Competitive [4 + 2] and [3 + 2] Cycloadditions of Nitrosoalkenes to the Imino Bond of Bicyclic 1,2-Oxazines

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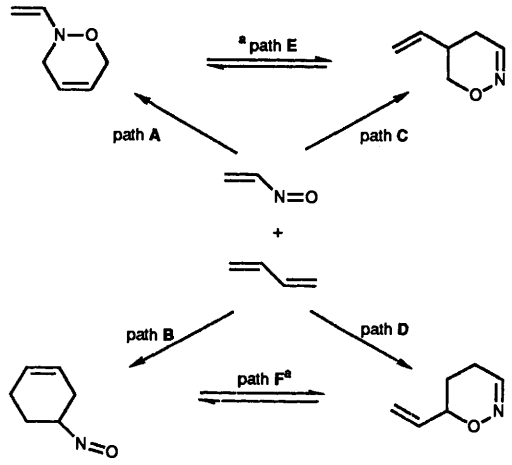
The bicyclic 1,2-oxazines derived from the cycloaddition of α-nitrosostyrene to either 2,5-dimethylfuran (**11**) or cyclopentadiene (**15**) react further with nitrosostyrene or other nitrosoalkenes. Only 3 + 2 addition is observed with (**11**) to give the tricyclic nitrones (**12**) and (**13**), shown by X-ray analysis of (**12**) to be *cis-anti-cis* fused, with a central boat conformation. The adduct (**15**) gives both nitrones (**16**)–(**18**) and the 4 + 2 cycloadducts of the 1,2,5 oxadiazines (**21**)–(**23**). The latter mode of addition is favoured by nitrosoalkenes with electron withdrawing α-substituents. The oxadiazine (**23**), derived from 3-nitrosobut-3-en-2-one is *cis-syn-cis* fused with a central chair conformation in the crystal state, but exists in solution in equilibrium with a small amount of the boat conformation.

The requirements for addition to the imino bond are demanding, many other model systems related to (**11**) or (**15**) failing to react.

Conjugated nitrosoalkenes can be obtained in a number of ways, of which the most important by far are the dehydrochlorination of α-chloro-aldoximes or -ketoximes, and the addition of nitrosyl chloride to alkenes.[1–3] They are, in general, unstable, but can be detected spectroscopically or chemically trapped in solution. They have been isolated only in a few cases, *e.g.* when substituted with bulky alkyl or aryl groups.[4,5] In the absence of trapping agents they usually undergo fragmentation through intramolecular condensation.[1,2] They are a synthetically useful species either as a Michael acceptor,[1,2] or as one component in cycloaddition with an unsaturated substrate.[1,2,6]

[2 + 2] Cycloadditions of nitrosoalkenes with alkenes are rare and are usually observed only if both components are highly halogenated or if the alkene is a ketene.[7] [4 + 2] Cycloadditions are by far the most important, especially with dienes. The possible thermally allowed reactions creating (paths **A**–**D**)[8] and interconverting (paths **E**, **F**) the dihydro-oxazines and cyclohexenes derived from nitrosoethylene and butadiene are shown in Scheme 1. A more complex set of regio- and



Scheme 1. [a] [3,3]-Sigmatropic rearrangement.

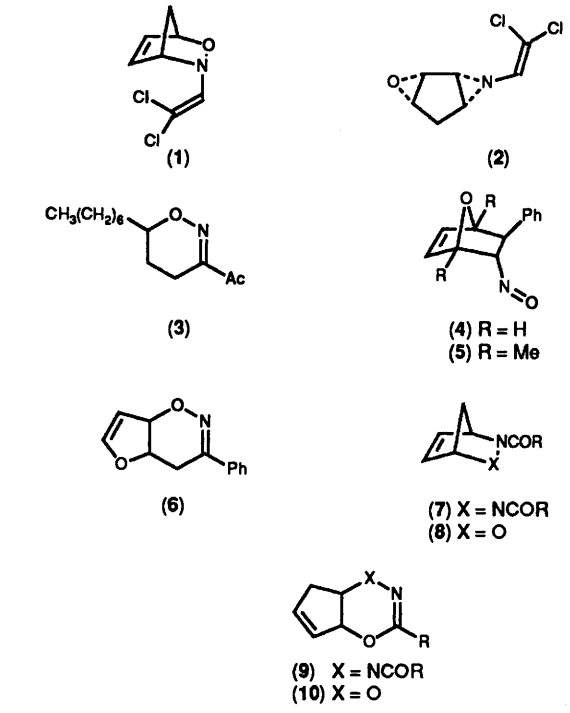
stereo-isomers arises if either the nitrosoalkene or the diene is substituted.

Path **A** has been clearly established in the formation of the unstable oxazine (**1**), which isomerizes to (**2**).[9] Path **D** must be followed to give the oxazines from simple alkenes, *e.g.* (**3**) from oct-1-ene;[10] it is likely also followed for the oxazines from a variety of cyclic dienes and electron rich heterocycles, including furans, pyrroles, and indoles,[2,8,10–14] though path **B** followed by a [3,3]sigmatropic rearrangement (path **F**) cannot be ruled out for some of these. There is no unequivocal evidence for the occurrence of path **C** in any reaction.

In the first reported synthesis of the dihydro-oxazines from furans or cyclopentadiene with nitrosoalkenes the pathway sequence **B**, **F** was suggested as plausible, for example from furan and nitrosostyrene to (**4**) to (**6**),[15] though it was later discounted on the basis of more extensive studies.[8,2] It drew our attention at the time because of our own studies on the reaction of cyclopentadiene with azodicarbonyl[16] and nitrosocarbonyl compounds.[17] In these the hetero system functioned as the dienophile to give the adducts (**7**) and (**8**) which could then be thermally isomerized to (**9**) and (**10**).

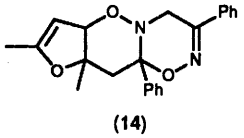
We investigated the reaction of nitrosostyrene with 2,5-dimethylfuran (Scheme 2) in the hope of detecting the adduct (**5**), and indeed found, as well as the oxazine (**11**), a second product in a low yield. This was not (**5**), but a bis-adduct derived from dimethylfuran and 2 equiv. of nitroso-styrene, the nitrone (**12**). Thus nitrosostyrene reacts successively with double bonds in a 4 + 2 and a 3 + 2 sense. This novel reaction of a nitrosoalkene has been described briefly in an earlier communication,[18] and some further examples of it have been uncovered since.[12,19] We wish to discuss the reaction in more detail, to outline some of its limitations, and to report that in some cases it competes with the expected Diels–Alder reaction in which the new ring formed in the tricyclic product is a dihydro-1,2,5-oxadiazine.

Treatment of dimethylfuran with 2 equiv. of nitrosostyrene or of the oxazine (**11**) with 1 equiv. gave the nitrone (**12**) (Scheme 2) which could be precipitated from the crude product mixture by addition of cold ether (10%, 35% isolated yield in each case).[18] Even with an excess of dimethylfuran (**12**) was a minor product, a 2:1 reaction between the furan and the nitroso compound giving 12% of (**12**) in the product mixture (high resolution NMR spectroscopy). The optimum practical



Scheme 2.

yield (*ca.* 50%) was obtained by addition of 2 equiv. of chloroacetophenone oxime in portions over 2 days to a solution of (**11**) in benzene in the presence of an excess of Na_2CO_3. The balance was the oxazine. A control reaction showed that reversal of (**12**) to (**11**) did not occur under the reaction conditions. We have no evidence that any of the expected bis-adduct (**14**) was formed.



(14)

A key spectroscopic feature characterizing (**12**) and the other nitrones reported here is the predictable downfield shifts

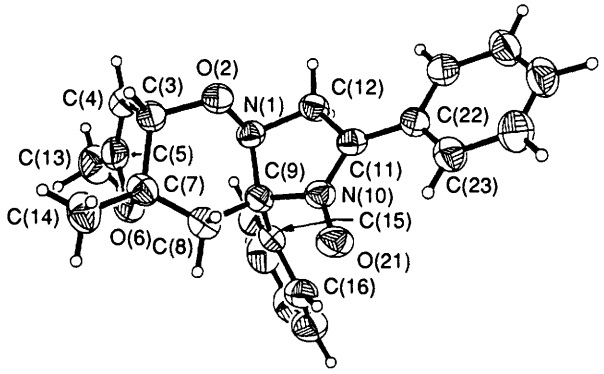


Figure 1. Molecular structure of compound (**12**).

Table 1. Crystal data.

	(12)	(23)
Formula	$C_{22}H_{22}N_2O_3$	$C_{17}H_{18}N_2O_3$
Molecular weight	362.432	298.345
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
Cell constants:		
a(Å)	12.021(2)	12.916(3)
b (Å)	12.459(2)	5.907(1)
c(Å)	13.015(2)	20.060(4)
β (°)	104.79(1)	95.07(2)
V (Å^3)	1 884.7(5)	1 524.5(5)
Z	4	4
ρ_c g cm^{-3}	1.277	1.300
F(000)	768	632
T K	294 ± 1	294 ± 1
μ(Mo-K_α) cm^{-1}	0.926	0.974
Crystal size (mm)	0.28 × 0.32 × 0.33	0.27 × 0.28 × 0.35
Scan type	θ–2θ	θ–2θ
2θ Range (°)	3.2–48.0	3.2–45.0
Scan width (° below $K\alpha_1$ to ° above $K\alpha_2$)	±0.8	±0.85
Scan speed (° min^{-1})	3.91–29.30	2.02–29.30
Standard reflections	300; 130	3 0$\bar{1}$0; 506
Variation of standards	±2%	±2%
Unique measured data	2 976	2 012
Observed data [$I \geqslant 3\sigma(I)$]	1 512	1 323
Number of variables	333	272
$R(= \Sigma\|\|F_o\| - \|F_c\|\|/\Sigma\|F_o\|)$	0.036	0.028
$R_w\{= [\Sigma w(\|F_o\| - \|F_c\|)^2/\Sigma w(F_o\|)^2]^{\frac{1}{2}}\}$	0.038	0.029
$w^{-1} = A - B\|F_o\| + C\|F_o\|^2$		
A	1.23	1.44
B	0.0162	0.0196
C	0.000 32	0.000 53
Residual electron density (e Å^{-3})	0.14	0.10

observed for the methylene protons (s, 4.48 in $CDCl_3$; q, 4.14, 4.29δ, J 17.5 Hz in C_6D_6) and the two *ortho* phenyl protons of its nitrone ring compared with the corresponding nitrosostyrene derived protons in (**11**); others are the absence both of the strong IR band at 1 170–1 280 cm^{-1} typical of the N–O group,[20] and of the intense $M - 16$ or $M - 17$ in the mass spectrum which are diagnostic of many heterocyclic *N*-oxides.[21] The presence of the nitrone ring, however, is confirmed by the X-ray crystallographic determination (Figure 1).

The end rings are almost planar* and are each *cis* fused to the boat-shaped oxazine ring in the stereochemically favoured

* Maximum deviation from planarity: A ring, ±0.07 Å; C ring, ±0.15 Å.

Table 2. Atomic co-ordinates (fractional, $\times 10^4$).

Atom	*x*	*y*	*z*
N(1)	6 913(2)	1 447(2)	832(2)
O(2)	6 136(2)	544(2)	856(2)
C(3)	6 766(3)	−436(3)	768(3)
C(4)	7 819(3)	−622(3)	1 640(3)
C(5)	8 737(3)	−505(3)	1 266(3)
O(6)	8 491(2)	−274(2)	200(2)
C(7)	7 249(3)	−403(3)	−219(3)
C(8)	6 795(3)	559(3)	−912(3)
C(9)	6 920(2)	1 610(3)	−283(2)
N(10)	5 852(2)	2 295(2)	−721(2)
C(11)	5 504(3)	2 755(3)	49(2)
C(12)	6 282(3)	2 392(3)	1 085(2)
C(13)	9 995(3)	−532(4)	1 791(4)
C(14)	7 068(3)	−1 450(3)	−842(3)
C(15)	7 982(3)	2 264(3)	−323(2)
C(16)	8 017(3)	2 835(3)	−1 231(3)
C(17)	8 985(3)	3 408(3)	−1 272(3)
C(18)	9 925(3)	3 424(3)	−425(4)
C(19)	9 909(3)	2 855(3)	482(4)
C(20)	8 935(3)	2 283(3)	538(3)
O(21)	5 420(2)	2 357(2)	−1 738(2)
C(22)	4 550(2)	3 495(3)	−61(2)
C(23)	3 778(3)	3 712(3)	−1 040(3)
C(24)	2 872(3)	4 434(3)	−1 094(3)
C(25)	2 736(3)	4 927(3)	−187(3)
C(26)	3 496(3)	4 720(3)	782(3)
C(27)	4 393(3)	4 001(3)	849(3)

Table 3. Selected bond lengths (Å) and bond angles (°) for compound (**12**).

N(1)–O(2)	1.467(3)	N(1)–C(9)	1.467(4)
N(1)–C(12)	1.483(4)	O(2)–C(3)	1.456(4)
C(3)–C(4)	1.487(5)	C(3)–C(7)	1.540(5)
C(4)–C(5)	1.322(5)	C(5)–O(6)	1.373(4)
C(5)–C(13)	1.493(5)	O(6)–C(7)	1.461(5)
C(7)–C(8)	1.515(5)	C(7)–C(14)	1.523(5)
C(8)–C(9)	1.531(4)	C(9)–N(10)	1.525(4)
C(9)–C(15)	1.527(4)	N(10)–C(11)	1.311(4)
N(10)–O(21)	1.295(3)	C(11)–C(12)	1.501(4)
C(11)–C(22)	1.450(4)		
O(2)–N(1)–C(9)	106.9(1)	O(2)–N(1)–C(12)	103.9(1)
C(9)–N(1)–C(12)	104.0(2)	N(1)–O(2)–C(3)	107.2(2)
O(2)–C(3)–C(4)	115.4(2)	O(2)–C(3)–C(7)	110.9(1)
C(4)–C(3)–C(7)	102.2(2)	C(3)–C(4)–C(5)	109.3(2)
C(4)–C(5)–O(6)	114.2(2)	C(4)–C(5)–C(13)	132.3(2)
O(6)–C(5)–C(13)	113.5(2)	C(5)–O(6)–C(7)	106.9(2)
C(3)–C(7)–O(6)	105.0(1)	C(3)–C(7)–C(8)	111.2(2)
C(3)–C(7)–C(14)	112.8(2)	O(6)–C(7)–C(8)	108.4(2)
O(6)–C(7)–C(14)	106.7(2)	C(8)–C(7)–C(14)	112.3(2)
C(7)–C(8)–C(9)	112.8(2)	N(1)–C(9)–C)8)	112.7(2)
N(1)–C(9)–N(10)	103.3(1)	N(1)–C(9)–C(15)	108.9(1)
C(8)–C(9)–N(10)	108.7(2)	C(8)–C(9)–C(15)	108.7(1)
N(10)–C(9)–C(15)	108.7(1)	C(9)–N(10)–C(11)	111.2(2)
C(9)–N(10)–O(21)	119.6(1)	C(11)–N(10)–O(21)	129.2(2)
N(10)–C(11)–C(12)	107.9(2)	N(10)–C(11)–C(22)	126.9(2)
C(12)–C(11)–C(22)	125.1(1)	N(1)–C(12)–C(11)	106.0(1)

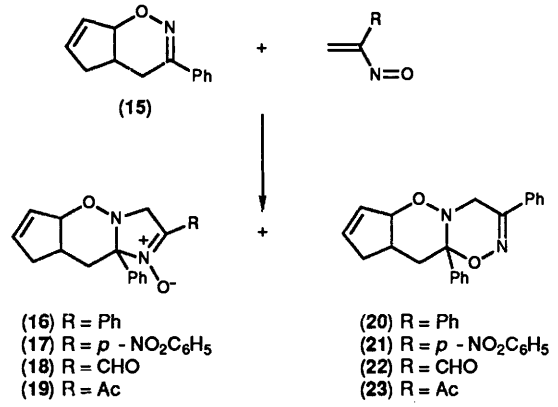
anti arrangement. The considerable diastereotopic shift between the methylene protons of the oxazine ring of (**12**) (2.77, 3.29δ, Δδ 0.52 ppm in C_6D_6), compared with that in the nitrone methylene group, is easily reconciled with the X-ray structure. Crystal data for (**12**) [and for compound (**23**) described later] are given in Table 1 and atomic co-ordinates of (**12**) in Table 2. Bond lengths and angles (Table 3) are unexceptional. The exocyclic N–O bond is 1.295(3) Å, typical of other *N*-oxides which range from 1.20 to 1.32 Å.[22]

The furo-oxazine (**6**) did not react with nitrosostyrene, but *p*-nitronitrosostyrene with (**11**) gave the nitrone (**13**), in a better yield (57%) than obtained for (**12**). Yields, spectroscopic data and elemental analyses of these and all other nitrones reported here are given in Table 4.

The cyclopent-oxazine (**15**) also gave a low yield (24%) of a nitrone (**16**) with nitrosostyrene. Its structure followed from its spectra, in particular the lowfield methylene absorption (very small diastereotopic shift, 4.50, 4.56δ) in the nitrone ring.

A nitrone (**17**) (57%) was also obtained from (**15**) with *p*-nitronitrosostyrene (Scheme 2), but in this reaction a second isomer was obtained (14%), these being separable by column chromatography. It showed no NH or OH in its IR spectrum, and its NMR spectrum still contained two vinylic protons, pointing clearly to the occurrence of a cycloaddition at the oxazine ring of (**15**). The major difference between this isomer and (**17**) was in the ^{1}H NMR absorptions of the methylene group in the newly formed ring which were shifted upfield approximately 1 ppm from the corresponding ones in the nitrone, and were well separated into a well defined AB quartet (*J* 18 Hz). Minor differences included a slight downfield shift of the vinyl protons, an upfield shift of the tertiary allylic proton, and a smaller downfield shift of the *ortho* protons, relative to the *meta* and *para*, of the phenyl group. Only a 1,2,5-oxadiazine ring, fused as in (**21**), can explain the observed spectra. The opposite mode of fusion, which would give a 1,2,6-oxadiazine, can be discounted since it is not in keeping with the polarity of the reacting fragments and would require the unlikely formation of a N to O bond.

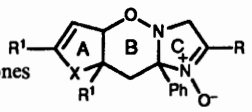
Since this 4 + 2 cycloaddition was observed with *p*-nitronitrosostyrene but not with nitrosostyrene itself [compound (**20**) was not detected], the reaction of (**15**) with nitrosoalkenes having even more strongly electron-withdrawing groups was examined (Scheme 3). α-Nitrosoacrolein and α-nitrosovinyl



Scheme 3.

methylketone are transient species, obtained by dehydrochlorination of β-chloro-α-hydroxyiminopropionaldehyde and β-chloro-α-hydroxyiminoethyl methyl ketone, and have been used in the synthesis of α-amino acid esters,[13] γ-hydroxy nitriles,[23] and oxazines.[10,19,29] They reacted with (**15**) to give the nitrones (**17**) and (**18**), but not (**19**) (Table 4) and oxadiazines (**21**)–(**23**) whose relative proportions are given in Table 5 and indeed show a growing bias towards oxadiazine formation as the nitrosoalkene substituent becomes more electronegative.

The compounds of Table 5 are formed in competition and are not in equilibrium. Both (**17**) and (**21**) were separately shown to be stable to the reaction conditions, though rearrangements of oxazines to nitrones[24,25] and of nitrones to oxazines[26] are known.

Table 4. Yields and physical data for tricyclic nitrones  (**12**) and (**13**) (R^1 = Me, X = O) and (**16**)–(**18**) (R^1 = H, X = CH_2).

Compd	R	Yield (%)[a]	M.p. (% C) (solvent)	$\nu_{C=C}$ cm^{-1} (Nujol)	$d^1H(CDCl_3)$ Ring A	Ring B
(**12**)	Ph	35	168–169 (iso-octane)	1 655[b]	1.33, s, Me; 1.88, d, Me (*J* 1.1); 4.55, m, tert. H (*J* 1.1, 1.1); 4.82, vinyl H (*J* 1.1)	2.77, 3.00, ABq, CH_2 (*J* 14.8)
(**13**)	*p*-$NO_2C_6H_4$	57	172–173 (EtOH)	1 673	1.32, s, Me; 1.87, d, Me; 4.54, m, tert. H; 4.84, m, vinyl H	2.79, 2.99, ABq, CH_2 (*J* 13.6)
(**16**)	Ph	12	177–178.5 ($EtOH/CHCl_3$)	*c*	2.38–2.79, m, $2CH_2$ and $CH(CH_2)_2$; 5.38, m, CHO; 5.58, m, 5.99, m, 2 vinyl H	
(**17**)	*p*-$NO_2C_6H_4$	57	151 (EtOH)	*c*	2.0–2.8, m, $2CH_2$ and $CH(CH_2)_2$; 5.36, m, CHO; 5.57, m, 5.98, m, 2 vinyl H	
(**18**)	CHO	12	Oil		2.1–2.6, m, $2CH_2$ and $CH(CH_2)_2$; 4.96, m, CHO; 5.61, m, 6.00, m, 2 vinyl H	

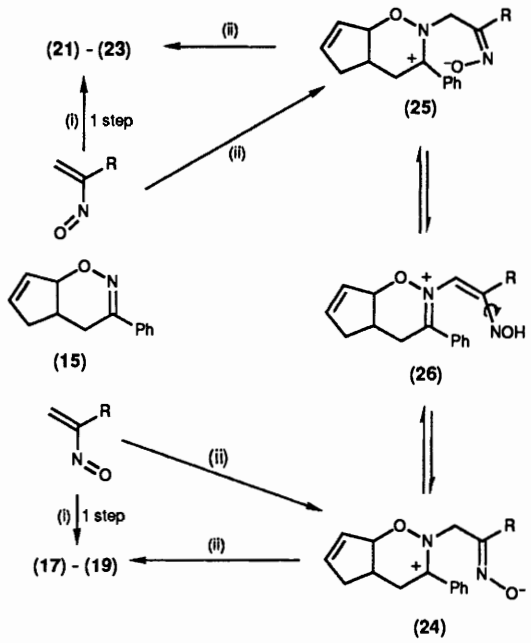
Compd	$\delta^1H(CDCl_3)$ Ring C	Phenyl and R	Calc./Required	C	H	N[d]
(**12**)	4.48, s, CH_2; 4.14, 4.29, ABq, [*J* 17.5 (C_6D_6)]	7.2–7.5, m, 8 Ph–H; 7.83, m, 1 Ph–H; 8.22, m, 1 Ph–H	$C_{22}H_{22}N_3O_3$	72.9 73.2	6.1 6.1	7.7 7.6
(**13**)	4.54, s, CH_2	7.2–8.5, m, 9 H, Ph + $NO_2C_6H_4$	$C_{22}H_{21}N_3O_5$	64.9 64.7	5.2 5.2	10.3 10.4
(**16**)	4.50, 4.56, CH_2, ABq (*J* 17.7)	7.2–8.3, m, 10 Ph-H	$C_{21}H_{20}N_2O_2$	75.9 75.6	6.1 6.0	8.4 8.2
(**17**)	4.57, s, CH_2	7.3–7.5, m, 3 (*m* + *p*) Ph–H; 7.7–8.0, m, 2 *o* Ph–H; 8.19, m, 8.33, m, $NO_2C_6H_4$	$C_{21}H_{19}N_3O_4$	66.8 66.9	5.1 5.2	11.1 11.3
(**18**)	4.30, s, CH_2	7.3–7.9, m, 5 Ph–H; 9.99, s, CH=O				

[a] As isolated by column chromatography with CH_2Cl_2 on silica gel, except for (**13**) for which alumina was used. [b] CCl_4. [c] No significant peak above 1 600 cm^{-1}. [d] All compounds gave the parent peak in the mass spectrum.

Table 5. Yield ratios of tricyclic nitrones (**16**)–(**19**) to tricyclic oxadiazines (**20**)–(**23**).

R	Compounds	Ratio
Ph	(**16**):(**20**)	>10:1[a]
p-$NO_2C_6H_4$	(**17**):(**21**)	4.1:1[b]
CHO	(**18**):(**22**)	0.38:1[c]
Ac	(**19**):(**23**)	<0.1:1[a]

[a] Minor isomer not detected. [b] Separated by chromatography. [c] Estimated from high resolution ^1H NMR spectrum of total reaction products.



Scheme 4.

Though addition of nitrosoalkenes to C=C has been judged to be one step,[12] it is less likely to be so [Scheme 4, pathway (i)] in the case of addition to the more polar C=N in (**15**) [or (**11**)]. α-Nitrososostyrene has been shown to react preferentially in the *transoid* form with morpholine,[27] and may also do so with the more weakly nucleophilic nitrogen in (**15**) to give (**24**) [pathway (ii)]. As R gets more electron withdrawing, however (Ph < *p*-$NO_2C_6H_4$ < CO) the *cisoid* forms may become preferred, as they avoid the repulsive interactions between the two strong dipoles of the system, thus explaining the increasing proportion of six- over five-membered rings. Even if (**24**) is preferred a crossover mechanism between it and (**25**) is possible, involving reversible protonation of these at oxygen and deprotonation at the β-carbon to give (**26**). The formation of (**26**) is particularly facilitated by conjugation when R contains the CO group. The considerable increase in the relative yield of (**23**) over (**22**) may be simply steric.

There was no evidence for the nitrone (**19**) as a co-product with (**23**) when the crude reaction mixture from the α-nitrosovinyl methyl ketone reaction was examined by high resolution ^1H NMR spectroscopy. The shifts for the nitrone could be predicted with some confidence by analogy with those of other nitrones, especially (**18**). A detection limit of 1% was conservatively estimated.

The spectrum of purified (**23**) (prisms from hexane or needles from methanol, m.p. 109.5–110 °C) did, however, show the

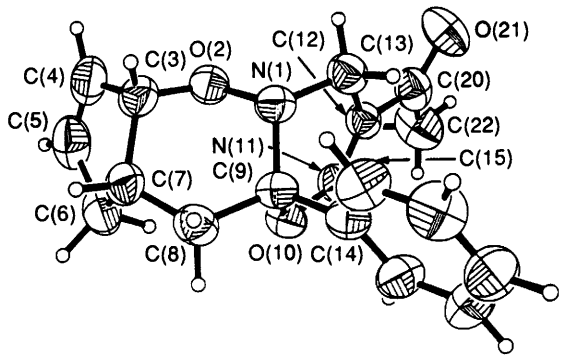


Figure 2. Molecular structure of compound (**23**).

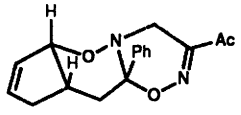


Figure 3.

Table 6. Atomic co-ordinates (fractional, $\times 10^4$) for compound (**23**).

Atom	*x*	*y*	*z*
N(1)	2 708(1)	1 314(3)	729(1)
O(2)	1 660(1)	1 513(3)	340(1)
C(3)	1 718(1)	1 507(4)	−316(1)
C(4)	630(2)	1 908(5)	−601(1)
C(5)	488(2)	4 058(6)	−748(1)
C(6)	1 458(2)	5 444(5)	−609(1)
C(7)	2 298(2)	3 606(4)	−526(1)
C(8)	3 281(2)	4 077(5)	−64(1)
C(9)	3 201(2)	3 506(4)	670(1)
O(10)	2 586(1)	5 344(2)	917(1)
N(11)	2 121(1)	4 990(3)	1 508(1)
C(12)	2 105(2)	2 969(4)	1 741(1)
C(13)	2 511(2)	894(4)	1 439(1)
C(14)	4 262(2)	3 434(4)	1 067(1)
C(15)	4 912(2)	1 604(5)	995(1)
C(16)	5 876(2)	1 498(5)	1 360(2)
C(17)	6 201(2)	3 221(6)	1 788(2)
C(18)	5 569(2)	5 044(5)	1 856(1)
C(19)	4 596(2)	5 159(5)	1 492(1)
C(20)	1 596(2)	2 736(4)	2 376(1)
O(21)	1 629(1)	901(3)	2 650(1)
C(22)	1 056(3)	4 717(6)	2 645(2)

Table 7. Selected bond lengths (Å) and bond angles (°) for compound (**23**).

N(1)–O(2)	1.458(2)	N(1)–C(9)	1.453(3)
N(1)–C(13)	1.469(3)	O(2)–C(3)	1.444(3)
C(3)–C(4)	1.489(3)	C(3)–C(7)	1.527(3)
C(4)–C(5)	1.313(5)	C(6)–C(6)	1.501(4)
C(6)–C(7)	1.535(4)	C(7)–C(8)	1.529(3)
C(8)–C(9)	1.524(3)	C(9)–O(10)	1.458(2)
C(9)–C(14)	1.524(3)	O(10)–N(11)	1.392(2)
N(11)–C(12)	1.283(3)	C(12)–C(13)	1.493(3)
C(12)–C(20)	1.489(3)	C(20)–O(21)	1.215(3)
C(20)–C(22)	1.488(4)		
O(2)–N(1)–C(9)	106.7(1)	O(2)–N(1)–C(13)	102.4(1)
C(9)–N(1)–C(13)	110.0(1)	N(1)–O(2)–C(3)	108.8(1)
O(2)–C(3)–C(4)	104.5(1)	O(2)–C(3)–C(7)	110.0(1)
C(4)–C(3)–C(7)	103.6(1)	C(3)–C(4)–C(5)	110.4(2)
C(4)–C(5)–C(6)	112.9(2)	C(5)–C(6)–C(7)	101.8(1)
C(3)–C(7)–C(6)	104.2(1)	C(3)–C(7)–C(8)	112.5(1)
N(1)–C(9)–C(8)	110.2(1)	N(1)–C(9)–O(10)	112.4(1)
N(1)–C(9)–C(14)	108.2(1)	C(8)–C(9)–O(10)	104.5(1)
C(8)–C(9)–C(14)	112.1(1)	O(10)–C(9)–C(14)	109.6(1)
C(9)–O(10)–N(11)	117.8(1)	O(10)–N(11)–C(12)	118.2(1)
N(11)–C(12)–C(13)	126.4(1)	N(11)–C(12)–C(20)	114.9(1)
C(13)–C(12)–C(20)	118.8(1)	N(1)–C(13)–C(12)	111.1(1)
C(12)–C(20)–O(21)	118.0(1)	C(12)–C(20)–C(22)	119.6(1)
O(21)–C(20)–C(22)	122.4(2)		

persistent presence of a small amount of an isomer in solution. Its chemical shifts were very similar to those of the major isomer, and quite different from those expected for (**19**). In particular the well spaced methylene AB quartet at 3.31 and 3.72, the 3° allylic multiplet at 5.00, and the vinylic multiplets at 5.91 and 6.04 [compare 3.35, 3.76, 4.94, 5.84, and 6.27 δ for (**23**), all in $CDCl_3$] implied that it was also a product of 5,6,6 fusion. The solution is clearly an equilibrium mixture of the two isomers since the proportions are (i) solvent dependent: 5:1 in $CDCl_3$, 6:1 in C_6D_6, 12:1 in CD_3COCD_3, >99:1 in C_2Cl_4 (minor isomer not detectable or else has shifts coincident with those of major), all at 24 °C, and (ii) temperature dependent (Boltzmann effect): 5.9:1 at 24 °C, 5.5:1 at 45 °C, 5.0:1 at 70 °C, in C_6D_6; no broadening of the lines was detectable at the latter temperature.

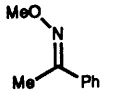
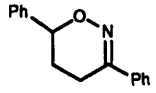
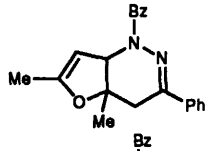
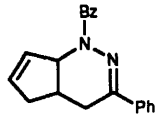
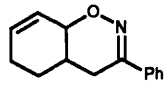
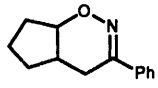
The most reasonable explanation for these observations is that the dioxazine is a mixture of conformational isomers with the conformation of Figure 2 (see ensuing discussion of X-ray analysis) being likely the major one. Models suggest that the only plausible dynamic process involved is the inversion of the chair form of Figure 2 into the boat form of Figure 3, derived by flipping 'down' of the CH_2 end. The other chair and boat forms, with the O atom 'up', are sterically extremely crowded. The variable temperature results above show that large barriers exist between these conformations of the central oxazine ring, predictably a lot larger than those found in monocyclic oxazines.[28]

The product distribution in these reactions is presumably unrelated to the configuration of the oxime precursors, by analogy with the results observed in the addition to 2-methoxypropene of nitrosostyrene generated from both *syn*- and *anti*-α-bromoacetophenone oximes.[12] The proportions of oxazine and nitrone were the same, indicating that the nitrosostyrene is long lived enough to give a conformational equilibrium independent of its origin. This conclusion is also consistent with the observation routinely of a transient blue–green colour in the stirred suspensions of sodium carbonate in the oxime solutions in the early stages of the reaction.

The structure of (**23**) and hence of (**21**) and (**22**), was confirmed by X-ray crystallography, which established its stereochemistry as the *cis-syn-cis* arrangement shown in the enantiomer in Figure 2. This contrasts with the *anti* fusion found in the dimethylfuran derived nitrone (**12**) (Figure 1). Whether the cyclopentadiene derived nitrones (**17**)–(**19**) are also *anti* fused, or *syn* as in (**23**), can be established only by a further X-ray analysis on one of them. The central ring of (**23**) is chair-like [contrast the boat form in (**12**)], the cyclopentene ring is very slightly twisted, and the oxadiazine ring is very nearly coplanar over five atoms, the ring junction N being well out of plane.* Atomic co-ordinates of (**23**) are given in Table 6 and bond lengths and angles of interest in Table 7.

* If all the other 5 atoms are arranged as close as possible in one plane the deviations from that plane of the six atoms (Å): C(9), 0.082; O(10), −0.097; N(11), 0.026; C(12), 0.057; C(13), −0.068; [(N)1, −0.570, not included in the plane calculation].

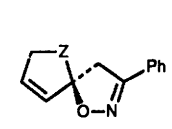
Table 8. Model imino compounds which failed to react with α-nitrososostyrene.

Compound		Ref.	Implied requirements for successful reaction with α-nitrososostyrene
(27)		32	Cyclic oxime (1,2-oxazine)
(28)		12	Fused bicyclic system
(29)		This work	Oxazine oxygen
(30)		33	Oxazine oxygen
(31)		14	*b*
(32)		*a*	Alkene function with allylic oxygen

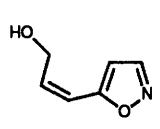
[a] By hydrogenation of (15).[8] [b] Ring junction stereochemistry unknown, but likely *cis*, and hence a rather flexible system. The more rigid cyclopenteno system may be necessary.

Efforts were made to establish the scope of these cycloadditions to the C=N in systems related to the dimethylfuran and cyclopentadiene adducts (**11**) and (**15**). The model compounds chosen, (**27**)–(**32**), listed in Table 8, are all known or were readily synthesized: compound (**29**) was formed quantitatively from 2,5-dimethylfuran and the benzoylhydrazone of α-chloroacetophenone with sodium carbonate, and (**32**) from (**15**) by hydrogenation. None of these compounds reacted with nitrososostyrene.* The structural limitations implied by each of these failures is indicated in Table 8. Taken together they suggest that the reaction is most favourable with the 1,2-oxazine ring system, which must be fused to a 5-membered ring having a double bond allylic to the oxazine oxygen. Notable also, however, is the fact that the furan adduct (**6**), unlike (**11**), did not react, another measure of the exclusiveness of these reactions.

A number of thermal and acid-catalysed reactions of the adducts of cyclopentadiene, furan and enol ethers with nitrosoalkenes have been described by Gilchrist and co-workers.[24,29] Most of these reactions depended on the presence of an angular proton α to the dihydrofuran oxygen. Thus (**15**) gave 3-phenylpyridine at 250 °C, and the spiro compound (**33**) on heating with acid.[29] The furan adduct (**6**) gave the isoxazolyl allylic alcohol (**35**) with acid, the α-(2-furyl)acetophenone and the spiro compound (**34**) being presumed to be intermediates; the analogous azoalkene adduct (**36**) with acid gave the analogous pyrazole (**37**).[29] Recently the furo-oxazine (**11**) has been shown to undergo isomerisation with the base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to the acetonyldihydro-oxazine (**38**) which underwent thermal dehydration in low yield to the pyridine (**39**) (pyridine formation was much more efficient in furo-oxazines having electron withdrawing groups in place of Ph).[30] The furopyridazine (**40**) with DBU gave the acetonyldihydropyridazine, related to (**38**), which did not aromatise.

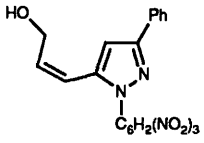


(**33**) Z = CH_2
(**34**) Z = O

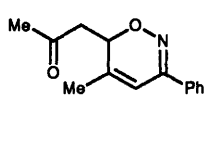


(**35**)

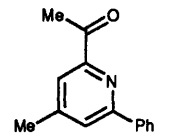
(**36**)



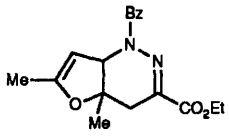
(**37**)



(**38**)



(**39**)



(**40**)

We have also examined isomerisations of furo-oxazines and furopyridazines, but under acidic conditions, specifically the compound (**11**) and (**29**).

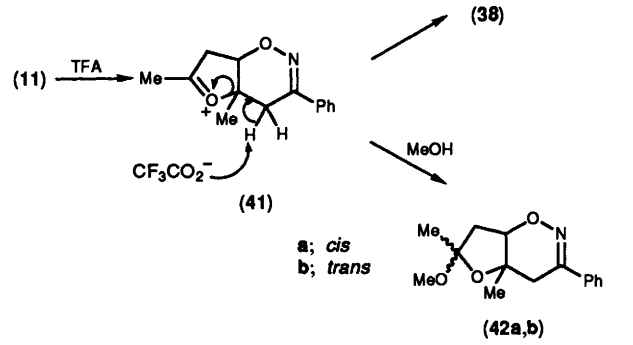
The oxazine (**11**) isomerised completely in 1 h in refluxing bromobenzene (154 °C) but was stable in refluxing tetrachloroethylene (TCE, 120 °C). Traces of acid in the PhBr might have been responsible since addition of trifluoroacetic acid (TFA, 1% v/v, 0.1 mol) caused complete isomerisation in 2 h in refluxing TCE. The product was the acetonyloxazine (**38**), extractable in high yield as a pale yellow oil with hot hexane (semicarbazone, m.p. 181–182 °C). The oxonium ion (**41**) (Scheme 5) is a reasonable intermediate.

Enol ether reactivity in (**11**) was also evident in the formation of the methyl ketals (**42a**) and (**42b**) by reaction with MeOH and catalytic TFA (Scheme 5). The diastereomeric ratio was about 2.7:1, the major isomer being separable by crystallization from MeOH. Complete ^{1}H NMR assignments were thus obtained for both isomers, though it was not possible to distinguish the *cis* from the *trans*.

The azoalkene adduct (**29**) displayed similar reactions to those of (**11**). Acidic MeOH gave the ketals (**43**) in a diastereoisomeric ratio of about 4:3. Refluxed in bromobenzene for 12 h, or more rapidly (½ h) in the presence of 0.2 equiv. TFA, (**29**) isomerized to the ketone (**44**) (semicarbazone m.p. 178–181 °C), whose ^{1}H NMR spectrum resembled that of (**38**) in all the obvious ways.

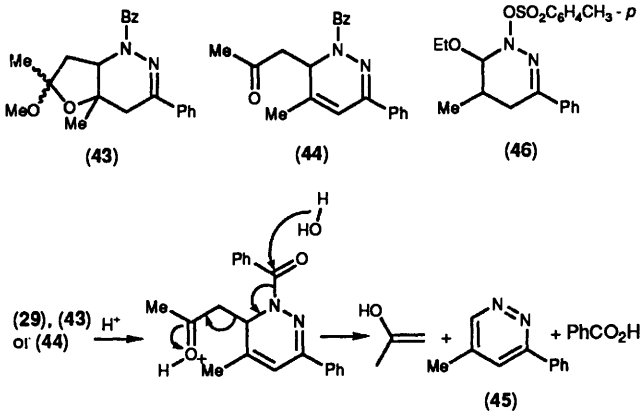
If 1 equiv. of TFA was present the ketone, its precursor (**29**), or the ketals (**43**), underwent rapid aromatization in refluxing bromobenzene to 5-methyl-3-phenylpyridazine, (**45**), in a good

* Starting material was largely recovered. Trace amounts of adducts might have been obscured in the NMR spectrum by the self-condensation products of nitrososostyrene. It should also be pointed out that these model compounds were not screened for reactivity with nitrosoalkenes other than nitrososostyrene.



Scheme 5.

yield. Acetone was detected and the other product was presumed to be benzoic acid (trace H_2O) (Scheme 6). The



Scheme 6.

pyridazine was also the major product when the adduct (**29**) was heated with sodium ethoxide in ethanol, methyl benzoate (and presumably acetone) being the co-product. This reaction is analogous to the ethoxide-catalysed formation of pyridazines from the adducts of enol ethers with tosylazoalkenes [but not from the related adducts with acylazoalkenes, in contrast with the reaction of (**29**)]; thus (**46**) gave (**45**).[31] Interestingly the regiochemistry of the addition of azoalkenes to enol ethers, as in (**46**), is opposite to that observed in the present work with the enol ether function in dimethylfuran.

Experimental

The following spectrometers were used: for IR, a Beckman IR 10 using mulls or $CHCl_3$ solutions; for NMR, Varian T60, Brucker WP 80, AC 200, or AM 250 instruments; for mass spectra, a Varian MATCH7 or VG-7070F. Column chromatography was in general carried out on silica gel, 70–270 mesh (Merck). M.p.s are uncorrected.

5,7-*Dimethyl*-9,11-*diphenyl*-2,6-*dioxa*-1,10-*diazatricyclo*-[7.3.0.$0^{3,7}$]*dodeca*-4,10-*dien*-10-*one* (**12**).—The synthesis of this compound was examined in some detail.

(a) *From* 2,5-*dimethylfuran*. A solution of the furan (107 μl, 1.0 mmol) and chloroacetophenone oxime (0.34 g, 2 mmol) in methylene dichloride (15 ml) was stirred with sodium carbonate (0.53 g, 5 mmol) for 1 day. Filtration and evaporation gave a residue whose ^1H NMR spectrum showed the presence of the mono- and bis-adducts, (**11**) and (**12**), in a ratio of *ca.* 3:1 (NMR analysis). A similar reaction with 3 mmol of the oxime to one of dimethylfuran gave (**11**) and (**12**) in a ratio of *ca.* 2:1, as well as the (unidentified) product(s) of self condensation recognisable in the spectrum (control reaction).

Control reaction with an excess of dimethylfuran. The furan (125 μl, 1.2 mmol and the oxime (100 mg, 0.59 mmol) were stirred in methylene dichloride (5 ml) with Na_2CO_3 (2 g) for 3 days. NMR analysis of the residue after work-up showed the presence of 12% of (**12**) *even though the furan had been used in excess*.

(*b*) *From the mono-adduct* (**11**). From a variety of solvents (CH_2Cl_2, benzene and dioxane), reaction times, and reagent ratios the optimum conditions were determined: addition of 2 to 3 equiv. of oxime portionwise over 3 days to a solution of 1 equiv. of dimethylfuran in dry benzene containing 7 equiv. of Na_2CO_3 led to the formation of (**11**) and (**12**) in a ratio of *ca.* 1:1.

Work-up consisted of filtering the suspension and chromatographing the residue on silica gel from methylene dichloride which gave the mono- and bis-adducts pure in that order. Alternatively, addition of cold ether to the reaction residue gave (**12**) as a colourless insoluble solid, which was recrystallized from iso-octane (see Table 4).

Stability of (**12**) *to conditions of synthesis*. In a control reaction (**12**) (10 mg) was stirred for 30 h in methylene dichloride (5 ml) containing Na_2CO_3 (200 mg). The suspension was filtered, the filtrate was evaporated, and the residue extracted with benzene. Removal of the benzene gave crystalline (**12**) whose 200 MHz ^1H NMR spectrum showed no trace of the retro product (**11**).

5,7-*Dimethyl*-9-*phenyl*-11-p-*nitrophenyl*-2,6-*dioxa*-1,10-*diazatricyclo*-[7.3.0.$0^{3,7}$]*dodeca*-4,10-*dien*-10-*one* (**13**).—The mono-adduct (**11**) (1.0 g, 4.4 mmol) and the α-chloroacetophenone oxime (0.75 g, 4.4 mmol) were stirred for 1 day in methylene dichloride (25 ml) containing sodium carbonate (2.3 g, 22 mmol). The suspension was filtered and the residual oil was chromatographed on Al_2O_3 using methylene dichloride to give the crystalline nitrone (**13**) (0.91 g, 57%). It was recrystallised from EtOH (see Table 4).

Competitive Formation of the Tricyclic Nitrones (**16**)–(**19**) *and the Tricyclic Oxadiazines* (**20**)–(**23**) *from the Tetrahydrocyclopentoxazine* (**15**).—The conditions described above for the synthesis of (**13**) were used, starting typically with (**15**) (1 g) and the appropriate oxime (1 equiv.): α-chloroacetophenone oxime, α-bromo-*p*-nitroacetophenone oxime, β-chloro-α- hydroxyiminopropionaldehyde, and β-chloro-α-hydroxyiminoethyl methyl ketone. The two latter were made from the unsaturated aldehyde and ketone using nitrosyl chloride.[10] The residue after filtration and evaporation was purified by column chromatography on silica gel using methylene dichloride in general.

The oxadiazine (**20**) was not observed in the reaction with chloroacetophenone oxime. With the other oximes the nitrones (**17**) and (**18**) and the dioxazines (**21**)–(**23**) were formed, but there was no evidence for the formation of the nitrone (**19**). The properties of the nitrones are described in Table 4.

12-p-*Nitrophenyl*-9-*phenyl*-2,10-*dioxa*-1,11-*diazatricyclo*-[7.3.0.$0^{3,7}$]*trideca*-4,11-*diene* (**21**).—From α-bromo-*p*-nitro acetophenone oxime [as a co-product with (**13**)]; 14%, from EtOH, m.p. 154–155.5 °C: ν_{max}(Nujol) clear above 1 600 cm^{-1}, other than CH; δ_H(80 MHz; $CDCl_3$) 2.0–3.0 (m, CH_2CHCH_2), 3.67, 3.89 (ABq, NCH_2, *J* 18.9), 5.00 (m, CHO), 5.88 (m, vinyl H), 6.30 (m, vinyl H), 7.2–7.7 (m, 5 H, Ph), 7.64 (m, 2 H, $NO_2C_6H_4$), and 8.12 (m, 2 H, $NO_2C_6H_4$); *m*/*z* 377 (M^+) 360

(M − 17) (Found: C, 66.7; H, 5.3; N, 11.0. $C_{21}H_{19}N_3O_4$ requires C, 66.8; H, 5.1; N, 11.1%).

For the nitrone (**17**) (57%) see Table 4.

Stability of (**17**) *and* (**21**) *to Conditions of Synthesis.*—The conditions were those employed in the similar control reaction on (**12**) above. There was no interconversion of (**17**) and (**21**), each being recovered completely.

12-*Formyl*-9-*phenyl*-2,10-*dioxa*-1,11-*diazatricyclo*-[7.4.0.0^{3,7}]-*trideca*-4,11-*diene* (**22**).—From α-chloro-α-hydroxyiminopropionaldehyde;[10] 32%, non-crystalline: δ(80 MHz; $CDCl_3$) 2.0–3.0 (m, CH_2CHCH_2), 3.33, 3.71 (ABq, NCH_2, J 18.4), 4.95 (m, CHO), 5.84 (m, vinyl H), 6.26 (m, vinyl H), 7.2–7.6 (m, 5 H, Ph), and 9.38 (s, CH=O); m/z 284 (M^+), 255 (M − 29), and 239 (M − 45).

For nitrone (**18**) (12%) see Table 4.

12-*Acetyl*-9-*phenyl*-2,10-*dioxa*-1,11-*diazatricyclo*[7.4.0.0^{3,7}]-*trideca*-4,11-*diene* (**23**).—The residue from the reaction of equimolar amounts of (**15**) (1 g) and β-chloro-α-hydroxyiminoethyl methyl ketone[10] with Na_2CO_3 in methylene dichloride for 1 day was analysed by 200 MHz ^{1}H NMR spectroscopy. It consisted of a *ca.* 1:1 mixture of starting material (**15**) and product (**23**), with small amounts of the self condensation product(s) of the reaction of the chloro oxime with Na_2CO_3. [This was established by a control reaction without (**15**) present. The product(s) were not identified.] The nitrone (**19**) was absent (detection limit 1%). Its shifts can be confidently predicted from those of the formyl nitrone (**18**), which are distinctively different from those of its isomer (**22**).

Chromatography on silica gel with hexane–methylene dichloride (1:1) gave the product (**23**); the unchanged starting material could be recovered by elution with methylene dichloride. Crystallisation from methanol or by slow evaporation from hexane gave large prisms, m.p. 109.5–110 °C with discolouration: ν_{max}(Nujol) 1 682 (C=O) and 1 591 cm^{-1} (C=N); δ_H(250 MHz; $CDCl_3$); major conformation: 1.90–2.85 (m, 6-, 7-, 8-H, 5 H), 2.33 (s, $COCH_3$), 3.35, 3.76 (ABq, 2 × 13-H, J 24.5 Hz), 4.94 (m, 3-H), 5.84 (m, 5-H), 6.27 (m, 4-H), and 7.20–7.80 (m, 5 H, Ph); minor conformation includes: 2.37 (s, $COCH_3$), 3.31, 3.72 (ABq, 2 × 13-H, J 24.2 Hz), 5.02 (m, 3-H), 5.92 (m, 5-H), and 6.05 (m, 4-H) (Found: C, 68.2; H, 6.4; N, 9.4. $C_{17}H_{18}N_2O_3$ requires C, 68.4; H, 6.1; N, 9.4%).

Attempted Reaction of α-*Nitrosostyrene with Model Compounds* (**27**)–(**32**).—The latter were made by published methods in the case of (*E*)-*O*-methylacetophenone oxime (**27**),[32] the styrene adduct (**28**),[12] the cyclopentadiene adduct (**30**),[33] and the cyclohexadiene adduct (**31**);[14] hydrogenation of (**11**)[8] with Pd/C gave (**32**). The preparation and some reactions of (**29**) are described below.

Each of the adducts (**27**)–(**32**) (1 g) and α-chloroacetophenone oxime (1 equiv.) were stirred for 16 h in methylene dichloride (50 ml) containing Na_2CO_3 (5 equiv.) Filtration and work up in each case gave a residue consisting mainly of the starting adduct and the self-condensation products from the oxime.

Thermal and Acid-catalysed Reactions of the Dimethylfuran Adducts (**11**) *and* (**29**).—(a) *Synthesis of* 6-*acetonyl*-5-*methyl*-3-*phenyl*-6H-1,2-*oxazine* (**38**). A sample of (**11**) (32 mg, 0.14 mmol) in tetrachloroethylene (0.5 ml) was heated in an NMR tube in refluxing tetrachloroethylene but its spectrum was unchanged after 2 h. The experiment was repeated with the inclusion of trifluoroacetic acid (TFA; 1.0 μl). Isomerisation was complete in 2 h.

The same result was obtained when (**11**) was refluxed in bromobenzene for 1 h on the same scale, using unpurified commercial solvent which may have contained traces of acid.

In either case evaporation of the solvent gave a slightly discoloured residue (quantitative) which on extraction with hexane yielded the oxazine (**38**) (90%). Since its spectra show some differences from the literature values,[30] they are reported here in detail: ν_{max}(film) 1 700 cm^{-1} (C=O); δ_H(200 MHz, $CDCl_3$) 1.975, 1.978, 1.983, 1.986 (dd, 5-CH_3, both J with 4-H, 6-H *ca.* 1 Hz), 2.26 (s, $COCH_3$), 2.48 (dd, A of ABq, $COCH_2$, J_{AB} 16.0 Hz, $J_{A,6\text{-}H}$ 4.2 Hz), 3.05 (dd, B of ABq, $COCH_2$, J_{AB} 16.0 Hz, $J_{B,6\text{-}H}$ 8.5 Hz), 5.00 (dd, 6-H, J 4.2 Hz, J 8.5 Hz), 6.18 (d, 4-H, J *ca.* 1 Hz), 7.3–7.5 (m, m + p-Ph), and 7.6–7.8 (m, o-Ph). A sample of (**38**) obtained by reaction with DBU,[30] in admixture with material from the TFA route, gave the spectrum just described, in every detail.

The semicarbazone of (**38**) gave prisms from aqueous EtOH, m.p. 181–182 °C (lit.,[30] m.p. 185–186 °C).

(b) cis- *and* trans-6-*Methoxy*-4a,6-*dimethyl*-3-*phenyl*-4a,6,7,7a-*tetrahydro*-4H-*furo*[2,3-e]-1,2-*oxazine* (**42a,b**). A solution of the adduct (**11**) (35 mg, 0.15 mmol) in MeOH (3 ml) containing TFA (4 μl, 0.05 mmol) was kept at room temperature for 2.5 h, neutralised with sodium acetate and evaporated. The residue was extracted with chloroform and shown by NMR spectroscopy to be a mixture of (**42a**) and (**42b**) in a ratio of *ca.* 2.7:1 and at least 90% purity. Crystallisation from MeOH gave the major isomer pure: δ_H(200 MHz; $CDCl_3$) 1.39, 1.47 (s, 4a-CH_3, s, 6-CH_3, in either order), 2.24 (dd, A of AMX, 7-H, J_{AM} 5.0 Hz, J_{AX} 14.1 Hz), 2.57 (dd, M of AMX, 7-H, J_{MX} 7.8 Hz), 2.59 (d, A of ABq, 4-H, J 14.7 Hz), 2.81 (B of ABq, 4-H), 3.21 (s, OCH_3), 4.44 (dd, X of AMX, 7a-H), 7.39–7.47 (m, m + p-Ph), 7.67–7.74 (m, o-Ph); minor isomer, partial assignments: (200 MHz; $CDCl_3$) 1.27, 1.49 (s, 4a-CH_3, s, 6-CH_3, in either order), 3.26 (s, OCH_3), and 3.94 (dd, 7a-H).

(c) 1-*Benzoyl*-4a,6-*dimethyl*-3-*phenyl*,1,4,4a,7a-*tetrahydrofuro*[2,3-e]*pyridazine* (**29**). α-Chloroacetophenone benzoylhydrazone was prepared in almost quantitative yield by refluxing the chloro ketone (10 g, 59 mmol) and benzhydrazide (10 g, 74 mmol) in 30% aqueous acetic acid for 30 min. The crude product was recrystallised from aqueous EtOH to give a mixture of *E* and *Z* isomers. Recrystallisation from MeOH containing dissolved sodium carbonate or acetic acid gave one stereoisomer, m.p. 129 °C: ν_{max}(Nujol) 1 654 cm^{-1} (C=O); δ_H(250 MHz; $CDCl_3$) 4.58 (s, CH_2), 7.3–8.3 (m, 10 H, Ph), and 9.67 (s, NH) (Found: C, 66.3; H, 5.0; Cl, 13.2; N, 10.5. $C_{15}H_{13}ClN_2O$ requires C, 66.1; H, 4.8; Cl, 13.0; N, 10.3%).

The hydrazone (1.0 g, 3.7 mmol) and 2,5-dimethylfuran (0.79 ml, 7.4 mmol) were stirred with Na_2CO_3 (5 g) in methylene dichloride (25 ml) for 12 h. The suspension was filtered through Celite and the filtrate evaporated to give the *product* in quantitative yield. Recrystallised from ether–iso-octane it had m.p. 123.5–125 °C: ν_{max}(Nujol) 1 637 cm^{-1}; δ_H($CDCl_3$) 1.65 (s, 4a-CH_3), 1.68 (s, 6-CH_3), 2.40, 3.38 (AXq, 4-H_2, J 15.3 Hz), 4.94 (br s, 7a-H), 5.32 (br s, 7-H), and 7.3–7.8 (m, 10 H, Ph) (Found: C, 76.0; H, 6.2; N, 8.4. $C_{21}H_{20}N_2O_2$ requires C, 75.9; H, 6.1; N, 8.4%).

(d) cis- *and* trans-1-*Benzoyl*-6-*methoxy*-4a,6-*dimethyl*-3-*phenyl*-1,4,4a,6,7,7a-*hexahydrofuro*[2,3-e]*pyridazine* (**43**). A solution of the adduct (**29**) (100 mg, 0.30 mmol) in MeOH (10 ml) containing TFA (10 μl, 0.13 mmol) was kept at room temperature for 2 h, and then treated with an excess of sodium acetate and evaporated. The residue was extracted thoroughly with ether from which a product (102 mg, 94%) was obtained which crystallised. Its NMR spectrum showed it to be a 4:3 mixture of the stereoisomeric ketals. Crystallisation by slow evaporation from hexane containing a trace of ether gave crystals enriched in the major isomer (Found: C, 72.5; H, 6.5; N, 7.7. $C_{22}H_{24}N_2O_3$ requires C, 72.5; H, 6.6; N, 7.7%), and on one occasion a pure sample of it, m.p. 105–106 °C, δ_H(200 MHz;

$CDCl_3$) 1.394, 1.514 (s, 4a-CH_3, s, 6-CH_3, in either order), 1.96 (dd, A of AMX, 7-H, J_{AM} 13.3 Hz, J_{AX} 8.2 Hz), 2.64, 2.85 (q, J 16.3 Hz, 4-H_2), 2.93 (dd, M of AMX, J_{MX} 7.3 Hz, 7-H), 3.29 (s, OCH_3), 4.97 (t, X of AMX, 7a-H), 7.31–7.50 (m, m + p-Ph), 7.60–7.77 (m, o-Ph); minor isomer: 1.386, 1.514 (s, 4a-CH_3, s, 6-CH_3, in either order), 2.16 (dd, A of AMX, 7-H, J_{AM} 13.6 Hz, J_{AX} 8.2 Hz), 2.68, 3.21 (q, J 17.1 Hz, 4-H_2), 2.81 (M of AMX, J_{MX} 8.2 Hz, 7-H), 3.23 (s, OCH_3), and 4.70 (t, X of AMX, 7a-H); Ph region as for major isomer.

(e) 6-*Acetonyl*-1-*benzoyl*-5-*methyl*-3-*phenyl*-1,6-*dihydropyridazine* (**44**). The adduct (**29**) (32 mg, 0.10 mmol) was heated in bromobenzene (0.5 ml) in an NMR tube at the reflux temperature, and its rearrangement was followed by ^1H NMR spectroscopy, being complete in *ca.* 12 h. If TFA (1.5 μl, 0.2 equiv.) was included at the start the reaction was complete in *ca.* 30 min. In either case evaporation gave a discoloured residue whose spectrum showed the presence of the ketone in at least 90% yield. Repeated extraction with hot hexane gave the ketone as a pale yellow oil: ν(film) 1 707 (C=O) and 1 668 cm^{-1} (C=N); δ_H(250 MHz; $CDCl_3$) 2.12 (s, 5-CH_3), 2.23 (s, $COCH_3$), 2.75 (d, $COCH_2$, J 7 Hz), 5.66 (t, 6-H, J 7 Hz), 6.42 (s, 4-H), 7.27–7.67 (m, m + p-Ph), and 7.67–7.80 (m, o-Ph). The *semicarbazone* gave prisms from EtOH, which melted and re-solidified between 150 and 160 °C, and remelted at 178–181 °C.

The ketone (**44**) could be similarly prepared by heating the ketals (**43**) in bromobenzene without, or more rapidly with, the inclusion of TFA (0.2 equiv.).

(f) 5-*Methyl*-3-*phenylpyridazine* (**45**). The adduct (**29**) (66 mg, 0.2 mmol) was heated at reflux in bromobenzene (0.5 ml) containing TFA (18.5 μl, 0.24 mmol) for 15 min, at which time NMR spectroscopy showed the reaction to be complete, the pyridazine being present in at least 90% yield. Evaporation, addition of MeOH, neutralisation with solid Na_2CO_3, and evaporation gave a residue which was extracted with ether to yield a dark solution. Purification was effected by extraction with dilute hydrochloric acid, basification of the extracts with KOH, and washing out of the free pyridazine from the alkali with methylene dichloride. Removal of the solvent gave (**45**) as a light brown solid which was crystallised as pale yellow prisms, m.p. 92–93 °C (lit.,[31] 85–87 °C): δ_H(200 MHz; $CDCl_3$) 2.44 (q, determined by selective decoupling, CH_3, $J_{CH_3,6\text{-}H}$ 0.4 Hz, $J_{CH_3,4\text{-}H}$ 0.8 Hz), 7.4–7.6 (m, m + p-Ph), 7.66 (q, 4-H, $J_{4\text{-}H,6\text{-}H}$ 2.1 Hz), 8.0–8.1 (*m*, o-Ph), 9.01 (q, 6-H).

The pyridazine (**45**) was prepared in exactly the same way using TFA from the ketals (**43**). The release of acetone (as well as methanol) was confirmed in a reaction monitored by NMR spectroscopy.

The intermediacy of the ketone (**44**) was confirmed in an NMR tube experiment in which the ketals were converted into the ketone using TFA (0.2 equiv.) and then further into the pyridazine by addition of TFA up to 1 equiv.

Pyridazine formation with sodium methoxide was also demonstrated. A solution of (**29**) (42 mg, 0.12 mmol) in 0.1M NaOMe (3 ml, 0.3 mmol) in MeOH was refluxed for 1 h, neutralised with acetic acid and evaporated. The residue had a strong odour of methyl benzoate. Its spectrum showed (**45**) to be the major product (*ca.* 70%) and confirmed the presence of the ester.

X-Ray Crystal Structure Analyses of (**12**) *and* (**23**).—Details of the crystal parameters, data collection, and refinement are listed in Table 1. Data were measured on a Syntex $P2_1$ automated diffractometer using graphite monochromated Mo-K_α radiation (λ = 0.710 73 Å). The standard Syntex centering, autoindexing and data collection programs were used. Accurate unit cell dimensions for each structure were derived from the least-squares fit of 15 general reflections ($10 < \theta < 15°$) well distributed in reciprocal space.

Intensity data were collected by the θ–2θ scan technique using variable scan rates (the rate being determined by a quick preliminary scan). Background measurements were made at the beginning and end of each scan for a total time of half the scan time. Crystal stability was checked by monitoring the intensities of two standard reflections every 100 measurements; only statistical fluctuations were observed for both compounds. Data were corrected for Lorentz and polarisation effects but not absorption.

Both structures were solved by direct methods (MULTAN80) and refined by full-matrix least-squares methods, the function minimised being $\Sigma w(|F_o| - |F_c|)^2$. Final agreement factors are shown in the Table. Complete listings of the bond lengths and angles together with anisotropic thermal parameters are available on request from the Cambridge Crystallographic Data Centre.

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