Tetrahedron Vol. 47, No. 24, pp. 4007-4030, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

X=Y-ZH SYSTEMS AS POTENTIAL 1,3-DIPOLES. PART 31.[1]

GENERATION OF NITRONES FROM OXIMES. BACKGROUND AND SCOPE OF THE TANDEM 1,2-PROTOTROPY-INTRAMOLECULAR CYCLOADDITION SEQUENCE.

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(*Received in UK* 25 *January* 1991)

Abstract. 1,2-Prototropy in aryl and aliphatic oximes generates a small equilibrium concentration of the corresponding NH nitrone. Examples of a tandem 1,2-prototropy-intramolecular cycloaddition sequence involving aryl and aliphatic oximes are described and steric and electronic factors that favour or disfavour such a sequence are discussed. Deuterium labelling studies with an aliphatic oxime rule out the involvement of an enehydroxylamine in the prototropic generation of the NH nitrone.

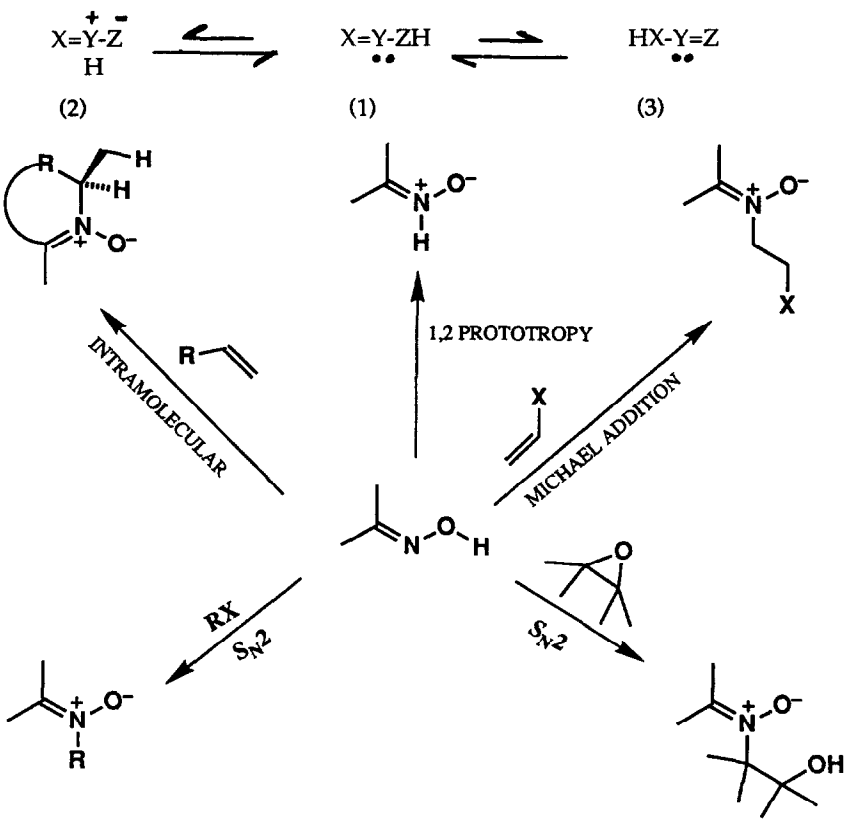
X=Y-ZH Systems can be classified into four classes according to the number of their constituent atoms that possess at least one lone pair of electrons (Table 1).[2] This classification provides a useful method of collating classes of compounds capable of undergoing 1,2-prototropy (1) ⇌ (2), in addition to the more common 1,3-prototropy (1) ⇌ (3), as well as other important properties such as ambident nucleophilicity. When the central Y atom in an X=Y-ZH system possesses a lone pair of electrons the 1,2-prototropic process (1) ⇌ (2) generates small amounts of a novel type of 1,3-dipole (2). We have reported extensively on such processes in imines[1,3], hydrazones[4] and oximes[5] and shown that such 1,3-dipoles can be trapped, in good yield, both inter- and intra-molecularly in 1,3-dipolar cycloaddition reactions.[2]

The type III X=Y-ZH systems are potentially ambident nucleophiles and bases, and those which possess lone pairs on contiguous atoms, such as oximes and hydrazones should show enhanced nucleophilicity.[6] Over the past few years we have developed five tandem nitrone generation-cycloaddition processes utilising oximes as the nitrone precursors (Scheme 1). Three of these five tandem processes, Michael addition-cycloaddition[7,8] and the S_N2 processes involving alkyl halides[9] and epoxides[10] have four distinct synthetic variants depending on whether nitrone generation and/or cycloaddition are inter- or intra-molecular. The remaining two tandem processes, cyclisation-cycloaddition,[11] and 1,2-prototropy-cycloaddition[11] have two synthetic variants. This paper is concerned with the latter tandem sequence.

The five processes summarised in Scheme 1 make use variously of the ambident nucleophilicity and basicity of the oxime moiety.

Table 1 Classification of X=Y-ZH Systems.

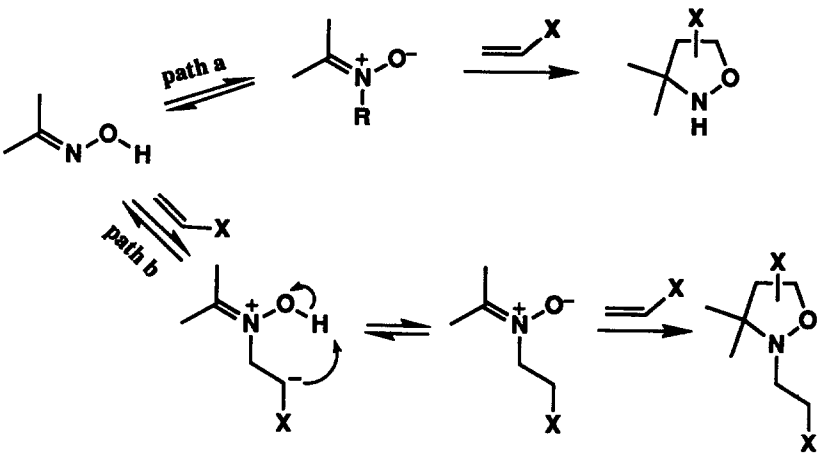
Type				No of lone pair atoms	Examples
I	X=Y-ZH			0	alkenes
II	X=Y-ZH	X=Y-ZH	X=Y-ZH	1	imines ketones nitroalkanes
III	X=Y-ZH	X=Y-ZH	X=Y-ZH	2	hydrazones oximes azo-compounds amidines
IV	X=Y-ZH			3	triazenes



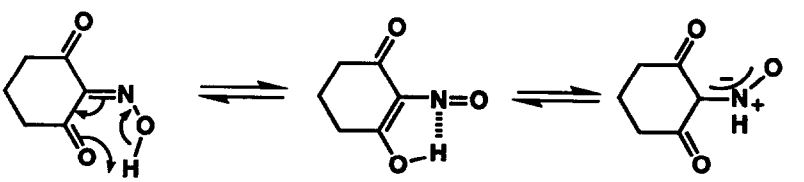
Scheme 1

Oximes, which are enols of nitroso compounds, have pka's of ca. 10-12, similar to those of enols of aldehydes and ketones.[12] This acidity coupled with the known very rapid proton transfer between electronegative atoms[13] and the ability of oximes to serve as effective bifunctional catalysts[14] suggest 1,2-prototropy in oximes (1) ⇌ (2) generating nitrones (2, X=C, Y=N, Z=O) should be a facile process. However, it is likely that the concentration of the nitrone in such an equilibrium mixture will be very small. Jencks has estimated that ca. 1-2% of the NH nitrone should be present in equilibrium with p-chlorobenzaldehyde oxime,[15] whilst later M.O. calculations concluded that NH nitrones should be observable.[16] Nevertheless, the operation of the 1,2-prototropy-cycloaddition mechanism in the presence of electronegative olefins is rare.

In our initial studies[5,7] of nitrone generation by 1,2-prototropy in the presence of electronegative olefins (Scheme 2, path a) a more facile Michael addition-cycloaddition sequence (Scheme 2, path b) intervened. However, we were successful in achieving the desired process by using monoximes of 1,2,3-triketones.[5] In these processes we postulated that the formal 1,2-prototropy was achieved via an intramolecular 1,5-H shift (Scheme 3). This is the sole example, to our knowledge, of a tandem 1,2-prototropy-cycloaddition involving an electronegative olefin.[17] The recently reported conversion of (4) → (5) appears to be the first intramolecular case.[18]

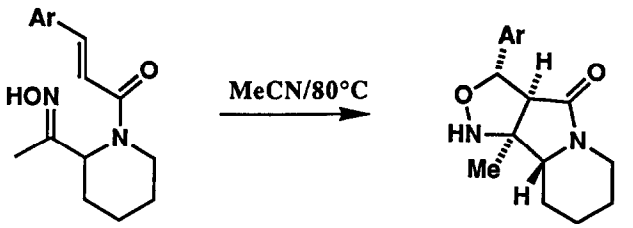


Scheme 2

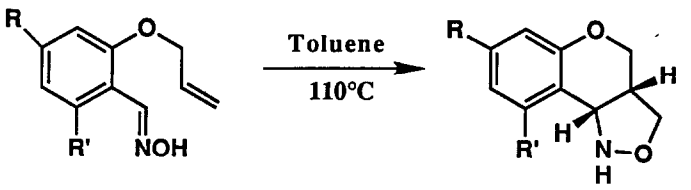


Scheme 3

The first reported example of the tandem 1,2-prototropy-cycloaddition process involving "non-activated" alkenes appears to be (6a) → (7a)[19]. We have attempted unsuccessfully to duplicate this reaction under various conditions.[7,20] Wildman[21] has reported an alkaloid example (8) → (9) and Christy et al.[22] reported the first transannular case (10) → (11) (92%). Recently Hassner et al. have provided further examples.[23]

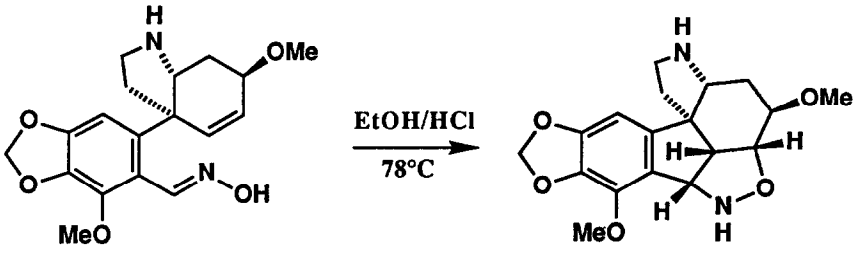


(4) (5)

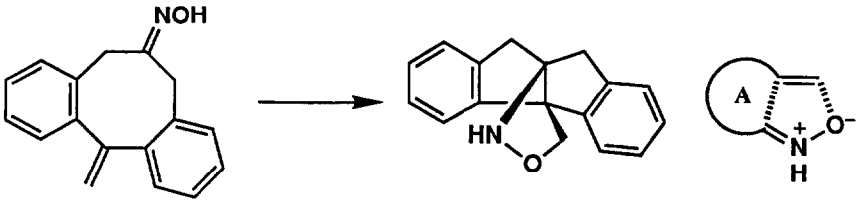


(6) a. R = R' = H
b. R = OEt, R' = H
c. R = R' = OMe

(7) a. R = R' = H
b. R = R' = OMe



(8) (9)

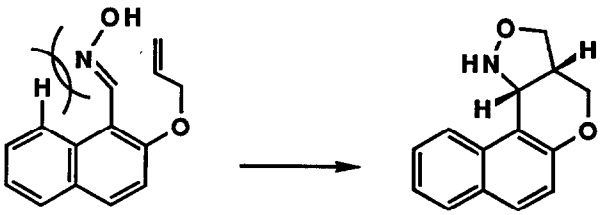


(10) (11) (12)

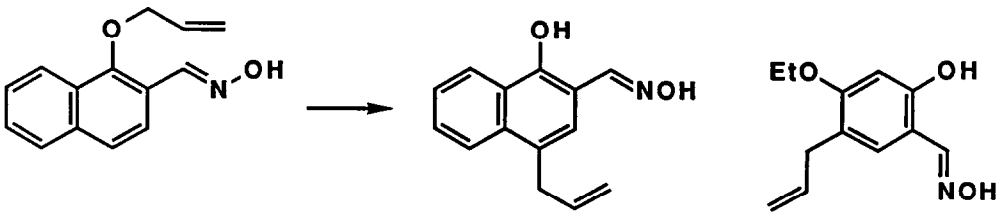
Our own studies[11] of the tandem 1,2-prototropy-intramolecular cycloaddition sequence have focussed on the influence of steric and electronic effects on the process with examples drawn from both aryl and alicyclic oximes.

1,2-Prototropy in Aryl Aldoximes

Aryl aldoximes were selected for study because of the reported conversion of (6a) → (7a) and because they had no α-hydrogen atoms available for tautomerism. We had previously suggested enehydroxylamines might play a role in the 1,2-prototropic process in aliphatic oximes although subsequent studies (below) ruled this out. Attempts to convert (6a) → (7a) under the reported conditions[19] or under more vigorous conditions (xylene, 140°C, 8d) were unsuccesful. The reported low yield, acid catalysed, (EtOH-HCl, 80°C) conversion of (13) to (14) (10%)[24] encouraged us to look at this process. We found that the conversion of (13) → (14) occurs in the absence of acid in boiling xylene over 2.5 h and in almost quantitative yield. However the isomeric oxime (15) undergoes a para-Claisen rearrangement furnishing (16) in almost quantitative yield in either xylene (140°C) or acetonitrile (80°C).



(13) (14)

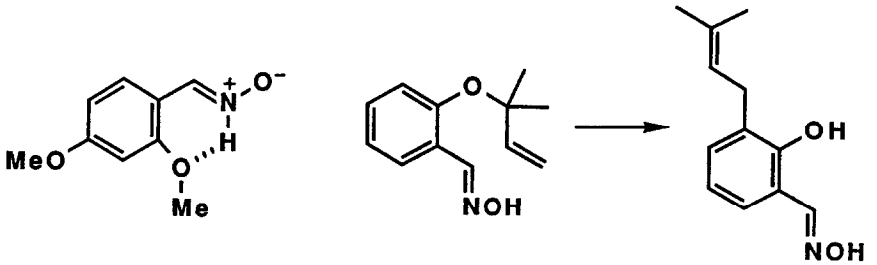


(15) (16) (17)

The different behaviour of (13) and (15) reflects the comparatively slow rate of cycloaddition of the intermediate nitrone to the unactivated terminal alkene, i.e. in the tandem 1,2-prototropy-cycloaddition process the cycloaddition step is rate determining with unactivated alkenes as dipolarophiles.

This is believed to be partly due to an unfavourable HOMO/LUMO energy gap in the interacting moieties and partly due to somewhat unfavourable transition state geometry [(12), ring A is six-membered in (13) and (15)]. In (13) the buttressing effect arising from steric interaction of the C(8)-H (peri-H) and oxime moiety assists attainment of the transition state geometry. The buttressing effect was again evident when the oximes (6b) and (6c) were heated in boiling mesitylene (160°C) and xylene (140°C) respectively The former underwent the para-Claisen rearrangement giving (17) (40%) whilst

the latter gave (7b) (ca. 70%). The increasing basicity of the oxime nitrogen atom in going from (6a) to (6c) together with the opportunity of bifurcated H-bonding (18) stabilising the nitrone are not considered to have a major effect on the rate determining cycloaddition.

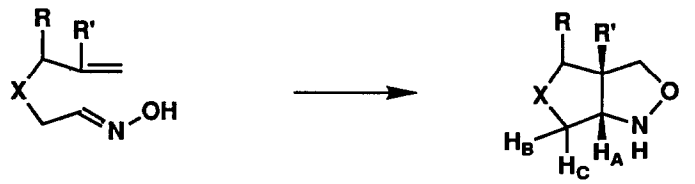


(18) (19) (20)

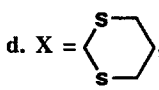
In a brief exploration of the Thorpe-Ingold effect in aryl aldoximes the oxime (19) was prepared[25] and heated at 80°C (MeCN) when a quantitative Claisen rearrangement to (20) occurred. This rearrangement also occurred on storing (19) at room temperature over several weeks.

1,2-Prototropy in Aliphatic Aldoximes

A more detailed study of steric effects was made with aliphatic aldoximes. We found that the δ-alkenyl oximes (21a) and (21b) are essentially unchanged, apart from a little decomposition, on heating in boiling xylene. In contrast (21c) is reported to give (22a) (25%) on heating at 80°C in benzene.[23]



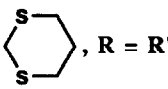
(21) a. X = CH_2, R = R' = H
b. X = S, R = R' = H
c. X = O, R = Ph, R' = H



d. X = , R = R' = H

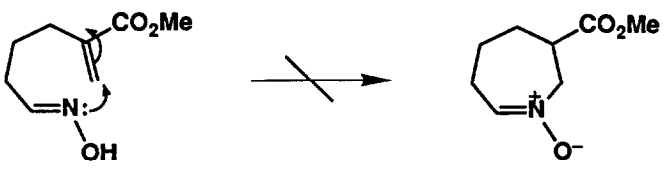
e. X = CH_2, R = H, R' = CO_2Me

(22) a. X = O, R = Ph, R' = H

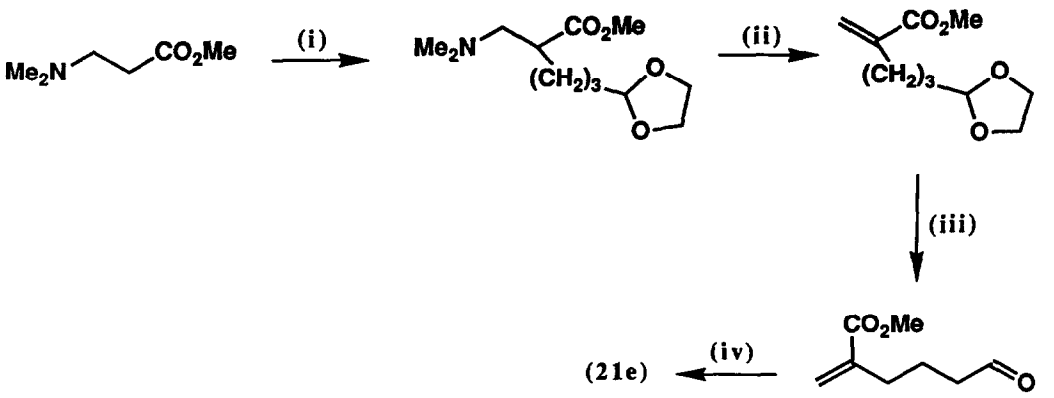


b. X = , R = R' = H

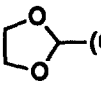
c. X = CH_2, R = H, R' = CO_2Me



(23) (24)



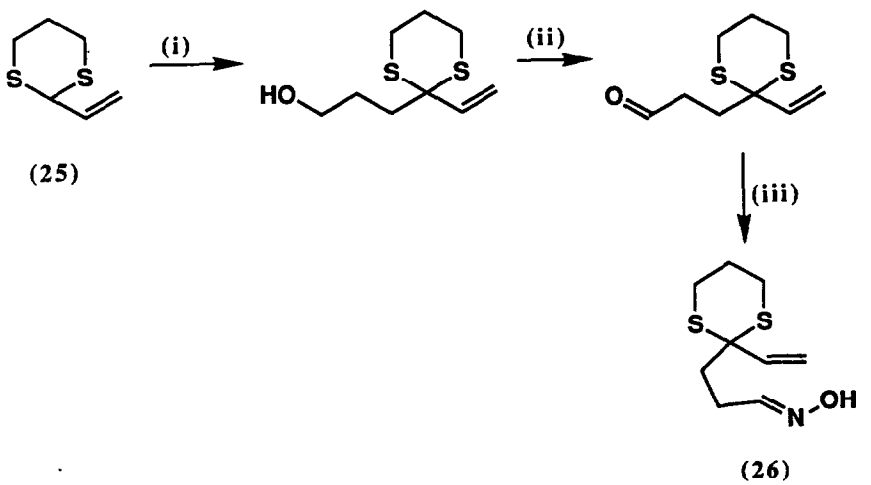
Scheme 4

Reagents: (i) LDA/  $-(CH_2)_3Br$/THF-HMPA/–78°C

(ii) MeI/MeOH/25°C/18h; then DBN/benzene/80°C/2.3h

(iii) aqueous THF-HCl,reflux 4.5h

(iv) N^+H_3OH Cl^-/NaOAc/H_2O/MeCN/25°C/3h.



(25)

(26)

Scheme 5

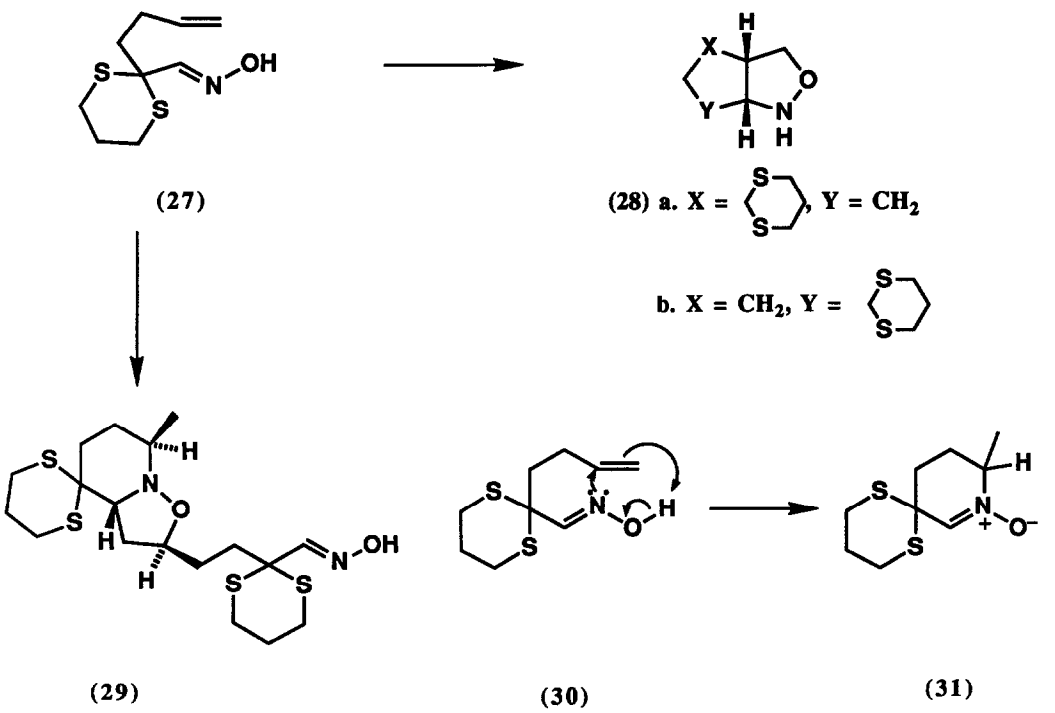
Reagents: (i) n-BuLi/THF/oxetane/–78°to25°C/20h

(ii) pyridinium chlorochromate/NaOAc/CH_2Cl_2/25°C/2.5h

(iii) N^+H_3OH Cl^-/NaOAc/MeCN/25°C/16h.

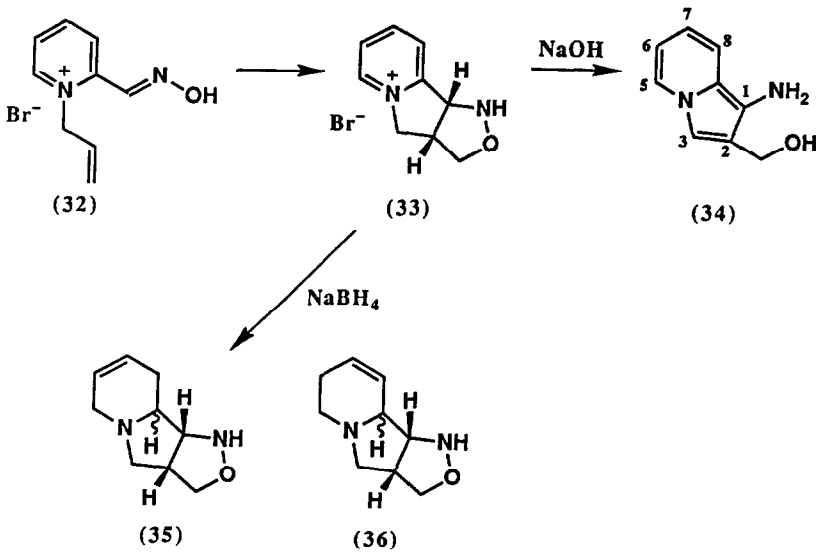
Oxime (21d) was prepared by standard dithiane methodology and, upon heating in boiling xylene for 7h, afforded (22b) (85%). Oxime (21e) was prepared as outlined in Scheme 4 and underwent tandem 1,2-prototropy-cycloaddition on heating in boiling acetonitrile for 16h to afford (22c) (80% yield, 60% conversion). The alternative 7-endo-trig cyclisation (23, arrows) to (24) was not observed. The successful tandem prototropy-cycloaddition sequence using (21d) prompted study of other dithiane positional isomers. Thus oxime (26) was prepared from (25) as outlined in scheme 5 and underwent (xylene, 140°, 16h) the desired tandem 1,2-prototropy-cyloaddition sequence giving (28a) (71%). In contrast to (21d) and (26), oxime (27) gives a 2.8:1 mixture (87%) of (28b) and the dimeric oxime (29) under identical (xylene, 140°C) conditions.

The formation of the dimeric oxime (29) implicates a cyclisation-cycloaddition sequence (30) → (31) with nitrone (31) then undergoing cycloaddition to the terminal double bond of another molecule of (27). The 6π-electron cyclisation (30) → (31) is the reverse of the known thermal fragmentation of N-alkyl nitrones[27] and will be discussed in more detail in a subsequent paper in this series.

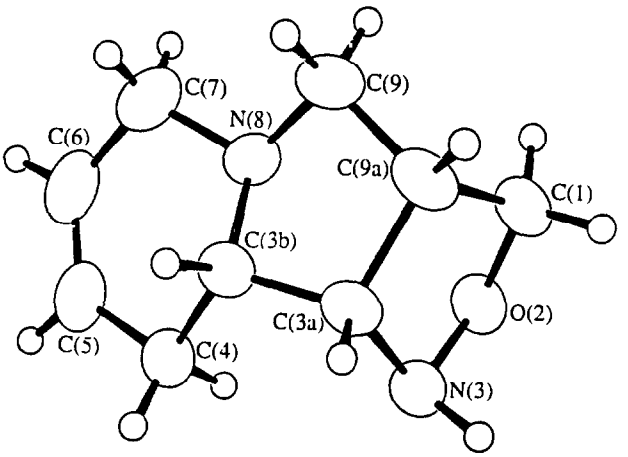


1,2-Prototropy in an Aldoxime of a Pyridinium Salt

The oxime of pyridine-2-carboxaldehyde was N-allylated with allyl bromide in hot ethanol to give (32).[28] This oxime underwent the desired tandem 1,2-prototropy-cycloaddition sequence on heating in boiling n-butanol for 3.5 h. The cycloadduct (33) was unstable but could be converted to an unstable dark green product, formulated as the indolizine (34), on treatment with cold aqueous sodium hydroxide. Reduction of (33) with sodium borohydride afforded a stable, colourless, crystalline tetrahydro-derivative for which two structures, (35) and (36) are possible. The former was favoured on mass spectral evidence (m/z 82, M-CH_2=O-butadiene). The tetrahydro-derivative gave a broad p.m.r. spectrum and the structure was therefore unambiguously confirmed as (35) by a single crystal X-ray structure determination (fig.).

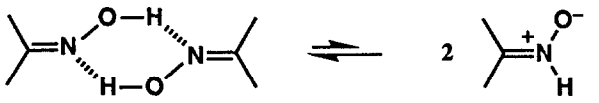


Figure

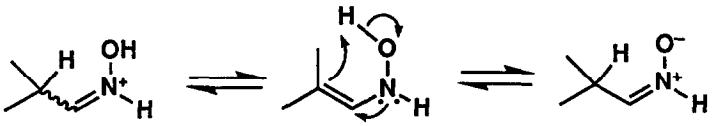


Mechanism and Steric and Electronic Effects.

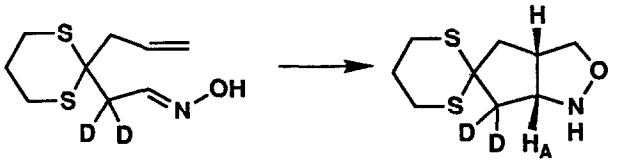
The mechanism of the 1,2-prototropy at its simplest must involve two moles of the oxime The well-known H-bonding dimeric association of oximes both in solution[29] and the solid state[30] suggests a possible concerted proton switch (37) → (38) may operate in non-polar solvents such as xylene.



(37) (38)



Scheme 6



(39) (40)

We suggested[11] that another, possibly important route to NH nitrones might be via the enehydroxylamine (Scheme 6). To probe this possibility we prepared the regiospecifically deuteriated oxime (39) (d_0 1%, d_1 25%, d_2 74%, by mass spectrometry). The labelled oxime (39) was heated in xylene in a sealed n.m.r. tube (140°C, 7h). Purification by preparative t.l.c. afforded (40) (d_0 1.5%, d_1 23%, d_2 75.5%, mass spec). Comparison of the ^{1}H n.m.r. spectra of the protio (22b)- and deuterio (40)-isomers showed that the quartet signal for H_A(δ 3.76) in (22b) appears as a doublet in (40) and the signals at δ 2.63 and 1.87 for H_B and H_c in (22b) are absent in (40). Thus the 1,2-prototropy generating the NH nitrone does not proceed via the enehydroxylamine (Scheme 6).

1,2-Prototropy generating NH nitrones seems to be a facile process in oximes and the comparative lack of examples of cycloadditions involving such prototropically generated nitrones is due to (i) a lower energy Michael addition process when dipolarophiles with electronegative substituents are used[8] (ii) an unfavourable HOMO/LUMO energy gap when unactivated alkenes are used as dipolarophiles. (iii)

although the unfavourable HOMO/LUMO energy gap can be ameliorated by carrying out the reaction intramolecularly the reaction is difficult to achieve if the chain connecting the reacting centres is larger than 3 atoms i.e. the favoured size of the secondary ring created in the intramolecular cycloaddition is 5-membered [ring A in (12)]. Kinetically favourable 5-membered ring formation is, of course, well known and a related "rule of five" is observed in radical cyclisations,[31] (iv) the presence of an allylic electronegative centre in the unactivated alkene such as oxygen in (6c), (8), (13), (21c) and the iminium nitrogen in (32) can result in a beneficial lowering of the alkene LUMO energy as well as creating a more favourable geometry for the cycloaddition as a result of the smaller C-O-C bond angle.[32] The failure of (21b) to cyclise may thus reflect the larger atomic radius of sulphur, the greater C-S-C bond angle and the smaller electronegativity difference between carbon and sulphur. More favourable geometry can be created by geminal disubstitution (Thorpe-Ingold effect) in the chain linking the reacting centres as in (21d), (26) and (27) or by buttressing effects as in (6c) and (13). An alternative method of accelerating the reaction is to carry it out at elevated pressures,[33] and there is evidence from work by Hassner that this is beneficial in the tandem 1,2-prototropy-cycloaddition process.

Experimental General details were as previously described.[34] Petroleum ether refers to the fraction with b.p. 60-80°C. Flash chromatography was performed using Sorbsil C60-40/60 (Rhone-Poulenc).

Oximes and Oxime Precursors

p-Ethoxy-O-allylsalicylaldehyde oxime (6b). To a stirred solution of p-ethoxy-O-allylsalicyl aldehyde (4.12g, 2.0mmol) and hydroxylamine hydrochloride (1.75g, 2.5mmol) in water (40ml) was added sodium acetate (2.12, 2.5mmol) in water (20ml). The resulting solution was stirred overnight at room temperature and then extracted with methylene chloride (2 x 100ml). The organic layers were combined, dried over sodium sulphate, and concentrated to afford a viscous yellow oil. Distillation of the oil furnished (6b) (50%) as a colourless oil, b.p. 134-136°C/0.01mmHg which solidified on standing, to a low melting solid. Accurate mass 221.1054. $C_{12}H_{15}NO_3$ requires 221.1052. m/z(%) 221(M^+, 49), 206(27), 180(42) and 152(100); δ 8.36(br s, 1H, OH), 8.06(s, 1H, HC=N), 7.26(s, 1H, ArH), 7.01 and 6.88(2 x m, 2 x 1H, ArH), 6.05(m, 1H, C<u>H</u>=CH_2), 5.39(m, 2H, CH=C<u>H_2</u>), 4.62(m, 2H, OCH_2), 4.13(q, 2H, O<u>CH_2</u>Me) and 1.45(t, 3H, OCH_2<u>Me</u>).

4,6-Dimethoxy-O-allylsalicylaldehyde oxime (6c). Anhydrous potassium carbonate (4.9g, 3.6mmol) and allyl bromide (4.0g, 3.5 mmol) were added to a solution of 2,4-dimethoxy-6-hydroxybenzaldehyde (5.46g, 3.6mmol) in acetone (200ml). The mixture was boiled under reflux for 14h., cooled, poured into water (100 ml) and extracted with ether (2 x 100 ml). The ether extracts were combined, dried over sodium sulphate, and concentrated to afford the crude product, a mobile orange oil (5.50g, 74%), whose p.m.r. spectrum indicated quantitative formation of the O-allyl ether. This material was used for the next stage

without further purification. A portion of the crude O-allyl ether (2.2g, 10.5 mmol) and hydroxylamine hydrochloride (1.05g, 15mmol) were dissolved in water (40ml) and a solution of sodium carbonate (1.5g, 15mmol) in water (20ml) added. The resulting solution was stirred overnight at ambient temperature and then extracted with chloroform (2 x 100 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated to afford a yellow gum. Trituration of the gum with ether, and subsequent crystallisation from ether, furnished (6c) (1.3g, 55%) as colourless plates, m.p. 166-167°C (Found C, 60.85; H, 6.45; N, 5.7. $C_{12}H_{15}NO_4$ requires C, 60.75; H, 6.35, N, 5.9%); m/z(%) 237(M^+, 37), 220(24), 205(100) and 41(33); δ 10.60(br s, 1H, OH), 8.55(s, 1H, HC=N), 6.15 and 6.13(2 x s, 2 x 1H, ArH), 6.04(m, 1H, C<u>H</u>=CH_2), 5.31(m, 2H, CH=C<u>H</u>$_2$), 4.59(m, 2H, OCH_2), 3.88 and 3.82(2 x s, 2 x 3H, 2 x OMe).

<u>1-Allyloxy-2-naphthaldehyde oxime (15)</u>. 1-Hydroxy-2-naphthaldehyde (5.2g, 30mmol) was dissolved in acetone (150ml) and anhydrous potassium carbonate (4.14g, 30mmol) and allyl bromide (4.20g, 35mmol) added. The resulting mixture was stirred and boiled under reflux for 4h. The mixture was then poured into water (100ml) and extracted with ether (2 x 200ml). The organic layers were combined, dried over sodium sulphate and concentrated to yield the crude O-allyl ether as a pale brown oil (6.4g, 100%), which was used for the next stage without further purification [δ, 10.58, (s, 1H), 8.20(dd, 1H), 7.85(d, 2H), 7.59(m, 3H), 6.20(m, 1h), 5.40(m, 2H) and 4.73(d, 2H)]. A portion of the crude O-allyl ether (2.8g, 14mmol) and hydroxylamine hydrochloride (1.12g, 16mmol) were dissolved in water (20ml) and a solution of sodium acetate (1.15g, 14mmol) in water (10ml) was added. The resulting solution was stirred at ambient temperature for 15h and then extracted with methylene chloride (3 x 100ml). The organic layers were combined, dried over sodium sulphate, and concentrated in vacuo to afford a brown gum. Trituration of the gum with ether-hexane, followed by crystallisation from ether-hexane, afforded (15) (1.8g, 60%) as buff needles, m.p. 89-90°C (Found: C, 73.75; H, 5.9; N, 5.95. $C_{14}H_{13}NO_2$ requires C, 74.0; H, 5.7; N, 6.15%); m/z(%) 227(M^+, 100), 212(33), 195(58), 186(50) and 169(96); δ(CD_3CN) 9.34(br s, 1H, OH), 8.73(s, 1H, HC=N), 8.47, 8.14, 7.88 and 7.77(4 x m, 6H, ArH), 6.43(m, 1H, C<u>H</u>=CH_2), 5.59(m, 2H, CH=C<u>H</u>$_2$), and 4.78(m, 2H, OCH_2).

<u>2-(1,1-Dimethylallyloxy) benzaldoxime (19)</u>. Prepared by adaptation of a literature method.[25]

a. <u>2-(1′,1′-Dimethylpropargyloxy)benzaldehyde</u>. 3-Chloro-3-methyl-1-butyne (45g, 44 mmol) was added dropwise with stirring over to a solution of salicyl aldehyde (15g, 12.2 mmol) and potassium hydroxide (18g, 32 mmol) in methanol (135ml) under a nitrogen atmosphere. The resulting mixture was stirred and heated at 70°C for 4 h. then cooled, filtered, acidified to pH2 with dilute hydrochloric acid and extracted with ether (2 x 100 ml). The combined ether layers were washed with dilute hydrochloric acid (50 ml), and then dried (Na_2SO_4). Evaporation of the ether and distillation of the residue afforded the *product* as a pale yellow oil (7.0g, 30%), b.p. 170-172°C/0.3mmHg(Found: C, 76.75; H, 6.65. $C_{12}H_{12}O_2$

requires C, 76.55; H, 6.4%); δ 10.44(s, 1H, CHO), 7.86(d, 1H, ArH), 7.25(m, 2H, ArH), 6.85(m, 1H, ArH), 2.62(s, 1H, ≡ CH) and 1.73(s, 6H, Me).

b. 2-(1′,1′-Dimethylallyloxy)benzaldehyde. A solution of 2-(1′,1′-dimethylpropargyloxy)benzaldehyde(2.0g) in benzene (10ml) and n-hexane(40ml) was hydrogenated over Lindlar catalyst (190 mg) for 10min. during which time 1 mol of hydrogen was absorbed. After removal of the catalyst, the solvent was removed under reduced pressure to afford the product (1.8g, 90%) as a pale yellow oil, b.p. 74%C/0.3mmHg. (Found: C, 75.45; H, 7.5. $C_{12}H_{14}O_2$ requires C, 75.75; H, 7.4%); m/z(%) 190(M^+, 10); δ 7.79(d, 1H, ArH), 7.4(t, 1H, ArH), 7.12(d, 1H, ArH), 6.99(t, 1H, ArH), 6.1(dd, 1H, J 10.5 and 17.6 Hz, C<u>H</u>=CH_2), 5.2(dd, 2H, CH=C<u>H_2</u>), and 1.51(s, 6H, Me); m/z(%) 190(M^+, 5), 122(90) and 69(100).

c. 2-(1′,1′-Dimethylallyloxy)benzaldoxime prepared in aqueous acetonitrile by reaction of 2-(1′,1′-dimethylallyloxy)benzaldehyde (1g), hydroxylamine hydrochloride (400mg), and sodium acetate (520mg). The *product* (930mg, 87%), was obtained as a colourless oil after purification by preparative t.l.c. (Found: C, 69.95; H, 7.55; N, 7.05. $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.35; N, 6.8%); m/z(%) 205(M^+, 5), 137(100) and 69(82); δ 8.54(s, 1H, CH=N), 7.74(dd, 1H, ArH), 7.21(t, 1H, ArH), 7.1(d, 1H, ArH), 6.98(t, 1H, ArH), 6.14(dd, 1H, J 10.9 and 17.6 Hz, C<u>H</u>=CH_2), 5.2(dd, 2H, CH=C<u>H_2</u>), and 1.49(s, 6H, Me).

3-Thiohex-5-ene-1-al oxime (21b)

a. 1,1-Diethoxy-3-thiohex-5-ene. Sodium hydride (60% in mineral oil, 2.8g, 70 mmol) was added to a stirred solution of allyl mercaptan (5g, 67 mmol) in DMF(100 ml) and the mixture stirred for a further 5 mins. Chloroacetaldehyde diethylacetal (10.3g, 67 mmol) was then added dropwise with stirring over 10 min. and the resulting mixture was heated at 70°C for 6h. The reaction mixture was then cooled, water (250 ml) added, and the mixture extracted with ether (2 x 70ml). The combined extracts were dried ($MgSO_4$), the ether evaporated, and the residual oil distilled to afford the product (9.28g, 72%) as a colourless oil, b.p. 58°C/0.45 mmHg (Found: C, 56.9; H, 9.75; S, 16.7. $C_9H_{18}O_2S$ requires, C, 56.8; H, 9.55; S, 16.85%); δ 5.77(m, 2H, CH=C<u>H_2</u>), 5.1(m, 1H, C<u>H</u>=CH_2), 4.5[t, 1H, $CH(Et)_2$], 3.67 and 3.53(2 x m, 2 x 2H, C<u>H_2</u>Me), 3.2(d, 2H, C<u>H_2</u>CH=CH_2), 2.64(d, 2H, C<u>H_2</u> CH) and 1.2(t, 6H, CH_2 <u>Me</u>); ν_{max}(film) 3080, 2970, 1630, 1340, 1120, 1060 and 930 cm^{-1}.

b 3-Thiohex-5-ene-1-al. The above diethyl acetal (4g) was dissolved in a mixture of 2M hydrochloric acid (40ml) and THF(60ml) and kept at room temperature for 24h. Work up by neutralisation with aqueous sodium carbonate and extraction with ether afforded the *product* (1.05g, 43%) as a colourless oil, b.p. 38-40°C/0.7 mm Hg (lit.[35] b.p. 81°C/14mm Hg).

c. 3-Thiohex-5-ene-1-al oxime. Prepared in the usual way in aqueous acetonitrile. The *product* (87%) was a colourless oil, b.p. 64-65°C/0.6mm Hg, which comprised a 1.8:1 mixture of E- and Z-isomers (Found: C, 45.55; H, 7.05; N, 10.55; S, 24.2. C_5H_9NOS requires C, 45.75; H, 6.9; N, 10.65; S, 24.45%), δ 8.3(br s, 1H, OH), 7.38(t, 1H, E-CH=N), 6.82(t, 1H, Z-CH=N), 5.8(m, 1H, $\underline{CH}=CH_2$), 5.15(m, 2H, $CH=C\underline{H_2}$), 3.37 and 3.18(2 x d, 2 x 2H, E- and Z- $C\underline{H_2}CH=N$), and 3.15 and 3.11(2 x d, 2 x 1H, $SC\underline{H_2}CH=CH_2$); ν_{max}(film) 3500-3150(br), 3080, 2900, 1630, 1480, 1460, 1300, 1240 and 940 cm^{-1}.

2-(2′-Propenyl)-2-(2′-oximinoethyl)-1,3-dithiane (21d)

a. 2-(2′-Propenyl)-2-[2′-(1′,3′-dioxolan) methyl]-1,3-dithiane n-Butyl lithium (34ml, 1.6M, 5.2mmol) was added to a stirred solution of 2-(2′-propenyl)-1,3-dithiane(7.9g, 4.9mmol)[36] in dry THF (150ml) at -78°C under an atmosphere of nitrogen. The solution was maintained at -22°C for 2.5h and then cooled to -78°C and anhydrous HMPA (17.2ml, 9.8mmol) added followed, after 15min., by the dropwise addition over 5 min. of 2-bromomethyl-1,3-dioxolan (5.6 ml, 5.4mmol). The resulting mixture was allowed to warm to room temperature over 15 h and then diluted with water (200 ml) and extracted with ether (2 x 100 ml). The combined ether extracts were dried ($MgSO_4$), the solvent removed under reduced pressure and the residual oil chromatographed (SiO_2) eluting with 4:1 ether-petroleum ether to afford the *product* as a colourless oil (9.0g, 72%). A small sample was molecularly distilled at 120°C/0.1mm Hg to provide an analytical sample (Found: C, 53.85; H, 7.5; S, 25.75. $C_{11}H_{18}O_2S_2$ requires C, 53.6; H, 7 35; S, 26.0%), m/z (%) 246(M^+, 7), 205(12), and 73(100); δ 5.9(m, 1H, $C\underline{H}=CH_2$), 5.17(m, 3H, $CH=C\underline{H_2}$ and OCHO), 3.9(m, 4H, 2 x CH_2O), 2.83(m, 4H, 2 x CH_2S), 2.7(d, 2H, $=CH-C\underline{H_2}$), 2.3(d, 2H, $CHC\underline{H_2}$) and 1.9(m, 2H, $CH_2C\underline{H_2}CH_2$).

b. 2-(2′-Propenyl)-2-(2′-oxoethyl)-1,3-dithiane 2-(2′-Propenyl)-2-[2′-(1′,3′-dioxolan)methyl]-1,3-dithiane (7.5g, 3mmol) was dissolved in THF (100ml) and 2M hydrochloric acid (100ml) and the solution boiled under reflux for 5h. The cooled reaction mixture was then neutralised with 5% aqueous sodium bicarbonate solution and extracted with ether (3 x 75ml). The combined ether extractes were dried ($MgSO_4$) and the ether removed under reduced pressure to afford the product (5.2g, 76%) which was contaminated with a small amount of unhydrolysed acetal. A small sample was purified by preparative t.l.c. and molecular distillation (100-105°C/0.2mmHg) (Found: C, 53.75; H, 7.15; S, 31.4. $C_9H_{14}OS_2$ requires C, 53.45; H, 6.95; S, 31.7%); δ 9.77(t, 1H, CHO), 5.89(m, 1H, $C\underline{H}=CH_2$), 5.17(m, 2H, $CH=C\underline{H_2}$), 2.9(m, 6H, 2 x CH_2S and $C\underline{H_2}$ CHO), 2.78(d, 2H, $=CHC\underline{H_2}$) and 1.98(m, 2H, $CH_2C\underline{H_2}CH_2$).

c. 2-(2′-Propenyl)-2-(2′-oximoethyl)-1,3-dithiane Prepared in the usual way from 2-(2′-propenyl)-2-(2′-oxoethyl)-1,3-dithiane, hydroxylamine hydrochloride and sodium acetate in aqueous acetonitrile at room temperature for 2h. The *product* (81%) was a pale yellow semi-solid which comprised a 5:4 mixture of

E- and Z-isomers (p.m.r.) (Found: C, 49.55; H, 6.95; N, 6.55; S, 29.65. $C_9H_{15}ONS_2$ requires C, 49.75; H, 6.95; N, 6.45; S, 29.5%); m/z (%) 217(M^+, 27), 176(100) and 159(65); δ 8.53 and 9.0(br s, 1H, =NOH), 7.5(t, 1H, E-CH=N), 6.97(t, 1H, Z-CH=N), 5.89(m, 1H, C<u>H</u>=CH_2), 5.2(m, 2H, CH=C<u>H_2</u>), 3.0(d, 2H, Z-C<u>H_2</u>CH=N), 2.82(m, 2H, E-C<u>H_2</u>CH=N), 2.86(m, 4H, 2 x CH_2S), 2.6(t, 2H, C<u>H_2</u>CH=CH_2) and 1.94(m, 2H, $CH_2C\underline{H_2}CH_2$).

<u>Oxime of 5-carbomethoxyhex-5-ene-1-al (21e)</u>

a. <u>2-(5′-N,N-Dimethyl-4′-carbomethoxypentyl)-1,3-dioxolan</u>. Methyl 3-dimethylaminopropionate (3.8g, 29mmol) was added to a stirred solution of lithium diisopropylamide (32mmol) [from 1.6M n-BuLi (19.9 ml) and $(Pr^i)_2$ NH(3.22g)] in dry THF (100ml) at -78°C under an atmosphere of nitrogen. After 30 min. a solution of 2-(3′-bromopropyl)1,3-dioxolan (5.9g, 30mmol) in HMPA (5.6ml) was added dropwise over 15min. The resulting mixture was stirred and allowed to warm to room temperature over 1h., quenched with saturated aqueous ammonium chloride (30 ml) and partitioned between ether and water. The aqueous layer was further extracted with ether and the combined ether extracts washed with brine and then with water, dried ($MgSO_4$), and the solvent removed under reduced pressure. The residual oil was purified by chromatography (SiO_2, ether) to afford the product as a colourless oil (2g, 28%), b.p. 67-70°C/0.1mmHg(molecular distillation) (Found: C, 58.45; H, 9.75; N, 5.55. $C_{12}H_{23}O_4N$ requires, C, 58.75; H, 9.45; N, 5.7%); m/z(%) 245(M^+,3); δ 4.83(t, 1H, OCHO), 3.88(m, 4H, CH_2O), 3.69(s, 3H, OMe), 2.64(m, 2H, CH_2N), 2.22(m, 1H, $CHCO_2Me$), 2.2(s, 6H, NMe_2) and 1.68-1.38(m, 6H, 3 x CH_2).

b. <u>2-(4′-Carbomethoxypent-4′-enyl)-1,3-dioxolan</u>. A solution of 2-(5′-N,N-dimethyl-4′-carbomethoxypentyl)-1,3-dioxolan (2.7g, 11mmol) and methyl iodide (18.77g, 132 mmol) in methanol (30ml) was kept at room temperature in the dark for 18h. The solvent and excess methyl iodide were then removed under reduced pressure, the residue suspended in a solution of diazabicyclononene(2g, 16.2 mmol) in benzene (30ml) and the mixture boiled under reflux for 2.5h. The cooled solution was then washed with 1M hydrochloric acid and water, dried ($MgSO_4$), and the solvent removed under reduced pressure. The residual oil was purified by molecular distillation to afford the *product* (1.3g, 60%), b.p. 32°C/0.2mm Hg(furnace temp.) (Found: C, 59.75; H, 8.1. $C_{10}H_{16}O_4$ requires C, 60.0; H, 8.05%); m/z(%) 200(M^+, 2), 139(60) and 73(100); δ 6.15 and 5.55(2 x s, 2 x 1H, $=CH_2$), 4.87(t, 1H, OCHO), 3.9(m, 4H, 2 x CH_2O), 3.75(s, 3H, OMe), 2.35(m, 2H, $=CCH_2$), and 1.66(m, 4H, 2 X CH_2).

c. <u>5-Carbomethoxyhex-5-ene-1-al</u>. 2-(4′-Carbomethoxy-4′-enyl)-1,3-dioxolan (1.3g) was dissolved in a mixture of THF (30ml) and 1M hydrochloric acid (40ml) and the solution boiled under reflux for 4.5 h. Work up in the usual way followed by molecular distillation afforded the *product* (0.79g, 80%) as a colourless oil, b.p. 30-32°C/0.2mmHg(furnace temp.) (Found: C, 61.7; H, 7.5. $C_8H_{12}O_3$ requires C, 61.5;

H, 7.75%); δ 9.8(t, 1H, CHO), 6.2 and 5.6(d and m, 2 x 1H, $=CH_2$), 3.7(s, 3H, OMe), 2.5(m, 2H, $C\underline{H}_2$ CHO), 2.3(t, 2H, $=C-CH_2$), and 1.85(m, 2H, CH_2).

d. Oxime(21e). Prepared from the aldehyde (above) in the usual manner in aqueous acetonitrile. The *product* (81%) was a colourless liquid which comprised a 3:2 mixture of E- and Z-isomers. (Found: C, 55.9; H, 7.65; N, 7.65. $C_8H_{13}NO_3$ requires C, 56.15; H, 7.65; N, 8.2%); δ 7.4(t, 1H, E-CH=N), 6.8(br s, 1H, Z-CH=N), 6.2 and 5.5 (2 x m, 2 x 1H, $C=CH_2$), 3.76 and 3.75(2 x s, 2 x 3H, E- and Z- CO_2Me), 2.3(t, 2H, $CH_2C=CH_2$), 2.2(q, 2H, $C\underline{H}_2$ CH=N), and 1.69(m, 2H, CH_2).

4-[2′-(1′,3′-dithianyl)]hex-5-ene-1-ol. 2-(Ethylidine)-1,3-dithiane (5.0g, 0.034 mmol)[26] in dry THF (60ml) was cooled to -78°C and 1.6M n-butyl lithium (25ml, 0.04 mmol) was added dropwise under nitrogen. The magnetically stirred solution was maintained below -20°C over 2 hrs, cooled to -78°C, HMPA (18ml. 0.098 mmols) added, and the solution stirred at -78°C for 15min. Oxetane (2.5 ml, 0.038mmol) was then added to the deep orange solution and the mixture allowed to warm to room temperature over 20 h. Saturated ammonium chloride solution (100 ml) was added to the reaction mixture and the product extracted with ether (2 x 50 ml), washed with brine, dried ($MgSO_4$), and solvent removed to leave a viscous orange liquid which was purified by flash-chromatography (ether) to give the *product* as a pale yellow liquid (6.39 g, 91%). A small amount of the sample was mole distilled for micro analysis, b.p. 140-150°C (furnace temp.)/0.5 mm Hg. (Found: C, 52.95; H, 8.0; S, 30.95. $C_9H_{16}OS_2$ requires C, 52.9; H, 7.9; S, 31.4%); ν_{max} (film): 3400(br), 2960, 2920, 1620, 1430, 1400, 1280, 1240, 1060, 1000, 940, 920 and 800 cm^{-1}; m/z (%) 204(M^+, 66), 147(14), 145(63), 143(16), 119(24), 111(11), 106(14), 99(14), 97(100), 88(24), 86(76), 74(18), 73(22), 71(41), and 69(10); δ 5.77(dd, 1H, $C\underline{H}=CH_2$), 5.42(m, 2H, $CH=C\underline{H}_2$), 3.61(t, 2H, $C\underline{H}_2OH$), 2.89 and 2.67(2 x m, 2 x 2H, CH_2S), 2.13(br s, 1H, OH) and 1.67-2.02(m, 6H, 3 x CH_2).

b. 4-[2′-(1′,3′-dithianyl)]hex-5-ene-1-al. A mixture of 4-[2′-(1′,3′-dithianyl)]hex-5-ene-1-ol(2.0g, 9.8mmol), pyridinium chlorochromate (3.18g, 14.75mmol) and sodium acetate (1.20g, 14.63mmol) in dry methylene chloride (125ml) was mechanically stirred at room temperature for 2.5 hrs. Dry ether (100ml) was added to the black solution and the mixture filtered through a column of florosil. The fitrate was evaporated to give a pale yellow liquid, (1 34g, 67%), which was mole distilled b.p. 140-150°C (furnace temp)/ 0.5mm Hg. (Found: C, 53.5; H, 7.0: S, 32.0. $C_9H_{14}OS_2$ requires C, 53.45; H, 6.7; S, 31.7%); ν_{max}(film): 2900, 2820, 2700, 1720, 1620, 1415, 1270, 990 and 930 cm^{-1}; m/z(%) 202(M^+, 100), 170(8), 160(10), 158(17), 147(71), 132(22), 128(15), 119(12), 107(18), 106(23), 99(20), 96(12), 86(86), 74(34) and 71(64); δ 9.78(t, 1H, CH=O), 5.76(dd, 1H, $C\underline{H}=CH_2$), 5.43(m, 2H, $CH=C\underline{H}_2$), 2.85 and 2.72(2 x m, 2 x 2H, CH_2S), 2.64 and 2.21(2 x t, 2 x 2H, 2 x CH_2), 2.03 and 1.92(2 x m, 2 x 2H, CH_2).

c. 4-[2′-(1′,3′-dithianyl)]hex-5-ene-1-al oxime (26). Prepared in the usual way from the aldehyde

(above), hydroxylamine hydrochloride, and sodium acetate in aqueous acetonitrile. The *product* (89%) was a colourless viscous oil which comprised a 1:1 mixture of E- and Z- oximes (p.m.r., below) (Found: C, 49.9; H, 7.2; N, 6.4; S, 29.2. $C_9H_{15}NOS_2$ requires C, 49.75; H, 6.95; N, 6.45; S, 29.5%); ν_{max} (film) 3300, 2900, 1620, 1410 and 1270 cm^{-1}, m/z(%) 217(M^+, 23), 145(22), 111(100), 110(29), 107(12), 94(30) and 71(16); δ 9.10 and 8.60(2 x br s, 2 x 1H, NOH), 7.43 and 6.73(2 x t, 2 x 1H, CH=N, E- and Z-isomers), 5.79(m, 1H, C<u>H</u>=CH_2), 5.45(m, 2H, CH=C<u>H_2</u>), 2.88 and 2.70(2 x m, 2 x 2H, 2 x CH_2S), 2.53 and 2.37(2 x m, 2H, C<u>H_2</u> CH=N, E- and Z-isomers), 2.03(m, 6H, 3 x CH_2) and 1.94(m, 2H, CH_2).

<u>2-(But-3′-enyl)-2-formyl-1,3-dithiane oxime (27)</u>. Prepared in the usual way from 2-(but-3′-enyl)-2-formyl-1,3-dithiane,[37] hydroxylamine hydrochloride, and sodium acetate in aqueous acetonitrile. The *product* (85%) crystallised from ether-petroleum ether as colourless prisms, m.p. 61°C, which comprised a 1:1 mixture of E- and Z-isomers (p.m.r., below) (Found: C, 49.7; H, 6.95; N, 6.3; S, 29.4. $C_9H_{15}NOS_2$ requires, C, 49.7; H, 6.95; N, 6.4; S, 29.5%); ν_{max} (nujol) 3265, 2920, 2840, 1630, 1450, 1365 and 1265 cm^{-1}; m/z(%) 217(M^+, 55), 200(43), 176(100), 173(16), 162(59), 145(26), 142(20), 132(36), 126(29), 111(15), 107(34), 106(31), 99(19), 88(14) and 73(32); δ 7.42 and 8.91(2 x s, 2 x 1H, CH=N, E- and Z-isomers), 5.76(m, 1H, C<u>H</u>=CH_2), 5.03(m, 2H, CH=C<u>H_2</u>), 3.06 and 2.66(2 x m, 2 x 4H, 4 x CH_2S), 2.27(m, 4H, 2 x CH_2), 2.14(m, 2H, CH_2), 2.01(m, 4H, 2 x CH_2) and 1.87(m, 2H, CH_2).

<u>2-(2′-Propenyl)-2-(1′,1′-dideuterio-2′-oximinoethyl)-1,3-dithiane(39)</u>.

a Sodium carbonate (520mg, 5 mmol) and deuterium oxide (3g) were added to a solution of 2-(2′-propenyl)-2-(2′-oxoethyl)-1,3-dithiane (above) (500mg, 2.5mmol) in dry THF(20ml) and the resulting mixture was stirred at room temperature for 5h. Work up in the usual way afforded the *product* (250mg, 50%) as a colourless oil; m/z(%) 204(M^+, 4), 203(monodeutereo, 3), 163(94), 162(62) and 73(100).

b. <u>Oxime(39)</u> Prepared as described above for (21d). Purification by preparative t.l.c. (1:1 ether-petroleum ether) afforded the *product* as a colourless semi-solid (69%); m/z(%) 219(M^+, 21), 218(monodeuterio, 7), 178(92), 177(29) and 159(84). The p.m.r. spectrum was identical to that described above for (21d) except for the absence of signals at δ 3.0 and 2.82 due to Z- and E-C<u>H_2</u> CH=NOH. The % deuterium incorporation was calculated from the mass spectrum to be 1% d_0, 25% d_1 and 74% d_2.

Intramolecular Cycloadditions of Aryl Oximes

<u>1,3,3a,9b-Tetrahydro-7,9-dimethoxy-3H-isoxazolo[3′,4′-d]benzo[b]pyran(7b)</u>. A solution of oxime (6c) (500mg) in xylene (15ml) was boiled under reflux for 6h. Removal of the solvent furnished an orange gum (100%) whose p.m.r. spectrum indicated it comprised (7b) (70%) and a second product, possibly

the product of an ene reaction. Purification of the crude product by flash chromatography (silica, 5:2 ethyl acetate-hexane) furnished the *product* which crystallised from ether-acetone as irregular crystals, m.p. 112-114°C. (Found: C, 60.6; H, 6.25; N, 5.65. $C_{12}H_{15}NO_4$ requires C, 60.75; H, 6.35; N, 5.9%); m/z(%) 237(M^+, 37), 205(100), and 191(10); δ 6.10(m, 2H, ArH), 4.35(d, 1H, J 6.91 Hz, ArCHN), 4.24(t, 1H, J 7.9Hz, OCH) 4.15(dd, 1H, J 11.54 and 5.01Hz, OCH), 3.82-3.760(m and 2 x s, 8H, 2 x 3H, 2 x OMe, and 2 x OCH) and 2.86(m, 1H, ring junction CH).

1,3,3a,11c-Tetrahydro-3H-isoxazolo[3′,4′-d]naphtho[b]pyran(14). A solution of 2-allyloxy-1-naphthaldehyde oxime (230mg) in xylene (15ml) was boiled under reflux for 2.5h. Removal of the solvent and crystallisation of the residue from ethyl acetate-hexane afforded the *product* (184mg, 80%) as colourless needles, m.p. 135°C. The spectroscopic date agreed with that previously reported.[24]

Attempted cycloaddition of 1-allyloxy-2-naphthaldehyde oxime(15). A solution of oxime (15) in xylene (25ml) was boiled under reflux for 2h. The solvent was then removed in vacuo to afford a brown gum. Purification by flash chromatography (silica, 1:1 ether-hexane) furnished 1-hydroxy-4-allyl-2-naphthaldehyde oxime (16) (0.15g, 56%) as buff needles, m.p. 118-119°C, from ether-hexane. Accurate mass: 227.0954. $C_{14}H_{13}NO_2$ requires 227.1052; m/z(%) 227(M^+, 100), 228(17), 210(25), 194(14) and 182(23); δ (xylene-d_{10}), 11.31(br s, 1H, ArOH), 8.95(m, 1H, ArH), 8.16(s, 1H, ArH), 7.95(m, 1H, ArH), 7.52(m, 3H, OH and 2 x ArH), 6.87(s, 1H, ArH), 6.20(m, 1H, olefinic H), 5.28(m, 2H, olefinic H), and 3.74(d, 2H, J 6.2Hz, $ArCH_2$).

Attempted cycloaddition of p-ethoxy-O-allylsalicylaldehyde Oxime (6b). A solution of oxime (6b) (1g) in mesitylene (15ml) was boiled under reflux for 20h. Removal of the solvent furnished a viscous dark brown oil whose p.m.r. spectrum indicated it comprised (6b) (30%) and (17) (70%) together with trace amounts of other products. Purification by flash chromatography (silica, 3:5 ether-petroleum ether) furnished 2-hydroxy-4-ethoxy-5-allylbenzaldoxime (17) (0.4g, 40%) as colourless needles from ether-petroleum ether, m.p. 91-93°C. (Found: C, 64.85; H, 6.55; N, 6.30. $C_{12}H_{15}NO_3$ requires C, 65.15; H, 6.8; N, 6.35%); m/z(%) 221(M^+, 100), 222(15), 206(33), 180(22), 152(63), 135(55) and 121(32); δ($CDCl_3$ + 1 drop D_2O), 8.01(s, 1H, HC=N), 7.06 and 6.88(2 x s, 2 x 1H, 2 x ArH), 5.98(m, 1H, olefinic H), 5.09(m, 2H, olefinic H), 4.12(q, 2H, OCH_2Me), 3.41(m, 2H, $ArCH_2$) and 1.45(t, 3H, Me).

Attempted cycloaddition of 2-(1′,1′-dimethylallyloxy)benzaldoxime(19). A solution of oxime (19) (500mg) in acetonitrile (10ml) was boiled under reflux for 5h. Evaporation of the solvent and flash chromatography (SiO_2, 3:2 petroleum ether-ether) afforded 2-hydroxy-3-(3′-methylbut-2-enyl) benzaldoxime (20)(470mg, 94%) which crystallised from ether-petroleum ether as colourless rods, m.p. 72-74°C. (Found: C, 70.1; H, 7.35; N, 6.55. $C_{12}H_{15}NO_2$ requires C, 70.22; H, 7.35; N, 6.8%); m/z(%)

205(M^+, 50), 188(100) and 150(30); δ 10.08(s, 1H, OH), 8.22(s, 1H, CH=N), 7.65(s, 1H, OH), 7.16(d, 1H, ArH), 7.03(dd, 1H, ArH), 6.85(t, 1H, ArH), 5.34(m, 1H, C<u>H</u>=CMe_2), 3.38(d, 2H, $ArCH_2$), and 1.75 and 1.72(2 x s, 2 x 3H, Me).

<u>Isoxazolidine (22b)</u>. A solution of oxime (21d) (1g) in xylene (20ml) was boiled under reflux for 7h. The solvent was then removed under reduced pressure and the residue purified by chromatography (SiO_2, ether). The *product* (850mg, 85%) crystallised from ether as colourless rods, m.p. 51-53°C (Found: C, 49.9; H, 6.85; N, 6.43. $C_9H_{15}NOS_2$ requires, C, 49.75; H, 6.95; N, 6.45%); m/z(%) 217(M^+, 100), and 147(97); δ 4.5(br s, 1H, NH), 3.76(q, 1H, CHN), 3.5 and 3.0(d, and br s, 2 x 1H, CH_2O), 2.77(m, 1H, ring junction-H), 2.63(dd, 1H, CH<u>H</u> CHN), 2.45(m, 5H, 2 x CH_2S and C<u>H</u>HCH), 1.87(dd, 1H, C<u>H</u>H CHN) and 1.62(m, 3H, CH_2 and CH<u>H</u>CH).

<u>Isoxazolidine (22c)</u>. A solution of oxime (21e) (500mg) in acetonitrile (10ml) was boiled under reflux for 16h. Removal of the solvent and flash chromatography of the residual oil (SiO_2, ether) afforded starting material (200mg) and *product* (240mg, 80%) as a colourless oil, b.p. 55-58°C/0.3mm Hg(molecular distillation) (Found: C, 56.3; H, 7.35; N, 7.9. $C_8H_{13}NO_3$ requires C, 56.15; H, 7.65; N, 8.2%); m/z(%) 171(M^+, 48), 140(38), 112(25), and 72(100); δ 4.26(br s, 1H, NH), 4.11(t, 1H, CHN), 4.09 and 3.7(2 x d, 2 x 1H, CH_2O), 3.67(s, 3H, Me), 2.19 and 1.92(2 x m, 2 x 1H) and 1.78-1.57(m, 4H, 2 x CH_2).

<u>Isoxazolidine (28a)</u>. A solution of the oxime (26) (250 mg) in xylene (10ml) was boiled under reflux for 16h. The solvent was then removed under reduced pressure and the residual oil purified by preparative t.l.c. to afford the *product* (178mg, 71%) as a viscous colourless oil (Found: C, 49.75; H, 7.1; N, 6.5; S, 29.4. $C_9H_{15}NOS_2$ requires C, 49.75; H, 6.95; N, 6.45; S, 29.5%); m/z(%) 217(M^+, 100), 185(41), 158(7), 145(19), 111(16), 110(18), 106(29), 94(11), 86(31), 84(45), 80(12), and 71(11); δ 5.2(br s, 1H, NH), 4.25(br s, 1H, CHN), 4.13 and 3.75(m and br s, 2 x 1H, CH_2O), 3.39(m, 1H), 2.9-2.75(m, 4H), 2.33(m, 1H), 2.18-1.92(m, 4H) and 1.82(m, 1H); ν_{max}(film) 3400, 3180, 2920, 1620(br), 1410, 1030 and 840 cm^{-1}.

<u>Isoxazolidine (28b) and oxime dimer (29)</u>. A solution of the oxime (27) (500mg) in xylene (15ml) was boiled under reflux for 16h. The solution was cooled whereupon a colourless solid separated out and was removed by filtration. The precipitate (115mg, 23%) was the oxime dimer (29). Evaporation of the mother liquor afforded the isoxazolidine (28b) (320mg, 64%).

(<u>28b</u>). Colourless viscous oil (Found: C, 49.8; H, 6.95; N, 6.15. $C_9H_{15}NOS_2$ requires C, 49.75; H, 6.95; N, 6.45%); m/z(%) 217(M^+, 63), 187(14), 186(36), 145(20), 140(12), 132(64), 127(13), 119(11), 114(16), 113(100), 112(28), 86(33), 84(46) and 80(19); δ 4.95(br s, 1H, NH), 4.11(d, 1H, CHN), 4.05 and 3.56(2 x m, 2 x 1H, CH_2O), 3.25(m, 1H), 2.89(m, 4H, 2 x CH_2S), 2.06(m, 5H) and 1.67(m, 1H).

(<u>29</u>). Colourless plates from methanol, m.p. 190-191°C (Found: C, 49.65; H, 6.9; N, 6.0. $C_{18}H_{30}N_2O_2S_4$ requires C, 49.75; H, 6.95; N, 6.45%); m/z(%), 434(M^+, 9), 416(18), 271(29), 244(38), 216(12), 200(19),

182(14), 174(19), 173(76), 168(20), 155(16), 145(34), 141(61), 140(52), 132(100), 119(11), 110(12), 106(20) and 99(27); δ 8.12(s, 1H, NH), 7.38(s, 1H, CH=N), 4.28(br s, 1H CHO), 3.97(br t, 1H, CHN), 3.15(m, 2H), 2.88(m, 1H), 2.82(m, 3H), 2.68(m, 1H, MeCH), 2.65(m, 2H), 2.34(br dd, 1H) and 2.12(m, 5H).

Isoxazolidine (35).

a. A solution of the oxime salt (32) (1g)[28] in n-butanol (20ml) was boiled and stirred under reflux for 3.5h. Decolourising charcoal (100mg) was then added and boiling continued for a further 10 min. The mixture was then cooled, filtered, and the solvent removed under reduced pressure to afford a black solid (930mg) which upon crystallisation from ethanol afforded (33) as a grey crystalline solid (230mg) which darkened on keeping in air for several hours. m/z(%) 242(1), 240(1), 161(21), 144(13) and 132(100); δ (DMSO-d_6), 9.03(d,1H, ArH), 8.59(t, 1H, ArH), 8.18(d, 1H, ArH), 8.10(t, 1H, ArH), 7.10(d, 1H, NH), 5.56(br t, 1H, ArCHN), 5.08 and 4.95(br dd and br d, 2 x 1H, CH_2O), 4.16(br d, 1H, NCHH) and 3.74(br d, 1H, NCHH) and 3.74(br m, 2H, NCHH and CH).

b. A solution of the salt (33) (730mg, 3mmol) (above) in methanol (7ml) was stirred and sodium borohydride (230mg, 6 mmol) was added portionwise over 10 min. The resulting mixture was stirred overnight, the solvent removed under pressure and the residue partitioned between chloroform and water. The organic phase was dried (Na_2SO_4), and evaporated to leave a black oil. Chromatography (SiO_2, Et_2O) followed by crystallisation from ether gave the *product* (300 mg, 60%) as colourless rods, m.p. 85-86°C (Found: C, 64.8; H, 8.6; N, 17.35. $C_9H_{14}N_2O$ requires C, 65.05; H, 8.5; N, 16.85%); m/z(%) 166(M^+, 39), 165(30), 136(100), 82(39) and 81(36); δ 5.73(m, 2H, CH=CH), 5.05 and 4.1(2 x br s, 2 x 1H, OH and NH), 3.88 and 3.55(br m and dd, 2 x 1H, CH_20), 3.45(dd, 1H, CHN), 3.04(m, 2H, CH_2N), 2.76(br d, 1H, CHN), 2.31(m, 3H) and 2.18(br m, 1H).

Indolizine(34). Sodium hydroxide (100mg, 25mmol) in water (1ml) was added to a stirred solution of the salt (33) (243mg, 1mmol) in water (1ml). A green sludge formed almost immediately. The mixture was allowed to stand for 10 min and then extracted with chloroform (3 x 10ml). The organic extracts were combined, dried(Na_2SO_4), and evaporated to leave the unstable *product* (100mg, 62%). m/z(%) 162(M^+, 100), 144(71), 105(23), 83(23), 79(25) and 78(20); δ(DMSO -d_6), 7.8 and 7.2(2 x d, 2 x 1H, 5-H and 8-H), 7.08(s, 1H, 3-H), 6.2(m, 2H, 6-H and 7-H), 4.7(br t, 1H, OH), 4.45(d, 2H, CH_2O) and 3.9(br s, 2H, NH_2).

Deuteriated Oxazolidine (40). A solution of the deuteriated oxime (39) (150mg) in xylene-d_{10} (1ml) was heated at 140°C for 7h in a sealed n.m.r. tube. Work up followed by preparative t.l.c. afforded the *product* as colourless rods (ether), m.p. 54-56°C. m/z(%) 219(M^+, 54), 218(16) and 217(1); δ 5.2(br s, 1H, NH), 4.17(d, 1H, CHN), 3.89 and 3.52 (d and t, 2 x 1H, CH_2O), 3.2(m, 1H, ring junction H), 2.87(m, 4H,

2 x CH_2S), 2.64 and 1.79(2 x dd, 2 x 1H, $C\underline{H_2}CH$) and 1.99(m, 2H, CH_2).

Crystal data for compound (35) - $C_9H_{14}N_2O$, M=162.22, monoclinic, space group $P2_1/c$ (no. 14), a=1193.1 (2), b=630.6(1), c=1301.0(2) pm, β=117.15(1)^0, U=.8708(3)nm^3, Z=4, D_c=1.27Mgm^{-3}, μ(Mo-K_a)=0.49 cm^{-1}, F(000)=360, crystal dimensions *ca.* 0.75 x 0.65 x 0.4 mm.

Data Collection - Intensity data were collected at 200 K on a Stoe STADI4 diffractometer operating in the ω/θ scan mode using graphite monochromated Mo=K_α X-radiation (λ=71.069 pm). A total of 1700 data were measured for one unique quadrant ($\pm h$, k, 1; 4.0^0 <2θ <50.0^0) with no significant variation observed in three standard reflections. After correction for Lorentz and polarisation factors (no absorption correction applied), 1343 intensities with I>2.0σ(I) were considered observed and used for the subsequent structure solution and refinement.

Structure solution and refinement - The structure was determined by direct methods (SHELXS86)[38] and was refined by full-matrix least-squares (SHELX76)[38] with anisotropic thermal parameters for all non-hydrogen atoms. All hydrogen atoms were included in calculated positions (C-H = 96 pm) apart from the hydrogen atom attached to N(3) (see Figure) which was located in a Fourier difference synthesis and freely refined. All hydrogen atoms were assigned an overall isotropic thermal parameter. The weighting scheme $w=[\sigma^2(F_0)+0.0006(F_0)^2]^{-1}$, where $\sigma(F_0)$ is derived from counting statistics, gave a satisfactory analysis of variance. At convergence, the final $R(=\Sigma(|F_0|-|F_c|)/\Sigma|F_0|)$ and $R_w(=\Sigma w(|F_0|-|F_c|)^2/\Sigma w|F_0|^2)$ values were 0.0537 and 0.0640 respectively. The Fourier difference synthesis contained no features of chemical significance with maximum and minimum residual densities of 0.20 and -0.24 eÅ^{-3}.

Atomic coordinates are listed in Table 3. Additional data to that listed in Table 2, including tables of anisotropic thermal parameters, hydrogen atom co-ordinates, and tables of observed and calculated structure factors have been deposited as supplementary data.

Table 2. Bond lengths (pm) and angles (°) for (**35**) with estimated standard deviations (e.s.d.'s) in parantheses.

O(2)-C(1)	144.3(3)	C(9a)-C(1)	152.0(5)
N(3)-O(2)	145.1(3)	H(3)-N(3)	95.2(27)
C(3a)-N(3)	146.6(3)	C(3b)-C(3a)	153.9(4)
C(9a)-C(3a)	155.4(4)	C(4)-C(3b)	151.5(4)
N(8)-C(3b)	145.9(3)	C(5)-C(4)	150.1(5)
C(6)-C(5)	130.0(4)	C(7)-C(6)	149.8(4)
N(8)-C(7)	145.4(3)	C(9)-N(8)	145.5(4)
C(9a)-C(9)	152.8(5)		

C(9a)-C(1)-O(2)	105.8(2)	N(3)-O(2)-C(1)	105.6(2)
H(3)-N(3)-O(2)	107.7(15)	C(3a)-N(3)-O(2)	104.8(2)
C(3a)-N(3)-H(3)	107.1(16)	C(3b)-C(3a)-N(3)	114.4(2)
C(9a)-C(3a)-N(3)	106.7(2)	C(9a)-C(3a)-C(3b)	103.9(2)
C(4)-C(3b)-C(3a)	117.6(2)	N(8)-C(3b)-C(3a)	104.0(2)
N(8)-C(3b)-C(4)	110.3(2)	C(5)-C(4)-C(3b)	109.9(3)
C(6)-C(5)-C(4)	122.9(3)	C(7)-C(6)-C(5)	123.3(3)
N(8)-C(7)-C(6)	110.9(3)	C(7)-N(8)-C(3b)	111.8(3)
C(9)-N(8)-C(3b)	104.3(2)	C(9)-N(8)-C(7)	114.9(3)
C(9a)-C(9)-N(8)	104.0(2)	C(3a)-C(9a)-C(1)	102.4(2)
C(9)-C(9a)-C(1)	114.6(3)	C(9)-C(9a)-C(3a)	104.3(2)

Table 3. Non-hydrogen atom co-ordinates ($x10^4$) for (**35**) with e.s.d.'s in parentheses

	x	y	z
C(1)	9944(2)	2607(3)	9189(2)
O(2)	9809(1)	1000(2)	8351(1)
N(3)	10631(1)	1649(2)	7862(1)
C(3a)	11749(2)	2520(2)	8839(1)
C(3b)	12789(2)	882(3)	9491(2)
C(4)	12923(2)	-956(3)	8806(2)
C(5)	13734(2)	-2652(3)	9612(2)
C(6)	14007(2)	-2712(4)	10700(2)
C(7)	13528(2)	-1123(4)	11261(2)
N(8)	12496(1)	104(3)	10398(1)
C(9)	12167(2)	2003(4)	10835(2)
C(9a)	11324(2)	3251(3)	9748(2)

We thank Rhone-Poulenc, SERC, and Queen's and Leeds Universities for support.

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latter proposes an unusual zwitterionic intermediate. We subsequently showed[7] these processes occurred by the tandem Michael addition-cycloaddition route (Scheme 1, path b).

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