Tetrahedron Vol 47, No 25, pp 4495-4518, 1991
Printed in Great Britain

0040-4020/91 $3 00+ 00

X=Y-ZH Systems As Potential 1,3-Dipoles. Part 33.[1,2]

Generation Of Nitrones From Oximes

Tandem Michael Addition-1,3-Dipolar Cycloaddition Reactions

Class 2 Processes In Which The Dipolarophile Is Located Within The Oxime

Paul Armstrong,[a] Ronald Grigg,[*b] Frances Heaney[a],

Sivagnanasundram Surendrakumar[b] and William J Warnock [a]

a Chemistry Department, Queens University, Belfast BT9 5AG

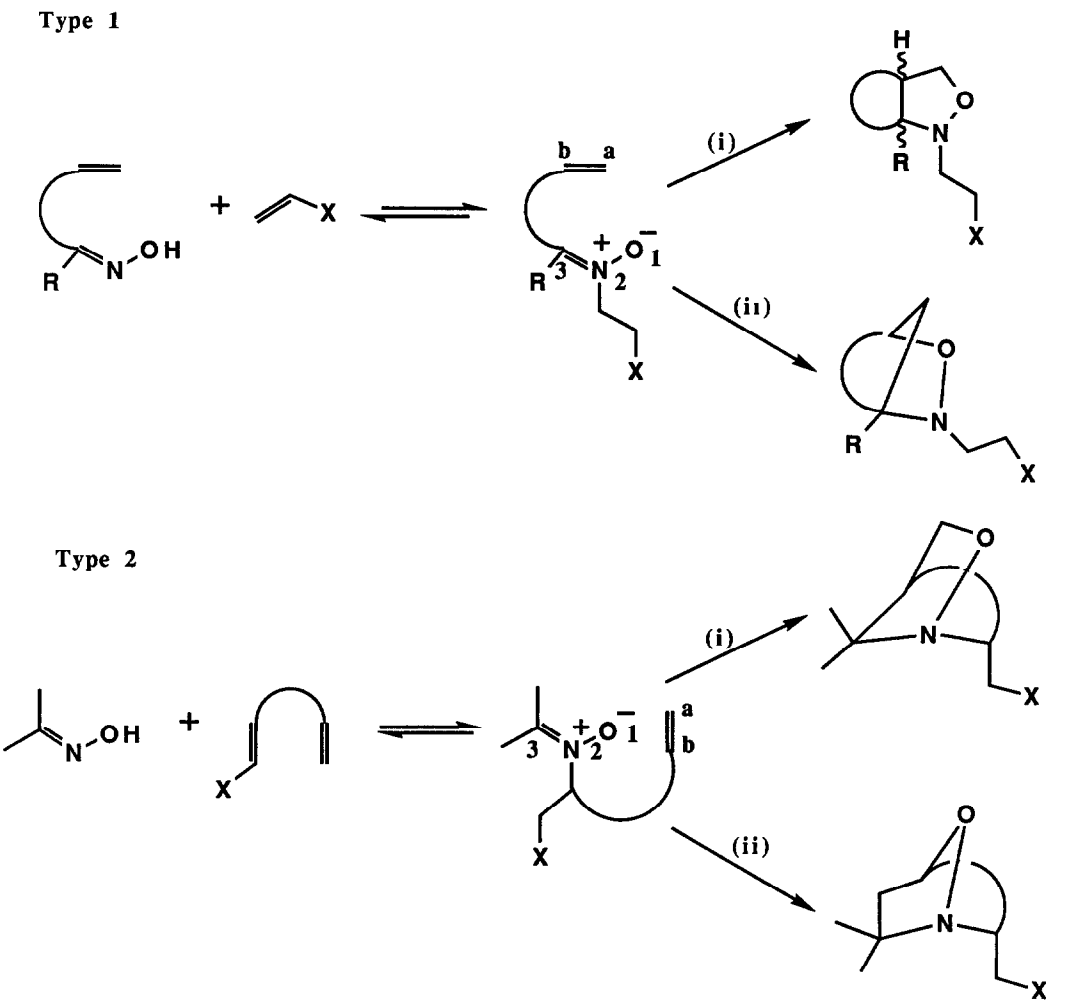
b School of Chemistry, Leeds University, Leeds LS2 9JT

(*Received in UK 22 March* 1991)

Abstract C-3, -4, -5, and -6-Alkenyl oximes react with electronegative olefins at the nitrogen atom via a Michael addition or ene-type process to generate the corresponding C-alkenyl nitrones which undergo an intramolecular cycloaddition The cycloaddition can occur by one of two modes leading to either bridged- or fused-isoxazolidines The latter is preferred in most cases except that of the C-(3-alkenyl) nitrone which gives exclusively the bridged-ring product and the C-(4-alkenyl)nitrones derived from N-allylpyrrole-2-carboxyaldehyde oxime which gives both bridged- and fused-ring isoxazolidines

In the preceding paper in this series the tandem Michael addition-1,3-dipolar cycloaddition process was analysed in terms of four broad synthetic variants depending on whether each component of the tandem process occurred in an inter-or intra-molecular fashion [1] This paper is concerned with a sub-set of Class 2 processes i e intermolecular Michael addition-intramolecular 1,3-dipolar cycloaddition Class 2 processes provide particularly attractive and flexible synthetic methodology because the dipolarophile can be located within the oxime (Scheme 1, type 1) such that when the oxime undergoes Michael addition a *C*-(n-alkenyl)-nitrone is generated Alternatively the dipolarophile and Michael acceptor can be located within the same molecule, in which case an *N*-(n-alkenyl)-nitrone is generated by the Michael addition reaction (Scheme 1, type 2) The former methodology is discussed in this paper whilst the latter approach forms the subject of the succeeding paper in this series [3]

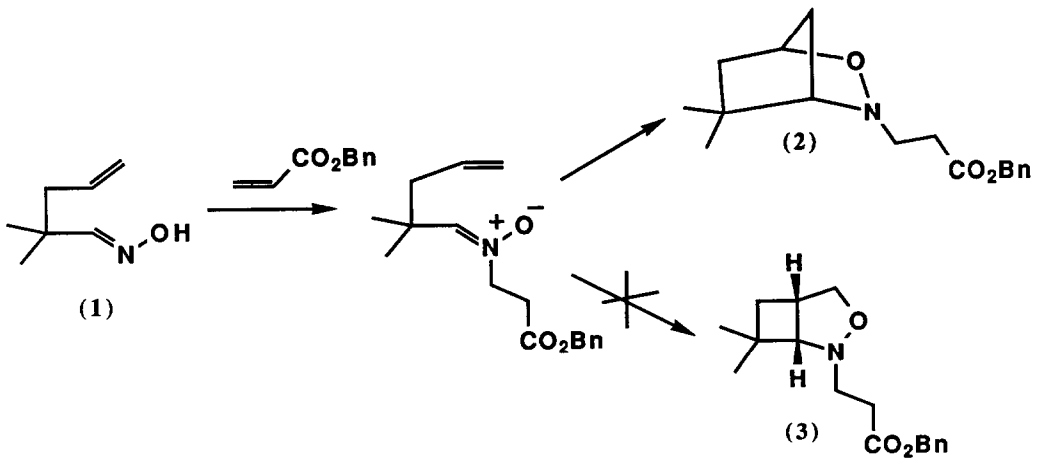
In the type 1 sub-set of the class 2 processes the intermediate *C*-(n-alkenyl)-nitrone can potentially give rise to a fused- or bridged-ring product (Scheme 1) whilst the type 2 sub-set involving an *N*-(n-alkenyl)-nitrone always leads to bridged-ring products although the cycloaddition can still occur by two regiochemically distinct processes (Scheme 1) Intramolecular cycloaddition reactions of nitrones have attracted much attention[4,5] as key steps in the synthesis of natural products and the methodology inherent in Scheme 1 provides a significant and substantial extension of such processes Invariably the



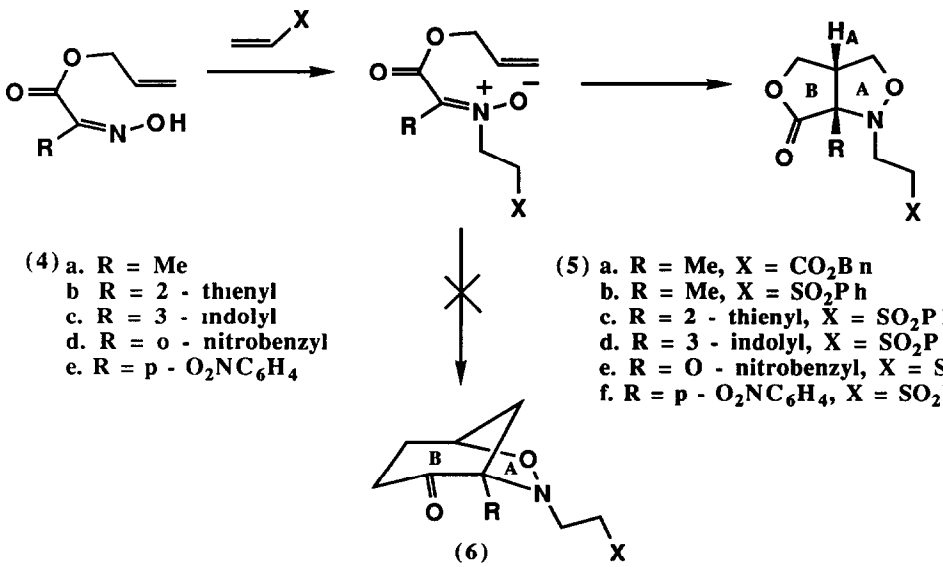
Scheme 1. (i) 1,a / 3,b - bonding (ii) 1,b / 3,a - bonding

oximes are mixtures of E- and Z-isomers but this has no untoward effect on the tandem processes since E ⇌ Z interconversion is facile under the reaction conditions employed

C-(3-Alkenyl)nitrones The reaction of (1) with benzyl acrylate was studied The type 1 tandem process (Scheme 1) could conceivably lead to either (2) or (3) In both cases a highly strained transition state would be involved and this was reflected in the high temperature (mesitylene, 165°C, 18h) necessary to bring about reaction and the low yield The reaction mixture comprised the bridged-ring isoxazolidine (2) (19%) together with a mixture of 2 1 adducts[1] and decomposition products The bridged-ring structure was assigned on the basis of ^{1}H-2D-COSY studies To our knowledge this is the first reported example of a successful C-(3-alkenyl) nitrone cycloaddition



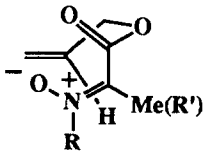
C-(4-Alkenyl)nitrones Pioneering work by LeBel had established that C-(4-alkenyl)nitrones derived from N-methyl hydroxylamine and the appropriate alkenyl aldehyde/ketone almost without exception undergo cycloaddition via the type 1(i) pathway (Scheme 1) to give cis-fused bicyclic isoxazolidines [6] It therefore came as no surprise that oximes of allyl esters of α-keto acids (4a-e), although differing in the nature of the linking chain [CO-O versus $(CH_2)_2$], react with benzyl acrylate or phenyl vinyl sulphone to give (5a-f) in 28-71% yield (Table 1) No bridged-ring products (6) were detected



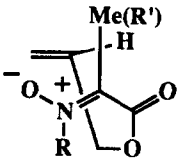
(4) a. R = Me
b R = 2 - thienyl
c. R = 3 - indolyl
d. R = o - nitrobenzyl
e. R = p - $O_2NC_6H_4$

(5) a. R = Me, X = CO_2Bn
b. R = Me, X = SO_2Ph
c. R = 2 - thienyl, X = SO_2Ph
d. R = 3 - indolyl, X = SO_2Ph
e. R = O - nitrobenzyl, X = SO_2Ph
f. R = p - $O_2NC_6H_4$, X = SO_2Ph

The stereochemistry of cycloadducts (5a, b) was established by n O e studies, in particular a positive n O e between the ring junction Me group and H_A (see experimental section), whilst that of (5c) was established by a single crystal X-ray structure determination [3] The remaining cycloadducts (5d-f) are assumed to have analogous stereochemistry The bicyclic isoxazolidines (5a-f) could arise from the Z-nitrone via an exo-transition state (7) or from the E-nitrone via an endo-transition state (8) In both transition states π-overlap between the carbonyl group and the nitrone moiety is essentially zero The initial configuration of the nitrone will be dictated by the developing steric interactions between R(or R^1) and the electronegative olefin in the Michael addition (or ene-type)[1] transition state (9) → (10) The E ⇌ Z nitrone interconversion barriers[4] are in the range 20-35 k cal mol^{-1} and are comparable to, though probably somewhat above, the activation energies for the cycloaddition step However, E ⇌ Z nitrone



(7)



(8)

(9) (10)

Table 1 Tandem Michael addition-cycloaddition of oximes of allyl esters of α-keto acids (4a-e) with monosubstituted electronegative olefins [a]

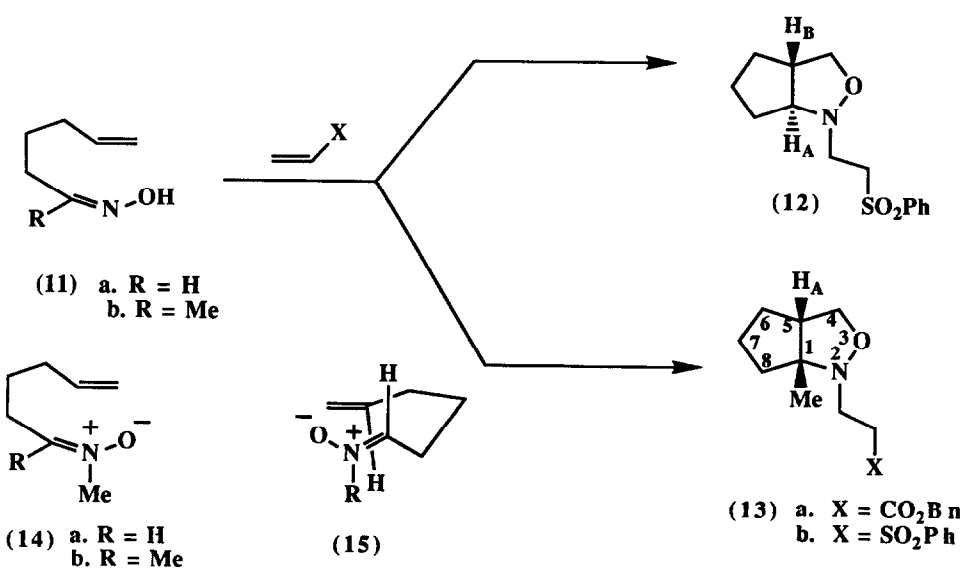
Oxime	Michael Acceptor	Time(h)	Product	Yield(%)[b]
4a	benzyl acrylate	24	5a	69(100)
4a	phenyl vinyl sulphone	11	5b	71(100)
4b	phenyl vinyl sulphone	10	5c	37(61)
4c	phenyl vinyl sulphone	18	5d	50(58)
4d	phenyl vinyl sulphone	16	5e	61(78)
4e	phenyl vinyl sulphone	20	5f	28(65)

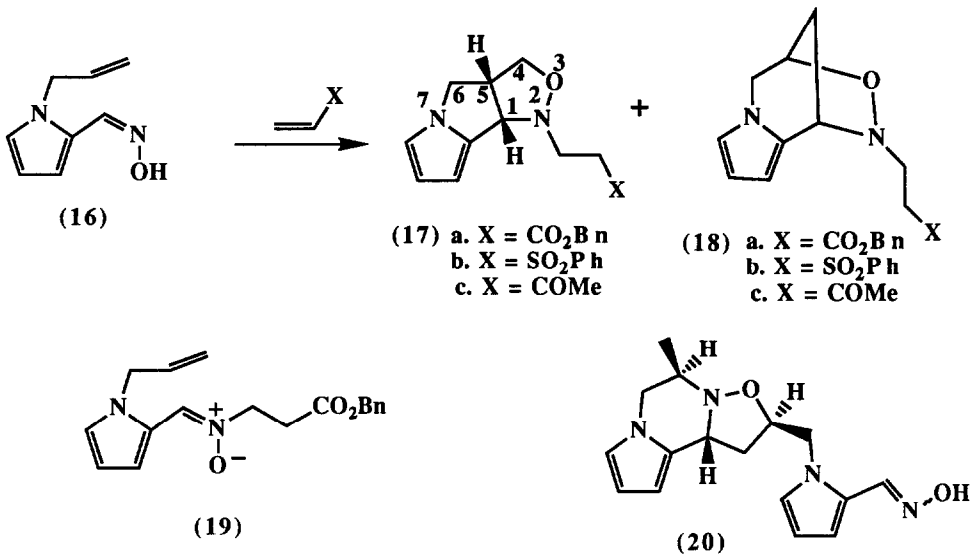
a All reactions carried out in boiling xylene under reflux

b Isolated yield, yield estimated by p m r in brackets

interconversion can also occur via fragmentation (10) → (9) and oxime isomerisation Both endo- and exo-transition states have been observed for nitrone cycloadditions,[7] with the former preferred in the absence of untoward steric effects The regiospecificity of the process, type 1(i) rather than type 1(ii) (Scheme 1), arises from the well known entropic bias for 5-versus 6-membered ring formation in the forming subsidiary ring (ring B) in (5) and (6)[1,8] together with the resultant superior frontier orbital overlap in the transition state leading to (5) compared to that leading to the alternative 6/5-bridged ring product (6) Weinreb has recently reported an example of an intramolecular nitrone cycloaddition to an allyl ester moiety [9]

The stereochemical outcome of analogous tandem processes on the oximes (11a) and (11b) was interesting Thus the aldoxime (11a) reacted (xylene, 140°C, 24h) with phenyl vinyl sulphone to give the trans-fused product (12) (74%), whilst the corresponding ketoxime (11b) reacts with benzyl acrylate and phenyl vinyl sulphone to give the cis-fused products (13a) (73%) and (13b) (78%) respectively The ring junction stereochemistry in (12) and (13 a,b) was assigned on the basis of n O e data In particular in the case of (12) the absence of an n O e between H_A and H_B, whilst in (13 a,b) positive n O e 's were observed between the ring junction Me group and H_A LeBel has reported that both of the corresponding N-methyl nitrones (14 a,b) give cis-fused oxazolidines [6] However, in these cases the reaction temperature was substantially lower (80-110°C), and nitrone cycloadducts are known to equilibrate at higher temperature [15] The trans-fused product (12) could arise from the Z-nitrone and an endo-transition state or the E-nitrone and an exo-transition state (15) The former transition state is geometrically unattainable (the four reacting centres cannot be suitably aligned)



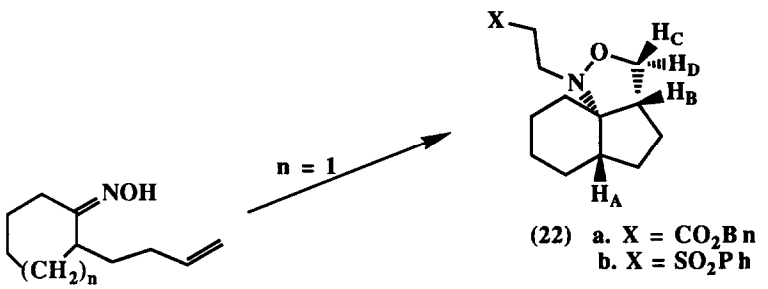


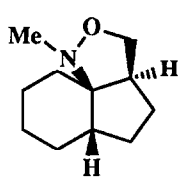
(19)

(20)

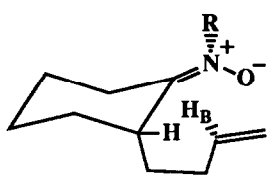
The N-allylpyrrole oxime (16), which comprised a ca 2 1 mixture of E- and Z-isomers, reacts (xylene, 140°C, 18h) with benzyl acrylate to give a complex mixture of products from which (17a) could be isolated in 30% yield No bridged ring isomer (18a) was isolated from this reaction However, carrying out the reaction at lower temperature (MeCN, 60°C) using the Z-oxime gave small amounts (9-12%) of both (17a) and (18a) together with the nitrone (19) (39%) Nitrone (19) was obtained as a single isomer, the stereochemistry of which was established by n O e studies Heating (19) in xylene at 110°C afforded a 1 1 6 mixture of (17a) and (18a) in quantitative yield A similar reaction (MeCN, 80°C, 18h) of Z-(16) with phenyl vinyl sulphone gave a 1 1 mixture of (17b) and (18b) in 86% yield Methyl vinyl ketone reacted (MeCN, 80°C, 16h) with Z-(16) in an analogous manner to give a 1 1 2 mixture of (17c) and (18c) in 81% yield In this case the conformational flexibility of the linking chain between oxime and dipolarophile is restricted by the pyrrole ring and this prevents the correct alignment of the four reacting centres in the E-nitrone exo-transition state analogous to (15) which would have lead to the trans-fused isomer of (17) The rigidity and angular disposition of the ring substituents imparted by the pyrrole ring also raises the fused-ring transition state energy of the type 1(i) process (scheme) allowing the bridged-ring transition state of the type 1(ii) (scheme) to compete effectively We have previously reported the formation of a dimeric cycloadduct (20) from (16) via a nitrone generated by an intramolecular ene-type process [10] The ^1H n m r spectra ($CDCl_3$) of the bridged ring cycloadducts (18) showed multiple signals, some of which were broad, indicating the operation of a stereodynamic process Addition of one drop of trifluoroacetic acid to the n m r sample resulted in both simplification of the spectrum and sharpening of the broad signals The resultant ^1H n m r spectrum was entirely consistant with one stereoisomer of the isoxazolidine (18) in which protonation had occured with high stereoselectivity on one face of the isoxazolidine ring nitrogen atom Both the ^1H and ^{13}C n m r spectra of protonated (18) showed only

traces of the epimeric N-protonated isomer in contrast to the spectra of the unprotonated compounds which showed substantial amounts of both stereoisomers Nitrogen inversion barriers in acyclic hydroxylamines range from ca 8 5-15 kcal mol^{-1} with hydroxylamines in which aryl substituents are conjugated to the nitrogen atom having the lowest inversion barrier [11] Thus the observed spectral changes when (18) is protonated indicate the stereodynamic process is nitrogen inversion and suggest the incorporation of the hydroxylamine moiety into the bicyclo [3 2 1] system of (18) increases the inversion barrier somewhat

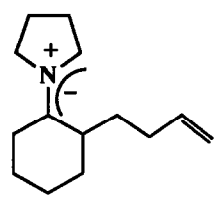




(24)



(25)



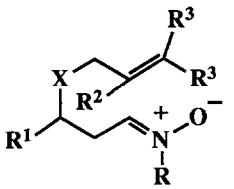
(26)

2-(3′-Butenyl)cyclohexanone oxime (21a) reacts stereospecifically with benzyl acrylate and phenyl vinyl sulphone in boiling xylene to give products formulated as (22a) (70%) and (22b) (69%) The relative stereochemistry of H_A and H_B is based on a positive n O e between the two protons The stereochemistry of (22a,b) differs from that tentatively assigned by Japanese workers to the corresponding N-methyl cycloadduct (24)[12] However, the latter stereochemistry was assigned without the benefit of n O e data The likely transition state for the formation of (22a,b) is one involving exo-addition to the Z-nitrone i e (25) or endo-addition to the E-nitrone In both transition states the 2-(3′-butenyl)-side chain

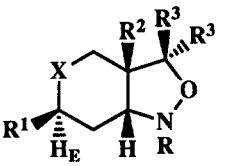
occupies an axial orientation which avoids the $A^{1,3}$-strain present in the equatorial conformers [13] We have observed a similar transition state geometry in the intramolecular cycloaddition of the related azomethine ylide (26) [14] It should also be noted that the Japanese work referred to above was carried out at 25°C whilst our reaction was performed at 140°C Nitrone cycloadducts are known to equilibrate at temperatures above 110°C [15]

The 2-(3′-butenyl) cycloheptanone oxime (21b) reacts with phenyl vinyl sulphone in boiling xylene over 20h to give a single tricyclic product (23) in ca 95% yield (p m r) (60% isolated yield) N O e studies did not show any enhancements between proton H_A and H_B and the relative stereochemistry of these two protons is therefore assigned as trans in (23) The corresponding N-methyl analogue has been reported previously[12] but its stereochemistry was not established

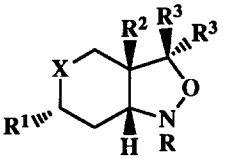
C-(5-Alkenyl)nitrones The N-methyl C-(5-hexenyl)nitrone (27a) is reported to give 3 1 1 mixture of (28a), (30a) and (31a) on heating at 110°C in toluene,[6,15] whilst nitrone (27b) gives the bridged ring product (30b) exclusively [16]



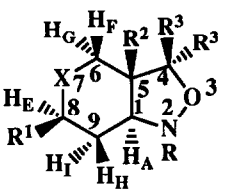
(27)



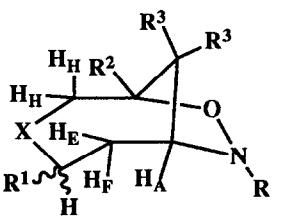
(28)



(29)

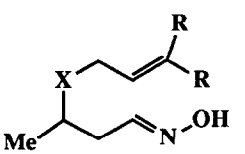


(30)



(31) $R^2 = H_B$
$R^3 = H_C, H_D$

(a) X = CH_2, R = Me, R^1=R^2=R^3= H
(b) X = CH_2, R = Me, R^2=Ph, R^1=R^3= H
(c) X = O, R = $(CH_2)_2CO_2Bn$, R^1=Me, R^2=R^3= H
(d) X = CH_2, R = R^1 =Me, R^2=R^3= H
(e) X = CH_2, R = $(CH_2)_2CO_2Bn$, R^1=R^3=Me, R^2= H_B
(f) X = CH_2, R = $(CH_2)_2SO_2Ph$, R^1=R^3=Me, R^2= H_B



(32) a. X = O, R = H
b. X = CH_2, R =Me

We examined the behaviour of the related oxime (32a) with benzyl acrylate in boiling xylene The tandem process, which is presumed to proceed via nitrone (27c) furnished a 3 1 5 2 mixture of (28c), (29c), (30c) and (31c) Preparative t l c of the mixture afforded pure samples of the three major isomers and detailed p m r studies [400 MHz, decoupling and NOEDS (Table 2)] established their stereochemistries LeBel has reported the intramolecular cycloaddition of (27d) at 110°C The product in this case is a 1 4 12 3 mixture of (28d), (29d), (30d) and (31) At higher temperatures increasing amounts of cis-fused isoxazolidines were observed [15] LeBel's studies lead him to conclude that trans-fused adducts

Table 2 NOEDS data ($CDCl_3$) for bicyclic isoxazolidines derived from C-(5-alkenyl)nitrones

		n O e (%)[a]												
Proton Irradiated		H_A	H_B	H_C	H_D	H_E	H_F	H_G	H_H	H_I	H_K	C(8)Me	Me[b]	NCH_2
	H_A			1					4	2				
28c	H_B	5		3			3							
	H_D			25										
C(8)Me						3			1	1				
	H_A							1		6				
30c	H_E							4		5		4		
C(8)Me						2				1				
	H_A					4		4		2			3	5
30e	H_C	3								3	5	3		
	H_I	3				4			18				3	
Me[b]		2						1						4
	H_A			4			3							3
	H_B			3						10				
	H_C	4	3		12									6
31c	H_G					5			2			5		
	H_E	4				7	20							
C(8)Me						2	1	3						

a For proton labelling see (29) and (30) X=H_J, H_K, R^2=H_B, R^3=H_C, H_D

b C(4)-α-Me

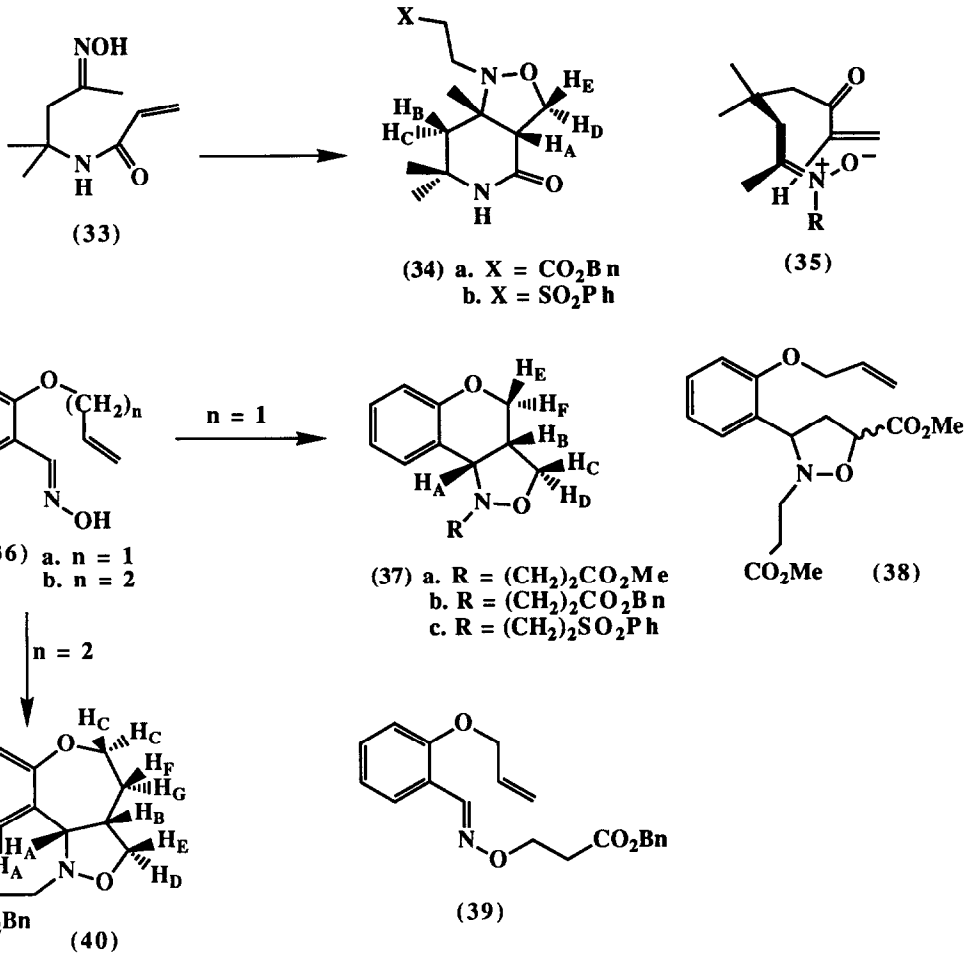
predominate under conditions of kinetic control whilst cis-fused adducts predominate under thermodynamic control This accords with observations on the relative stability of cis- and trans-hydrindenes [17] The most noticeable difference between the two sets of results is the increased amount of cis-isomer (28c) and the decreased amount of trans-isomer (30c) in our case relative to LeBel's results This reflects the higher temperature (140°C versus 110°C) in our reaction which results in more of the thermodynamically more stable cis-isomer

(+)-Citronellal oxime (32b) (1 1 mixture of E- and Z-isomers) reacts (xylene, 140°C, 24h) with benzyl acrylate to give a 5 5 1 mixture (95%) of (30e) and (28e), a result entirely consistant with LeBel's results using the corresponding N-methylnitrone [6,15] The isomer mixture was not separated but NOEDS data (Table 2) confirm the trans-ring junction and the equatorial position of the methyl group in (30e) The stereochemistry of (28e) is based on that given by LeBel for the N-methyl analogue An analogous reaction (xylene, 140°C, 14h) (32b) with phenyl vinyl sulphone afforded isoxazolidine (30f) as the major component (ca 60% by p m r) of a complex mixture

The oxime of diacetone acrylamide (33) (E/Z-isomer mixture) reacts with benzyl acrylate and phenyl vinyl sulphone in boiling xylene to give a single cycloadduct, (34a) (52%) and (34b) (100%) respectively, in each case Ring junction stereochemistry is assigned on the basis of a positive n O e between H_A and the ring junction Me group Examination of molecular models suggests the most favourable transition state is probably that involving the Z-nitrone and an exo-transition state (35) In this transition state the incipient 6-membered ring assumes a boat-conformation

We have previously reported the reaction of (36a) with methyl acrylate in pyridine at 80°C to give a mixture of (37a) and (38) [18] Acrylonitrile gives an analogous mixture In these previous studies an excess of methyl acrylate was employed In contrast, heating (36a) with benzyl acrylate (1 mol) in boiling xylene afforded (37b) as the sole product A similar reaction in toluene using phenyl vinyl sulphone as the dipolarophile gave (37c) (90%) The cis-ring junction stereochemistry was established by n O e studies The ring junction coupling constants [J_{AB} (37b), J_{AB} 6 9Hz, (37c), J_{AB} 6 6 Hz] compare favourably with that (J 7Hz) reported for (37, R=H)[19] Padwa[20] has independently reported the preparation of (37c) using our methodology The possible role of the O-Michael adduct (39) in the tandem process was briefly explored Heating (39) in boiling xylene (140°, 24h) failed to give any cycloadduct (37b) A more extensive study of O-Michael adducts will be reported at a later date

C-(6-Alkenyl)nitrones One example of this type was studied Thus the oxime (36b) reacted sluggishly with benzyl acrylate in boiling xylene However, when the reaction was repeated in boiling mesitylene (165°C, 18h) a 54% yield of the cis-fused isoxazolidine (40) was obtained together with a mixture of 2 1 acrylate oxime cycloadducts and decomposition products The N-methyl nitrone counterpart has been described by Oppolzer[19] although the ring junction stereochemistry was not specified The ring junction stereochemistry of (40) was indicated by the value of J_{AB} (9 4 Hz) and confirmed by n O e data



Experimental General details were as previously described [21]

Oximes and their Precursors.

Allyl Esters of α-Keto Acids General Procedure

A solution of α-keto acid (10mmol) and allyl alcohol (15mmol) in benzene (20ml) was boiled under reflux for 4-20h with a catalytic amount of p-toluene sulphonic acid using a Dean-Stark apparatus The reaction mixture was allowed to cool, and then washed with saturated aqueous sodium bicarbonate solution (2 x 100ml) and water (1 x 100ml) The organic layer was separated, dried (Na_2SO_4) and concentrated to furnish the crude product which was purified as detailed below

Allyl 2-thiopheneglyoxylate The product (88%), b p 94-100°C/0 5 mmHg, was obtained as a pale yellow oil after a reaction time of 6h (Found C, 54 85, H, 4 0 $C_9H_8O_3S$ requires C, 55 1, H, 4 1%), m/z (%) 196(M^+, 7), 111(100) and 83(7), δ 8 13, 7 84 and 7 20(3 x m, thienyl-H), 6 10 and 4 86(2 x m, $CH=CH_2$), and 5 41(m, 2H, OCH_2)

Allyl 3-indoleglyoxylate After a 20h reaction time the product (68%) was obtained as golden plates, m p 161-163°C) (Found C, 68 35, H, 4 6, N, 5 9 $C_{13}H_{11}NO_3$ requires C, 68 1, H, 4 8, N, 6 1%), m/z(%) 229(M^+, 12), 144(100), and 116(13), δ[$(CD_3)_2CO$] 11 34(br s, 1H, NH), 8 41(d, 1H, ArH), 8 27, 7 54 and 7 25(3 x m, 4H, ArH), 5 38 and 5 24(2 x m, $CH=CH_2$), and 3 80(m, 2H, OCH_2)

Allyl 2-nitrophenylpyruvate The product (64%) distilled as a viscous pale orange oil, b p 266°C/0 1 mmHg, after a reaction time of 20h (Found C, 57 75, H, 4 2, N, 5 65 $C_{12}H_{11}NO_5$ requires C, 57 85, H, 4 45, N, 5 6%), m/z(%) 294(M^+, 0 5), 164(42), 136(72) and 41(100), δ 8 11, 7 62, 7 50 and 7 43(4 x m, ArH), 6 0 and 5 38(2 x m, $CH=CH_2$), 4 80(m, 2H, OCH_2) and 4 54(m, 2H, $ArCH_2$)

Allyl 4-nitrophenylglyoxylate After a 4h reaction time the product (84%) was obtained as a pale orange oil, b p 150°C/0 8mmHg (Found C, 56 0, H, 3 9, N, 5 95 $C_{11}H_9NO_5$ requires C, 56 15, H, 3 85, N, 5 95%), m/z(%) 235(M^+, 0 5), 150(100), 104(37) and 41(32), δ 8 35 and 8 25(2 x m, 2 x 2H, ArH), 6 0 and 5 42(2 x m, $CH=CH_2$), and 4 92(m, 2H, OCH_2)

General Procedures for Oxime Formation

Two general procedures were employed

A A solution of the allyl ester (10mmol), and hydroxylamine hydrochloride (11mol) in a mixture of pyridine (2g) and ethanol (25ml) was boiled under reflux for 3h The solvent was then removed under reduced pressure, the residue taken up in 1 1 ethyl acetate/chloroform (100ml), and washed with saturated brine (50ml) The organic phase was separated, dried (Na_2SO_4), and evaporated to dryness The residue was purified as noted below

B. To a stirred suspension of the aldehyde or ketone (50mmol) and hydroxylamine hydrochloride (3 82g, 55mmol) in water (40ml) was added a solution of sodium carbonate (5 77g, 55mmol) in water (20ml) The mixture was stirred overnight at room temperature and the product extracted into methylene chloride (2 x 50ml) After washing with water (2 x 50ml) and drying (Na_2SO_4) the solvent was evaporated to leave the crude oxime which was either distilled under reduced pressure or crystallised from an appropriate solvent

2,2-Dimethyl-4-pentenal oxime(1) Prepared by method B The product (66%) distilled as a colourless

2,2-Dimethyl-4-pentenal oxime(1) Prepared by method B The product (66%) distilled as a colourless oil, b p 52-54°C/0 05mmHg, which comprised the pure E-oxime (Found C, 66 25, H, 10 15, N, 11 2 $C_7H_{13}NO$ requires C, 66 0, H, 10 3, N, 11 0%), ν_{max} 3300, 1633, 1430, 1380, 1360, 992 and 945 cm^{-1}, m/z(%) 127(M^+, 13), 112(8), 95(6), 86(100), 69(13), 55(10) and 41(46), δ 8 9(br s, 1H, OH, exchanges in D_2O), 7 34(s, 1H, CH=N), 5 83(m, 1H, CH=CH_2), 5 04(m, 2H, CH=CH_2), and 2 13(d, 2H, CH_2), 1 09(s, 6H, 2 x Me)

Allyl pyruvate oxime (4a) Prepared from allyl pyruvate[22] using method B After stirring over-night the oxime precipitated as a white solid (64%) which crystallised as colourless plates of the Z-isomer (presumably H-bonded) from petroleum ether-benzene, m p 86°C (Found C, 50 65, H, 6 6, N, 9 75 $C_6H_9NO_3$ requires C, 50 35, H, 6 35, N, 9 8%), ν_{max} 3240, 1715, 1415, 1171, 1030, 940, 776 and 750 cm^{-1}, m/z(%) 143(M^+, 4), 98(5), 87(22), 86(22), 58(29), 57(24), 41(100) and 39(19), δ 10 30(br s, 1H, OH, exchanges with D_2O), 5 96(m, 1H, CH=CH_2) 5 31(m, 2H, CH=CH_2), 4 74(m, 2H, OCH_2), 2 12(s, 3H, Me)

Allyl 2-thiopheneglyoxylate oxime (4b) Prepared by method A The product (54%) crystallised as colourless needles from benzene-pentane, m p 80-88°C (Found C, 51 45, H, 4 15, N, 6 5 $C_9H_9NO_3S$ requires C, 51 2, H, 4 3, N, 6 65%), m/z(%) 221(M^+, 32), 126(13) and 41(100), δ 9 01(br s, 1H, OH), 8 07, 7 62 and 7 10(3 x m, thienyl-H), 6 12 and 5 43(2 x m, 3H, CH=CH_2) and 4 82(m, 2H, OCH_2)

Allyl 3-indoleglyoxylate oxime (4c) Prepared by method A The product (37%) crystallised as fawn plates from chloroform, m p 141-142°C (Found C, 63 6, H, 4 95, N, 11 4 $C_{13}H_{12}N_2O_3$ requires C, 63 9, H, 4 95, N, 11 45%), m/z(%) 244(M^+, 44), 159(12), 142(100) and 116(11), δ[$(CD_3)_2CO$] 11 19 and 10 91(2 x br s, OH, E- and Z-isomers), 8 23(s, 1H, ArH), 7 38 and 7 12(2 x m, 2 x 2H, ArH), 6 03 and 5 37(2 x m, 3H, CH=CH_2), 4 85(m, 2H, OCH_2) and 2 99(br s, 1H, NH)

Allyl 2-nitrophenylpyruvate oxime (4d) Prepared by method A The product (60%) crystallised as colourless needles from chloroform, m p 106°C (Found C, 54 4, H, 4 6, N, 10 65 $C_{12}H_{12}N_2O_5$ requires C, 54 55, H, 4 6, N, 10 6%), m/z(%) 264(M^+, 2), 218(5), 207(6) and 41(100), δ 9 92(br s, 1H, OH), 7 94 and 7 40(2 x m, 2 x 2H, ArH), 5 92 and 5 34(2 x m, CH=CH_2), 4 68(m, 2H, OCH_2) and 4 32(s, 2H, $ArCH_2$)

Allyl 4-nitrophenylglyoxylate oxime (4e) Prepared by method A The product (65%) crystallised from methylene chloride-hexane-ethyl acetate as colourless rods, m p 165-170°C (Found C, 52 8, H, 4 0, N, 10 85 $C_{11}H_{10}N_2O_5$ requires C, 52 8, H, 4 05, N, 11 1%), m/z(%) 250(M^+, 13), 165(4), and 41(100), δ 12 0(br s, 1H, OH), 8 29 and 7 82(2 x m, 2 x 2H, ArH), 5 98 and 5 42(2 x m, CH=CH_2), and 4 70(m, 2H, OCH_2)

N-Allylpyrrole-2-carboxyaldehyde oxime (16) A mixture of N-allylpyrrole-2-carboxaldehyde (10 0g, 0 074 mol), hydroxylamine hydrochloride (6 4 g, 0 092 mol) and sodium acetate (9 4 g, 0 115 mol) was stirred in aqueous acetonitrile (50 ml) for 16 hrs After the usual work-up N-allyl pyrrole-2-carboxaldehyde oxime was isolated as a viscous liquid (8 33 g, 75%) The p m r spectrum of the product indicated it comprised a 3 2 mixture of (E)- and (Z)-oximes On distillation under reduced pressure (b p 86-92° at 0 5 mm) it

(several months) was accompanied by slow isomerisation to the pure Z-isomer (Found C, 64 05, H, 6 75, N, 18 5 $C_8H_{10}N_20$ requires C, 64 0, H, 6 7, N, 18 65%), ν_{max} 3300, 1615, 1400, 1305, 1075, 930, 820 and 730 cm^{-1}, m/z(%) 150(M^+, 100), 133(40), 118(82), 106(25) 93(57), 79(2) and 41(34), δ 8 16(br s, 1H, OH, exchanges in D_2O), 8 06(E) and 7 36(Z) (s, 1H, CH=N), 7 34-6 17(m, 3H, ArH), 5 94(m, 1H, C<u>H</u>=CH_2), 5 18 and 4 96(m, 2H, CH=C<u>H</u>$_2$) and 4 75 and 4 62(m, 2H, NCH_2)

<u>2-(3′-Butenyl)cyclohexanone oxime (21a)</u> A mixture of 2-(3′-butenyl)-cyclohexanone (50mmol),[23] hydroxylamine hydrochloride (5 21g, 75 mmol) and sodium acetate (6 15g, 75 mmol) in water (50ml) was heated to 50° for 3 hr After cooling the mixture was extracted with methylene (2 x 50ml), the organic layer washed with water (2 x 50ml), dried($NaSO_4$) and the solvent evaporated The residual oil was distilled to afford the product (67%) as a colourless oil, b p 72-76°C/0 05mmHg (Found C, 71 6, H, 10 55, N, 8 6 $C_{10}H_{17}NO$ requires C, 71 8, H, 10 25, N, 8 4%), ν_{max} 3250, 1645, 1438, 990 and 908 cm^{-1}, m/z(%), 167(M^+, 4), 152(12), 113(69), 98(13), 81(43), 67(34), 55(45) and 41(100), δ 8 95(br s, 1H, OH, exchanges in D_2O), 5 81(m, 1H, C<u>H</u>=CH_2), 4 98(m, 2H, CH=C<u>H</u>$_2$), 2 68-1 36[m, 13H, CH, $(CH_2)_6$]

<u>2-(3′-Butenyl)cycloheptanone oxime (21b)</u> Prepared in an analogous manner to that described above but stirring and heating at 60°C for 6h The product (51%) distilled as a colourless oil, b p 84-88°C/0 03mmHg, which comprised a 7 3 mixture of geometric isomers (Found C, 72 95, H, 10 75, N, 7 55 $C_{11}H_{19}NO$ requires C, 72 9, H, 10 55, N, 7 75%), m/z(%) 181(M^+, 18), 166(15), 164(18), 153(12), 152(10), and 127(100), δ 8 99(br s, 1H, OH), 5 80(m, 1H, C<u>H</u>=CH_2), 4 98(m, 2H, CH=C<u>H</u>$_2$), 3 26 and 2 87(m, 1H, methine CH isomers), and 2 45-1 08(m, 14H, 7 x CH_2)

<u>3-Allyloxybutyraldehyde oxime (32a)</u> Prepared by method B from 3-allyloxybutyraldehyde [24] The product (64%) was a colourless oil, b p 64-65°/0 2mmHg, which comprised a 1 1 mixture of E- and Z-isomers (Found C, 58 8, H, 9 45, N, 9 75 $C_7H_{13}NO_2$ requires C, 58 7, H, 9 15, N, 9 8%), ν_{max} 3300, 1638, 1420, 1081, 993 and 923 cm^{-1}, m/z(%) 85(55), 69(3), 57(3), 55(3), 43(27), 41(100) and 39(11), δ 9 40(br s, 1H, OH, exchanges with D_2O), 7 49(E) and 6 88(Z) (2 x t, 1H, CH=N), 5 90(m, 1H, C<u>H</u>=CH_2), 5 23(m, 2H, CH=C<u>H</u>$_2$), 4 00(m, 2H, OCH_2), 3 70(m, 1H, OC<u>H</u>(Me), 2 49(m, 2H, <u>CH_2</u>-CH=N), and 1 21(2 x d, 3H, Me)

<u>Diacetone acrylamide oxime (33)</u> Prepared from diacetone acrylamide (Aldrich) using method B After stirring overnight the oxime precipitated as a white amorphous solid which was crystallised from ether to yield the product as colourless prisms (54%), m p 85-95°C, comprising a 65 35 mixture of the geometric isomers (Found C, 58 45, H, 8 6, N, 15 5 $C_9H_{16}N_2O_2$ requires C, 58 65, H, 8 75, N, 15 2%), ν_{max} 3500-3000(br), 1655, 1621, 1561, 1408, 1244, 967, 882 and 811 cm^{-1}, m/z(%) 184(M^+, 1), 167(10), 112(71), 98(15), 72(12), 58(100), and 55(40), δ 9 5(br s, 1H, OH, exchanges in D_2O), 5 39 and 6 09(2 x br s, 1H, NH), 6 27-5 92(m, 2H, CH=C<u>H</u>$_2$), 5 55(m, 1H, C<u>H</u>=CH_2), 2 65 and 2 61(2 x s, 2H, <u>CH_2</u> C=N), 1 98 and 1 93(2 x s, 3H, Me), and 1 53 and 1 44(2 x s, 6H, 2 x Me)

Cycloadducts.

General Procedure A solution of the alkenyloxime (10mmol) and the electronegative olefin (benzyl acrylate, phenyl vinyl sulphone) (10mmol) in dry xylene (60-120ml) was boiled under reflux for 10 - 24h The solvent was then evaporated under reduced pressure and the residue purified as noted below Yields and reaction times for (5a - f) are collected in Table 1

2-(2′-Benzyloxycarbonylethyl)-6,6-dimethyl-2-aza-3-oxabicyclo[2 2 1]heptane (2) A solution of oxime (1) (2 54g, 20mmol) and benzyl acrylate (3 24g, 20mmol) in mesitylene (50ml) was boiled under reflux for 18h under an argon atmosphere The solvent was removed in vacuo to leave a dark brown oil which on distillation afforded the product (1 1g, 19%) as a pale yellow oil, b p 120-130°C/0 01mmHg (Found 70 8, H, 8 1, N, 4 8 $C_{17}H_{23}NO_3$ requires C, 70 55, H, 8 0, N, 4 85%), ν_{max} 2940, 1725, 1460, 1448, 1162, 920, 750, 730, 699 and 408 cm^{-1}, m/z(%), 289(M^+, 16), 233(17), 232(66), 95(8), 91(100) and 41(11), δ 7 32(m, 5H, ArH), 5 12(s, 2H, CH_2Ar), 4 32(m, 1H, 4-H), 2 92 and 2 84(2 x m, 2H, NCH_2), 2 86(m, 1H, 1-H), 2 58(t, 2H, CH_2CO), 1 93(m, 1H, 7-H), 1 86(d, 1H, J 22Hz, 7-H), 1 35(m, 1H, 5-H), 1 21(dd, 5-H), and 1 11 and 0 97(2 x s, 2 x 3H, Me) These assignments were made with the aid of the ^{1}H-2D-COSY spectrum

1-Methyl-2-(2′-benzyloxycarbonylethyl)-8-oxo-2-aza-3,7-dioxabicyclo[3 3 0]octane(5a) The product distilled as a pale yellow oil, b p 175-180°C/0 01mmHg (Found C, 63 0, H, 6 3, N, 4 6 $C_{16}H_{19}NO_5$ requires C, 62 95, H, 6 25, N, 4 6%), m/z(%) 305(M^+, 6), 261(7), 170(10), 156(14) and 91(100), δ 7 33(m, 5H, ArH), 5 13(s, 2H, $ArCH_2$), 4 42 and 4 15(2 x dd, 2 x 1H, J_{gem} 9 7Hz, J_{vic} 7 4 and 2 9Hz, 2 x 6-H), 4 0 and 3 77(2 x dd, 2 x 1H, J_{gem} 8 9 Hz, J_{vic} 7 1 and 1 8 Hz, 2 x 4-H), 3 35(m, 1H, NCHH), 3 0(m, 2H, NCH and 5-H), 2 68(m, 2H, CH_2 CO), and 1 42(s, 3H, Me)

1-Methyl-2-(2′-phenylsulphonylethyl)-8-oxo-2-aza-3,7-dioxabicyclo[3 3 0]octane (5b) The product (71%) crystallised from benzene as colourless prisms, m p 113-114°C (Found C, 53 9, H, 5 4, N, 4 55 $C_{14}H_{17}NO_5S$ requires C, 54 0, H, 5 5, N, 4 5%), m/z(%) 311(M^+, 16), 267(44), 238(38), 169(34), 126(60), 112(37), 77(84) and 43(100), δ 7 92(m, 2H, ArH), 7 59(m, 3H, ArH), 4 41(dd, 1H, J 7 6 and 9 7Hz, 4-H), 4 09(dd, 1H, J 2 9 and 9 7 Hz, 4-H), 3 67(d, 2H, 2 x 6 - H), 3 44 and 3 15(m, 4H, CH_2CH_2), 2 95(m, 1H, 5-H), and 1 41(s, 3H, Me)

1-(2′-Thienyl)-2-(2′-phenylsulphonylethyl)-8-oxo-2-aza-3,7-dioxabicyclo[3 3 0]octane(5c) The crude product, obtained as a maroon oil, was triturated, with ether-hexane to furnish a purple solid which crystallised from ethyl acetate-hexane to give the product (37%) as colourless rods, m p 114°-115°C (Found C, 53 85, H, 4 65, N, 3 5 $C_{17}H_{17}NO_5S_2$ requires C, 53 65, H, 4 75, N, 3 7%), m/z(%) 379(M^+, 5), 335(21), 194(79) and 77(100), δ 7 87 and 7 60(2 x m, 5H, ArH), 7 39, 7 15 and 7 02(3 x m, 3 x 1H,

ArH), 4 46(dd, 1H, J 9 6 and 7 0Hz, 2-H), 4 23(dd, 1H, J 9 7 and 2 2Hz, 2-H), 4 06(dd, 1H, J 8 3Hz, 4-H), 3 87(dd, 1H, J 8 9 and 2 3 Hz, 4-H), 3 40 and 3 22(2 x m, 5H, NCH_2CH_2 and 3-H)

1-(3′-Indolyl)-2-(2′-phenylsulphonylethyl)-8-oxo-2-aza-3,7-dioxabicyclo[3 3 0]octane(5d) The crude product was obtained as a black viscous oil Flash chromatography (silica, ether-hexane, 3 2) afforded the product (50%) which crystallised from benzene as colourless plates, m p 157-158°C (Found C, 60 8, H, 4 85, N, 6 5 $C_{21}H_{20}N_2O_5S$ requires C, 61 15, H, 4 9, N, 6 8%), m/z(%) 412(M^+, 3), 368(8), 227(41), 199(27), 77(69) and 43(100), δ 8 60(br s, 1H, NH), 7 10-7 75(m, 10H, ArH), 4 35(m, 3H, 2 x 2-H and 4-H), 3 92(dd, 1H, J 8 7 and 2 5 Hz, 4-H), 3 66(m, 1H, 3-H) and 3 35 and 3 25(2 x m, 2 x 2H, NCH_2CH_2)

1-(2′-Nitrobenzyl)-2-(2′-phenylsulphonylethyl)-8-oxo-2-aza-3,7-dioxabicyclo[3 3 0]octane(5e) The crude product was obtained as a brown oil Flash chromatography (silica, ether-hexane, 5 3) afforded the product (61%) which crystallised from hexane-methanol as buff plates, m p 145-146°C (Found C, 55 6, H, 4 75, N, 6 35, $C_{20}H_{20}N_2O_7S$ requires C, 55 55, H, 4 65, N, 6 5%), m/z(%), 432(M^+, 5), 296(24), 141(45) and 77(100), δ 7 90 and 7 52(2 x m, 9H, ArH), 4 1(dd, 1H, J 9Hz, 2-H), 3 9(dd, 1H, J 9 5 and 3 8Hz, 2-H), 3 52(m, 5H, 2 x 4-H, $ArCH_2$ and $CHSO_2Ph$) and 3 21(m, 4H, NCH_2, $CHSO_2Ph$ and 3-H)

1-(4′-Nitrophenyl)-2-(2′-phenylsulphonylethyl)-8-oxo-2-aza-3,7-dioxabicyclo[3 3 0]octane(5f) The crude product was obtained as a yellow solid Crystallisation from ethyl acetate-hexane furnished the product (28%) as colourless hexagonal plates, m p 200-202°C (Found C, 54 5, H, 4 25, N, 6 4 $C_{19}H_{18}N_2O_7S$ requires C, 54 55, H, 4 35, N, 6 7%), m/z(%) 418(M^+, 2), 374(6), 223(21), 205(13), 141(14), and 43(100), δ 8 11, 7 68 and 7 52(3 x m, 9H, ArH), 4 5(dd, 1H, J 9 8 and 7 2Hz, 2-H), 3 90(m, 2H, 4-H), 3 42(m, 3H, NCH, CH_2SO_2Ph) and 3 00(m, 2H, NCH and 3-H)

2-(2′-Phenylsulphonylethyl)-2-aza-3-oxabicyclo[3 3 0]octane(12) Prepared from 5-hexenal oxime and phenyl vinyl sulphone Purification by flash chromatography (SiO_2), eluting with 7 3 v/v ether-hexane afforded the product (74%) as colourless prisms, m p 43°C (Found C, 60 0, H, 6 9, N, 5 0 $C_{14}H_{19}NO_3S$ requires C, 59 75, H, 6 8, N, 5 0%), ν_{max} 1493, 1483, 1290, 1330, 1016, 855, 730, 684 and 522 cm^{-1}, m/z(%) 281(M^+, 27), 139(76), 126(100), 81(37), 77(46), 67(21), 60(20) and 41(21), δ(C_6D_6), 7 80(m, 2H, ArH), 6 97(m, 3H, ArH), 3 60(t, 1H, J 8 4Hz, 4-H), 3 42(m, 2H, CH_2SO_2), 3 16 and 2 92(2 x m, 2H, NCH_2), 2 85(dd, 1H, $J_{4,5}$ 6 2Hz, 4-H), 2 65(br t, 1H, J 6 5Hz, 1-H), 2 38(m, 1H, 5-H), 1 54-1 02(m, 6H, 3 x CH_2), ^{1}H NOEDSY(%) irradiation of 1-H resulted in enhancement of the signal for NCH_2(6), irradiation of 5-H caused enhancement of the signals of the cis-4-H(5) and the cis-6-H(6)

1-Methyl-2-(2′-benzyloxycarbonylethyl)-2-aza-3-oxabicyclo[3 3 0]octane(13a) Prepared from methyl pent-4-enyl ketone oxime[25] and benzyl acrylate with a 24h reaction time The product (73%) distilled as a

colourless oil, b p 125-129°C/0 1mmHg (Found C, 70 25, H, 7 95, N, 5 05 $C_{17}H_{23}NO_3$ requires C, 70 55, H, 8 0, N, 4 85%), ν_{max} 2940, 1725, 1446, 1160, 750, 732 and 696 cm^{-1}, m/z(%) 289(M^+, 25), 274(9), 140(40), 95(36), 91(100) and 55(12), δ 7 34(m, 5H, ArH), 5 13(s, 2H, CH_2 Ar), 3 92(br t, 1H, J 8 1Hz, 4-H), 3 29(dd, 1H, $J_{4,5}$ 5 0Hz, 4-H), 2 95(t, 2H, NCH_2), 2 67(t, 2H, CH_2CO), 2 42(m, 1H, 5-H), 1 85-1 20(m, 6H, $(CH_2)_3$), 1 16(s, 3H, Me), ^{1}H NOEDSY(%) irradiation of 5-H caused enhancement of the signal for 1-Me(5), irradiation of 1-Me caused enhancement of the signals for 5-H(3) and NCH_2(3)

1-Methyl-2-(2′-phenylsulphonylethyl)-2-aza-3-oxabicyclo[3 3 0]octane(13b) Prepared from methyl pent-4-enyl ketone oxime and phenyl vinyl sulphone with a reaction time of 7h Flash chromatogrpahy (SiO_2) eluting with 1 1 v/v ether-petroleum ether afforded the cycloadduct (78%) as a colourless oil (R_f 0 3) (Found C, 61 15, H, 7 2, N, 4 8 $C_{15}H_{21}NO_3S$ requires C, 61 0, H, 7 15, N, 4 75%), m/z(%) 295(M^+, 7), 277(18), 140(36) and 83(100), δ 7 84(m, 2H, ArH), 7 50(m, 3H, ArH), 3 63(br t, 1H, 4-H), 3 41(m, 2H, CH_2SO_2Ph), 2 97(t, 3H, NCH_2 and 4-H), 2 28(m, 1H, 5-H), 1 80-1 09(m, 6H, 3 x CH_2) and 1 05(s, 3H, Me), ^{1}H NOEDSY (%) irradiation of 5-H caused enhancement of the signal for 1-Me (3) and vice versa

Cycloadducts (17a) (18a) and nitrone (19)

a A 3 2 mixture of (E)- and (Z)-N-allylpyrrole-2-carboxaldehyde oxime and benzyl acrylate were reacted in boiling xylene for 24h according to the general procedure The resulting dark brown oil was purified by flash chromatography (SiO_2) eluting with ether to afford the product (17a)(30%) as colourless prisms, m p 76-78°C (Found C, 68 95, H, 6 35, N, 8 85 $C_{18}H_{20}N_2O_3$ requires C, 69 2, H, 6 45, N, 8 95%), ν_{max} 2870, 1731, 1452, 1350, 1217, 1365, 745 and 720 cm^{-1}, m/z(%) 312(M^+, 17), 118(100), 91(14), 105(7) and 65(3), δ 7 34(m, 5H, ArH), 6 54-5 98(3 x m, 3H, pyrrole-H), 5 13(s, 2H, CH_2Ar), 4 45(br m, 1H, 4-H), 4 14(m, 2H, 1-H and 4-H), 3 99-3 73(m, 3H, 5-H and 2 x 6-H), 3 16(m, 2H, NCH_2) and 2 73(m, 2H, CH_2CO)

b A solution of (Z)-N-allylpyrrole-2-carboxaldehyde oxime (500 mg, 3 33 mmol) in dry acetonitrile (25 ml) was stirred and heated to 60°C under a nitrogen atmosphere for 36 hrs Removal of the solvent gave an orange viscous oil (0 99g) whose p m r spectrum indicated a mixture of compounds including signals for the unreacted oxime Purification by flash chromatography (SiO_2, 9 1 v/v ether-ethyl acetate) afforded unreacted starting materials followed by (17a) and then (18a) When the column was eluted further (1 1 v/v ether-ethyl acetate) the nitrone (19) was obtained as a viscous liquid

(17a) Colourless prisms (123 mg, 12%), m p 76-78°C, identical to that described above

(18a) Obtained as a colourless viscous liquid (97 mg, 9%) (Found C, 69 15, H, 6 4, N, 9 15%), m/z(%) 312(M^+, 42), 221(7), 136(20), 118(100), 106(27), 91(83), and 77(25) The p m r spectrum of this compound contains broad signals due to a conformational equilibrium and shows the presence of a 1 1 25 mixture of two invertomers When one drop of trifluoroacetic acid was added to the $CDCl_3$ solution, the spectrum simplified and sharpened and showed the presence of mainly one N-protonated species δ($CDCl_3$ + 1 drop CF_3CO_2H) 7 29-7 38(m, 5H, ArH), 6 76(t, 1H, J 1 1 Hz, pyrrole-H), 6 40(dd, 1H, J 1 3

and 3 6 Hz, pyrrole-H), 6 27(t, 1H, J 3 2Hz, pyrrole-H), 5 45(d, 1H, J 4 6Hz, NCH-pyrrole), 5 25(d, 1H, J 5 96 Hz, OCH), 5 11(s, 2H, CH_2 Ph), 4 16(dd, 2H, J 1 5 and 6 2 Hz, pyrrole NCH_2), 3 46 and 3 08(2 x q, 2 x 1H, bridge CH_2), 2 95(m, 1H, NHCH CH_2), 2 83(m, 2H, CH_2CO_2), and 2 59(d, 1H, J 12 8 Hz, NHCHCH_2)

(19) Obtained as a colourless viscous liquid (403 mg, 39%) (Found C, 69 05, H, 6 35, N, 9 1 $C_{18}H_{20}N_2O_3$ requires C, 69 2, H, 6 45 and N, 8 95%), ν_{max}(nujol) 1740, 1650, 1600, 1525, 1310, 1155, 735 and 700 cm^{-1}, m/z(%), 312(M^+, 33), 296(6), 295(10), 162(6), 150(6), 133(11), 118(100), 106(21), 91(68) and 77(18), δ 7 83(d, 1H, J 3 7 Hz, pyrrole-H), 7 41(s, 1H, CH=N), 7 31(s, 5H, ArH), 6 80(d, 1H, J 1 7 Hz, pyrrole-H), 6 28(t, 1H, J 3 2 Hz, pyrrole-H), 5 90(m, 1H, CH=CH_2), 5 19(d, 1H, J 10 6 Hz, =CH), 5 12(s, 2H, CH_2Ph), 4 94(dd, 1H, J 1 0 and 17 1 Hz, =CH), 4 51(d, 2H, J 4 8 Hz, pyrrole-NCH_2), 4 16(t, 2H, J 6 2 Hz, NCH_2), 3 09(t, 2H, J 6 2 Hz, CH_2CO_2), δ(^{13}C) 170 6(carbonyl carbon), 135 1, 128 1(2C), 127 9, 127 7(2C), (phenyl carbons), 123 6, 116 8, 116 1, 108 8(pyrrole carbons), 125 2(C=N-O^-), 133 1, 125 5(olefinic carbons), and 66 2, 59 9, 49 1 and 31 4(aliphatic carbons)

c A solution of nitrone (19) (50 mg) in xylene (0 5 ml) was heated at 110°C for 16 h to give a 1 1 6 mixture of (17a) and (18a) in quantitative yield

Cycloadducts (17b) and (18b) A solution of N-allylpyrrole-2-carboxaldehyde oxime (500 mg, 3 33 mmol) and phenyl vinyl sulphone (560 mg, 3 33 mmol) in dry acetonitrile (25ml) was boiled under reflux, under a nitrogen atmosphere for 18 hrs Removal of the solvent afforded an orange gum, whose p m r spectrum indicated the presence of two isomers in the ratio 1 1 Purification by flash chromatography (ether) afforded (17b) (423 mg, 40%) and (18b) (372 mg, 35%), together with a mixed fraction (117 mg, 11%)

(17b) Obtained as colourless rods, from methanol m p 122-124°C (Found C, 60 5, H, 5 65, N, 8 9 $C_{16}H_{18}N_2O_3S$ requires C, 60 35, H, 5 7 and N, 8 8%), m/z(%) 318(M^+, 52), δ 7 85(d, 2H, J 7 7 Hz, ArH), 7 63(t, 2H, J 7 2Hz, ArH), 7 52(t, 2H, J 7 7 Hz, ArH), 6 54(t, 1H, J 1 2Hz, pyrrole-H), 6 24(t, 1H, J 3 1 Hz, pyrrole-H), 5 91(d, 1H, J 2 8 Hz, pyrrole-H), 4 32(br s, 1H, NCH), 4 09(dd, 1H, J 8 5 and 10 7Hz, OCH), 4 02(br s, 1H, OCH), 3 79(m, 2H, pyrrole-NCH_2), 3 60(br d, 1H, J 8 6 Hz, CH), 3 46(t, 2H, J 7 1 Hz, NCH_2), and 3 20(t, 2H, J 6 3 Hz, CH_2 SO_2 Ph) Addition of a drop of trifluoroacetic acid to the $CDCl_3$ solution sharpens the broad singlet at δ4 32 to a doublet at δ5 60(J 6 6 Hz)

(18b) Obtained as colourless viscous oil (Found C, 60 0, H, 5 5, N, 8 4%), m/z(%) 318(M^+, 39), 150(8), 136(9), 125(5), 118(100), 106(9), 91(10) and 77(30), the ^{1}H NMR ($CDCl_3$) spectrum of this compound shows broad signals due to conformational equilibrium δ 7 83(2H), 7 62(1H) and 7 53(2H) (ArH), 6 52, 6 08 and 5 91(3 x 1H, pyrrole H), 4 62 and 4 81(br s, 1H, NCH), 4 21(br d, 1H, OCH), 3 92(br s, 2H, pyrrole NCH_2), 3 35(br m, 2H), 2 40-2 90(br m, 3H), 2 20(d, 1H, J 11 3 Hz), δ($CDCl_3$ + 1 drop TFA) 7 80(d, 2H, J 7 6 Hz, ArH), 7 66(t, 1H, J 7 4Hz, ArH), 7 55(t, 2H, J 7 6 Hz, ArH) 4 91(d, 1H, J 5 6 Hz, NHCH-pyrrole), 4 75(d, 1H, J 4 2 Hz, OCH), 4 03(s, 2H, pyrrole NCH_2), 3 36-3 58(m, 2H, bridge CH_2), 3 11(m, 1H, NHCH), 2 63-2 83(m, 2H,), and 2 36(d, 1H, 11 9Hz, CH SO_2Ph), δ(^{13}C, $CDCl_3$ + 1 drop

TFA) 138 5, 134 4, 129 6(2C), 128 2(2C), (phenyl carbons), 123 2, 121 9, 109 6, 109 1 (pyrrole carbons), 76 0, 58 3, 52 2, 52 1, 47 9 and 35 7(aliphatic carbons)

Cycloadducts (17c) and (18c) A solution of N-allyl pyrrole-2-carboxaldehyde oxime (500 mg, 3 33 mmol) and methyl vinyl ketone (233 mg, 2 8 ml, 3 33 mmol) in dry acetonitrile (30 ml) was stirred and boiled under reflux under a nitrogen atmosphere for 16 hrs Removal of the solvent gave an orange viscous oil, whose p m r spectrum indicated the presence of two regio-isomeric cycloadducts in the ratio 1 1 2 Purification by flash chromatography (SiO_2, 9 1 v/v ether-ethylacetate) afforded both isomers

(17c) Obtained as colourless needles (270 mg, 37%), from ether-petroleum ether (40-60°), m p 73-74°C (Found C, 65 55, H, 7 55, N, 12 80 $C_{12}H_{16}N_2O_2$ requries C, 65 43, H, 7 32 and N, 12 72%), m/z(%) 220(M^+, 55), 163(7), 133(10), 118(100), 106(22), 105(45), 104(38), and 91(9), δ 6 56(s, 1H, pyrrole-H), 6 27(t, 1H, J 3 0 Hz, pyrrole-H), 5 99(d, 1H, J 3 3 Hz, pyrrole-H), 4 43(br s, 1H, pyrrole-NCH), 4 17(dd, 2H, J 8 1 and 10 6Hz, OCH_2), 3 97(dd, 1H, J 3 4 and 10 7 Hz, pyrrole-NCH)< 3 89(m, 1H, OCH_2CH), 3 77(dd, 1H, J 3 5 and 8 7 hz, pyrrole-NCH), 3 11(m, 2H, N-CH_2), 2 87 and 2 71(2 x m, 2H, $COCH_2$), and 2 18(s, 3H, $COCH_3$)

(18c) Obtained as a colourless viscous oil (324 mg, 44%), (Found C, 65 1, H, 7 25, N, 12 75%) m/z(%) 220(M^+, 32), 119(9) and 118(100), this compound exists as a 1 1 2 equilibrium mixture of two invertomers at room temperature The p m r spectrum in $CDCl_3$ shows signals due to both the invertomers δ 6 61 and 6 51(1H, 6 14 and 6 10(1H, 6 00 and 5 94(1H, (3 x 1H, pyrrole H), 4 81 and 4 71(2 x d, 1H, J 4 4 and 4 9 Hz, OCH), 4 27(d, 1H, J 4 1 Hz, NCH), 3 86-4 07(m, 2H), 3 03(m, 1H), 2 57-2 95(m, 4H), 2 21-2 46(m, 1H), and 2 17 and 2 14(2 x s, 3H, $COCH_3$) Addition of a drop of CF_3CO_2H to the $CDCl_3$ solution sharpens the spectrum and shows signals for mainly one protonated isomer The solution eventually becomes blue in colour δ($CDCl_3$ + 1 drop CF_3CO_2H) 6 80, 6 41 and 6 28(3H, pyrrole H), 5 44(d, 1H, J 4 6Hz, NHCH), 5 31(d, 1H, J 6 0 Hz, OCH), 4 24(AB d, 2H, J 13 6Hz, pyrrole-NCH_2), 3 38(m, 1H, NH $CHCH_2$), 2 91-3 11(m, 4H), 2 62(d, 1H, J 12 8Hz, COCH), and 2 22(s, 3H, $COCH_3$)

12-(2′-Benzyloxycarbonylethyl)-11-oxa-12-azatricyclo[7 3 0 $0^{1,6}$]dodecane (22a) Prepared from oxime (21a) and benzyl acrylate and a reaction time of 24h The resulting pale yellow oil was purified by preparative t l c(SiO_2) eluting with 1 1 v/v ether-petroleum ether to afford the product (70%) as a viscous colourless oil (Found C, 73 05, H, 8 05, N, 4 05 $C_{20}H_{27}NO_3$ requires C, 73 05, H, 8 25, N, 4 25%) ν_{max} 2915, 1725, 1447, 1163, 1005, 750, 735 and 697 cm^{-1}, m/z(%), 329(M^+, 100), 286(13), 180(61), 150(13), 135(84) and 91(69), δ 7 35(m, 5H, ArH), 5 13(s, 2H, CH_2Ar), 3 99(t, 1H, J 8 2 Hz, H_C), 3 37(dd, 1H, J_{DB} 3 9Hz, H_D), 2 97(m, 2H, NCH_2), 2 67(m, 2H, CH_2CO), 2 52(m, 1H, H_B), 2 06(m, 1H, H_A) and 1 86-1 25(m, 12H, $(CH_2)_6$), ^1H NOEDSY(%) irradiation of H_A caused enhancement of the signal for H_B (7), irradiation of H_B caused enhancement of the signals for H_C(7) and H_A(5)

12-(2′-Phenylsulphonylethyl)-11-oxa-12-azatricyclo[7 3 0 0 ^{1,6}]dodecane (22b) Prepared in an identical manner to that described above but using phenyl vinyl sulphone as the Michael acceptor The product (69%) crystallised from ether as colourless prisms, m p 79-81°C (Found C, 64 5, H, 7 65, N, 4 2 $C_{18}H_{25}NO_3S$ requires C, 64 45, H, 7 5, N, 4 15%), m/z(%), 335(M^+, 55), 292(21), 278(14), 194(15), 193(14) and 180(100), δ 7 94(m, 2H, ArH), 7 58(m, 3H, ArH), 3 80(t, 1H, H_C, J 8 1Hz), 3 94(t, 2H, CH_2SO_2Ph), 3 24(dd, 1H, H_D, J 3 8Hz and 8 2Hz), 3 09(m, 2H, CH_2N), 2 46(m, 1H, H_B), 2 03(m, 1H, H_A) and 1 99-1 20(m, 12H, 6 x CH_2), ^{1}H NOEDSY(%) irradiation of H_B caused enhancement of the signals for H_A(5) and H_C(6) but had no effect on H_D, irradiation of H_C resulted in enhancements of H_D(26) and H_B(8)

13-(2′-Phenylsulphonylethyl)-12-oxa-13-azatricyclo[8 3 0 0 ^{1,7}]tridecane (23) Prepared from oxime (21b) and phenyl vinyl sulphone with a 20 h reaction time The product (60%) crystallised from ether at -20°C as colourless prisms, m p 74-75°C (Found C, 65 35, H, 7 75, N, 3 95 $C_{19}H_{27}NO_3S$ requires C, 65 3, H, 7 8, N, 4 0%), m/z(%) 349(M^+, 100), 292(30), 208(37) and 194(69), δ 7 93(m, 2H, ArH), 7 58(m, 3H, ArH), 3 62(br t, 1H, H_C), 3 46(m, 2H, CH_2SO_2Ph), 3 16 and 3 05(m, 3H, NCH_2 + H_D), 2 40(m, 1H, H_B), 1 89(m, 1H, H_A), 1 80-1 36(m, 13H) and 1 24(m, 1H), ^{1}H NOEDSY (%) irradiation of H_B caused enhancement of the signal for H_C(4), irradiation of H_A caused enhancement of H_D(1)

Cis- and trans- 2-(2′-benzyloxycarbonylethyl)-8-methyl-2-aza-3,7-dioxabicyclo[4 3 0]nonane (28c) and (30c) and 2-(2′-benzyloxycarbonylethyl)-7-methyl-2-aza-3,6-dioxabicyclo[4 2 1]nonane (31c) Prepared from oxime (32a) and benzyl acrylate with a reaction time of 24h Work up afforded a pale yellow oil (100%) whose p m r spectrum showed it to comprise a 3 1 5 2 mixture of (28c), (29c), (30c) and (31c) Distillation afforded a colourless oil (65%), b p 150-158°C/0 05mmHg whose p m r spectrum showed the composition was approximately unchanged Preparative t l c (SiO_2) eluting with ether afforded pure samples of (28c), (30c) and (31c) Isomer (29c) was not isolated but is characterised by a p m r doublet at δ 1 25 (J 6 2 Hz) for the C(Me) group (Found (mixture) C, 67 0, H, 7 4, N, 4 55 $C_{17}H_{23}NO_4$ requires C, 66 85, H, 7 6, N, 4 6%), ν_{max} (mixture) 2920, 1725, 1447, 1375, 1162, 750, 737 and 700 cm^{-1}, m/z (%) (mixture) 305(M^+, 17), 248(12), 232(12), 178(13), 156(15), 91(100) and 55(18)

Cycloadduct (28c) δ 7 36-7 29 (m, 5H, ArH), 5 12(d, 2H, CH_2Ar), 3 90(dd, 1H, H_C, J_{CB} 5 9Hz, J_{CD} 8 0Hz), 3 83(dd, 1H, H_F, J_{FG}, 11 4Hz, J_{FB} 6 7Hz), 3 58(m, 1H, H_E), 3 56(t, 1H, H_G), 3 40(dd, 1H, H_D, J_{DB} 1 5 Hz), 3 22 and 2 85(2 x m, 2H, NCH_2), 2 88(m, 1H, H_A), 2 70(m, 2H, CH_2CO), 2 64(m, 1H, H_B), 1 65(m, 1H, H_I), 1 56(m, 1H, H_H), and 1 11(d, 3H, Me, J 6 2Hz) Decoupling experiments on H_B and Me support the assignments

Cycloadduct (30c) δ 7 37-7 29(m, 5H, ArH), 5 12(d, 2H, CH_2Ar), 4 05(dd, H_C, J_{CD} 7 1 Hz, J_{CB} 9 9Hz), 3 93(br d, 1H, H_F, J_{FG} 12 5 Hz), 3 76(dd, 1H, H_D, J_{DB} 9 4 Hz), 3 72(dd, 1H, H_G, J_{BG} 3 3 Hz), 3 34(m, 1H, H_E), 3 25(br m, 1H, H_A), 3 12 and 2 83(2 x m, 2H, NCH_2), 2 73(br m, 1H, H_B), 2 65(m, 2H, CH_2CO),

1 74(br m, 1H, H_I), 1 38(br m, 1H, H_H), and 1 18(d, 3H, Me, J 6 2Hz) Decoupling experiments on H_A, H_H, H_C and Me support the assignments

Cycloadduct (31c) δ 7 36-7 29(m, 5H, ArH), 5 12(d, 2H, CH_2Ar), 4 35(dd, 1H, H_B, J_{BC} 8 7Hz, J_{BI} 2 9Hz), 3 88(m, 1H, H_G), 3 55(d, 1H, H_H, J_{HI}, 13 0Hz), 3 48(dd, 1H, H_I), 3 35(m, 1H, H_A), 3 07 and 2 85(2 x m, 2H, NCH_2), 2 66(m, 2H, CH_2CO), 2 43(m, 1H, H_C), 2 26(d, 1H, H_D, J_{DC} 12 0Hz), 1 75(m, 1H, H_E) 1 38(m, 1H, H_F), and 1 10(d, 3H, Me, J 6 3Hz) Decoupling experiments on H_B, H_C and Me support the assignments

Cis- and trans-2-(2′-benzyloxycarbonylethyl)-4,4,8-trimethyl-2-aza-3-oxabicyclo[4 3 0]nonane (28e) and (30e) Citronellal oxime (32b) reacted with benzyl acrylate over 24h to give a pale yellow oil (95%) whose p m r spectrum showed it to comprise a 1 5 5 mixture of (28e) and (30e) Distillation afforded a colourless oil (56%), b p 140-144°C/0 05mmHg whose composition was essentially unchanged Isomer (28e) was not isolated but is characterised by a p m r doublet at δ 1 11(J 6 6Hz) (Found (mixture) C, 72 6, H, 9 0, N, 4 2 $C_{20}H_{29}NO_3$ requires C, 72 45, H, 8 8, N, 4 25%], ν_{max} (mixture) 2910, 1725, 1448, 1151, 870, 750, 735 and 697 cm^{-1}, m/z(%) (mixture) 331(M^+, 38), 316(8), 240(10), 195(20), 182(86), 137(42), 109(19), 91(100) and 81(35)

30e 7 37-7 26(m, 5H, ArH), 5 10(d, 2H, CH_2Ar), 3 24 and 2 85(2 x m, 2H, NCH_2), 2 70(m, 2H, CH_2CO), 2 37(br m, 1H, H_A), 1 85(m, 1H, H_I) 1 80-1 60(m, 3H, H_B, H_J, H_K), 1 41(m, 1H, H_E), 1 23(s, 3H, 4-Me), 1 17(m, 1H, H_G), 1 04(s, 3H, 4-Me), 1 00-0 90(m, 2H, H_H and H_F), 0 95(d, 3H, 8-Me, J 6 6 Hz)

Trans-2-(2′-phenylsulphonylethyl)-4,4,8-trimethyl-2-aza-3-oxabicyclo[4 3 0]nonane (30f) Prepared from oxime (32b) and phenyl vinyl sulphone with a reaction time of 14h Work up followed by flash chromatography (SiO_2) eluting with 1 1 v/v ether-hexane afforded the product (27%) which crystallised from hexane as colourless prisms, m p 99-101°C (Found C, 63 9, H, 8 1, N, 4 2 $C_{18}H_{27}NO_3S$ requires C, 64 05, H, 8 05, N, 4 15%), m/z(%) 337(M^+, 53), 254(34), 195(23) and 182(100), δ 7 89(m, 2H, ArH), 7 58(m, 3H, ArH), 3 51 and 3 41(br m, 2H, CH_2SO_2), 3 30 and 2 85(br m, 2H, CH_2N), 2 29(br m, 1H, H_A), 1 76(m, 2H, 2 x ring-H), 1 60(m, 2H, H_B and ring-H), 1 38(m, 1H, CHMe), 1 14(m, 1H, ring-H), 1 10(s, 3H, Me), 0 96(s, 3H, Me), 0 96(m, 1H, ring-H), 0 93(d, 3H, Me) and 0 90(m, 1H, ring-H), ^1H NOEDSY(%) irradiation of H_A caused enhancement of the signal of CHMe(4) but not of H_B, irradiation of CHMe caused enhancement of the signal for H_A(3)

2-(2-Benzyloxycarbonylethyl)-1,8,8-trimethyl-6-oxo-2,7-diaza-3-oxabicyclo[4 3 0]nonane (34a) Prepared from oxime (33) and benzyl acrylate with a reaction time of 24h Work up followed by flash chromotography (SiO_2) eluting with 3 97 v/v methanol-ether afforded the product (52%) which crystallised as colourless prisms from ether, m p 75-78°C (Found C, 65 8, H, 7 5, N, 8 15 $C_{19}H_{26}N_2O_4$ requires C, 65 85, H, 7 55, N, 8 1%), ν_{max} 3380, 1718, 1650, 1410, 1310, 1170, 951, 761 and 710 cm^{-1}, m/z(%),

346(M^+, 37), 331(38), 197(28), 140(30), 139(22), 124(20), 91(100), 88(30) and 58(13), δ 7 34(m, 5H, ArH), 6 85(br s, 1H, NH), 5 11(s, 2H, CH_2Ar), 4 23(dd, 1H, H_D, J_{DE} 3 5Hz, J_{DA} 9 7Hz), 3 81(dd, 1H, H_C, J_{CA} 6 63Hz), 2 93(m, 2H, NCH_2), 2 86(dd, 1H, H_A), 2 66(t, 2H CH_2CO), 1 83(d, 1H, H_C, J 14 3Hz), 1 63(d, 1H, H_B), 1 33 and 1 26(2 x s, 2 x 3H, CMe_2) and 1 18(s, 3H, Me)

2-(2-Phenylsulphonylethyl)-1,8,8-trimethyl-6-oxo-2,7-diaza-3-oxabicyclo[4 3 0]nonane (34b) Prepared from oxime (33) and vinyl sulphone with a reaction time of 16h Work up afforded the product (100%) as a colourless solid which crystallised from ethanol as colourless prisms, m p 155-157°C (Found C, 57 9, H, 6 7, N, 8 1 $C_{17}H_{24}N_2O_4S$ requires C, 57 95, H, 6 85, N, 7 95%), m/z(%) 352(M^+, 16), 152(44), 139(35), 124(36), 112(51), 77(64), 58(80), 55(34) and 43(100), δ 7 91(m, 2H, ArH), 7 59(m, 3H, ArH), 6 31(br s, 1H, NH), 4 06(t, 1H, H_E), 3 67(dd, 1H, H_D, J 6 2 and 8 4 Hz), 3 43(m, 2H, CH_2SO_2Ph), 3 03(m, 2H, CH_2N), 2 80(dd, 1H, H_A, J 6 1 and 9 7 Hz), 1 72(ABq, 2H, H_B and H_C), 1 32 and 1 27(2 x s, 2 x 3H, CMe_2) and 1 17(s, 3H, Me), ^{1}H NOEDSY(%) irradiation of H_A caused enhancement of 1-Me(5) and H_E(6), irradiation of 1-Me caused enhancement of H_A(9)

1-(2-Benzyloxycarbonylethyl)-1,3a,4,9b-tetrahydro-3H-isoxazolo[3,4-d]benzo[b]pyran(37b) Prepared from O-allyl-salicylaldehyde oxime (36a) and benzyl acrylate with a reaction time of 24h The product (100%) was a pale yellow oil A small sample was further purified by ptlc (SiO_2) eluting with 4 1 v/v petroleum ether-ether to yield a colourless oil (Found C, 70 75, H, 6 35, N, 4 1 $C_{20}H_{21}NO_4$ requires C, 70 8, H, 6 25, N, 4 15%), ν_{max} 2940, 1720, 1480, 1443, 1162, 1059, 755 and 697 cm^{-1}, m/z(%) 339(M^+, 9), 283(22), 160(33), 145(24), 132(23), 131(49), 91(100) and 88(42), δ 7 38-6 86(m, 4H, ArH), 7 32(s, 5H, ArH), 5 11(s, 2H, CH_2Ar), 4 18(t, 1H, H_C, J 8 2 Hz), 4 15(dd, 1H, H_F), 4 10(dd, 1H, H_E), 3 8(d, 1H, H_A, J_{AB}, 6 9Hz), 3 71(dd, 1H, H_D, J_{DB} 4 6Hz), 3 36 and 3 16(2 x m, 2H, NCH_2), 3 02(m, 1H, H_B), and 2 73(m, 2H, CH_2CO)

1-(2′-Phenylsulphonylethyl)-1,3a,4,9b-tetrahydro-3H-isoxazolo[3,4-d]-benzo[b]pyran (37c) Prepared in analogous manner to that described above from O-allylsalicylaldehyde oxime (36a) and phenyl vinyl sulphone in toluene with a reaction time of 16h Work up afforded an orange gum which upon flash chromatography with ether afforded the product (90%), m p 101-103°C, as colourless plates from ethanol (Found C, 62 45, H, 5 65, N, 3 8 $C_{18}H_{19}O_4S$ requires C, 62 6, H, 5 55, N, 4 05%), m/z(%) 345(M^+, 7), 289(15), 190(11), 160(29) and 131(100), δ 7 85-6 88(m, 9H, ArH), 4 10(t, 1H, OCH), 4 05(dd, 1H, OCH), 3 83(dd, 1H, OCH), 3 66(d, 1H, H_A, J 6 6Hz), 3 48(m, 4H, OCH, CH_2SO_2Ph, CHN), 3 17(m, 1H, CHN) and 2 94(m, 1H, H_B), ^{1}H NOEDSY (%) irradiation of H_A results in enhancement of the signal for H_B(8) and vice versa

Michael Adduct (39) A solution of oxime (36a) (1 77g, 1 mmol) in dioxan (10 ml) containing 20% aqueous sodium hydroxide (0 4 ml, 2 mmol) was stirred for 15 mins Benzyl acrylate (8 1g, 5 mmol) was

then added dropwise over 5 min and the resulting mixture stirred at room temperature for 16h After neutralising with 2N hydrochloric acid the solvent was removed under reduced pressure and the residue partitioned between chloroform and water The organic phase was separated, washed with water, dried (Na_2SO_4) and evaporated The residual oil was purified by flash chromatography to afford the Michael adduct (1 8g, 54%) (R_f 0 27) as a colourless oil (Found C, 70 55, H, 6 4, N, 3 85 $C_{20}H_{21}NO_4$ requires C, 70 8, H, 6 25, N, 4 15%), m/z(%) 339(M^+, 5), 160(24), 145(31), 107(23), 92(34) and 91(100), δ 8 51(s, 1H, CH=N), 7 78(dd, 1H, ArH), 7 32(m, 6H, ArH), 6 92(m, 2H, ArH), 6 02(m, 1H, C<u>H</u>=CH_2), 5 32(m, 2H, CH=C<u>H</u>$_2$), 5 14(s, 2H, Ar<u>CH</u>$_2$), 4 51(m, 2H, OC<u>H</u>$_2$CH=CH_2), 4 45(t, 2H, O<u>CH</u>$_2$) and 2 79(t, 2H, CH_2CO_2R) Heating the Michael adduct (50 mg) in xylene-d_{10} at 140°C for 24h failed to yield any (37b)

<u>Cycloadduct (40)</u> A solution of oxime (36b) (1 91g, 10 mmol) and benzyl acrylate (1 62g, 10 mmol) in mesitylene (40ml) was boiled under reflux for 18 hr under argon The solvent was removed in vacuo to leave a dark brown oil which comprised the product (60%) together with uncharacterised material The crude oil was purified by flash chromatography (SiO_2) eluting with 3 7 v/v ether-hexane to yield the product (1 91g, 54%) as a pale yellow oil which was too thick for distillation (Found C, 71 6, H, 6 65, N, 3 85 $C_{21}H_{23}NO_4$ requires C, 71 35, H, 6 55, N, 3 95%), ν_{max} 2910, 1720, 1595, 1445, 1160, 1010, 742 and 700 cm^{-1}, m/z(%) 353(M^+, 21), 191(15), 161(37), 159(32), 146(12), 119(15), 117(30), 107(28), 91(100), 79(21) and 55(56), δ 7 49-6 91(m, 9H, ArH), 5 15(s, 2H, CH_2Ar), 4 35(d, 1H, H_A, J_{AB} 9 4Hz), 4 16(t, 1H, H_E, J 8 3 Hz), 4 05(m, 2H, H_C), 3 40(t, 1H, H_D), 3 24-3 15(m, 2H, NCH_2), 3 07(m, 1H, H_B), 2 77(t, 2H, CH_2CO), 1 75(m, 1H, H_G), and 1 62(m, 1H, H_F), ^{1}H NOEDSY(%) irradiation of H_A results in enhancement of the signals for H_B(8) and H_H(3), irradiation of H_D produced enhancements in the signals for H_E(24) and H_G(4)

We thank the Department for Education for Northern Ireland, and Queen's and Leeds Universities for support and Dr O Howarth, SERC 400 MHz service, Warwick University, for p m r spectra

<u>References</u>

1 Part 32 Grigg, R , Heaney, F , Surendrakumar, S , and Warnock, W J , *Tetrahedron,* in press
2 Preliminary communication Armstrong, P , Grigg, R , and Warnock, W J , *J Chem Soc , Chem Commun ,* 1987, 1325-1327
3 Armstrong, P , Dorrity, M J R , Grigg, R , Malone, J F , Rajviroongit, S , Surendrakumar, S , and Warnock, W J , in preparation
4 Tufariello, J J , in "1,3-Dipolar Cycloaddition Chemistry", ed A Padwa, Wiley, New York, 1984, Vol 2, p 83
5 Padwa, A , *Angew Chem , Int Ed Engl ,* 1976, <u>15</u>, 123-136 Oppolzer, W , *ibid,* 1977, <u>16</u>, 10-23
6 LeBel, N A , Post, M E , and Whang, J J , *J Am Chem Soc ,* 1964, <u>86</u>, 3759-3767
7 Tufariello, J J , Ali, Sk A , *Tetrahedron Letters,* 1978, <u>19</u>, 4647-4650, Tufariello, J J , Puglis, J M , *ibid,* 1986, <u>27</u>, 1265-1268, Burdisso, M , Gandolfi, R , Grunager, P , and Rastelli, A , *J Org*

Chem., 1990, 55, 3427-3429; Jung, M.E.; Gervay, J., *Chemtracts,* 1990, 3, 284-287.

8 March, J., "Advanced Organic Chemistry", Wiley, New York 3rd Edn., 1985, p. 359 and 890,

9 Tschaen, D.M.; Whittle, R.R., and Weinreb, S.M., *J. Org. Chem.,* 1986, 51, 2604-2605.

10 Grigg, R.; Markandu, J., Perrior, T., Surendrakumar, S., and Warnock, W.J., *Tetrahedron Letters,* 1990, 31, 559-562.

11 Raban, M.; Kenny, G.W., *Tetrahedron Letters,* 1969, 1295-1298; Fletcher, J.R.; Sutherland, I.O., *J. Chem. Soc., Chem. Commun.,* 1970, 687-688; Raban, M.; Kost, D., *J. Org. Chem.,* 1972, 37, 499-501; Posner, T.B.; Couch, D.A., and Hall, C.D., *J. Chem. Soc., Perkin Trans. 2,* 1978, 450-453; Iwanura, M.; Katoh, M., Iwamura, H., *Org. Mag. Reson.,* 1980, 14, 392-397.

12 Takahashi, S.; Kusumi, T., Sato, Y., Inouye, Y., and Kakisawa, H., *Bull. Chem. Soc. Jpn.,* 1981,54, 1777-1780; Kusumi, T., Takahashi, S., Sato, Y., and Kakisawa, H., *Heterocycles,* 1978, 10, 257-260.

13 Johnson, F.; *Chem. Revs.,* 1968, 68, 375-413.

14 Ardill, H.; Grigg, R., Sridharan, V., and Surendrakumar, S., *Tetrahedron,* 1988, 44, 4953-4966.

15 LeBel, N.A.; Banucci, E.G., *J. Org. Chem.,* 1971, 36, 2440-2448; Burdisso, M.; Gandolfi, R., and Grunager, P., *Tetrahedron,* 1989, 45, 5579-5594.

16 Baldwin, S.W.; Wilson, J.D., and Aube, J., *J. Org. Chem.,* 1985, 50, 4432-4439.

17 Eliel, E.L.; Allinger, N.L., Angyal, S.J., and Morrison, G.A., "Conformational Analysis", Wiley-Interscience, 1965, p. 230.

18 Grigg, R.; Jordan, M., Tangthongkum, A., Einstein, W.B., and Jones, T., *J. Chem. Soc., Perkin Trans. 1,* 1984, 47-57; note that there is an error in the reported coupling constants for the ring junction protons of (36a) in this paper.

19 Oppolzer, W.; Keller, K., *Tetrahedron Letters,* 1970, 1117-1120, Oppolzer, W.; Weber, H.B., *ibid,* 1970, 1121-1124.

20 Padwa, A.; Norman, B.H., *Tetrahedron Letters,* 1988, 29, 2417-2420.

21 Grigg, R.; Gunaratne, H.Q.N.; and Kemp, J., *J. Chem. Soc., Perkin Trans. 1.,* 1984, 41-46.

22 Louw, R.; Kooyman, E.C., *Rec. Trav. Chim. Pays-Bas,* 1967, 86, 1041-1046.

23 Harding, K.E.; Ligon, R.C., Tseng, C.-Y., and Wu, T.-C., *J. Org. Chem.,* 1973, 38, 3478-3481.

24 Hall, R.H.; Stern, E.S., *J. Chem. Soc.,* 1952, 4083-4085.

25 House, H.O.; Lee, L.F., *J. Org. Chem.,* 1976, 41, 863-869.