-tetrahydro-2,1-benzoxazepine (22) via (21). The position of the methyl group was established by 500MHz ^{1}H nmr spectroscopy. The upfield aromatic region of the ^{1}H nmr (Figure 6) depicted a typical ABX spin system which could accord with either (22) or the 8-methyl analogue (23). However a COSY spectrum showed coupling between the X proton at δ7.05 and both sets of benzylic protons. In addition the methyl protons coupled to the B proton at δ6.81. This accords with (22).



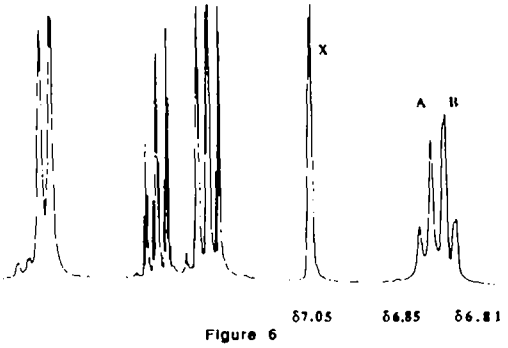


Figure 6

^{13}C spectroscopy indicated that the A,B and X protons at δ6.81, δ6.85 and δ7.05 were correlated with methine carbons at δ127.45, δ127.3 and δ130.76ppm and conclusive proof that the methyl was in the 7-position came from Selective Population Inversion (SPI) experiments. [11] Application of a 180° decoupler pulse close to the ring benzylic proton resonance frequency (δ3.04) resulted in selective inversion of two quaternaries at δ138.49 and δ139.49 as well as the aromatic methine at δ130.76 (Figure 7a). Polarisation transfer from the methyl protons inverted this carbon as well as the quaternary at δ138.05 and the methine carbon at δ127.3 ppm (Figure 7b). Since these experiments result in enhancement/inversion of carbons only two or three bonds removed from the protons in question, the structure was therefore that indicated in (22) in which the carbon at δ130.8 is two bonds from both the methyl and

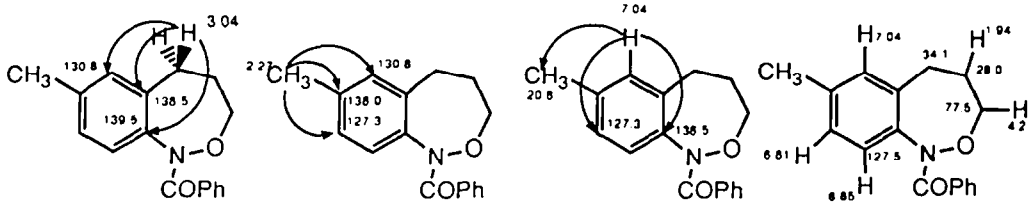
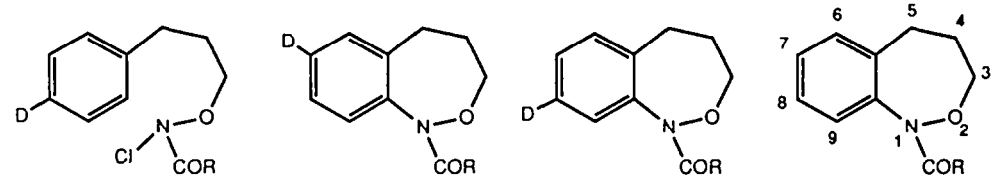


Figure 7

benzylic protons. A further SPI experiment (Figure 7c) resulted in final assignments shown in Figure 7d.

This mode of cyclisation could be ascribed to the *para* directing effect of the methyl group. More definitive evidence for this mechanism was derived from the cyclisation of N-chloro-O-(3-(4-deuteriophenyl)propyl)benzohydroxamate (24a) which was synthesised in analogous fashion to (12) from 3-(*p*-bromophenyl)propylbromide and potassium benzohydroxamate. Cyclisation with silver tetrafluoroborate in ether afforded a deuterated N-benzoyl-1,3,4,5-tetrahydrobenzoxazepine, (25a) or (26a).



(a) R=Ph
(b) R=CH_3 (24) (25) (26) (27)

Structural elucidation required the complete assignment of the ^1H and ^{13}C nmr resonances for the parent compound (27a). At 298K, the proton nmr spectrum showed considerable broadening in both the aliphatic and aromatic regions. However the aromatic region was comprised of a four spin system to high field of and overlapping the benzoyl proton resonances. (δ7.27 to δ6.9) (Figure 8a). At 370K in hexadeuterio DMSO, aliphatic ^1H resonances were sharp but slight broadening of the upfield aromatic doublet (δ6.93) and triplet (δ7.05) as well as the *ortho* protons on the benzoyl ring (δ7.48) was still evident (Figure 8b). X-ray analysis has shown that in the solid state this novel fused heterocycle is in a chair conformation with the benzoyl substituent in a pseudo axial orientation and the phenyl ring folded over the aromatic portion of the molecule (Figure 9c). [9] Line broadening of these protons could therefore be ascribed to a relatively slow rotation about the amide bond as H_9 and H_8 as well as the *ortho* protons would be expected to be more

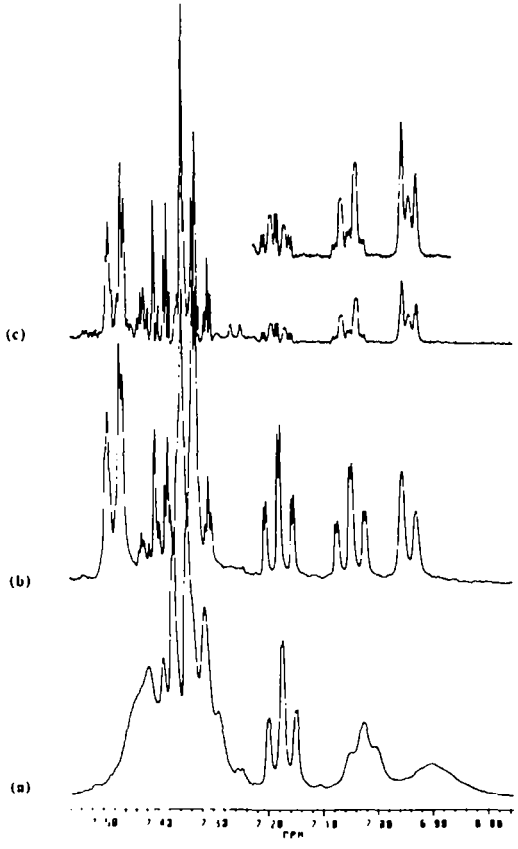


Figure 8. (a) (27a) at 298K; (b) (27a) at 370K; (c) (25-27a) at 370K.

influenced by varying magnetic anisotropies as a consequence of these conformational changes. Broadening of the aliphatic methylenic resonances at room temperature is on the other hand attributable to flipping between two chair conformations of the seven-membered ring. At 219K both methylene multiplets at δ3.08 and δ4.18 were resolved into axial and equatorial components. From their coalescence temperatures, a typical $\Delta G^{\ddagger}$ of 13 kcal mol^{-1}(E_A *ca* 8.1 kcal mol^{-1}) was obtained. [12]

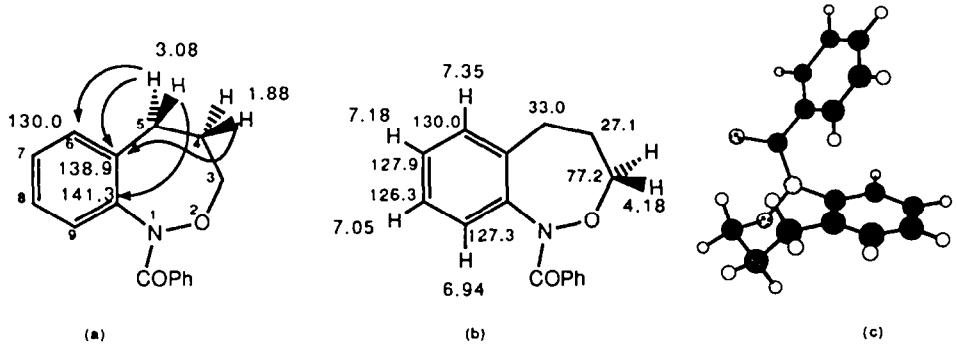


Figure 9

The tentative assignment of H_8 and H_9 was confirmed by CH-correlated spectroscopy at 370K. A $^1J_{CH}$ correlated spectrum allowed assignment of the ^{13}C resonances corresponding to the four spin system and in particular those due to either C_6 and C_9 as those at δ130.0 and δ127.29. A $^3J_{CH}$ spectrum showed a correlation between the benzylic protons and the carbon resonance at δ130.0 (Figure 9a) which enabled assignment of C_6 as well as the other carbons and protons of the four-spin system. Other long range correlations depicted in Figure 9a gave the final assignments shown in Figure 9b

Benzoxazepine deuterated at the 8 position (26a) would remove the upfield triplet of the four-spin system and as well as one vicinal coupling from the resonances at δ6.94 and δ7.18. 7-deuteriobenzoxazepine (25a) would not display a low-field triplet at δ7.18 and would have simplified resonances at δ7.05 and δ7.35 as a broadened doublet and singlet respectively. The ^1H nmr spectrum of the product was in the main attributable to the 7-deuterio species (25a) (Figure 8c). Analysis of the residual signal at δ7.18 as well as the upfield doublet at δ6.94 suggests the presence of some of the 8-deuterio species(26a). The signal at δ7.18 is a crude doublet while at δ6.94 the doublet due to H_9 of (25a) is superimposed upon a broadened singlet. An unexpected feature though was the presence of fully protonated material (27a) as evidenced by the residual triplets of doublets at both δ7.19 and δ7.05 (Figure 8c). The molecular ion for (27a) (m/z 253) constituted *ca.*16% of the total molecular ion intensity. Furthermore the mass spectrum of (27a) itself displayed a negligible [M-1] fragment and since the molecular ion (m/z 256) in the mass spectrum of the uncyclised hydroxamic ester was consistent with 100% deuterated material, deuterium exchange appears to have occurred during the cyclisation process (*vide infra*) .

The N-acetyl analogue (24b) was cyclised to a similar mixture of the 7-deuterio- (25b), 8-deuterio-(26b) and deuterium free N-acetylbenzoxazepine (27b). The aromatic region of (27b) was strongly second order at 300MHz and unresolved at 370K in D_6-DMSO. However identification of the mixture was made on the basis of ^{13}C deuterium isotope shifts in the broad-band decoupled ^{13}C spectrum (Figure 10a). [13] These were similar to those observed for the mixture of (25a) and (26a) (Figure 10b,Table 1).

Table 1.^{13}C deuterium isotope shifts in N-acetyl-and N-benzoylbenzoxazepines.[1]

position	6	7	8	9
25a	112(β)	n.d.[2]	99(β)	n.d.[3]
25b	115(β)	281(α)	100(β)	70(γ)
26a	76(γ)	n.d.[2]	n.d.[3]	95(β)
26b	76(γ)	90(β)	n.d.[3]	109(β)

1.Isotopic shifts in ppb; 2. Signals concealed by phenyl carbons; 3. Unresolved.

The major isomer proved to be the 7-deuterio species since the $^{13}C_7$ signal (δ127.2) was strongly attenuated and both $^{13}C_6$(δ129.3) and$^{13}C_8$(δ125.69) experienced β -isotope shifts. The minor isomer deuterated at C_8 (26b) resulted in a smaller γ -isotope shift for $^{13}C_6$(δ129.3) and β-isotope shifts for $^{13}C_7$ (δ127.2) and $^{13}C_9$(δ126.11) respectively. The formation of (27b) by loss of deuterium in the cyclisation was indicated by ^{13}C n.m.r. (Figure 10a) as well as a 17% contribution of m/z=191 to the molecular ion of the mixture.

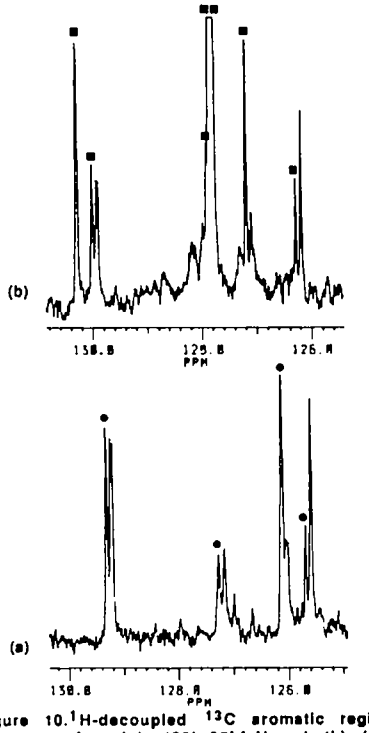
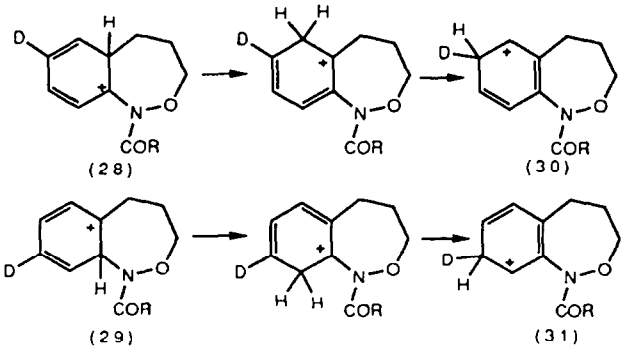


Figure 10.^1H-decoupled ^{13}C aromatic regions for (a) (25b-27b[a]) and (b) (25a-27a[a]) at 370K in D_6-DMSO.

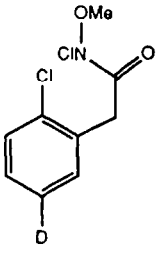
It can be concluded from this study that the major pathway in the formation of the benzoxazepines is that involving attack at the *ipso* carbon rather than direct attack at the *ortho* position however some direct attack or nitrogen migration (Scheme 2 n=3, i or iii) is indicated. The formation of deuterium free material from both cyclisations is interesting and clearly indicates a circumambulation of proton in the intermediate σ complexes (28) or (29) (Scheme 4). Stepwise 1,2 migration (which can be construed as a symmetry allowed suprafacial 1,6 sigmatropic rearrangement about the pentadienyl cation) would lead to intermediates (30) and (31) which could lose deuterium or hydrogen upon rearomatisation (Scheme 4). 1,2-migration of deuterium in (30) to give (31) [or in (31) to give (30)], while possible is likely to be a minor pathway considering the selective nature of the thermoneutral rearrangement and the magnitude of primary deuterium isotope effects. [14] The obvious preponderence of the 7-deuterio isomer in both product mixtures can therefore be accounted for by carbon migration in the spirane intermediates from *ipso* attack.

Re-analysis of the ^{13}C nmr spectra of the deuterated benzoxazines and the mass spectra of (13,R=Ph,Me) confirmed the presence of small quantities of (15) and (16) which are presumably formed in similar fashion. However only the 7-deuterio isomers could be detected by n.m.r. thus confirming that deuterium migration is not a competitive process.

In the course of our study, Kikugawa reported a similar 1,2(1,6) proton migration in the generically similar silver catalysed cyclisation of N-chloro-2-(2-chloro-5-deuteriophenyl)-N-methoxyacetamide (32). In TFA this reaction gave 4-Chloro-7-deuterio-1-methoxy-2-oxindole 55%, 4-chloro-1-methoxy-2-oxindole 17% and 7-chloro-5-deuterio-1-methoxy-2-oxindole 12%. [15] It is possible therefore that circumambulation of proton generally competes with aromatisation in σ- complex intermediates of this type in much the same way as has been found in benzenium ions from protonation of benzene. [16]



Scheme 4



(32)

Acknowledgements:

We are grateful to Prof. A. Goosen and Dr. C.W. McCleland for fruitful discussions, to Dr P.L.Wessels of the South African C.S.I.R.O for running the SPI experiments and to Mr. M. Smythe of the Mass Spectrometry Unit at the University of Sydney for providing Mass Spectra. In addition we are grateful to the Australian Research Council and the South African C.S.I.R. (J.L.S.) for financial support.

Experimental Details

Ir spectra were recorded on a Perkin-Elmer 502 Infrared Spectrometer. 300 MHz ^1H and 75 MHz ^{13}C n.m.r. spectra were recorded on a 60MHz Perkin-Elmer R12A, Bruker AC-300P and Bruker WM500 spectrometers. Mass Spectral data was obtained on an upgraded Kratos MS902 spectrometer through the Mass Spectrometry Unit of Sydney University.

Melting points were determined on a Reichert Microscopic Hot-Stage and are uncorrected.

H.p.l.c analyses were performed on a Waters 510 Analytical instrument using a model 481 UV absorbance detector linked to a Waters 740 data module. Preparative separations were performed on a Waters Prep500 h.p.l.c.

Ether refers to anhydrous diethyl ether. Benzene and tetrahydrofuran (THF) were distilled and dried over sodium wire. Methylene chloride (DCM) was dried over molecular sieve. Petroleum spirit (Pet. sp.) refers to petroleum spirit of the boiling range 60-70°C. Anhydrous sodium sulphate was used for drying of all mixtures. Preparative plates were coated with Kiesegel 60 with indicator (Merck). Flash chromatography was executed on columns loaded with Kiesegel 60 (Merck).

Syntheses.

Tributyltin Deuteride.

Tri-*n*-butyltin chloride (9.76g, 30mmol), dissolved in ether (25ml) was added to an ice cooled suspension of lithium aluminium deuteride (0.50g,120mmol) in ether over a period of 15 minutes. The mixture was stirred at room temperature for 18 hours and then hydrolysed with ice cold water. The ethereal layer was washed twice with ice cold water, dried and concentration under reduced pressure. High vacuum distillation of the resultant oil (b.p.75°C/0.1mm) yielded tri-*n*-butyltin deuteride (3.77g,13mmol). ν_{max} 1320 cm^{-1}(Sn-D).

2-(4-Bromophenyl)ethanol.

4-Bromophenylacetic acid (6.0g, 28mmol) in THF (25ml) was added dropwise to a suspension of lithium aluminium hydride (1.25g,37mmol) in THF (50ml). The reaction was stirred under reflux for 12 hours after which the mixture was poured onto crushed ice (100g), acidified (conc. HCl, 10ml) and extracted with ether (50ml). The extracts were washed with water, saturated sodium carbonate, water and dried. Concentration under reduced pressure gave a clear oil (4.65g) which was a mixture (h.p.l.c., n.m.r.) of phenylethanol and the 4-bromo adduct. Fractional distillation (b.p.70°C/0.04mm) (Lit.[17] b.p.104°/1mm) afforded 2-(4-bromophenyl) ethanol (98.9% pure by analytical h.p.l.c.), ν_{max} ($CHCl_3$) 3450 cm^{-1} (br, OH); δ ($CDCl_3$) 2.8 (2H,t), 3.2 (1H,s), 3.75 (2H,t), 7.25 (4H,2xd)

4-Bromocinnamic Acid.

4-Bromocinnamic acid was synthesised from 4-bromobenzaldehyde, acetic anydride and potassium acetate according to a standard procedure [18] and was isolated as pale yellow crystals from water/acetone, m.p. 256-258° (Lit. [19] m.p.262-264°).

3-(4-Bromophenyl)propan-1-ol.

4-Bromocinnamic acid (5g, 22mmol) in THF (50ml) was added to a suspension of lithium aluminium hydride (0.5g,13mmol) in THF (100ml). The mixture was refluxed for 1h, cooled and poured onto crushed ice/water (50g) which was acidified (dil. HCl) and extracted with ether. The ethereal solution was washed with water, saturated sodium carbonate, water and dried. Concentration resulted in an oil (3.42g,16mmol) which distilled under reduced pressure (b.p.162°/2.5mm) (Lit. [20] b.p.105.9/0.05mm) as 3-(4-bromophenyl) propan-1-ol, ν_{max} ($CHCl_3$) 3350 cm^{-1}; δ($CDCl_3$) 1.81 (2H,q), 2.62(2H,t), 3.60(2H,t), 7.01-7.39 (4H, 2xd).

3-(4-Methylphenyl)propan-1-ol.

Lithium aluminium hydride reduction of 4-methylcinnamic acid (25,0g, 154 mmol) according to the above procedure afforded 3-(4-methylphenyl)-1-propanol (21.2g,141mmol) , (b.p. 140°C /15 mm) (Lit. [21] b.p.136°/16mm). ν_{max} ($CHCl_3$) 3625, 3425 and 2950 cm^{-1}; δ(60MHz,$CDCl_3$) 1,71 (2H, m), 2,27(1H, s), 2,57(2H, t), 3,49(2H, t), 6,99(4H, s).

Phenylalkyl Bromides.

2-(4-Bromophenyl)ethyl Bromide , 3-(4-bromophenyl)propyl Bromide and **3-(4-methylphenyl)propyl Bromide** were prepared from 2-(4-bromophenyl) ethanol, 3-(4-bromophenyl) propanol and 3-(4-methylphenyl) propanol by digestion in HBr/H_2SO_4 according to standard procedures. [22] 2-(4-Bromo-phenyl)ethyl bromide distilled as a clear oil (b.p. 64°/ 0.07mm) (Lit. [23] b.p.127°/6mm) , δ($CDCl_3$) 3.45 (4H,m), 7.4 (4H,2xd). 3-(4-Bromophenyl)-propyl bromide was isolated pure by flash chromatography and was used without further purification, δ($CDCl_3$) 2.15 (2H,quintet), 2.7 (2H,t), 3.35 (2H,t), 7.04 (2H,d), 7.4(2h,d). 3-(4-Methylphenyl)-1-bromopropane was distilled (b.p. 130°C/19mm) (Lit. [24] b.p.127/18mm). ν_{max} ($CHCl_3$) 2925 and 1620 cm^{-1} (weak); δ (60MHz,$CDCl_3$) 2.15 (2H, quintet), 2.27 (3H, s), 2.79 (2H, t), 3.29 (2H, t), 7.00 (4H, s).

Synthesis of Hydroxamic Esters.

The general synthesis of hydroxamic esters from potassium salts of the hydroxamic acids and the appropriate alkylbromides [8,25] has been described previously as have the syntheses of O-(2-phenylethyl) benzohydroxamate, O-(2-phenylethyl) acetohydroxamate and O-(3-phenylpropyl) benzohydroxamate. [1,2]

O-(3-(4-Methylphenyl)-1-propyl) Benzohydroxamate.

3-(4-Methylphenyl)-1-bromopropane (14.9g,70mmol) and potassium benzohydroxamate (12.26g,70mmol) afforded O-(3-(4-methylphenyl)-1-propyl) benzohydroxamate which was recrystallised from ether-pet.sp. (8.1g,30mmol) m.p. 74-75°C. ν_{max} ($CHCl_3$) 3400, 3250, 2925, 1680 and 1605 cm^{-1}; δ(60MHz,$CDCl_3$) 1.95 (2H, m), 2.28 (3H, s), 2.69 (2H, t), 3.99 (2H, t), 7.02 (4H, s), 7.20 - 7.55 (3H, m), 7.60 - 7.85 (2H, m); M^+ 269 (trace), $^m/_z$ 224, 118, 105, 91 and 77. (Found: C 76.0; H 7.1; N 5.25%. $C_{17}H_{19}NO_2$ requires C 75.81; H 7.11; N 5.20%).

O-(2-(4-Bromophenyl)ethyl) Benzohydroxamate.

2-(4-Bromophenyl)ethyl bromide (3.0g, 11.4mmol) and potassium benzohydroxamate (2.0g,11.4mmol) afforded a colourless solid which crystallised from benzene m.p.

103.5-105 °C. δ ($CDCl_3$) 3.02 (2H,t), 4.25 (2H,t), 7.2-7.9 (9H,m), 9.2 (1H,br s); M^+319/321, m/z 182,184,137,105,77,51. (Found: C 55.7; H 4.2; Br 24.7; N 4.1%. $C_{15}H_{14}BrNO_2$ requires C 56.25; H 4.37; Br 25.0; N 4.37%.)

O-(2-(4-Bromophenyl)ethyl) Acetohydroxamate.

2-(4-Bromophenyl)ethyl bromide (3.0g,11.4mmol) and potassium acetohydroxamate (1.28g,11mmol) afforded after chromatography ($CHCl_3$) and recrystallization from benzene/pet.sp., pale yellow crystals of O-(2-(4-bromophenyl)ethyl) acetohydroxamate, m.p. 80-81.5°C. δ ($CDCl_3$) 1.87 (3H,s), 2.9 (2H,t), 4.2 (2H,t), 7.3 (4H,2xd), 9.35 (1H, br); M^+257, m/z 182/184, 169/171, 104, 90, 77, 51, 43. (Found: C 46.47; H 4.82; Br 30.7 ; N 5.06 %. $C_{10}H_{12}BrNO_2$ requires C 46.53; H 4.69 ; Br 30.96; N 5.43 %.)

O-(3-(4-Bromophenyl)propyl) Benzohydroxamate.

3-(4-Bromophenyl)propyl bromide (5.0g,18mmol) and potassium benzohydroxamate (2.93g,16.7mmol) afforded after work up and recrystallization pure O-(3-(4-bromophenyl)propyl) benzohydroxamate (1.84g,5.5mmol), m.p. 110.5-112.0°. ν_{max} ($CHCl_3$) 3200 and 1650 (s) cm^{-1} ; δ($CDCl_3$) 1.85 (2H,q), 2.6 (2H,t), 4.0 (2H,t), 6.95-7.2 (2H,d), 7.35-7.6 (5H,m), 7.8-8.05 (2H,d) ; M^+ 333/335, m/z 288/290, 105,77.

O-(3-(4-Bromopheny)propyl) Acetohydroxamate.

3-(4-Bromophenyl)propyl bromide (5.0g,18mmol) and potassium acetohydroxamate (4.06g,35mmol) afforded after work up and flash chromatography pure O-(3-(4-bromopheny)propyl) acetohydroxamate (2.71g,10mmol) as a pale yellow oil. ν_{max} ($CHCl_3$) 3200,1675 (s)cm^{-1}; δ ($CDCl_3$) 2.05 (5H,m), 2.7 (2H,t), 3.9(2H,t), 7.05-7.6(4H,2xd) ; [M^++1] 272/274, m/z 196/198, 182/184, 169/171. (Found: C 48.2; H 5.2; Br 29.4; N 5.0%. $C_{11}H_{14}BrNO_2$ requires C 48.5; H 5.1; Br 29.4; N 5.1%.)

O-(3-Phenylpropyl) Acetohydroxamate.

3-Phenylpropyl bromide (10.0g,50mmol) and potassium acetohydroxamate (11g, 94mmol) afforded, after work up and flash chromatography, pure O-(3-phenylpropyl) acetohydroxamate (4.14g,21mmol) as a clear oil. ν_{max} ($CHCl_3$) 3403, 3223(br)1685(s)cm^{-1}; δ^1H ($CDCl_3$) 1.67 and 2.08 (3H,s,Me), 1.94(2H,quintet), 2.68(2H,t), 3.88(2H,t),7.14-7.27(5H,m); $\delta^{13}C$ 19.4(q), 29.29(t)31.59(t), 75.16(t), 125.6(d), 128.0(d), 141.0(s), 167.0(s); M^+ 193, m/z 134,118,117,105,104,91,41.

General procedure for deuteration of 4-bromo derivatives.

Brominated hydroxamic ester, a 10 % molar excess of AIBN and a 20 % molar excess of tributyltin deuteride in anhydrous benzene were degassed by the 'freeze-thaw' method and refluxed overnight under nitrogen. The benzene was removed under reduced pressure to yield a mixture of the deuterated hydroxamate, excess AIBN and tributyltin bromide. Separation from the tributyltin bromide was achieved by passing a mixture of the reaction products in pet. sp. through a flash column, followed by elution with methanol. Further purification was carried out on preparative plates using first hexane and then chloroform as mobile phase. [7]

O-(2-(4-Deuteriophenyl)ethyl) Acetohydroxamate.

O-(2-(4-Bromophenyl)ethyl) acetohydroxamate (0.48g,1.86mmol), tributyltin deuteride (0.64g,2.2mmol) and AIBN (0.29g) were reacted as above in benzene (20ml). Final purification on plates and crystallisation from ether/pet.sp. gave pure O-(2-(4-deuteriophenyl)ethyl) acetohydroxamate (0.10g,0.5mmol), m.p.87-89°C. (Lit. [1] m.p. of protio analogue 91-93°). δ ($CDCl_3$) 1.9 (3H,s), 2.94 (2H,t), 4.1 (2H,t), 7.3 (4H,s), 10.2 (1H,br. s); M^+180, m/z 106, 105, 92, 66, 43.

O-(2-(4-Deuteriophenyl)ethyl) Benzohydroxamate.

O-(2-(4-Bromophenyl)ethyl) benzohydroxamate (0.75g, 3mmol), AIBN (0.48g) and tributyltin deuteride (1.05g,3.6mmol) in benzene (50ml) were reacted as above to yield crude product which was purified by preparative h.p.l.c. to yield a colourless oil. δ ($CDCl_3$) 2.9 (2H,t), 4.15 (2H,t), 7.2-7.5 (8H,m), 7.6-7.8 (2H,m), 10.1 (1H,s); M^+242 , m/z 137, 105, 92, 77, 66.

O-(3-(4-Deuteriophenyl)propyl Benzohydroxamate.

O-(3-(4-Bromophenyl)propyl) benzohydroxamate (1.6g, 4.5mmol), AIBN (0.70g) and tributyltin deuteride (1.60g,5.5mmol) in benzene (50ml) yielded after plate chromotography the title compound (0.6g,2.3mmol) as an oil. δ($CDCl_3$) 1.91(2H,q), 2.64(2H,t), 3.92(2H,t) 7.09(2h,d), 7.18(2H,d), 7.2-7.4(3H,m), 7.63(2h,d), 9.27(1H,s); M^+256, m/z 226,211,119,105,92,77

O-(3-(4-Deuteriophenyl)propyl) Acetohydroxamate.

O-3-(4-Bromophenyl)propyl acetohydroxamate (1.6g, 5.5mmol), AIBN (0.9g) and tributyltin deuteride (1.8g,6.2mmol) in benzene (50ml) gave after workup and plate chromatography the title compound (0.56g,2.9mmol). as an oil. δ ($CDCl_3$)1.67 (3H,s), 1.91 (2H,m), 2.68 (2H,t), 3.68 (2H,t), 7.15 (2H,d), 7.23(2h, broadened d); M^+194, m/z 162,149,135,119,105,92.

N-Chlorination of Hydroxamates.

N-Chlorination was achieved by stirring the appropriate hydroxamates with a three molar excess of t-butyl hypochlorite in benzene at room temperature for 2-3 hours. Removal of the benzene under reduced pressure at 35°C afforded yellow oils in almost quantitative yield. (n.m.r.) The chlorination of O-(2-phenylethyl) acetohydroxamate, O-(2-phenylethyl) benzohydroxamate and O-(3-phenylpropyl) benzohydroxamate has been described previously. [1,2] Their n.m.r. data are reported for the first time.

N-Chloro-O-(2-phenylethyl) Acetohydroxamate. δ ($CDCl_3$) 2.1 (3H,s), 3.02 (2H,t), 4.3 (2H,t), 7.34 (5H,s).

N-Chloro-O-(2-phenylethyl) Benzohydroxamate. δ ($CDCl_3$) 2.96 (2H,t), 4.4 (2H,t), 7.3-7.5 (8H,m), 7.7-7.9 (2H,m).

N-Chloro-O-(3-phenylpropyl) Benzohydroxamate. δ ($CDCl_3$) 1.93 (2H,m), 2.6 (2H,t), 4.14 (2H,t), 7.09-7.59 (7H,m), 7.74-7.77 (2H, dd).

N-Chloro-O-(3-(4-methylphenyl)-1-propyl) Benzohydroxamate was a yellow oil. ν_{max} ($CHCl_3$) 1730 cm^{-1}; δ (60MHz,$CDCl_3$) 1.82 (2H, m), 2.24 (3H, s), 2.51 (2H, t), 4.01 (2H, t), 6.90 (4H, s), 7.15 - 7.48 (3H, m), 7.60 - 7.81 (2H, m). (Found: Cl (by iodometry), 11.4%. $C_{17}H_{18}NO_2$ requires Cl, 11.67%).

N-Chloro-O-(3-phenylpropyl) Acetohydroxamate was a yellow oil δ ($CDCl_3$) 2.02 (2H,m), 2.16 (3H,s), 2.69 (2H,t), 4.06 (2H,t), 7.18(2H,d), 7.27(2H,d).

N-Chloro-O-(2-(4-deuteriophenyl)ethyl) Acetohydroxamate.
O-(2-(4-Deuteriophenyl)ethyl) acetohydroxamate and t-butyl hypochlorite gave the chloride as a yellow oil. δ ($CDCl_3$) 2.1 (3H,s), 3.02 (2H,t), 4.3 (2H,t), 7.35 (4H,2xd).

N-Chloro-O-(2-(4-deuteriophenyl)ethyl) Benzohydroxamate .
O-(2-(4-Deuteriophenyl)ethyl) benzohydroxamate and t-butyl hypochlorite gave a yellow oil. N.m.r.data not available.

N-Chloro-O-(3-(4-deuteriophenyl)propyl) Benzohydroxamate was a yellow oil. ν_{max} ($CHCl_3$)1740cm-1(s); δ($CDCl_3$) 1.93 (2H,q), 2.60 (2H,t), 4.10 (2H,t), 7.1-7.6 (7H,m), 7.7-7.8 (2H,d).

N-Chloro-O-(3-(4-deuteriophenyl)propyl) Acetohydroxamate.
O-(3-(4-Deuteriophenyl)propyl) acetohydroxamate and t-butyl hypochlorite gave a yellow oil. ν_{max} ($CHCl_3$)1750cm-1 (s); δ($CDCl_3$) 1.99 (2H,quintet), 2.25(3H,s), 2.71(2H,t), 4.03(2H,t), 7.18(2H,d), 7.28 (2H,broadened d).

Cyclisation of N-Chlorohydroxamates.

Cyclisation of the N-chlorohydroxamates was achieved by dissolving the N-chlorohydroxamate in anhydrous ether and adding a molar equivalent of silver tetrafluoroborate. Stirring overnight at room temperature resulted in the formation of the desired product occluded onto the silver chloride precipitate. The precipitate was extracted with chloroform which was washed with water until the aqueous layer was clear, dried and concentrated.

The syntheses of **N-Acetyl-3,4-dihydro-*1H*-2,1-benzoxazine**, **N-Benzoyl-3,4-dihydro-*1H*-2,1-benzoxazine** and **N-Benzoyl-1,3,4,5-tetrahydro-2,1-benzoxazepine** from silver tetrafluoroborate and the N-chloro derivatives of O-(2-phenylethyl) acetohydroxamate, O-(2-phenylethyl) benzohydroxamate and O-(3-phenylpropyl) benzohydroxamate respectively have been described previously. [1,2]

N-Acetyl-1,3,4,5,-tetrahydro-2,1-benzoxazepine.

N-Chloro-O-(3-phenylpropyl) acetohydroxamate (2.0g, 8.8mmol) and silver tetrafluoroborate (1.70g,8.8mmol) gave a mixture which was separated on silica gel plates. The major component was N-acetyl-1,3,4,5,-tetrahydro-2,1-benzoxazepine which crystallized from benzene/pet.sp. (0.68g,3.6mmol) m.p. 88-91° (Found: C 69.45; H 7.03; N 7.07%. $C_{11}H_{13}NO_2$ requires: C 69.09; H 6.85; N 7.32%) N.m.r. data presented in the discussion.

N-Benzoyl-7-methyl-1,3,4,5-tetrahydro-2,1-benzoxazepine.

N-Chloro-O-(3-(4-Methylphenyl)-1-propyl) benzohydroxamate (2.13g; 7.0 mmol) and silver tetrafluoroborate (1.36g,7mmol) gave a brown oil which afforded two major

components upon preparative t.l.c. The more polar of these was identified as the parent hydroxamate (29%) by comparison with authentic material (n.m.r. i.r., t.l.c.). The second component was isolated as a solid (0.32g,1.2mmol) which recrystallised from benzene-pet.sp. as N-benzoyl-7-methyl-1,3,4,5-tetrahydro-2,1-benzoxazepine (17%) m.p. 103.5-105°C. ν_{max} ($CHCl_3$) 1660 and 1350 cm^{-1}; δ (500MHz; $CDCl_3$) 1.92 - 1.97 (2H, m), 2.27 (3H, s), 3.03-3.05 (2H, br t), 4.207 (2H,br t), 6.81 (1H, dd), 6.85(1H, d), 7.05 (1H, m), 7.24 - 7.27 (2H, m, *m*H), 7.31-7.34(1H,m,*p*H),7.53-7.55(2H,br d,*o*H) (N.m.r. data presented in the discussion); M^+ 267, m/z 162, 132, 105 and 77. (Found: C 75.85; H 6.5; N 5.25%. $C_{17}H_{17}NO_2$ requires C 76.38; H 6.41; N 5.24%).

N-Acetyl-7-deuterio-3,4-dihydro-1*H*-2,1-benzoxazine.

N-Chloro-O-(2-(4-deuteriophenyl)ethyl) acetohydroxamate (0.07g, 0.33mmol), and silver tetrafluoroborate (0.06g) gave after chromatographic separation on plates and crystallization from ether/pet.sp., N-acetyl-7-deuterio-3,4-dihydro-1*H*-2,1-benzoxazine (0.02g) m.p. 75-85° (Lit. [1] m.p. protio analogue 90-92) M^+ 178 (*ca*20% 177), m/z 136, 119, 105, 93, 79, 43. N.m.r. data presented in the discussion.

N-Benzoyl-7-deuterio-3,4-dihydro-1*H*-2,1-benzoxazine.

N-Chloro-O-(2-(4-deuteriophenyl)ethyl) benzohydroxamate (0.08g, 0.3mmol) and silver tetrafluoroborate (0.06g,3.1mmol) resulted in a solid, which after recrystallization from benzene/pet.sp. gave the product (0.02g). m.p.142-146° (Lit.[1] m.p. protio analogue149-151°). M^+ 240 (5% 239), m/z 105, 77 . N.m.r. data presented in the discussion.

N-Benzoyl-7(8)-deuterio-1,3,4,5-tetrahydro-2,1-benzoxazepine.

N-Chloro-O-(3-(4-deuteriophenyl)ethyl) benzohydroxamate (0.29g, 1mmol), and silver tetrafluoroborate (0.19g,1mmol) gave after chromatographic separation on plates a crystalline solid (from ether/ pet. sp.) (0.08g). M^+254 (253 16%), m/z 205, 105, 77. N.m.r. analysis of the mixture of the 7-deuterio- and 6-deuterio-N-benzoyl benzoxazepines is described in the discussion

N-Acetyl-7(8)-deuterio-1,3,4,5-tetrahydro-2,1-benzoxazepine.

N-Chloro-O-(3-(4-deuteriophenyl)ethyl) acetohydroxamate(0.35g,1.50mmol), and silver tetrafluoroborate (0.32g,1.6mmol) yielded an oil from plates (0.15g). M^+ 192 (191, 27%), m/z 151,150,149,133,121,120,119,107,92,78,77. N.m.r. analysis of the mixture of the 7-deuterio- and 6-deuterio-N-acetyl benzoxazepines is described in the discussion.

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