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X=Y-ZH SYSTEMS AS POTENTIAL 1,3-DIPOLES. PART 32[1,2] GENERATION OF NITRONES FROM OXIMES. TANDEM MICHAEL ADDITION-1,3-DIPOLAR CYCLOADDITION REACTIONS. BACKGROUND AND CLASS 1 PROCESSES.

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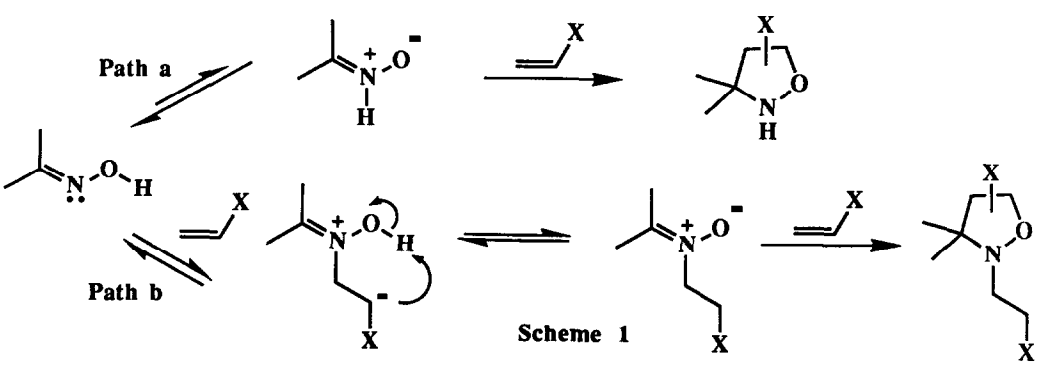
Abstract. Intermolecular Michael addition of aldoximes and ketoximes to electronegative olefins generates nitrones The keto nitrones can be trapped in regiospecific intermolecular cycloaddition reactions giving single cycloadducts in good yield Chemospecific 1 1 1 cycloadducts are obtained from ketoximes, monosubstituted electronegative olefins (Michael acceptor) and N-methylmaleimide (dipolarophile), whilst the chemoselectivity of the corresponding reactions with aldoximes is dependent on the oxime stereochemistry Z-Aldoximes show high chemospecificity whilst E-aldoximes are much less chemoselective

In the preceding paper[1] we discussed the general background of nitrone formation from oximes and focussed on the 1,2-prototropic route to nitrones (Scheme 1, path a) When an oxime is reacted in either an inter- or an intra-molecular manner with an alkene two tandem processes are possible (Scheme 1, paths a and b) The low energy path depends on the particular combination of oxime and alkene and whether the process is inter- or intra-molecular [1] In general δ-alkenyl oximes in which the alkene is unactivated react by path a [1,3] The analogous unactivated ω-alkenyl oximes also react by path a[4] under moderate pressures When γ- or δ-alkenyl oximes have electron withdrawing groups located on the alkene terminus or an oxime reacts intermolecularly with an electronegative olefin the reaction invariably



Scheme 1

occurs by path b (Scheme 1) [2,5] This latter process forms the subject of this paper

Intermolecular cycloaddition reactions of oximes to electronegative olefins were briefly reported by three groups in 1967, each of which interpreted their results in terms of a different mechanism [6] Our own systematic study[7] showed that aldoximes and ketoximes (1) react with 2 mol of an electronegative olefin to give regio- and stereo-isomeric mixtures of cycloadducts (2) and (3) in good yield In cycloadditions with acrylonitrile the 4-substituted isoxazolidines (2) predominate whilst with methyl acrylate the major isomers are the 5-substituted compounds (3) It was proposed that the formation of (2) and (3) occurred by path b (Scheme 1) The 1 1 adducts (4) were not observed even when a 1 1 molar ratio of oxime and monosubstituted electronegative olefin was used

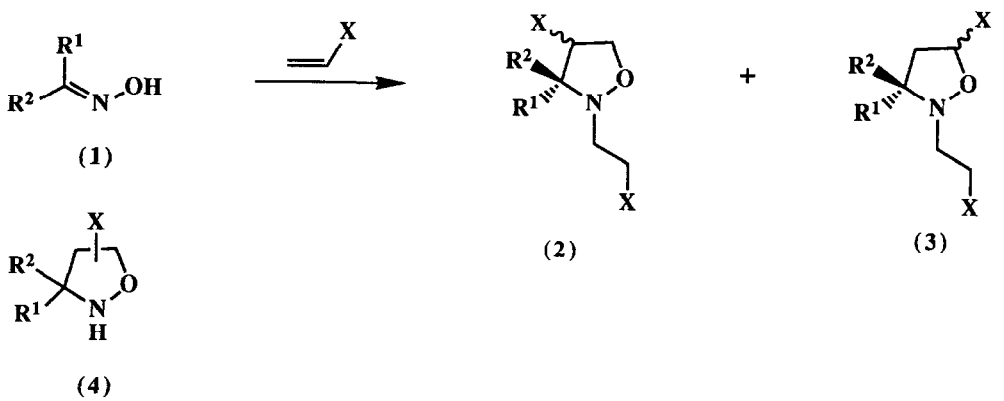


Table Synthetic Variants of the Tandem Michael Addition-1,3-Dipolar Cycloaddition Methodology

Class	Michael Addition	Cycloaddition
1	intermolecular	intermolecular
2	intermolecular	intramolecular
3	intramolecular	intermolecular
4	intramolecular	intramolecular

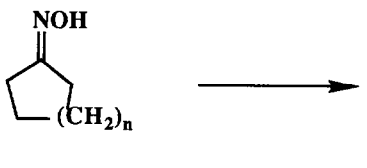
Path b (Scheme 1) formally consists of a tandem Michael addition-1,3-dipolar cycloaddition sequence and potentially provides four broad classes of synthetic methodology (Table) For maximum synthetic utility these four classes require chemospecific discrimination, by the oxime, between the Michael component and the dipolarophile We have now achieved this for all four classes of tandem

processes Although we represent path b (Scheme 1) as proceeding via an initial Michael addition[2,7] our studies thus far do not rule out an ene-like reaction as the first step This mechanistic problem is considered in more detail later in this paper Class 1 processes (Table) form the subject of this paper

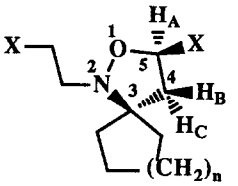
Class 1 Processes. Identical Michael Acceptor and Dipolarophile

Our initial non-stereo- and non-regio-specific cycloadditions were carried out in pyridine as solvent and involved acyclic oximes[7] When cycloalkanone oximes (5) were reacted (dry acetonitrile, 80°C) with phenyl vinyl sulphone a regiospecific tandem process occurred giving (6a, b) in > 75% yield The same reactions in xylene at 140°C were less efficient and gave in addition small amounts of other products, possibly the corresponding O-Michael adducts (7a, b) The regiochemistry of (6a, b) is readily assigned from their p m r spectra The signal for the C(5) methine proton H_A occurs at ca δ 4 8 whilst the C(4) methylene protons occur between δ 2 4 and 2 8 An analogous reaction occurs when either benzyl acrylate or methyl vinyl ketone are used in place of phenyl vinyl sulphone Thus (5, n=2) gives (MeCN, 80°C, 20h) (6c)(73%) together with trace amounts (ca 5%) of the hydroxylamine [NH(OH)$CH_2CH_2CO_2CH_2$Ph], whilst (6d) is obtained (MeCN, 80°C, 24h) as a single isomer in 60% yield An analogous reaction (MeCN, 80°C, 16h), of (5, n=2) with N-methylmaleimide (NMM) (2 mol) afforded a 6 1 mixture (51%) of (8a) and the N-unsubstituted isoxazolidine (9a), together with ca 15% of a third product whose mass spectrum showed it to be a 1 2 adduct of cyclohexanone oxime and NMM The spectral data (ir, n m r , and mass) of the 1 2 adduct could be accommodated by structure (10a) In particular a DEPT spectrum confirmed the presence of three CH groups whilst a D_2O shake revealed the presence (p m r) of one rapidly exchangeable proton (OH) and one more slowly exchanging proton (NH) The amount of (10a) present in the reaction mixture was minimal but the quantity of (10a) increased upon chromatography on silica Thus (10a) apparently arises from (8a) by an acid catalysed rearrangement The small initial amount of (10a) is probably generated by traces of the precursor maleamic acid in the NMM The 2 1 adduct (8a) comprised a 5 1 mixture of two diastereomers Only the major diastereomer was obtained pure

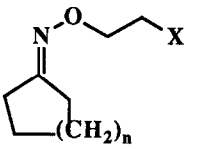
The regiospecific formation of the 5-substituted isoxazolidines (6a-c) invites comment since it is well documented that cycloadditions of nitrones with electronegative olefins generally afforded considerable quantities of the 4-substituted regioisomer[9] This latter orientation is disfavoured in cycloadditions of (5, n=1 or 2) because of the steric interaction between the carbocyclic ring and olefin substituent X in the transition state Thus formation of (6a-c) involves a transition state in which the least hindered terminal carbon of the dipolarophile reacts with the most hindered nitrone centre Similar effects have been observed and discussed by us in more detail with respect to azomethine ylide cycloadditions[10] The



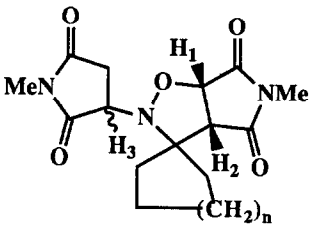
(5) n = 1 or 2



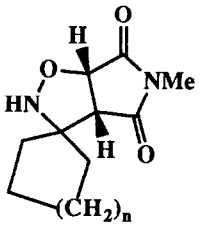
(6) a. n = 1, X = SO_2Ph
b. n = 2, X = SO_2Ph
c. n = 2, X = CO_2CH_2Ph
d. n = 2, X = COMe



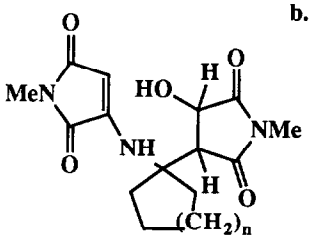
(7) a. X = SO_2Ph



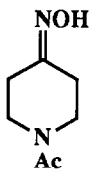
(8) a. n = 2
b. n = 1



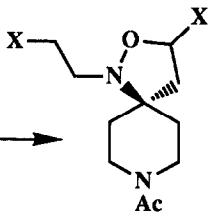
(9) a. n = 2
b. n = 1



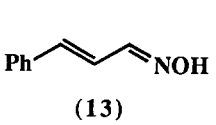
(10) a. n = 2
b. n = 1



(11)



(12) a. X= SO_2Ph
b. X = CO_2CH_2Ph



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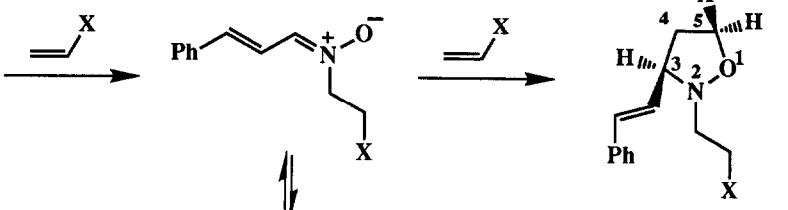
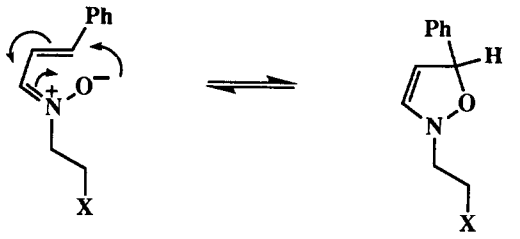


(14) a. X = SO_2Ph
b. X = CO_2CH_2Ph



Scheme 2

formation of ca 8% of (9a) in the reaction of (5, n=2) with NMM (2 mol) demonstrates the ability of very reactive dipolarophiles to trap the small equilibrium concentration of the NH nitrone (Scheme 1, path a)[1] in competition with the Michael addition (or ene) reaction

N-Acetyl-4-piperidone oxime (11) reacts (xylene, 140°C, 10-12h) with phenyl vinyl sulphone and with benzyl acrylate to give the analogous spirocyclic adducts (12a) and (12b) respectively in good yield (65-75%) together with trace amounts of the regioisomeric cycloadducts It was of interest to examine the behaviour of cinnamaldehyde oxime (13) with electronegative olefins to probe the relative importance of the tandem Michael addition-cycloaddition process and the possible Michael addition-1,5-electrocyclisation sequence (Scheme 2) We have recently demonstrated the synthetic utility of related 1,5-electrocyclisations in azomethine ylide chemistry [11]

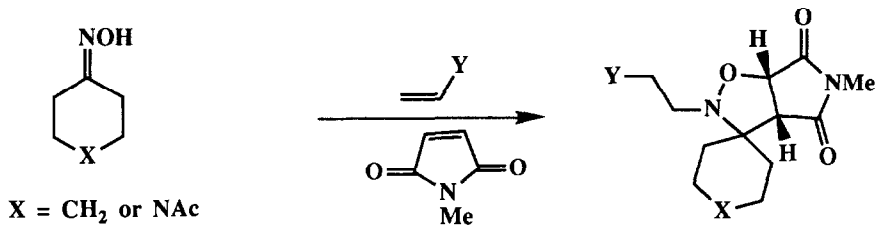
When equimolar amounts of (13) and phenyl vinyl sulphone were heated in boiling xylene the major product was the 1 2 cycloadduct (14a) When two mol of the dipolarophile was used the yield of (14a) was 60%, and in addition trace amounts of a second product were detected (p m r) possibly a regio/stereo-isomer of (14a) Although we have good evidence for facile oxime E ⇌ Z-isomer interconversion in xylene at 140°C which would allow the electrocyclisation (Scheme 2) to proceed, the use of such high temperatures, not surprisingly, favours (14a) since the electrocyclisation is reversible The regio- and stereo-chemistry of (14a) is assigned on the basis of n m r studies involving ^{1}H-2D-COSY spectra, NOEDS results and decoupling studies In contrast to phenyl vinyl sulphone when (13) was reacted with benzyl acrylate (xylene, 140°C, 8h) the product (58%) consisted of a mixture of all four possible regio- and stereo-isomeric products but one in which (14b) was the predominant isomer No attempt was made to separate this mixture The major factor in the different behaviour of the two dipolarophiles is apparently the greater steric demand of the $PhSO_2$ group compared to the CO_2CH_2Ph moiety in the cycloaddition transition state

Thus the regio- and stereo-specificity observed in these Class 1 processes is due to steric effects operating in the cycloaddition transition states

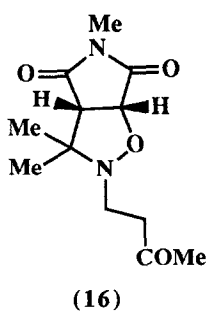
Class 1 Processes with Non-identical Michael Acceptor and Dipolarophile.

As a natural development of the class 1 synthetic variant we explored the potential for a chemospecific reaction in which the Michael acceptor and dipolarophile were different The key to success in this endeavour lies in identifying pairs of reactants, one of which functions as a good Michael acceptor or enophile but a relatively poor dipolarophile, and the other of which is a reactive dipolarophile but a poor Michael acceptor (enophile) (or one for which the Michael addition is readily reversible) The work

of Ring et al [12] outlining a measure of the relative electrophilicity of activated vinyl compounds ($RR^1C{=}CR^2A$) toward nucleophilic attack showed the rate enhancing effect of the activating group A (withdrawing group) increases in the order $CONHR<CONR_2<CO_2H<CN<SO_2R<COR$, and directed our attention to methyl vinyl ketone as the Michael acceptor (enophile) After a series of exploratory experiments we found that boiling a solution of equimolar amounts of cyclohexanone oxime (5, n=2),



(15) a. X = CH_2, Y = COMe
b. X = NCOMe, Y = COMe
c. X = CH_2, Y = SO_2Ph
d. X = CH_2, Y = CO_2CH_2Ph



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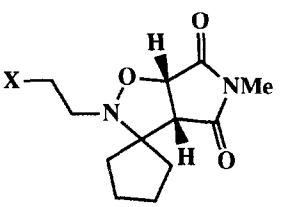
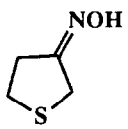


(17) a. X = SO_2Ph
b. X = CO_2CH_2Ph



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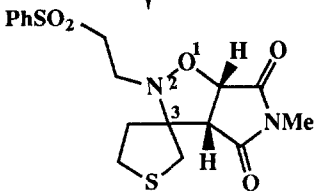


(19)

methyl vinyl ketone and N-methylmaleimide (NMM) in acetonitrile under reflux (18h) afforded the 1 1 1 adduct (15a) as a colourless crystalline solid in 75% yield

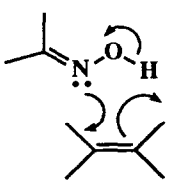
The same Michael acceptor-dipolarophile combination afforded (15b) (60%) from reaction with (11), and (16) (75%) from reaction with acetone oxime Phenyl vinyl sulphone in combination with NMM proved an efficient combination for chemoselective processes Thus this combination afforded (15c) (60%) from cyclohexanone oxime (MeCN, 80°C, 20h), and (17a) (60%) from cyclopentanone oxime under the same

conditions Interestingly when the reaction of phenyl vinyl sulphone, NMM and cyclohexanone oxime was carried out in deuterioacetonitrile over 30 days at room temperature the cycloadduct (15c) was formed in quantitative yield (n m r tube experiment)

When benzyl acrylate is used as the Michael acceptor in combination with NMM as the dipolarophile a much lower degree of chemoselectivity is observed Thus the cycloadducts (15d) and (17b) were obtained (MeCN, 80°C) in only 40 and 57% yield respectively In the case of cyclohexanone oxime ca 20% of (8a) the 2 1 adduct with NMM was detected together with trace amounts of other products whilst with cyclopentanone the by-products were the 2 1 adduct (8b) (8%, two diastereomers), a trace of the NH isoxazolidine (9b) and (10b) (18%) The tetrahydrothiophene oxime (18) reacted slowly (MeCN, 80°C, 18h) with phenyl vinyl sulphone and NMM to give the corresponding 1 1 1 adduct (19) as a 2 1 mixture of C(3) epimers The p m r spectrum of the reaction mixture after 18h indicated ca 62% conversion to products

Mechanism

The question of whether the 1 1 1 adducts were chemo-selective/specific kinetic products or the products of an equilibration process was briefly probed The 2 1 adduct (6b) was heated (xylene-d_{10}, 140°C, n m r tube) with NMM (1 mol) Monitoring the reaction for 20h by p m r did not reveal formation of any 1 1 1 adduct (15c), only some decomposition products An analogous experiment with (8) and phenyl vinyl sulphone (xylene -d_{10}, 130°C) showed no change after 16h whilst on longer heating (22-32h) signals corresponding to NMM and (9) began to appear Repeating both these reactions in deuterioacetonitrile at 80°C gave identical results but decomposition was suppressed These observations support the conclusion that the 1 1 1 adducts (15) and (17) are kinetic products The formation of the nitrone could occur by a Michael addition reaction (Scheme 1, path b) or by a concerted ene-like process involving the nitrogen lone pair, e g (20, arrows) This latter type of process has recently been observed by us[13] and by Bishop[14] in certain δ-alkenyl oximes, e g (21) → (22),[13] in which the alkene moiety is unactivated



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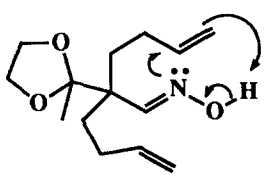

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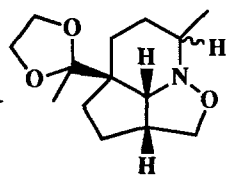

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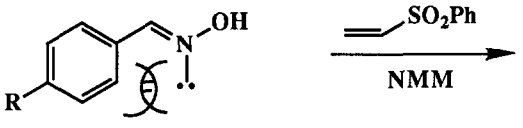
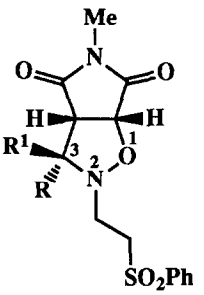
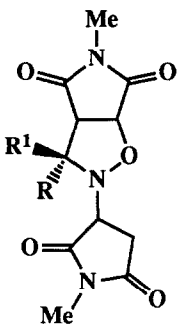
Both possible mechanisms involve attack of the nitrogen lone pair on the electonegative olefin and should therefore be sensitive to oxime geometry in aldoximes This is readily demonstrated using aryl aldoximes The chemoselective cycloadditions of the aryl aldoximes (23 a-c) with equimolar amounts of phenyl vinyl sulphone and NMM were briefly studied Complex mixtures of cycloadducts were formed in xylene at 140°C whilst in acetonitrile at 80°C the reaction was very slow (<10% conversion after 24h) In all cases in xylene 2 1 adduct-formation competes with the desired 1 1 1 cycloaddition reaction Only in the case of (23a) was separation of the mixture deemed worthwhile Flash chromatography (SiO_2, 3 2 ethyl acetate-hexane) of the reaction mixture in this case afforded (24a) (12%)



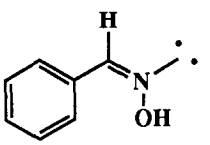
(23) a. R = H
b. R = OMe
c. R = NO_2



(24) a. R = Ph, R^1 = H
b. R = H, R^1 = Ph



(25) a. R = Ph, R^1 = H
b. R = H, R^1 = Ph



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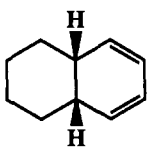


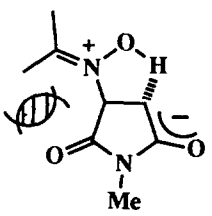
(27)

and (24b) (25%) Trace amounts of (25a) and (25b) were detected in the p m r spectra but these compounds were not isolated

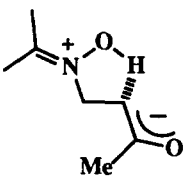
The reactions with aryl aldoximes are complicated by the formation of C(3)-epimers of (24) but are also clearly less chemospecific than those of cyclic ketoximes even though 1 1 1 adducts still predominate

The origin of the reduced chemoselectivity was believed to be steric in origin, i e the enforced eclipsing of the nitrogen lone pair and the aryl ring (23) Indeed, it seemed likely that the high reaction temperature was necessary to produce a small equilibrium concentration of the Z-isomer (26) which would be much more reactive The Z-isomer was therefore reacted with phenyl vinyl sulphone and NMM in acetonitrile at 80°C A rapid reaction ensued giving a 9 1 mixture of (24a) and (24b) together with a trace amount (>10%) of (25a)

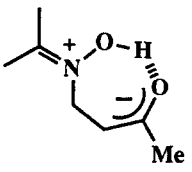
The distinction between the Michael addition and ene-type mechanisms is difficult to make on our present evidence There is literature data[15] which shows that for reaction of a range of enophiles/dienophiles with the sterically hindered diene (27), maleimides clearly prefer the Diels-Alder pathway over the ene reaction (ca 98 2) whilst for methyl acrylate the reactivity is more evenly balanced (45 55) In the case of Michael addition of nitrogen nucleophiles a direct comparison of maleimides and acrylates is lacking although there is some evidence that hydroxylamine addition to maleimides via the nitrogen atom is a fast reversible process [16] The Michael addition, if operative, is clearly related to the well known Baylis-Hillman reaction [17] The concerted process and the Michael addition with intramolecular proton transfer differ only in the concertedness of the proton transfer step Whilst proton transfers between electronegative atoms are known to be very rapid,[18] proton transfer from an electronegative atom to a carbon centre is much slower and is dependant on the extent to which the negative charge is delocalised [19] Moreover, the most favourable geometry for an intramolecular proton transfer is via an 8-membered transition state[20] where the donor- proton-acceptor array can attain a linear arrangement The proton transfer transition states for the Michael addition of an oxime to NMM, and to a monosubsitituted electronegative olefin, such as methyl vinyl ketone, are (28), and (29) or (30) respectively Transition state (28), in addition to being more strained than (29) and (30) suffers more steric hindrance and would appear less favoured on these grounds A decision between the Michael addition and ene-type mechanisms awaits a more detailed kinetic study of these reactions



(28)



(29)



(30)

Experimental General details were as previously described [1,21]

Cycloadducts in which the Michael Acceptor and Dipolarophile are Identical

2-(2′-Phenylsulphonylethyl)-3,3-spirotetramethylene-5-phenylsulphonylisoxazolidine (6a) A solution of cyclopentanone oxime (990 mg, 10 mmol) and phenyl vinyl sulphone (3 36g, 20 mmol) in dry acetonitrile (60 ml) was stirred and boiled under reflux for 20h The solvent was removed and the residual solid purified by flash chromatography (silica, 9 1 ether-hexane) to afford the cycloadduct as a colourless solid (3 3g, 76%) which crystallised from ether as colourless prisms, m p 100-102°C (Found C, 57 7, H, 5 7, N, 3 15 $C_{21}H_{25}NO_5S_2$ requires C, 57 9, H, 5 8, N, 3 2%), m/z(%) 435(M^+, 2), 294(23), 264(20), 141(34), 125(41), 110(63), 78(22) and 77(100), δ 7 93-7 52(m, 10H, ArH), 4 84(t, 1H, H_A, J 8 1Hz), 3 43(br t, 2H, CH_2SO_2Ph), 3 24 and 3 11(br m, 2H CH_2N), 2 73(dd, 1H, H_B, J 8 3 and 12 9Hz), 2 47(dd, 1H, H_C, J 7 8 and 12 9Hz), and 1 67 and 1 39(br m, 8H, 4 x CH_2)

2-(2′-Phenylsulphonylethyl)-3,3-spiropentamethylene-5-phenylsulphonylisoxazolidine (6b) - A solution of cyclohexanone oxime (560 mg, 5 mmol) and phenyl vinyl sulphone (1 68g, 10 mmol) was boiled under reflux in dry acetonitrile (30ml) for 20h Removal of the solvent followed by flash chromatography (silica, 9 1 ether-hexane) of the solid residue afforded (6b) as a colourless solid (1 79g, 80%) which crystallised from ether as colourless prisms, m p 101-103°C (Found C, 58 55, H, 5 85, N, 3 25 $C_{22}H_{27}NO_5S_2$ requires C, 58 8, H, 6 05, N, 3 1%), m/z(%) 449(M^+, 0 5), 218(25), 141(82), 125(89) and 77(100), δ 7 93-7 51(m, 10H, ArH), 4 83(t, 1H, H_A), 3 48-3 24(br m, 2H, CH_2SO_2Ph), 3 23-2 92(br m, 2H, CH_2N), 2 56(m, 2H, H_B, H_C) and 1 80-1 10(m, 10H, 5 x CH_2)

2-(2′-benzyloxycarbonylethyl)-3,3-spiropentamethylene-5-benzyloxycarbonylisoxazolidine (6c) A solution of cyclohexanone oxime (500 mg, 4 42mmol) and benzyl acrylate (1 43g, 8 84 mmol) in dry acetonitrile (30ml) was boiled under reflux under a nitrogen atmosphere for 20h Removal of the solvent afforded a pale yellow oil which was purified by flash chromatography (1 1 ether-petroleum ether) to give the *product* (1 41g, 73%) as a colourless oil (Found C, 71 4, H, 7 2, N, 3 2 $C_{26}H_{31}NO_5$ requires C, 71 4, H, 7 15, N, 3 2%), m/z(%) 437(M^+, 10), 394(10) and 91(100), δ 7 39-7 31(m, 10H, ArH), 5 17 and 5 13(2 x s, 2 x 2H, 2 x Ch_2Ph), 4 57(dd, 1H, H_A, J 6 7 and 9 5Hz), 2 98(br m, 2H, CH_2N), 2 77(br t, 2H, $\underline{CH_2}CO_2CH_2Ph$), 2 43(dd, 1H, H_C, J 9 5 and 12 7Hz), 2 27(dd, 1H, H_B, J 6 7 and 12 6Hz) and 1 9-1 2(m, 10H, 5 x CH_2) The presence of the hydroxylamine [$NH(OH)CH_2CH_2CO_2CH_2Ph$] was inferred from following signals in the p m r spectrum of the crude reaction mixture, δ 7 35(br s, 5H, ArH), 5 10(s, 2H, CO_2CH_2Ph), 2 98(t, 2H, CH_2N) and 2 62(t, 2H, CH_2CO)

2-(3′-Oxobutyl)-3,3-spiropentamethylene-5-acetylisoxazolidine (6d) A solution of cyclohexanone oxime

(1 13g, 10mmol) and methyl vinyl ketone (1 40g, 20mmol) was boiled under reflux in acetonitrile (60ml) for 22h Removal of the solvent afforded a pale yellow oil (2 2g, 87%) whose p m r spectrum indicated the presence of >90% of a single isoxazolidine (6d) together with trace amounts of a second product Preparative t l c (silica, 7 6 ether-hexane) afforded the *product* (1 50g, 60%) as a mobile pale yellow oil (R_f 0 64) (Found C, 66 55, H, 9 4, N, 5 35 $C_{14}H_{23}NO_3$ requires C, 66 4, H, 9 1, N, 5 55%), m/z(%) 253(M^+, 29), 210(100), 151(15), 59(24) and 43(49), δ 4 30(dd, 1H, J 9 6 and 5 6 Hz, H-5), 2 86(m, 4H, NCH_2CH_2), 2 35(dd, 1H, J 12 6 and 9 8 Hz, H-4), 2 23 and 2 20(2 x s, 2 x 3H, 2 x Me), and 1 55(m, 11H, H-4 and 5 x CH_2)

Cycloadducts (8a) (9a) and (10a) A solution of cyclohexanone oxime (500 mg, 4 42 mmol) and N-methylmaleimide (980 mg, 8 82 mmol) in dry acetonitrile (30 ml) was boiled under reflux under a nitrogen atmosphere for 16h Work up in the usual way afforded a yellow solid whose p m r spectrum indicated it comprised a 5 1 1 1 mixture of (8a), (9a) and (10a) Work up by flash chromatography (ether) and crystallisation from ether afforded the three products

(8a) (750mg, 51%) was obtained as colourless rods, m p 174-176°C (Found C, 57 2, H, 6 25, N, 12 55 $C_{16}H_{21}N_3O_5$ requries C, 57 3, H, 6 3, N, 12 55%), m/z(%) 335(M^+, 22), 292(20), 250(17), 209(14), 207(24), 126(16), 123(12), 112(16), 111(28), 96(15), 83(17), 81(25), 68(22), 67(27), 55(59), 54(51) and 40(100), δ 4 77(d, 1H, J 8 1 Hz, CHO), 4 15(dd, 1H, J 5 0 and 9 2 Hz, $CH_2\underline{CH}CO$), 3 84(d, 1H, $\underline{CH}CHO$), 3 0 and 2 99(2 x s, 2 x 3H, NMe), 2 97(m, 2H, $CO\underline{CH_2}CHCO$), 2 08(m, 2H, CH_2) and 1 69-1 39(m, 8H, 4 x CH_2), ν_{max}(nujol) 2910, 2840, 1780, 1760, 1690, 1455, 1370, 1270, 1105 and 940 cm^{-1}

(9a) Colourless prisms (165mg, 17%), m p 165-167°C (Found C, 58 75, H, 7 15, N, 12 3 $C_{11}H_{16}N_2O_3$ requires C, 58 9, H, 7 2, N, 12 5%), m/z(%) 224(M^+, 77), 209(9), 195(49), 181(88), 168(63), 153(43), 138(42), 125(26), 112(66), 96(100) and 83(32), δ 5 20(br s, 1H, NH), 4 95 and 3 27(2 x d, 2 x 1H, J 7 3 Hz, COCHCHCO), 3 03(s, 3H, NMe), 1 74-1 82(m, 4H, 2 x CH_2) and 1 37-1 60(m, 6H, 3 x CH_2)

(10a) Pale yellow prisms (150mg, 10%), m p 178-180°C (ether-chloroform), accurate mass 335 1852 $C_{16}H_{21}N_3O_5$ requires 335 1481, m/z(%) 335(M^+, 21), 292(37), 274(6), 250(10), 207(100), 150(8), 129(7), 121(13), 112(10), and 81(36), δ 5 88(br s, 1H, NH), 4 92(s, 1H, C=CH), 4 71(dd, 1H, J 2 6 and 7 9 Hz, COC$\underline{H}$OH), 3 68(d, 1H, J 2 3 Hz, OH), 3 25(d, 1H, J 8 0Hz, CHCO), 2 99 and 2 98(2 x s, 2 x 3H, 2 x NMe), and 1 25-2 32(m, 10H, 5 x CH_2)

N-Acetyl-4-piperidone oxime (11) To a stirred solution of N-acetyl-4-piperidone (10g, 71mmol) and hydroxylamine hydrochloride (4 9g, 71mmol) in water (70ml) was added an aqueous solution of sodium carbonate (7 5g, 71mmol) in water (40ml) The resulting mixture was stirred overnight at 25°C, then

saturated with sodium chloride and extracted with methylene chloride (4 x 100ml) The organic layers were combined, dried over anhydrous sodium sulphate and concentrated to afford a colourless solid which was crystallised from methylene chloride to give the *product* as colourless needles, m p 173-175^{0}C, (6 6g, 62%), (Found C, 53 45, H, 7 8, N, 17 65 $C_7H_{12}N_2O_2$ requires C, 53 85, H, 7 75, N, 17 95%), m/z(%) 156(M^+, 0 5), 141(93), 113(30), 57(64) and 43(100), δ 3 72 and 3 56(2 x m, 2 x 2H, 2 x NCH_2), 2 68 and 2 44(2 x m, 2 x 2H, 2 x CH_2) and 2 16 and 2 15(2 x s, 3H, NCOMe isomers)

2-(2′-Phenylsulphonylethyl)-3,3-spiro(pentamethylene-3′-azaacetyl)-5-phenylsulphonylisoxazolidine (12a) A solution of N-acetyl-4-piperidone oxime (0 25g, 1 6mmol) and phenyl vinyl sulphone (0 53g, 3 2mmol) was boiled under reflux in xylene (15ml) for 12h Removal of the solvent afforded a yellow gum whose p m r spectrum indicated the presence of (9a) (90%) together with a small amount of a second compound Flash chromatography (silica, 7 2 ethyl acetate-hexane) afforded the *product* as a colourless solid (0 6g, 75%), which crystallised from ethyl acetate-hexane as colourless needles, m p 77-78^{0}C (Found C, 56 3, H, 5 6, N, 5 4 $C_{23}H_{28}N_2O_6S_2$ requires C, 56 1, H, 5 7, N, 5 7%), m/z(%) 332(43(M-SO_2Ph-Me)), 289(11), 274(12), 261(43), 141(28) and 77(100), δ 7 88, 7 66 and 7 54(3 x m, 10H, ArH), 4 90(dd, 1H, J 7 3 and 8 1 Hz, H-5), 3 38(m, 8H, $NCH_2CH_2SO_2Ph$ and 2 x NCH_2), 2 61(m, 2H, 2 x H-4), 2 07(2 x S, 3H, NCOMe isomers) and 1 50(m, 4H, 2 x CH_2)

2-(2′-Benzyloxycarbonylethyl)-3,3-spiro(pentamethylene-3′-azaacetyl)-5-benzyloxycarbonyl isoxazolidine (12b) A solution of N-acetyl-4-piperidine oxime (1 0g, 6 4mmol) and benzyl acrylate (2 07g, 12 8mmol) was boiled under reflux in degassed xylene (50ml) for 20h Removal of the solvent afforded a brown gum (3 07g) whose p m r spectrum indicated the presence of (9b) as the major product (80% together with a small amount of other unidentified products A sample (0 5g) of the crude material was purified by preparative t l c (silica, ethyl acetate) to afford the *product* (0 3g, 65%) as a colourless viscous oil (R_f, 0 28) (Found C, 67 15, H, 6 3, N, 6 0 $C_{27}H_{32}N_2O_6$ requires C, 67 5, H, 6 7, N, 5 85%), m/z(%) 480(M^+, 1), 162(40), 139(42), 107(25), 91(100) and 55(100), δ 7 34(m, 10H, ArH), 5 16 and 5 11(2 x s, 2 x 2H, 2 x CH_2Ar), 4 60(m, H, H-5), 3 53 and 3 29(2 x m, 4H, 2 x NCH_2), 2 93(m, 2H, $N\underline{CH_2}CH_2CO_2CH_2Ph$), 2 73(m, 2H, $\underline{CH_2}CO_2CH_2Ph$), 2 34(m, 2H, 2 x H-4), 2 06 and 2 07(2 x s, 3H, NCOMe isomers) and 1 75 and 1 56(2 x m, 4H, 2 x NCH_2)

2-(2′Phenylsulphonylethyl)-3α-styryl-5α-phenylsulphonylisoxazolidine (14a) A solution of cinnamaldehyde oxime (13) (0 72g, 5mmol) and phenyl vinyl sulphone (1 68g, 10mmol) was boiled under reflux in xylene (35ml) for 5h Removal of the solvent afforded a brown oil whose p m r spectrum showed it to comprise (13a) (75%) as the major product, together with minor amounts of unidentified material Flash chromatography (silica, 7 3 ether-hexane) afforded a colourless solid (1 9g, 60%) which crystallised from benzene-petroleum ether as colourless needles, m p 151-153^{0}C (Found C, 61 8, H,

5 4, N, 2 6 $C_{25}H_{25}NO_5S_2$ requires C, 62 1, H, 5 2, N, 3 0%) m/z (%) 483(M^+, 0 5), 314(17), 342(5), 125(73) and 77(100), δ 7 89, 7 61, 7 32 and 7 15(4 x m, 15H, ArH), 6 21(d, 1H, J 16 OHz, PhCH=CH), 5 72(dd, 1H, J 15 6 and 8 5Hz, PhCH), 4 35(dd, 1H, J 9 0 and 2 6Hz, H-5), 3 9(dd, 1H, J 16 5 and 8 0Hz, H-4), 3 80(m, 1H, H-4), 3 50(m, 3H, H-3 and CH_2SO_2Ph), and 3 42 and 2 98(2 x m, 2 x 1H, NCH_2), ^{1}NOEDSY(%) irradiation of 6-H caused enhancements of H-5 (14%) and H-4(11%), irradiation of H-3 caused enhancements of H-5(15%) and H-4(5%)

Reaction between cinnamaldehyde oxime and benzyl acrylate A solution of cinnamaldehyde oxime, (0 72g, 5mmol) and benzyl acrylate (1 62g, 10mmol) in xylene (35ml) was boiled under reflux for 8h Evaporation of the solvent afforded a brown oil whose p m r spectrum showed it to comprise the stereoisomers of (13b) (58%, combined yield) together with unreacted starting materials Flash chromatography (silica, 3 5 ether hexane) afforded (14b), (0 9g, 38%) as an inseparable mixture of isomers (Found C, 73 75, H, 6 2, N, 2 75 $C_{29}H_{29}NO_5$ requires C, 73 85, H, 6 2, N, 2 95%), m/z(%) 471(M^+, 1) 308(3), 202(4), 162(23), 117(23), 91(100) and 77(15)

Cycloadducts in which the Michael Acceptor and Dipolarophile are Different.

2,2-Spiropentamethylene-3-(3′-oxobutyl)-7-methyl-3,7-diaza-4-oxabicyclo[3 3 0]octane-6,8-dione(15a) A solution of cyclohexanone oxime (1 13g, 10mmol), methyl vinyl ketone (0 7g, 10mmol) and NMM (1 11g, 10mmol) in acetonitrile (75ml) was boiled under reflux for 18h Removal of the solvent afforded a pale brown solid which was purified by flash chromatography (silica, 4 1 ether-hexane) The product (14a) (2 2g, 75%), was obtained as colourless plates, from ethyl acetate, m p 94-96°C (Found C, 61 0, H, 7 4, N, 9 8 $C_{15}H_{22}N_2O_4$ reqiores C 61 2, H, 7 55, N, 9 5%), m/z(%) 294(M^+, 13), 251(100), 237(15), 181(14) and 113(9), δ 4 67(d, 1H, J 7 48Hz, H-5), 3 45(d, 1H, J 7 49Hz, H-4), 3 00(s, 3H, OMe), 2 94(m, 2H, NCH_2), 2 76[t, 2H, J 6 5Hz, $CH_2C(O)Me$], 2 16(s, 3H, NMe), and 1 95, 1 75, 1 45 and 1 25(4 x m, 10H, 5 x CH_2)

2,2-Spiro(pentamethylene-3′-azaacetyl)-3-(3′-oxobutyl)-7-methyl-3,7-diaza-4-oxabicyclo[3 3 0]octane-6,8-dione(15b) A solution of N-acetyl-4-piperidone oxime (0 39g, 2 5mmol), NMM (0 28g, 2 5mmol) and methyl vinyl ketone (0 18g, 2 5mmol) in acetonitrile (20ml) was boiled under reflux for 30h Removal of the solvent afforded a yellow oil Purification of the crude mixture by flash chromatography (silica, 95 5 ethyl acetate-ethanol) followed by crystallisation from benzene afforded the *product* (0 51g, 60%) as colourless plates (Found C, 57 15, H, 6 85, N, 12 1 $C_{16}H_{23}N_3O_5$ requires C, 56 95, H, 6 85, N, 12 45%), m/z(%) 337(M^+, 46), 266(34), 251(48) and 209(100), δ 4 74(d, 1H, J 7 5Hz, H-5), 3 74(m, 3H, 3 x NCH), 3 50(m, 2H, H-4 and NCH), 3 02(s, 3H, NMe), 2 82(m, 4H, NCH_2CH_2), 2 16 and 2 13(2 x s, 2 x 3H, 2 x Me), 1 69 and 1 58(2 x m, 2 x 2H, 2 x CH_2)

2,2-Spiropentamethylene-3-(2′-phenylsulphonylethyl)-7-methyl-3,7-diaza-4-oxabicyclo[3 3 0]octane-6,8-dione(15c) A solution of cyclohexanone oxime (0 56g, 5mmol), phenyl vinyl sulphone (0 86g, 5mmol) and NMM (0 56g, 5mmol) in acetonitrile (35ml) was boiled under reflux for 20h under an atmosphere of argon Removal of the solvent afforded an orange solid whose p m r spectrum showed it to comprise (14c) as the major product (82%) together with some unreacted starting materials and a trace amount of a second product Crystallisation of the solid from benzene yielded (14c) (1 2g, 60%) as colourless plates, m p 168-170°C (Found C, 57 5, H, 6 1, N, 6 95 $C_{19}H_{24}N_2O_5S$ requires C, 58 15, H, 6 2, N, 7 15%), m/z(%) 392(M^+, 34), 250(21), 223(8) and 77(100), δ 7 91 and 7 67(2 x m, 5-H, ArH), 4 61(d, 1H, J 7 5Hz, H-5), 3 45(m, 3H, H-4 and CH_2SO_2Ph), 3 14(m, 2H, NCH_2), 2 93(s, 3H, NMe), and 1 75 and 1 34(2 x m, 10H, 5 x CH_2)

2,2-Spiropentamethylene-3-(2′-benzyloxycarbonylethyl)-7-methyl-3,7-diaza-4-oxabicyclo[3 3 0]octane-6,8-dione(15d) A solution of cyclohexanone oxime (0 31g, 2 5mmol), benzyl acrylate (0 45g, 2 5mmol), and NMM(0 3g, 2 5mmol), in acetonitrile (20ml) was boiled under reflux for 15h Removal of the solvent afforded an orange gum whose p m r spectrum showed it to comprise (14d) as the major product (50%) together benzyl acrylate (20%), (8) (20%), and trace amounts of another cycloadduct Purification of the crude reaction mixture by flash chromatography (silica 1 1 ether-hexane) yielded the *product* (0 38g, 40%) as a colourless solid which crystallised from ether-petroleum ether as colourless needles, m p 87-88°C (Found C, 65 0, H, 6 7, N, 7 4 $C_{21}H_{26}N_2O_5$ requires C, 65 25, H, 6 8, N, 7 25%), m/z(%) 386(M^+, 42), 343(47) and 91(100), δ 7 24(br s, 5H, ArH), 5 04(s, 2H, CH_2Ar), 4 58(d, 1H, J 7 4Hz, H-5), 3 34(d, 1H, J 7 4Hz, H-4), 2 91(m, 5H, NCH_3 and NCH_2), 2 57(m, 2H, CH_2CO_2R), and 1 72 and 1 43(2 x m, 10H, 5 x CH_2)

2,2,7-Trimethyl-3-(3′-oxobutyl)-3,7-diaza-4-oxabicyclo[3 3 0]octane-6,8dione(16) A solution of acetone oxime (0 73g, 10mmol), methyl vinyl ketone (0 7g, 10mmol), and NMM(1 11g, 10mmol) in acetonitrile (75ml) was boiled under reflux for 22h Removal of the solvent afforded a yellow gum which was purified by flash chromatography (silica, ether) to afford the *product* (1 90g, 75%) which crystallised from ethyl acetate as colourless chunky prisms, m p 99-100°C (Found C, 57 15, H, 6 8, N, 10 8 $C_{12}H_{18}N_2O_4$ requires C, 56 7, H, 7 1, N, 11 0%), m/z(%) 254(M^+, 22), 239(64), 197(34) and 43(100), δ 4 68(d, 1H, J 7 31Hz, H-5), 3 07(d, 1H, J 7 32Hz, H-4), 2 99(s, 3H, OMe), 2 84 and 2 74(2 x m, 2 x 2H, NCH_2CH_2), 2 15(s, 3H, NMe), and 1 19 and 1 17(2 x s, 2 x 3H, CMe_2)

2,2-Spirotetramethylene-3(2′-phenylsulphonylethyl)-7-methyl-3,7-diaza-4-oxabicyclo[3 3 0]octane-6,8-dione(17a) A solution of cyclopentanone oxime (0 5g, 5mmol) phenyl vinyl sulphone (0 8g, 5mmol), and NMM (0 55g, 5mmol), in acetonitrile (35ml) was boiled under reflux for 21h under argon Removal of the solvent afforded a yellow solid Crystallisation of this material from benzene yielded the *product*

(1 1g, 60%) as irregular prisms, m p 159-161°C (Found C, 57 15, H, 5 85, N, 7 35 $C_{18}H_{22}N_2O_5S$ requires C, 57 15, H, 5 85, N, 7 4%), m/z(%) 378(M^+, 1), 237(3), 125(65) and 77(100), δ 7 87 and 7 60(2 x m, 5H, ArH), 4 63(d, 1H, J 7 4Hz, H-5), 3 40(m, 2H, CH_2SO_2Ph), 3 14(m, 3H, H-4 and NCH_2), 2 93(s, 3H, NMe), and 1 90 and 1 42(2 x m, 8H, 4 x CH_2)

2,2-Spirotetramethylene-3-(2′-benzyloxycarbonylethyl)-7-methyl-3,7-diaza-4-oxabicyclo[3 3 0]octane-6,8-dione(17b) A solution of cyclopentanone oxime (0 5g, 5 05mmol), benzyl acrylate (0 82g, 5 06mmol) and NMM(0 56g, 5 04mmol) in acetonitrile (30ml) was boiled under reflux for 18h Work up in the usual way afforded a solid whose p m r spectrum showed 80% conversion to products Purification by flash chromatography afforded the *product* (0 86g, 57%) as an oil which solidified on refrigeration and crystallised from ether-petroleum ether colourless needles, m p 43-45°C (Found C, 64 25, H, 6 6, N, 7 15 $C_{20}H_{24}N_2O_5$ requires C, 64 5, H, 6 5, N, 7 5%), m/z(%) 372(M^+, 30), 343(16), 223(17) and 91(100), δ 7 18(br s, 5H, ArH), 5 07(s, 2H, CH_2Ar), 4 61(d, 1H, J 7 4Hz, H-5), 3 11(d, 1H, J 7 4Hz, H-4), 2 91(m, 5H, NCH_3 and NCH_2), 2 50(m, 2H, CH_2CO_2R), and 2 00, 1 81 and 1 42(3 x m, 8H, 4 x CH_2)

Further elution of the column afforded (8b) and (10b)

(8b) Colourless prisms from ether (121 mg, 8%), accurate mass 321 1873 $C_{15}H_{19}N_3O_5$ requires 321 1324, m/z(%) 321(M^+, 100), 304(5), 292(88), 279(78), 207(31), 193(99), 165(31) and 109(49), δ 4 82(d, 1H, J 8 0Hz, COCHO), 4 05(dd, 1H, J 5 1 and 8 9 Hz, COCHN), 3 79(d, 1H, J 8 0 Hz, CHCO), 3 00 and 3 01(2 x s, 2 x 3H, NMe), 2 94(m, 2H, CH_2), 2 05(m, 1H, CH), 1 66-1 86(m, 5H, 2 x CH_2 and CH) and 1 58(m, 1H, CH)

(10b) Pale yellow rods (242mg, 18%), from ether-chloroform, m p 222-224°C (Found C, 56 15, H, 5 95, N, 13 1 $C_{15}H_{19}N_3O_5$ requires C, 56 05, H, 5 95, N, 13 2%), m/z(%) 321(M^+, 23), 292(11), 193(100), 134(8), 127(22), 107(15), 81(8) and 67(27), ν_{max}(nujol) 3540, 3400, 3340, 3120, 1770, 1750(sh), 1715(sh), 1690 and 1630cm^{-1}, δ(^{1}H), 5 73(s, 1H, NH), 4 87(s, 1H, C=CH), 4 69(dd, 1H, J 2 5 and 8 1Hz, COCHOH), 3 38(d, 1H, J 2 4Hz, OH), 3 35(d, 1H, J 8 3Hz, CHCO), 2 97 and 2 96(2 x s, 2 x 3H, 2 x NMe), 2 14-2 30(m, 3H, CH_2 and CH), 1 95(m, 1H, CH), and 1 65-1 78(m, 4H, 2 x CH_2) δ(^{13}C) 23 5, 23 8, 35 3, 38 8 (methylene carbon atoms), 25 2, 68 9, 86 0(methine carbon atoms), 23 6, 50 2(NMe groups), 66 6, 145 5(quaternary carbon atoms), 167 8, 172 5, 174 5, 177 3(carbonyl carbon atoms)

Tetrahydrothiophen-3-one oxime (18) A mixture of tetrahydrothiophen-3-one (2 0g, 19 6 mmol), hydroxylamine hydrochloride (1 49g, 21 4 mmol) and sodium carbonate (2 5g) in 1 1 v/v aqueous acetonitrile (30ml) was stirred at room temperature for 16h The solvent was then removed under reduced pressure, the residue dissolved in methylene chloride, washed with water, dried ($MgSO_4$), and the solvent evaporated The residual oil was distilled to afford the *product* (1 67g, 73%), b p 78-

80°C/0 4mmHg, as a colourless oil which solidified on standing (Found C, 40 9, H, 6 1, N, 11 95, S, 27 55 C_4H_7NOS requires C, 41 0, H, 6 0, N, 11 95, S, 27 35%); m/z(%) 117(M^+, 100), 100(59), 86(26), 72(48), 59(24), 54(85) and 45(36), δ(E/Z isomer mixture) 2 79-3 02(m, 4H, S CH_2CH_2, 3 51 and 3 64(s, S CH_2 C=N, E and Z), and 9 23 and 9 29(s, OH, E and Z) The ^{1}H n m r of the oxime before distillation indicated it comprised a 1 25 1 mixture of E- and Z-isomers After distillation the product comprised mainly the Z-isomer

Cycloadduct (19) A solution of tetrahydrothiophen-3-one oxime (259mg, 2 2 mmol), phenyl vinyl sulphone (372mg, 2 2mmol), and NMM(250mg, 2 25mmol) in dry acetonitrile (15ml) was boiled under reflux under a nitrogen atmosphere for 18h Work up in the usual way afforded an orange solid (800mg) whose p m r spectrum indicated 62% conversion and the presence of a 2 1 mixtue of stereoisomeric cycloadducts Flash chromatography (SiO_2) eluting with 95 5 ether-ethyl acetate followed by crystallisation from methanol afforded the *major isomer* (219mg, 40%) as colourless prisms, m p 189-191°C (Found C, 51 65, H, 5 1, N, 7 1, S, 16 4 $C_{17}H_{20}N_2O_5S_2$ requires C, 51 5, H, 5 1, N, 7 05, S, 16 15%), m/z(%) 396(M^+, 13), 368(35), 349(21), 269(12), 227(40), 209(63), 181(8), 169(11), 154(17), 141(30), 125(23) and 77(100), δ 7 86(d, 2H, ArH), 7 68 and 7 58(2 x t, 1H, and 2H, ArH), 4 71 and 3 59(2 x d, 2 x 1H, J 7 5Hz, CHCH), 3 40(m, 2H, NCH_2), 3 12-3 28(m, 2H, CH_2SO_2Ph), 3 02(m, 1H, J 11 2Hz, CHS), 2 91(s, 3H, NMe), 2 82(m, 1H, CH), 2 51(d, 1H, J 11 2Hz, CHS), 2 07(m, 2H, CH_2) and 1 82(m, 1H, CH)

The *minor isomer* was not isolated in the pure form δ 7 97-7 54(m, 5H, ArH), 4 69 and 3 61(2 x d, 2 x 1H, J 7 5Hz, CHCH), 2 95(s, 3H, NMe), 3 53-2 76(m, 5H, 2 x CH_2 and CH), 2 49(d, 1H, J 11 3Hz, CHS) and 2 15 and 1 84(2 x m, 2 x 2H, 2 x CH_2)

Reaction of E- and Z-benzaldehyde oximes with phenyl vinyl sulphone and NMM

a A solution of E-benzaldehyde oxime (1 12g, 10mmol), phenyl vinyl sulphone (1 68g, 10mmol) and NMM(1 11g, 10mmol) in xylene (100ml) was boiled under reflux for 20h Removal of the solvent in vacuo afforded an orange gummy solid (100%) whose p m r spectrum indicated it comprised (24a) and (24b) as major products, together with trace amounts of the 2 1 adducts (25a and b) and other unidentified products The crude mixture was separated by flash chromatography (silica, ethyl acetate-hexane 3 2) to furnish (24a) (0 5g, 12%) and (24b) (1 1g, 25%)

(24a) Obtained as straw coloured prisms, from ethyl acetate-hexane, m p 178-179°C (Found C, 59 85, H, 4 7 N, 6 8 $C_{20}H_{20}N_2O_5S$ requires C, 60 0, H, 5 05, N, 7 0%), m/z(%) 400(M^+, 30), 258(40), 141(15) and 43(100), δ 7 84, 7 63, 7 34 and 7 03(4 x m, 10H, ArH), 4 82(d, 1H, J 7 3Hz, H-3), 3 92(d, 1H, J 8 6Hz, H-5), 3 67(dd, 1H, J 8 2 and 7 7Hz, H-4), 3 50(m, 2H, NCH_2), 3 26 and 2 97(2 x m, 2 x 1H, CH_2SO_2Ph) and 2 92(s, 3H, NMe)

(24b) This isomer was isolated as an amorphous colourless solid but could not be obtained pure The following p m r assignments were made from a slightly impure sample δ 7.57, 7 48, 7 36, 7 25 and 7 15(5 x m, 10H, ArH), 4 73(d, 1H, J 7 3Hz, H-3), 4 05(m, 2H, H-4 and H-5), 3 56(dd, 1H, J 7 3 and 3 4, NCH), 3 25(m, 2H, NCH and $CHSO_2Ph$) and 2 86(m, 4H, NMe and $CHSO_2Ph$)

b A solution of Z-benzaldehyde oxime (4 13mmol), phenyl vinyl sulphone (4 11mmol) and NMM(4 14mmol) in dry acetonitrile (25ml) was boiled under reflux under a nitrogen atmosphere for 18h Standard work up afforded a colourless viscous oil whose p m r spectrum showed it to have undergone 68% conversion to a 9 1 mixture of (24a) and (24b) Other isomers, if present, are only formed in trace amounts

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