X=Y–ZH Systems as Potential 1,3-Dipoles. Part 2. Oxime Cycloadditions: Formation of 2:1 Adducts

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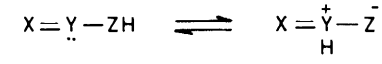
Cycloaddition of aldehyde and ketone oximes are shown to give mixtures of all possible isoxazolidine regioisomers and stereoisomers. The products are 2:1 adducts with the second molecule of the dipolarophile attached to the isoxazolidine *N*-atom. The stereochemistry of the major isomer from benzaldehyde oxime and acrylonitrile was established by an *X*-ray crystal structure analysis. The cycloaddition is shown to be weakly catalysed by 2,4-dinitrophenol and to proceed best in acetonitrile. More polar solvents slightly favour the 5-isoxazolidine regioisomer. The mechanism of the reaction is discussed.

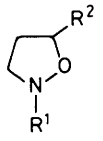
We have recently proposed that X=Y–ZH systems (1), in which the central Y atom possesses a lone pair of electrons, are potential sources of 1,3-dipolar species *via* tautomeric equilibration of neutral (1) and dipolar (2) species.[1] Application of this concept further extends the scope of 1,3-dipolar cycloaddition reactions which are the most versatile reactions for synthesising five-membered heterocycles.[2] To date we have provided preliminary accounts of examples of imines (1a) ⇌ (2a) [1,3] and hydrazones (1b) ⇌ (2b) [1] and the current paper is concerned with oximes (1c) ⇌ (2c).



(1) (2)

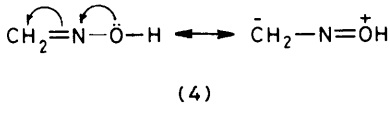
a; X = Z = >C; Y = N
b; X = >C, Y = N, Z = NR
c; X = >C, Y = N, Z = O

Prior to our own work on oximes there were relevant publications from three other groups.[4-6] Japanese workers treated formaldehyde oxime, formed *in situ*, with methyl acrylate and acrylonitrile and obtained mixtures of the 5-substituted isoxazolidines (3a,b) and (3c,d) [4] in which 2:1 adducts (3a) and (3c) predominated [(3a):(3b), 5.2:1 and (3c):(3d), 10.7:1].



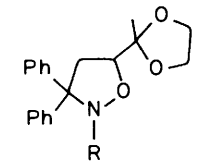
(3)

a; R^1 = CH_2CH_2CN, R^2 = CN
b; R^1 = H, R^2 = CN
c; R^1 = $CH_2CH_2CO_2Me$, R^2 = CO_2Me
d; R^1 = H, R^2 = CO_2Me



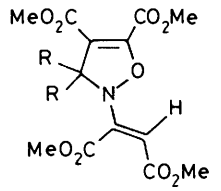
(4)

Cycloadducts were also obtained from dimethyl maleate and dimethyl fumarate. Cycloaddition to maleate and fumarate occurred stereospecifically and the canonical form (4) of the oxime was thought to be important in the cycloaddition. French workers studied the cycloaddition of benzophenone oxime with methyl vinyl ketone and protected the unstable cycloadducts as ethylene acetals before isolation.[5] They report regiospecific formation of the 5-isoxazolidines (5a,b) in which the 1:1 adduct (5a) predominates with only trace amounts of the 2:1 adduct (5b) (5a:5b, 300:1). Finally, German workers report only 2:1 adducts (6a,b) are formed from cyclohexanone and acetone oximes and dimethyl acetylenedicarboxylate (ADE).[6]



(5)

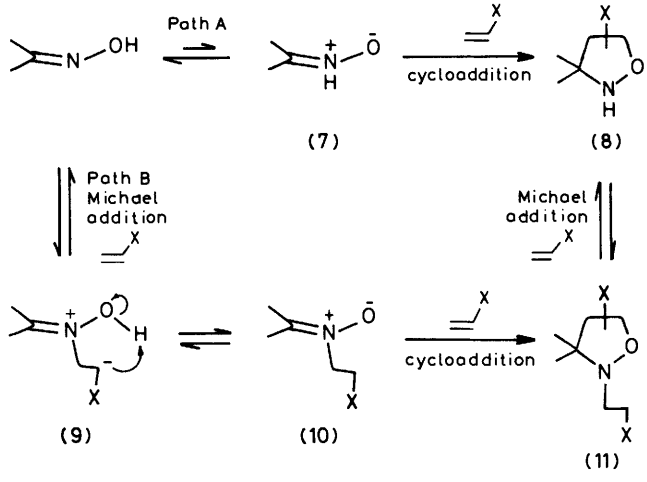
a; R = H
b; R = $CH_2C(Me)CH{\cdot}O{\cdot}(CH_2)_2{\cdot}O$



(6)

a; R = Me
b; R = $-(CH_2)_5-$

Lablache-Combier and Villaume [5] suggested that (5a,b) arise *via* tautomeric equilibration of benzophenone oxime with the corresponding nitrone and that the 2:1 adduct (5b) arises *via* Michael addition of the 2*H*-isoxazolidine (1:1 adduct) to methyl vinyl ketone. In contrast Winterfeldt and Krohn, who observed only 2:1 adducts with ADE, suggest Michael addition to the oxime nitrogen atom occurs first. Thus two pathways to 2:1 adducts are possible as shown in the Scheme.



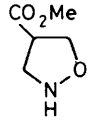
Scheme.

Table 1. Isoxazolidines (15), (16) from cycloaddition of oximes (14) to acrylonitrile and methyl acrylate

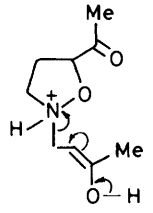
R^1	R^2	X	Yield (%) *
2-Furyl	H	CN	78.5
2-Furyl	H	CO_2Me	82.0
2-Thienyl	H	CN	77.0
2-Thienyl	H	CO_2Me	77
Ph	H	CN	81.0
Ph	H	CO_2Me	83.0
p-$MeOC_6H_4$	H	CN	82.0
p-$MeOC_6H_4$	H	CO_2Me	82.0
Me	H	CN	71.0
Me	H	CO_2Me	73.5
Et	H	CN	76.5
Et	H	CO_2Me	82.5
Pr^n	H	CN	81.0
Pr^n	H	CO_2Me	84.5
Pr^i	H	CN	72.5
Pr^i	H	CO_2Me	77.5
Me	Me	CN	75.0
Me	Me	CO_2Me	81.0
Et	Me	CN	77.0
Et	Me	CO_2Me	82.0
Et	Et	CN	74.0
Et	Et	CO_2Me	81.0
p-$Me_2NC_6H_4$	H	CN	81.0
p-$Me_2NC_6H_4$	H	CO_2Me	85.0
p-$CF_3C_6H_4$	H	CN	79.5
p-$CF_3C_6H_4$	H	CO_2Me	84.0

* Total yield of regioisomeric and stereoisomeric isoxazolidines.

Our own work was directed towards providing data on the regioselectivity and stereoselectivity of oxime cycloadditions and to seeking evidence for the importance of path A and path B (Scheme) in the formation of 2 : 1 adducts. We have repeated and confirmed the Japanese results with formaldehyde oxime and methyl acrylate. The 2 : 1 adduct (3e) comprises >90% of the product and small amounts of (3d) and a further 1 : 1 adduct, possibly the regioisomer (12), were also detected [(3d) + (12) < 5% of product]. On repeating the French work we isolated the isoxazolidines (5a,b) (23%) but in our hands the 2 : 1 adduct predominated (5a) : (5b), 1 : 2. The major discrepancy in the ratio of (5a) to (5b) could possibly be due to the 1 : 1 adduct arising from an acid catalysed retro-Michael addition reaction of the 2 : 1 adduct during acetalisation or isolation (13; arrows).



(12)



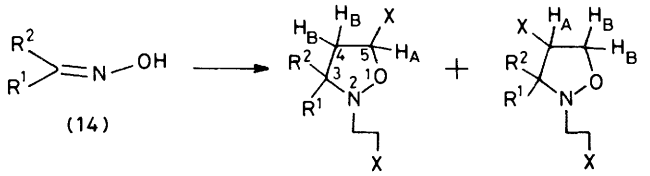
(13)

We have studied the reaction of aldehyde oximes or ketone oximes (14) with unsymmetrical dipolarophiles (acrylonitrile, methyl acrylate) in pyridine at 80—85 °C for 3—12 d and observe the formation of mixtures of regioisomeric and stereoisomeric isoxazolidines (15), (16) in high yield (Table 1) in each case. The 2 : 1 adducts (15), (16) are sometimes accompanied by a minor amount (1—5%) of Michael adduct (17). 1 : 1 Adducts (18) were not observed even when a 1 : 1 molar ratio of oxime and acrylate or acrylonitrile were used.

Table 2. Regioisomer ratios in oxime cycloadditions to methyl acrylate and acrylonitrile (pyridine, 80—85 °C, 3—7 d)

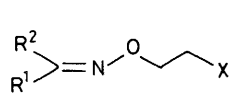
Isoxazolidines (15) and (16)			Ratio of
R^1	R^2	X	(15) : (16) [a]
Me	Me	CN	7 : 9
Me	Me	CO_2Me	5 : 2
Et [b]	Me	CN	3 : 4
Et [b]	Me	CO_2Me	9 : 3.5
Et	Et	CN	3 : 4
Et	Et	CO_2Me	5 : 1

[a] Ratios based on integration of ^1H n.m.r. spectra of crude products after passage through a silica column (ether–light petroleum). [b] No attempt made to separate the stereoisomers.



(14) (15) (16)

a; $R^1 = R^2 = Me$, X = CN a; $R^1 = R^2 = Me$, X = CN



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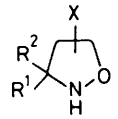


(18)

The isoxazolidines (15) and (16), depending on the nature of R^1 and R^2, can also give rise to stereoisomers. Hence these cycloadditions can result in a mixture of two ($R^1 = R^2$) or four ($R^1 \neq R^2$) isoxazolidines. The mixtures of isoxazolidines were first cleaned up by column chromatography (silica, ether–light petroleum), and then separated by p.t.l.c. or h.p.l.c. In some instances one pure stereoisomer usually (15; X = CN) crystallised spontaneously from the mixture.

The regiochemistry of the isoxazolidines (15), (16) is readily assigned on the basis of their ^1H n.m.r. spectra. The 5-substituted isoxazolidines (15) exhibit a signal for the 5-methine proton H_A at δ 4.3—4.9. whilst the 4-methylene protons H_B occur at δ 2.3—3.0. The 4-substituted regioisomers (16) exhibit signals for the 5-methylene protons H_B at δ 4.0—4.4 and for the 4-methine proton H_A at δ 3.0—3.8. The ratio of regioisomers obtained in some preparative reactions is shown in Table 2.

We find that both methyl acrylate and acrylonitrile react with oximes to give substantial amounts of both regioisomeric isoxazolidines. In the preparative-scale runs (Table 2) with acrylonitrile the 4-substituted isoxazolidine (16) predominates whilst with methyl acrylate the 5-substituted isomer (15) comprised the major product. ^1H N.m.r. kinetic experiments to study the effect of solvent polarity on rate and regiochemistry (Table 3) show it would be misleading to draw conclusions from the regioisomer ratios in Table 2 (compare entry one Table 2 with entry two Table 3) which refer to preparative-scale experiments of longer duration (than the kinetic experiments in Table 3) and after partial purification by column chromatography. Huisgen's studies have shown that 1,3-dipolar cycloadditions are only moderately influenced by solvent polarity.[8] Our studies (Table 3)

Table 3.[a] Solvent effects on the rate and regiochemistry of cycloaddition of acetone oxime and acrylonitrile at 80 °C [b]

Solvent	Dielectric constant	E_T (kcal/mol) [c]	(15a) $t_{\frac{1}{2}}$ (h) [d]	(16a) $t_{\frac{1}{2}}$ (h) [d]	Ratio of (15a) : (16a)
[$^2H_8$]Toluene	2.38	33.9	7.25	9.60	1.5 : 1
[$^2H_5$]Pyridine	12.30	40.2	21.67	38.77	2 : 1
[$^2H_6$]Acetone	20.70	42.2	17.70	35.63	2.4 : 1
[$^2H_3$]Acetonitrile	36.20	46.0	4.52	9.46	2.8 : 1
[$^2H_6$]DMSO	49.00	45.0	19.26	49.12	3 : 1

[a] Kinetics were measured in the probe of a Bruker WM250 MHz FT spectrometer, spectral width 3 012 Hz, 8K data points, on solutions of acrylonitrile (43.6 mg, 2 mol) and acetone oxime (30 mg, 1 mol) in the appropriate solvent (1.1 ml). [b] Temperature accurate to ±0.5 °C. [c] Empirical parameters of solvent polarity (ref. 7). [d] Time for conversion into 50% product.

Table 4.[a] Effect of Lewis acids and bases (1 mol) on the rate and regiochemistry of the cycloaddition of acetone oxime and acrylonitrile in [$^2H_3$]acetonitrile at 80 °C

Additive	(15a) $t_{\frac{1}{2}}$ (h) [b]	(16a) $t_{\frac{1}{2}}$ (h) [b]	Ratio of (15a) : (16a)
$Zn(OAc)\cdot 2H_2O$	28.3	32.6	*ca.* 2 : 1 (initially) 1.2 : 1 (finally)
N-Methylpyrrolidine	13.25	31.02	2.7 : 1
4-Dimethylaminopyridine	11.92	28.57	2.65 : 1 [c]
[$^2H_4$]Acetic acid	7.25	12.6	2.45 : 1
2,4-Dinitrophenol	3.05	5.94	2.4 : 1

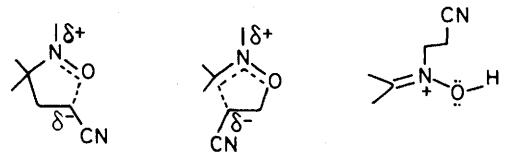
[a] Spectral parameters and quantities of reactants as in Table 3. [b] Time for conversion into 50% product. [c] Approximately 40% of Michael adduct is also found.

show a rate variation of *ca.* 5 with change in solvent polarity in broad agreement with Huisgen's findings but there is no correlation between $t_{\frac{1}{2}}$ and solvent polarity. However, a correlation between regioselectivity and solvent polarity is observed (Table 3) with more polar solvents favouring the 5-substituted isoxazolidine (15a). This trend would accord with unequal degrees of bond formation in the transition states (19) and (20), thus resulting in partial charge separation. Transition state (19) has more charge localisation than (20) and thus might be slightly more stabilised by polar solvents; this would lead to more of the 5-substituted isoxazolidine.

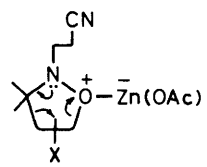
The effect of Lewis acids and bases on the cycloaddition of acetaldehyde oxime and acrylonitrile was also briefly studied (Table 4). All the added Lewis acids and bases retard the rate of formation of both isomeric isoxazolidines except 2,4-dinitrophenol (pK_a 4).[9] This increased rate with 2,4-dinitrophenol and rate retardation with acetic acid (pK_a 4.76) suggested acids with lower pK_a values might exert a stronger catalytic effect. However, toluene-*p*-sulphonic acid (pK_a −7) caused hydrolysis of acetaldehyde oxime. The catalytic effect of 2,4-dinitrophenol might be to stabilise an intermediate such as (21) which could undergo a ($4\pi + 2\pi$) cycloaddition reaction by utilising the imine electrons and an oxygen lone pair. A similar suggestion has been made by Hamelin for the acid-catalysed cycloaddition of hydrazones to dipolarophiles.[10] Alternatively, the acid may promote the Michael addition (Scheme, Path B) giving a more favourable equilibrium concentration of nitrone. Examples of acid-catalysed Michael additions are known.[11]

Addition of Lewis acids and bases causes very little variation in regiochemistry except in the case of zinc acetate which gives an initial ratio (15a) : (16a) of *ca.* 2 : 1 and a final ratio of 1.2 : 1 This variation is shown in more detail in Table 5. Thus zinc acetate catalyses cycloreversion leading to an equilibrium mixture of (15a) and (16a), presumably *via* co-ordination to the isoxazolidine oxygen atom (22; arrows).

Aldehyde oximes and unsymmetrical ketone oximes can give rise to four products (23)—(26). Results of cycloaddition reactions between aldehyde oximes and acrylonitrile or methyl acrylate in which separation of the isomeric isoxazolidines was undertaken are collected in Table 6.



(19) (20) (21)



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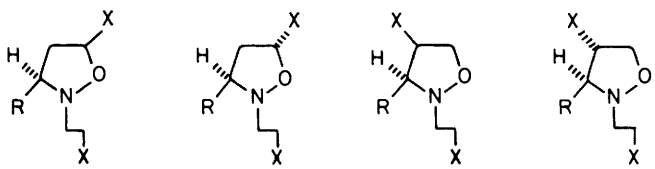


(23) (24) (25) (26)

The stereoisomeric mixtures (Table 6) of isoxazolidines (23)—(26) were separated by h.p.l.c. or p.t.l.c. and the isomer ratio determined by area measurement (planimeter) of the u.v. detector trace (h.p.l.c.) or by weight and ^1H n.m.r. spectra (p.t.l.c. separation). Assignment of regiochemistry to the products presented no difficulties as discussed above. However, the assignment of stereochemistry to each pair of stereoisomeric regioisomers poses a more difficult problem which was greatly simplified by the determination of the *X*-ray

Table 5.[a] Variation in regiochemistry with time during the cycloaddition of acetone oxime and acrylonitrile in the presence of $Zn(OAc)_2 \cdot 2H_2O$ (1 mol) (acetonitrile, 80 °C) [a]

Time (h)	Ratio of (15a) : (16a)
5	2 : 1
10	2 : 1
15	1.8 : 1
20	1.74 : 1
25	1.6 : 1
30	1.49 : 1
35	1.36 : 1
40	1.29 : 1
45	1.24 : 1
50	1.21 : 1
55	1.20 : 1
60	1.20 : 1

[a] Spectral parameters and quantities of reactants as in Table 3.

Table 6. Regio- and stereo-isomer ratios of isoxazolidines (23)—(26) from cycloaddition of aldehyde oximes to acrylonitrile and methyl acrylate

Isoxazolidine (23)—(26)		Product ratio
R	X	(23) : (24) : (25) : (26)
2-Furyl	CN	10 : 3 : 7 : 2 [a]
2-Furyl	CO_2Me	5 : 1.7 : 5 : 6 [a]
Ph	CN	9 : 5 : 4.2 : 2.8 [b]
Ph	CO_2Me	4 : 3 : 2.3 : 2.7 [b]
p-$MeOC_6H_4$	CN	4 : 2 : 3.5 : 5.6 [c]
p-$MeOC_6H_4$	CO_2Me	8.5 : 3 : 8.4 : 6.5 [a]
p-$CF_3C_6H_4$	CN	9 : 7 : 5 [b,d]
p-$CF_3C_6H_4$	CO_2Me	13 : 3.5 : 1 [b,e]

[a] Separation by h.p.l.c., two isomers obtained pure. [b] Two isomers obtained pure by p.t.l.c. [c] Separation by h.p.l.c., all four isomers obtained pure. [d] Ratio of (23) : (24) : (26). [e] Ratio of (23) : (25) : (26).

crystal structure of the major isomer from benzaldehyde oxime and acrylonitrile which established the *cis*-relationship between the benzene ring and the 5-cyano group, *i.e.* (23; R = Ph, X = CN).

The molecular structure and numbering scheme is shown in the Figure. The bond parameters do not appear out of the ordinary and, furthermore, the distances and angles within the five-membered heterocyclic ring compare favourably with similar ring systems previously reported.[12,13] The five-membered ring in the present molecule has an envelope conformation (flap angle = 49.9°) as found in 5-*p*-bromophenyl-3-cyano-*N*-methoxyisoxazolidine.[13] The stereochemical arrangement found here is such that the phenyl and cyano substituents are *cis*- with respect to one another and with respect to N(1) in the heterocyclic ring. This arrangement differs from that found in 5-*p*-bromophenyl-3-cyano-*N*-methoxyisoxazolidine in that, although the cyano and bromophenyl substituents are *cis*- with respect to one another the N atom of the heterocyclic ring is *trans*- with respect to both these groups.

With the *X*-ray crystal structure of (23; R = Ph, X = CN) to hand and n.m.r. spectra of the stereoisomers (23)—(26) it was possible to complete the stereochemical assignments. The ^1H n.m.r. spectra of *cis*-(23)- and *trans*-(24)-isoxazolidines can be differentiated as follows. (*i*) The difference in chemical shifts ($\Delta\delta$) of the 4-methylene protons in the *cis*-isomer (23) is greater than that in the *trans*-isomer (24) (Table 7), *e.g.* for (23; R = Ph, X = CN), $\delta\Delta$ (4-H) = 0.5 and for (24; R = Ph, X = CN), $\delta\Delta$(4-H) = 0.26. (ii) The difference in

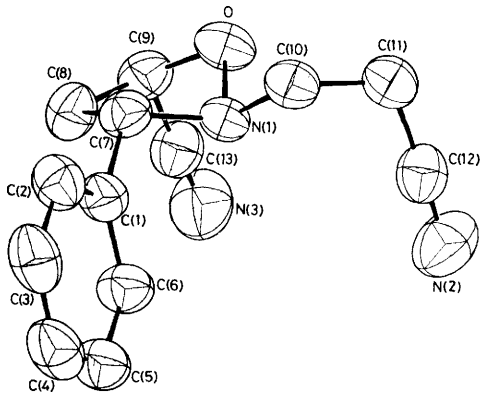


Figure. ORTEP diagram [23] of 2-(2-cyanoethyl)-*cis*-5-cyano-3-phenylisoxazolidine (23; R = Ph, X = CN), showing the atomic numbering scheme. Thermal ellipsoids enclose 50% of probability

chemical shifts of the 3- and 5-methine protons is greater in the *cis*-isomer (23) than in the *trans*-isomer (24), *e.g.* (23; R = 2-furyl, X = CN), $\delta\Delta$ (3-H/5-H) = 1.11 and (24; R = 2-furyl, X = CN) $\delta\Delta$ (3-H/5-H) = 0.53 (Table 7). Whilst the ^1H n.m.r. chemical shifts of the ester methyl groups in the methyl acrylate cycloadducts are not diagnostic for the stereochemistry of the 5-substituted isoxazolidines (23) and (24), they are indicative of stereochemistry in the 4-substituted isoxazolidines (25) and (26) and similar structural information is provided by the chemical shift of 4-methine proton in the 4-substituted isoxazolidines. These chemical-shifts differences are due to the shielding effect of a 3-aryl substituent on an adjacent *cis*-4-H or *cis*-4-CO_2Me group.[14] Thus, the *cis*-isomer (25; R = 2-furyl, X = CO_2Me) exhibits signals for its two OMe groups at δ 3.66 and 3.45, whilst the *trans*-isomer (26; R = 2-furyl, X = CO_2Me) has two signals at δ 3.72 and 3.65. Similar chemical-shift differences are shown by the 4-methine protons, *e.g.* (25; R = 2-furyl, X = CO_2Me) 4-H, δ 2.61 and (26; R = 2-furyl, X = CO_2Me) 4-H, δ 2.46 (Table 7). Although the 4-substituted isoxazolidines derived from acrylonitrile (25) and (26) (X = CN) lack the 4-CO_2Me n.m.r. probe the stereoisomers can be differentiated on the basis of the chemical shift of the 4-methine protons as indicated above. Thus the signal for the 4-methine proton in the *cis*-isomer, *e.g.* (25; R = *p*-$MeOC_6H_4$, X = CN), δ 3.72, occurs at lower field than that of the *trans*-isomer (26; R = *p*-$MeOC_6H_4$, X = CN), δ 3.36 (Table 7).

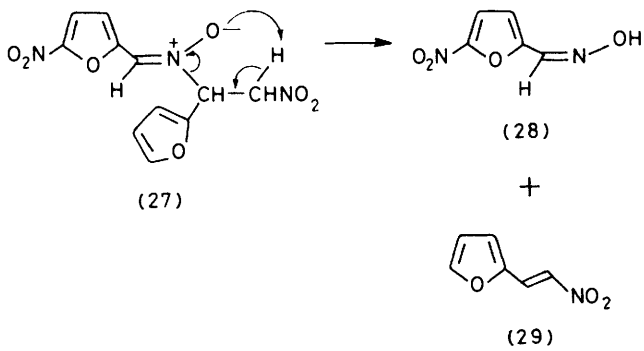
In our experiments only isomeric *N*-substituted isoxazolidines (*i.e.*, 2 : 1 adducts) were observed and these could arise *via* path A or path B (Scheme). Path A involves a formal 1,2-hydrogen shift and recent MO calculations [15] predict high activation energies for intramolecular 1,2-shifts generating formaldonitrone ($CH_2 = \overset{+}{N} - \overset{-}{O}$) from either nitrosomethane or formaldehyde oxime. This suggests that generation of nitrones by tautomerisation of oximes will not normally occur by an intramolecular process. However the calculations suggest that once generated such nitrones may be observable. Thus in the context of the scheme, nitrone (7) formation by path A would be an intermolecular process. Cycloaddition of the nitrone to a dipolarophile (Path A) then leads to the *N*-unsubstituted isoxazolidine (8) in which the enhanced nucleophilicity (α-effect) of the hydroxylamino moiety [16] would be expected to facilitate the Michael addition step (8) ⟶ (11). Indeed Lablache-Combier and Villaume [5] demonstrated that (5a) undergoes Michael addition to methyl vinyl ketone in boiling benzene.

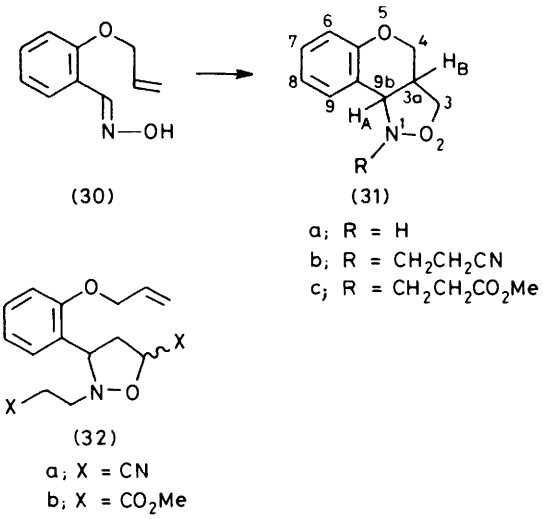
Path B generates (10) *via* a Michael addition involving the nitrogen atom. Reports in the literature indicate that frag-

Table 7. Chemical shifts (250 MHz, δ, $CDCl_3$) and coupling constants of protons in stereoisomeric isoxazolidines

	3-H	$J_{3,4}$ (Hz)	4a-H	4b-H	5a-H	5b-H	$J_{4,5}$ (Hz)
(23; R = 2-furyl, X = CN)	3.78 (t)	8.18	2.91	2.82	4.89 (q)	—	8.17, 4.9
(24; R = 2-furyl, X = CN)	4.38 (t)	6.5	3.0	3.0	4.91 (q)	—	6.5, 3
(25; R = 2-furyl, X = CN)	4.16 (d)	6.0	3.87	—	4.36	4.11	9.0
(26; R = 2-furyl, X = CN)	4.1 (d)	3.6	3.68	—	4.34	4.29	3.0
(23; R = 2-furyl, X = CO_2Me)	3.74 (t)	7.37	2.85	2.64	4.69 (q)	—	8.6, 6.2
(24; R = 2-furyl, X = CO_2Me)	4.13 (t)	3.36	2.87	2.75	4.65 (t)	—	7.7
(25; R = 2-furyl, X = CO_2Me)	4.28 (d)	7.68	2.61	—	4.42	4.18	—
(26; R = 2-furyl, X = CO_2Me)	4.24 (d)	1.7	2.46	—	4.14	4.14	—
(23; R = Ph, X = CN)	3.67 (t)	8.46	3.1	2.6	4.89 (q)	—	9.19, 4.04
(24; R = Ph, X = CN)	4.09 (q)	9.19, 6.99	2.94	2.68	4.86 (q)	—	8.82, 4.41
(25; R = Ph, X = CN)	3.85 (d)	8.8	3.75	—	4.4	4.19	—
(26; R = Ph, X = CN)	3.84 (d)	8.0	3.34	—	4.29	4.29	—
(23; R = Ph, X = CO_2Me)	3.72 (t)	7.5	2.94	2.62	4.63 (q)	—	9.19, 5.15
(24; R = Ph, X = CO_2Me)	3.92 (t)	7.5	2.9	2.78	4.67 (q)	—	8.82, 5.15
(25; R = Ph, X = CO_2Me)	4.02 (d)	8.8	3.72	—	4.42	4.2	—
(26; R = Ph, X = CO_2Me)	3.97 (d)	7.35	3.4	—	4.23	4.23	—
(23; R = *p*-$MeOC_6H_4$, X = CN)	3.63 (t)	8.46	3.06	2.55	4.88 (q)	—	9.19, 4.04
(24; R = *p*-$MeOC_6H_4$, X = CN)	4.03 (t)	7.9	2.89	2.71	4.86 (q)	—	8.82, 4.04
(25; R = *p*-$MeOC_6H_4$, X = CN)	3.82 (d)	9.0	3.72	—	4.39	4.19	—
(26; R = *p*-$MeOC_6H_4$, X = CN)	3.79 (d)	7.2	3.36	—	4.29	4.22	—
(23; R = *p*-$MeOC_6H_4$, X = CO_2Me)	3.72 (t)	9.9	2.87	2.58	4.62 (q)	—	9.19, 5.50
(24; R = *p*-$MeOC_6H_4$, X = CO_2Me)	3.8 (t)	8.09	2.67	2.59	4.68 (q)	—	8.82, 5.50
(25; R = *p*-$MeOC_6H_4$, X = CO_2Me)	3.98 (d)	9.56	3.72	—	4.38	4.14	—
(26; R = *p*-$MeOC_6H_4$, X = CO_2Me)	4.2 (d)	6.0	3.35	—	4.21	4.2	—
(23; R = *p*-$CF_3C_6H_4$, X = CN)	3.78 (t)	8.46	3.17	2.57	4.94 (q)	—	9.19, 3.68
(24; R = *p*-$CF_3C_6H_4$, X = CN)	4.20 (t)	7.0	2.85	2.51	4.89 (q)	—	8.82, 4.40
(26; R = *p*-$CF_3C_6H_4$, X = CN)	3.97 (d)	7.7	3.39	—	4.32	4.32	—
(23; R = *p*-$CF_3C_6H_4$, X = CO_2Me)	4.0 (t)	7.5	3.0	2.85	4.67 (q)	—	9.19, 5.15
(25; R = *p*-$CF_3C_6H_4$, X = CO_2Me)	4.14 (d)	7.5	3.8	—	4.38	4.22	—
(26; R = *p*-$CF_3C_6H_4$, X = CO_2Me)	4.06 (d)	7.2	3.12	—	4.23	4.23	—

mentation of nitrones (10) to oximes occurs thermally [17] and is especially facile when X is an electron-withdrawing group [*e.g.* (27) ⟶ (28) + (29) at room temperature].[18] Thus any equilibrium concentration of (10) (Scheme) must be small.

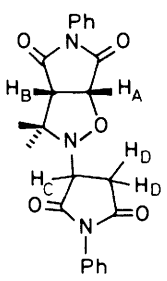




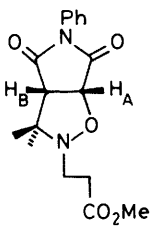
Oppolzer has provided evidence for the operation of path A in the intramolecular cycloaddition (30) ⟶ (31a) which occurs at 210 °C in moderate yield.[19] We have also studied the intramolecular cycloaddition of the oxime (30) and found that disappearance of starting material was slow in xylene at 140 °C (8 d) and resulted in a complex mixture of products. No (31a) could be isolated. Reaction in pyridine (80 °C) also failed to yield any (31a). In contrast when (30) was allowed to react in pyridine (80 °C; 3 d) in the presence of acrylonitrile (1.5 mol) a mixture (79%) of (31b) and (32a) (65 : 35), separable by p.t.l.c., was obtained. The 2 : 1 adduct (32a) comprised mainly a *ca.* (1 : 1) mixture of *E*- and *Z*-stereoisomers together with minor amounts of the other regioisomer. An analogous reaction between (30) and methyl acrylate afforded a mixture (82%) of (31c) and (32b) (57 : 43). In this case the regioisomer (32b) again comprised the major component of the 2 : 1 adduct with minor amounts of the alternative regioisomer but overlapping peaks in the 250 MHz ^1H n.m.r. spectrum of the product made more detailed analysis impossible. The ^1H n.m.r. coupling constants for the ring junction protons $J_{H_AH_B}$ suggests a *cis*-fused ring system [(31b), 4.7 Hz and (31c), 3.9 Hz]. These results, taken together with Oppolzer's observations,[19] suggest that both paths A and B (Scheme) can operate, but that path A is the higher energy process.

Further evidence was provided on this point by cycloaddition experiments with acetone oxime, *N*-phenylmaleimide and methyl acrylate. Heating acetone oxime with *N*-phenylmaleimide (boiling acetonitrile; 3 d) in both 1 : 1 and 1 : 2 *molar* ratios, afforded in each case the 2 : 1 adduct (33) with none of the 1 : 1 adduct being observed.

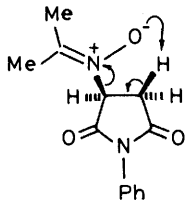
Acetone oxime, methyl acrylate, and *N*-phenylmaleimide (molar ratio 1 : 1 : 1) heated (CD_3CN, 80 °C, 2 d) in a sealed n.m.r. tube gave (34) (30%) together with acetone (50%) formed by hydrolysis of the oxime. A similar reaction (CH_3CN, 80 °C, 41 h) with acetone oxime, methyl acrylate, and *N*-phenylmaleimide in the ratio 1 : 1 : 2 gave a 43 : 57 mixture (60%) of (33) and (34); no 1 : 1 adducts were observed.



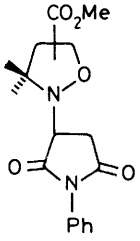
(33)



(34)



(35)



(36)

These results are interpretable in terms of path B of the Scheme. With *N*-phenylmaleimide the concentration of the nitrone (35) is expected to be much smaller than that of nitrone (10; X = CO_2Me, Scheme) due to a more facile fragmentation to oxime (35; arrows). Thus in the mixed cycloadditions the nitrone (10; X = CO_2Me, Scheme) is able to compete more effectively than (35) for the available dipolarophiles. *N*-Phenylmaleimide is a more reactive dipolarophile than methyl acrylate, and thus the order of ease of formation is (34) > (33) > (36).

Experimental

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. N.m.r. spectra were obtained in deuteriochloroform on Bruker WH90 and Bruker WM250 instruments. Chemical shifts are given in p.p.m. (δ) downfield from tetramethylsilane (TMS) as internal standard with the usual abbreviations. I.r. spectra were recorded on Perkin-Elmer model 157G and Perkin-Elmer model 598-SP instruments. Mass spectra were run by direct insertion into the ion source of an AEI MS902 mass spectrometer operating at 70 eV. High performance liquid chromatography (h.p.l.c.) was performed on a Spectra-Physics SP3500 instrument using an analytical column (250 mm × 4.6 mm i.d.; Sperisorb silica S5W or Partisil 5 silica) or a semi-preparative Partisil 10M9 column (500 mm × 9.4 mm i.d.; Whatman Ltd.). Solvents used for h.p.l.c. were purified according to established procedures. Some batches of pentane were further purified to spectroscopic grade simply by slow passage through an activated alumina column followed by fractional distillation. Column chromatography was conducted with silica gel (Sorbsil 200—300 mesh, J. Crossfield Ltd.) and preparative t.l.c. with silica gel PF 254 + 366 (Merck). Oximes were prepared by established procedures.

General Method for the Synthesis of Isoxazolidines by Reaction of Aldehyde or Ketone Oximes with Acrylonitrile or Methyl Acrylate.—A mixture of aldehyde oxime (8.3×10^{-2} mol) or ketone oxime (8.3×10^{-2} mol) and acrylonitrile (8.8 g, $2 \times 8.3 \times 10^{-2}$ mol) or methyl acrylate (14.3 g, $2 \times 8.3 \times 10^{-2}$ mol) was heated at 80—85 °C in pyridine (60 ml) under an atmosphere of argon for 3—12 d. The solvent was evaporated under reduced pressure and the residue treated with 2% aqueous hydrochloric acid (200 ml) and methylene chloride (200 ml). The aqueous layer was extracted with methylene chloride (3 × 150 ml), and the extract washed with water (3 × 200 ml) and dried ($MgSO_4$). After removal of methylene chloride under reduced pressure, the crude cycloadduct was purified by passage through a silica gel column (1 : 30), eluting first with ether–light petroleum (b.p. 40—60 °C) (1 : 1) and then pure ether. The stereo- and regio-isomers were separated by h.p.l.c. or p.t.l.c. (ether–pentane, 2 : 3)

2-(2-*Cyanoethyl*)-3-(2-*furyl*)-4- *and* 5-*cyanoisoxazolidine* (23)—(26) (R = 2-furyl, X = CN).—The pale yellow oily product (79%) was obtained as a mixture of isomers (see Table 6) which were separated by h.p.l.c. on a Partisil 10M9 (19 μm) column, mobile phase ether–pentane (35 : 65), flow rate 6 ml/min, u.v. detector set at 230 nm: (23; R = 2 furyl, X = CN), m.p. 85—86 °C (from ether); δ, 7.42 and 6.4 (m, 3 H, furyl-H), 4.89 (q, 1 H, $J_{4,5}$ 8.17, 4.9 Hz, 5-H), 3.78 (t, 1 H, $J_{3,4}$ 8.18 Hz, 3-H), 2.91 and 2.82 (m, 2 H, 2 × 4-H), 3.16, 2.94, and 2.72 (m, 4 H, CH_2CH_2).

(24; R = 2-furyl, X = CN), colourless oil, δ 7.5 and 6.4 (d and m, 3 H, furyl-H), 4.91 (q, 1 H, $J_{4,5}$ 6.5, 3 Hz, 5-H), 4.38 (t, 1 H, $J_{3,4}$ 6.5 Hz, 3-H), 3.0 (m, 2 H, 2 × 4-H), 3.0 and 2.7 (m, 4 H, CH_2CH_2).

(25; R = 2-furyl, X = CN), colourless oil, δ, 7.5, 6.6, and 6.46 (d, 3 H, furyl-H), 4.36 and 4.11 (t, 2 H, $J_{4,5}$ 9 Hz, 5-H), 4.16 (d, 1 H, $J_{3,4}$ 6 Hz, 3-H), 3.87 (q, 1 H, 4-H), 3.0, 2.9, and 2.74 (m, 4 H, CH_2CH_2).

(26; R = 2-furyl, X = CN), colourless oil, δ, 7.5, 6.56, and 6.45 (d, 3 H, furyl-H), 4.34 and 4.29 (t, 2 H, $J_{4,5}$ 3 Hz, 2 × 5-H), 4.1 (d, 1 H, $J_{3,4}$ 3.6 Hz, 3-H), 3.68 (m, 1 H, 4-H), 3.29 and 2.74 (m, 4 H, CH_2CH_2); *m/z* (%) (mixture), 217 (M^+, 18), 177 (14), 133 (17), and 132 (100) [Found (mixed isomers): C, 60.65; H, 5.1; N, 19.35. $C_{11}H_{11}N_3O_2$ requires C, 60.80; H, 5.10; N, 19.35%].

2-(2-*Methoxycarbonylethyl*)-3-(2-*furyl*)-4- *and* 5-*methoxycarbonylisoxazolidine* (23)—(26) (R = 2-furyl, X = CO_2Me).—The pale yellow oily product (82%) was obtained as a mixture of isomers (see Table 6) which were separated by h.p.l.c. [Partisil 10M9, mobile phase ether-pentane (20 : 80), flow rate 6.4 ml/min]. All four isomers are colourless oils: (23; R = 2-furyl, X = CO_2Me), δ 7.39 and 6.3 (d, 3 H, furyl-H), 4.69 (q, 1 H, $J_{4,5}$ 8.6, 6.2 Hz, 5-H), 3.74 (t, 1 H, $J_{3,4}$ 7.37 Hz, 3-H), 2.85 and 2.64 (m, 2 H, 2 × 4-H), 3.09 and 2.76 (m, 4 H, CH_2CH_2), 3.78 and 3.65 (s, 6 H, 2 × OMe).

(24; R = 2-furyl, X = CO_2Me), δ 7.37 and 6.28 (d, 3 H, furyl-H), 4.65 (t, 1 H, $J_{4,5}$ 7.7 Hz, 5-H), 4.13 (t, 1 H, $J_{3,4}$ 3.36 Hz, 3-H), 2.87 and 2.75 (m, 2 H, 2 × 4-H), 2.87 and 2.68 (m, 4 H, CH_2CH_2), 3.77 and 3.65 (s, 6 H, 2 × OMe).

(25; R = 2-furyl, X = CO_2Me), δ 7.37 and 6.27 (d, 3 H, furyl-H), 4.42 and 4.18 (t, 2 H, 2 × 5-H), 4.28 (d, 1 H, $J_{3,4}$

7.68 Hz, 3-H), 2.61 (q, 1 H, 4-H), 3.0 and 2.6 (m, 4 H, CH_2-CH_2), 3.66 and 3.45 (s, 6 H, 2 × OMe).

(26; R = 2-furyl, X = CO_2Me), δ 7.4, 6.3 (d, 3 H, furyl-H), 4.14 (t, 2 H, 2 × 5-H), 4.24 (d, 1 H, $J_{3,4}$ 1.7 Hz, 3-H), 2.46 (m, 1 H, 4-H), 3.07 and 2.66 (m, 4 H, CH_2CH_2), 3.72, 3.65 (s, 6 H, 2 × OMe); *m/z* (%) (mixture), 283 (M^+, 29), 224 (24), 210 (33), and 165 (100) [Found (mixed isomers): C, 54.95; H, 6.25; N, 4.95. $C_{13}H_{17}NO_6$ requires C, 55.10; H, 6.05; N, 4.95%].

2-(2-*Cyanoethyl*)-3-*phenyl*-4- *and* 5-*cyanoisoxazolidine* (23)—(26) (R = Ph, X = CN).—The pale yellow oily product (81%) was obtained as a mixture of isomers (see Table 6) which were separated by p.t.l.c. (ether–pentane, 40 : 60): (23; R = Ph, X = CN), m.p. 128—129 °C (from ether), δ 7.4 (m, 5 H, Ph), 4.89 (q, 1 H, $J_{4,5}$ 9.19, 4.04 Hz, 5-H), 3.67 (t, 1 H, $J_{3,4}$ 8.46 Hz, 3-H), 3.1 and 2.6 (m, 2 H, 2 × 4-H), 3.08, 2.9, and 2.72 (m, 4 H, CH_2CH_2).

(24; R = Ph, X = CN), colourless oil, δ 7.4 (m, 5 H, Ph), 4.86 (q, 1 H, $J_{4,5}$ 8.82, 4.41 Hz, 5-H), 4.09 (q, 1 H, $J_{3,4}$ 9.19, 6.99 Hz, 3-H), 2.94, 2.68 (m, 2 H, 2 × 4-H), 3.0, 2.84, 2.66 (m, 4 H, CH_2CH_2).

(25; R = Ph, X = CN), colourless oil, δ 7.45 (m, 5 H, Ph), 4.4, 4.19 (t, 2 H, 2 × 5-H), 3.85, (d, 1 H, $J_{3,4}$ 8.8 Hz, 3-H), 3.75 (q, 1 H, 4-H), 3.08, 2.84, 2.65 (m, 4 H, CH_2CH_2).

(26; R = Ph, X = CN), colourless oil, δ 7.38 (m, 5 H, Ph), 4.29 (m, 2 H, 2 × 5-H), 3.84 (d, 1 H, $J_{3,4}$ 8.0 Hz, 3-H), 3.34 (m, 1 H, 4-H), 3.0, 2.63 (m, 4 H, CH_2CH_2); *m/z* (%) (mixture) 227 (M^+, 45), 187 (35), and 142 (100) [Found (mixed isomers): C, 68.65; H, 5.75; N, 18.60. $C_{13}H_{13}N_3O$ requires C, 68.70; H, 5.75; N, 18.50%].

2-(2-*Methoxycarbonylethyl*)-3-*phenyl*-4- *and* 5-*methoxycarbonylisoxazolidine* (23)—(26) (R = Ph, X = CO_2Me).—The pale yellow oily mixture (83%) of products (isomer ratio, Table 6) was separated by p.t.l.c. (ether–pentane, 40 : 60). All four isomers are colourless oils: (23; R = Ph, X = CO_2Me), δ 7.2 (m, 5 H, Ph), 4.36 (q, 1 H, $J_{4,5}$ 9.19, 5.15 Hz, 5-H), 3.72 (t, 1 H, $J_{3,4}$ 7.5 Hz, 3-H), 2.94, 2.62 (m, 2 H, 2 × 4-H), 3.78, 3.62 (s, 6 H, 2 × OMe), 3.0, 2.87, 2.65 (m, 4 H, CH_2-CH_2).

(24; R = Ph, X = CO_2Me), δ 7.24 (m, 5 H, Ph), 4.67 (q, 1 H, $J_{4,5}$ 8.82, 5.15 Hz, 5-H), 3.92 (t, 1 H, $J_{3,4}$ 7.5 Hz, 3-H), 2.9, 2.78 (m, 2 × 4-H), 3.7 and 3.6 (s, 6 H, 2 × OMe), 3.0, 2.8, 2.6, (m, 4 H, CH_2CH_2).

(25; R = Ph, X = CO_2Me), δ 7.2 (m, 5 H, Ph), 4.42, 4.2 (t, 2 H, 2 × 5-H), 4.02 (d, 1 H, $J_{3,4}$ 8.8 Hz, 3-H), 3.72 (q, 1 H, 4-H), 3.67, 3.17 (s, 6 H, 2 × OMe), 3.0, 2.8, 2.6 (m, 4 H, CH_2CH_2).

(26; R = Ph, X = CO_2Me), δ 7.3 (m, 5 H, Ph), 4.23 (m, 2 H, 2 × 5-H), 3.97 (d, 1 H, $J_{3,4}$ 7.35 Hz, 3-H), 3.4 (q, 1 H, 4-H), 3.73, 3.65 (s, 6 H, 2 × OMe), 2.98, 2.61 (m, 4 H, CH_2CH_2); *m/z* (%) (mixture), 293 (M^+, 38), 220 (54), 174 (8), and 84 (100); [Found (mixed isomers): C, 61.2; H, 6.7; N, 4.5. $C_{15}H_{19}NO_5$ requires C, 61.40; H, 6.55; N, 4.80%].

2-(2-*Cyanoethyl*)-3-(p-*methoxyphenyl*)-4- *and* 5-*cyanoisoxazolidine* (23)—(26) (R = p-$MeOC_6H_4$, X = CN).—The pale yellow oily mixture (82%, isomer ratio Table 6) was separated by h.p.l.c. [Partisil 10M9, mobile phase ether–pentane (35 : 65), flow rate 6 ml/min].

(23; R = *p*-$MeOC_6H_4$, X = CN), colourless needles, m.p. 105—106 °C (from ether), δ 7.26, 6.98 (ABq, 4 H, C_6H_4), 4.88 (q, 1 H, $J_{4,5}$ 9.19, 4.04 Hz, 5-H), 3.63 (t, 1 H, $J_{3,4}$ 8.46 Hz, 3-H), 3.06, 2.55 (m, 2 H, 2 × 4 H), 3.72 (s, 3 H, OMe), 3.0, 2.6 (m, 4 H, CH_2CH_2).

(24; R = *p*-$MeOC_6H_4$, X = CN), δ 7.2, 6.8 (ABq, 4 H, C_6H_4), 4.86 (q, 1 H, $J_{4,5}$ 8.82, 4.04, 5-H Hz), 4.03 (t, 1 H, $J_{3,4}$ 7.9 Hz, 3-H), 2.89 and 2.71 (m, 2 H, 2 × 4-H), 3.76 (s, 3 H, OMe), 2.96 and 2.66 (m, 4 H, CH_2CH_2).

(25; R = *p*-$MeOC_6H_4$, X = CN), δ 7.4, 6.98 (ABq, 4 H, C_6H_4), 4.39, 4.19 (t, 2 H, 2 × 5-H), 3.82 (d, 1 H, $J_{3,4}$ 9.0 Hz, 3-H), 3.72 (q, 1 H, 4-H), 3.8 (s, 3 H, OMe), 3.0, 2.8, 2.65 (m, 4 H, CH_2CH_2).

(26; R = *p*-$MeOC_6H_4$, X = CN), δ 7.27, 6.98 (ABq, 4 H, C_6H_4), 4.29, 4.22 (m, 2 H, 2 × 5-H), 3.79 (d, 1 H, $J_{3,4}$ 7.2 Hz, 3-H), 3.36 (m, 1 H, 4-H), 3.77 (s, 3 H, OMe), 2.9, 2.6 (m, 4 H, CH_2CH_2); *m/z* (%) (mixture) 257 (M^+, 18), 204 (22), and 172 (100) [Found (mixed isomers): C, 65.2; H, 5.9; N, 16.05. $C_{14}H_{15}N_3O_2$ requires C, 65.35; H, 5.90; N, 16.35%].

2-(2-*Methoxycarbonylethyl*)-3-(p-*methoxyphenyl*)-4- *and* 5-*methoxycarbonylisoxazolidine* (23)—(26) (R = *p*-$MeOC_6H_4$, X = CO_2Me).—The pale yellow oily mixture (82%; isomer ratio Table 6) was separated by h.p.l.c. [Partisil 10M9, mobile phase ether–pentane (25 : 75), flow rate 6.2 ml/min]. All four isomers are colourless oils: (23; R = *p*-$MeOC_6H_4$, X = CN), δ 7.2, 6.82 (ABq, 4 H, C_6H_4), 4.62 (q, 1 H, $J_{4,5}$ 9.19, 5.5 Hz, 5-H), 3.72 (t, 1 H, $J_{3,4}$ 9.9 Hz, 3-H), 2.87, 2.58 (m, 2 H, 2 × 4-H), 3.78, 3.6 (s, 9 H, 3 × OMe), 3.0, 2.64 (m, 4 H, CH_2CH_2).

(24; R = *p*-$MeOC_6H_4$, X = CN), δ 7.18, 6.8 (ABq, 4 H, C_6H_4), 4.68 (q, 1 H, $J_{4,5}$ 8.82, 5.5 Hz, 5-H), 3.8 (t, 1 H, $J_{3,4}$ 8.0 Hz, 3-H), 2.67, 2.59 (m, 2 H, 2 × 4-H), 3.79, 3.6 (s, 9 H, 3 × OMe), 2.86, 2.6 (m, 4 H, CH_2CH_2).

(25; R = *p*-$MeOC_6H_4$, X = CN), δ 7.14, 6.67 (ABq, 4 H, C_6H_4), 4.38, 4.14 (t, 2 H, 2 × 5-H), 3.98 (d, 1 H, $J_{3,4}$ 9.56, 3-H), 3.72 (m, 1 H, 4-H), 3.78, 3.65, 3.21, (s, 3 H, 3 × OMe), 2.9, 2.6 (m, 4 H, CH_2CH_2).

(26; R = *p*-$MeOC_6H_4$, X = CN), δ 7.24, 6.84 (ABq, 4 H, C_6H_4), 4.21, 4.14 (dd, 2 H, 2 × 5-H), 4.2 (d, 1 H, $J_{3,4}$ 6.0 Hz, 3-H), 3.35 (q, 1 H, 4-H), 3.8, 3.69, 3.6 (s, 9 H, 3 × OMe), 3.0, 2.88, 2.58 (m, 4 H, CH_2CH_2); *m/z* (%) (mixture) 323 (M^+, 66), 264 (14), 250 (40), and 145 (100) [Found (mixed isomers): C, 59.55; H, 6.45; N, 4.2. $C_{16}H_{21}NO_6$ requires C, 59.45; H, 6.55; N, 4.35%].

2-(2-*Cyanoethyl*)-3-(p-*trifluoromethylphenyl*)-4- *and* 5-*cyanoisoxazolidine* (23), (24), (26) (R = *p*-$CF_3C_6H_4$, X = CN).—The yellow oily mixture (79%) of three isomers (Table 6) was separated by p.t.l.c. (ether–pentane, 40 : 60): (23; R = *p*-$CF_3C_6H_4$, X = CN), colourless rods, m.p. 125—126 °C (from ether), δ 7.68, 6.8 (ABq, 4 H, C_6H_4), 4.94 (q, 1 H, $J_{4,5}$ 9.19, 3.68 Hz, 5-H), 3.78 (t, 1 H, $J_{3,4}$ 8.46 Hz, 3-H), 3.17 2.57 (m, 2 H, 2 × 4-H), 3.0, 2.72 (m, 4 H, CH_2CH_2).

(24; R = *p*-$CF_3C_6H_4$, X = CN), colourless oil, δ 7.6, 6.8 (ABq, 4 H, C_6H_4), 4.89 (q, 1 H, $J_{4,5}$ 8.82, 4.4 Hz, 5-H), 4.2 (t, 1 H, $J_{3,4}$ 7.0 Hz, 3-H), 2.85, 2.51 (m, 2 H, 2 × 4-H), 3.0, 2.74 (m, 4 H, CH_2CH_2).

(26; R = *p*-$CF_3C_6H_4$, X = CN), colourless oil, δ 7.7, 6.7 (ABq, 4 H, C_6H_4), 4.32 (m, 2 H, 2 × 5-H), 3.97 (d, 1 H, $J_{3,4}$ 7.7 Hz, 3-H), 3.39 (m, 1 H, 4-H), 3.0, 2.74 (m, 4 H, CH_2CH_2); *m/z* (%) (mixture), 295 (M^+, 21), 255 (84), 210 (100), and 190 (14) [Found (mixed isomers): C, 56.8; H, 4.05; N, 14.0. $C_{14}H_{12}F_3N_3O$ requires C, 56.95; H, 4.05; N, 14.25%].

2-(2-*Methoxycarbonylethyl*)-3-(p-*trifluoromethylphenyl*)-4- *and* 5-*methoxycarbonylisoxazolidine* (23), (25), (26) (R = *p*-$CF_3C_6H_4$, X = CO_2Me).—The yellow oily mixture (79%) of three isomers was separated by p.t.l.c. (ether–pentane, 40 : 60). All three isomers are colourless oils: (23; R = *p*-$CF_3C_6H_4$, X = CO_2Me), δ 7.5, 6.6 (ABq, 4 H, C_6H_4), 4.67 (q, 1 H, $J_{4,5}$ 9.19, 5.15 Hz, 5-H), 4.0 (t, 1 H, $J_{3,4}$ 7.5 Hz, 3-H), 3.0, 2.85 (m, 2 H, 2 × 4-H), 3.0, 2.7 (m, 4 H, CH_2CH_2), 3.79, 3.65 (s, 6 H, OMe).

(25; R = *p*-$CF_3C_6H_4$, X = CO_2Me), δ 7.5, 6.7 (ABq, 4 H, C_6H_4), 4.38, 4.22 (t, 2 H, 2 × 5-H), 4.14 (d, 1 H, $J_{3,4}$ 7.5 Hz,

3-H), 3.8 (q, 1 H, 4-H), 3.0, 2.7 (m, 4 H, CH_2CH_2), 3.78, 364 (s, 6 H, OMe).

(26; R = *p*-$CF_3C_6H_4$, X = CO_2Me), δ 7.56, 6.65 (ABq, 4 H, C_6H_4), 4.23 (dd, 2 H, 5-H), 4.06 (d, 1 H, $J_{3,4}$ 7.2 Hz, 3-H), 3.12 (q, 1 H, 4-H), 3.0, 2.66 (m, 4 H, CH_2CH_2), 3.7, 3.6 (s, 6 H, 2 × OMe); *m/z* (%) (mixture) 361 (M^+, 37), 302 (30), 288 (100) and 243 (20) [Found (mixed isomers): C, 53.4; H, 5.1; N, 4.0. $C_{16}H_{18}F_3NO_5$ requires C, 53.20; H, 5.00; N, 3.90%].

2-(2-*Cyanoethyl*)-3,3-*dimethyl*-4- *and* 5-*cyanoisoxazolidine* (15a) *and* (16a).—The yellow oily product mixture (75%) was separated (isomer ratio Table 2) by p.t.l.c. (ether–pentane, 40 : 60) to give pure samples of (15a) and (16a), both of which are colourless oils: (15a), δ 4.69 (q, 1 H, $J_{4,5}$ 8.18, 6.56 Hz, 5-H), 2.49 (m, 2 H, 2 × 4-H), 1.34 and 1.27 (s, 6 H, 2 × Me), 2.88 and 2.66 (m, 4 H, CH_2CH_2).

(16a), δ 4.19 (q, 1 H, $J_{4,5}$ 8.18, 7.36 Hz, 5-H), 3.98 (q, 1 H, $J_{4,5}$ 7.36, 6.55 Hz, 5-H), 3.25 (q, 1 H, 4-H), 1.24, 1.08 (s, 6 H, 2 × Me), 2.88, 2.66 (m, 4 H, CH_2CH_2); *m/z* (%) (mixture) 179 (M^+, 10), 164 (27), 139 (30) [Found (mixed isomers): C, 60.25; H, 7.2; N, 23.45. $C_9H_{13}N_3$ requires C, 60.30; H, 7.30; N, 23.45%].

2-(2-*Methoxycarbonylethyl*)-3,3-*dimethyl*-4- *and* 5-*methoxycarbonylisoxazolidine* (15) *and* (16) (R¹ = R² = Me, X = CO_2Me).—The oily mixture (81%) was separated (isomer ratio Table 2) by p.t.l.c. (ether–pentane, 40 : 60) to give pure samples of both isomers as colourless oils: (15; R¹ = R² = Me, X = CO_2Me), δ 4.51 (q, 1 H, $J_{4,5}$ 7.8, 6.55 Hz, 5-H), 2.31 (m, 2 H, 2 × 4-H), 3.66, 3.6 (s, 6 H, 2 × OMe), 1.26, 1.1 (s, 6 H, 2 × Me), 2.85, 2.64 (m, 4 H, CH_2CH_2).

(16; R¹ = R² = Me, X = CO_2Me), δ 4.24 (t, 1 H, $J_{4,5}$ 7.36 Hz, 5-H), 3.9 (t, 1 H, $J_{4,5}$ 6.55 Hz, 5-H), 3.22 (q, 1 H, $J_{4,5}$ 7.36, 6.55 Hz, 4-H), 3.64, 3.6 (s, 6 H, 2 × OMe), 1.08, 0.98 (s, 6 H, 2 × Me), 2.85, 2.64 (m, 4 H, CH_2CH_2); *m/z* (%) (mixture), 245 (M^+, 8), 230 (40), and 172 (28) [Found (isomer mixture): C, 53.75; H, 7.85; N, 5.60. $C_{11}H_{19}NO_5$ requires C, 53.85; H, 7.80; N, 5.70%].

2-(2-*Cyanoethyl*)-3,3-*diethyl*-4- *and* 5-*cyanoisoxazolidine* (15) *and* (16) (R¹ = R² = Et, X = CN).—The oily mixture (74%) of two regioisomers was separated (isomer ratio Table 2) by p.t.l.c. (ether–pentane, 40 : 60) to give pure samples of both isomers as colourless oils: (15; R¹ = R² = Et, X = CN), δ 4.74 (q, 1 H, $J_{4,5}$ 9.56, 5.15 Hz, 5-H), 2.52, 2.36 (m, 2 H, 2 × 4-H), 1.5 (m, 4 H, 2 × CH_2Me), 1.0 (m, 6 H, 2 × Me), 1.82, 1.7 (m, 4 H, CH_2CH_2).

(16; R¹ = R² = Et, X = CN), δ 4.28, 4.1 (t, 2 H, $J_{4,5}$ 7.5 Hz, 2 × 5-H), 3.29 (q, 1 H, $J_{4,5}$ 9.56, 5.88 Hz, 4-H), 1.5 (m, 4 H, 2 × CH_2Me), 1.0 (m, 6 H, 2 × Me), 1.82, 1.7 (m, 4 H, CH_2CH_2); *m/z* (%) (mixture) 207 (M^+, 6) and 178 (100) [Found (isomer mixture): C, 63.5; H, 8.3; N, 19.95. $C_{11}H_{17}N_3O$ requires C, 63.75; H, 8.30; N, 20.25%].

2-(2-*Methoxycarbonylethyl*)-3,3-*diethyl*-4- *and* 5-*methoxycarbonylisoxazolidine* (15) *and* (16) (R¹ = R² = Et, X = CO_2-Me).—The mixture (81%) of regioisomers (isomer ratio Table 2) was separated by p.t.l.c. (ether–pentane, 40 : 60) to give both regioisomers as colourless oils: (15; R¹ = R² = Et, X = CO_2Me), δ 4.59 (q, 1 H, $J_{4,5}$ 9.56, 6.61 Hz, 5-H), 2.38, 2.26 (m, 2 H, 2 × 4-H), 3.7, 3.6 (s, 6 H, 2 × OMe), 1.54 (m, 4 H, 2 × CH_2), 0.98 (m, 6 H, 2 × Me), 2.86, 2.6 (m, 4 H, CH_2CH_2).

(16; R¹ = R² = Et, X = CO_2Me), δ 4.18, 4.07 (t, 2 H, 2 × 5-H, $J_{4,5}$ 8.75 Hz), 3.2 (q, 1 H, 4-H), 3.72, 3.65 (s, 6 H, 2 × OMe), 1.54 (m, 4 H, 2 × CH_2), 0.98 (m, 6 H, 2 × Me), 2.86, 2.6 (m, 4 H, CH_2CH_2); *m/z* (%) (mixture) 273 (M^+, 9), 244 (100), 200 (12), and 87 (22) [Found (isomer mixture): C, 57.3; H, 8.45; N, 5.25. $C_{13}H_{23}NO_5$ requires C, 57.10; H, 8.50; N, 5.15%].

2-(2-*Cyanoethyl*)-3-(2-*thienyl*)-4- *and* 5-*cyanoisoxazolidine* (15) *and* (16) (R¹ = 2-*thienyl*, R² = H, X = CN).—The product (77%) was obtained as a pale yellow oily mixture of regio- and stereo-isomers which were not separated [Found: C, 56.50; H, 4.80; N, 18.10. $C_{11}H_{11}N_3OS$ requires C, 56.65; H, 4.7; N, 18.05%); $\nu_{max.}$ 2 250, 1 180, and 1 070 cm^{-1}; *m/z* (%), 233 (M^+, 17), 192 (10), 148 (100), and 124 (12).

2-(2-*Methoxycarbonylethyl*)-3-(2-*thienyl*)-4- *and* 5-*methoxycarbonylisoxazolidine* (15) *and* (16) (R¹ = 2-thienyl, R² = H, X = CO_2Me).—This was obtained as a pale yellow oily mixture (77%) of regio- and stereo-isomers which were not separated (Found: C, 52.45; H, 5.9; N, 4.50. $C_{13}H_{17}NO_5S$ requires C, 52.15; H, 5.70; N, 4.70%); $\nu_{max.}$ 1 745, 1 200, and 1 050 cm^{-1}; *m/z* (%), 299 (M^+, 5), 240 (16), 226 (27), and 181 (100).

2-(2-*Cyanoethyl*)-3-*methyl*-4- *and* 5-*cyanoisoxazolidine* (15) *and* (16) (R¹ = Me, R² = H, X = CN).—The pale yellow oily product (71%) consisted of a mixture of regio- and stereo-isomers which were not separated (Found: C, 58.25; H, 6.95; N, 25.7. $C_8H_{11}N_3O$ requires C, 58.15; H, 6.70; N, 25.45%); $\nu_{max.}$ 2 250, 1 170, and 1 020 cm^{-1}; *m/z* (%) 165 (M^+, 1) and 124 (88).

2-(2-*Methoxycarbonylethyl*)-3-*methyl*-4- *and* -5-*methoxycarbonylisoxazolidine* (15) *and* (16); (R¹ = Me, R² = H, X = CO_2Me).—The product (73%) was obtained as a mixture of regio- and stereo-isomers which were not further separated (Found: C, 51.95; H, 7.4; N, 6.05. $C_{10}H_{17}NO_5$ requires C, 51.85; H, 7.45; N, 5.95%); $\nu_{max.}$ 1 740, 1 200, and 1 050 cm^{-1}; *m/z* (%) 231 (M^+, 29), 216 (44), and 158 (81).

2-(2-*Cyanoethyl*)-3-*ethyl*-4- *and* -5-*cyanoisoxazolidine* (15) *and* (16) (R¹ = Et, R² = H, X = CN).—This was obtained as a pale yellow oily mixture (76%) of regio- and stereo-isomers (Found: C, 60.0; H, 7.5; N, 23.45. $C_9H_{13}N_3O$ requires C, 60.30; H, 7.30; N, 23.45%); $\nu_{max.}$ 2 250, 1 200, and 1 070 cm^{-1}; *m/z* (%) 179 (M^+, 14), 150 (95), 139 (76), and 28 (100).

2-(2-*Methoxycarbonylethyl*)-3-*ethyl*-4- *and* -5-*methoxycarbonylisoxazolidine* (15) *and* (16) (R¹ = Et, R² = H, X = CO_2Me).—The pale yellow oily product (82%) consisted of a mixture of regio- and stereo-isomers which were not separated (Found: C, 53.9; H, 7.95; N, 5.7. $C_{11}H_{19}NO_5$ requires C, 53.85; H, 7.80; N, 5.70%); $\nu_{max.}$ 1 750, 1 200, and 1 030 cm^{-1}; *m/z* (%) 245 (M^+, 15), 216 (82), and 172 (58).

2-(2-*Cyanoethyl*)-3-*n*-*propyl*-4- *and* -5-*cyanoisoxazolidine* (15) *and* (16) (R¹ = Pr^n, R² = H, X = CN).—The product (81%) was obtained as a pale yellow oily mixture of stereo- and regio-isomers which were not further separated (Found: C, 62.3; H, 8.05; N, 21.5. $C_{10}H_{15}N_3O$ requires C, 62.15; H, 7.90; N, 21.75%); $\nu_{max.}$ 2 245, 1 245, and 1 040 cm^{-1}; *m/z* (%), 193 (M^+, 2) and 151 (42).

2-(2-*Methoxycarbonylethyl*)-3-*n*-*propyl*-4- *and* -5-*methoxycarbonylisoxazolidine* (15) *and* (16); (R¹ = Pr^n, R² = H, X = CO_2Me).—This was obtained as a pale yellow oily mixture (84%) of regio- and stereo-isomers (Found: C, 55.6; H, 8.35; N, 5.3. $C_{12}H_{21}NO_5$ requires C, 55.60; H, 8.15; N, 5.40%); $\nu_{max.}$ 1 740, 1 200, and 1 035 cm^{-1}; *m/z* (%) 259 (M^+, 16), 216 (94), and 186 (38).

2-(2-*Cyanoethyl*)-3-*isoropyl*-4- *and* -5-*cyanoisoxazolidine* (15) *and* (16) (R^1 = Pr^i, R^2 = H, X = CN).—The pale yellow oily product (72%) comprised a mixture of regio- and stereo-isomers (Found: C, 62.15; H, 7.9, N, 21.5. $C_{10}H_{15}N_3O$ requires C, 62.15; H, 7.85; N, 21.75%); $\nu_{max.}$ 2 247, 1 230, and 1 045 cm^{-1}; *m/z* (%) 193 (M^+, 3) and 150 (100).

2-(2-*Methoxycarbonylethyl*)-3-*isopropyl*-4- *and* -5-*methoxycarbonylisoxazolidine* (15) *and* (16) (R^1 = Pr^i, R^2 = H, X = CO_2Me).—The product (77%) consisted of a pale yellow oily mixture of regio- and stereo-isomers (Found: C, 55.75; H, 8.4; N, 5.45. $C_{12}H_{21}NO_5$ requires C, 55.60; H, 8.15; N, 5.40%); $\nu_{max.}$ 1 735, 1 200, and 1 050 cm^{-1}; *m/z* (%) 259 (M^+, absent) and 216 (25).

2-(2-*Cyanoethyl*)-3-(p-*dimethylaminophenyl*)-4- *and* -5-*cyanoisoxazolidine* (15) *and* (16) (R^1 = *p*-$Me_2NC_6H_4$, R^2 = H, X = CN).—This was obtained as a pale yellow oily mixture (81%) of regio- and stereo-isomers (Found: C, 66.6; H, 6.85; N, 20.8. $C_{15}H_{18}NO_4$ requires C, 66.65; H, 6.70; N, 20.75%); $\nu_{max.}$ 2 240, 1 170, and 1 050 cm^{-1}; *m/z* (%) 270 (M^+, 43), 217 (90), and 185 (100).

2-(2-*Methoxycarbonylethyl*)-3-(p-*dimethylaminophenyl*)-4- *and* -5-*methoxycarbonylisoxazolidine* (15) *and* (16) (R^1 = *p*-$Me_2NC_6H_4$, R^2 = H, X = CN).—The pale yellow oily product (85%) comprised a mixture of regio- and stereo-isomers which were not separated (Found: C, 61.0; H, 7.35; N, 8.3. $C_{17}H_{24}N_2O_5$ requires C, 60.70; H, 7.20; N, 8.35%); $\nu_{max.}$ 1 735, 1 200, and 1 060 cm^{-1}; *m/z* (%) 336 (M^+, 11), 250 (60), 218 (24), and 148 (100).

2-(2-*Cyanoethyl*)-3-*ethyl*-3-*methyl*-4- *and* -5-*cyanoisoxazolidine* (15) *and* (16) (R^1 = Me, R^2 = Et, X = CN).—The product (77%) consisted of a pale yellow oily mixture of regio- and stereo-isomers (Found: C, 62.25; H, 7.95; N, 21.7. $C_{10}H_{15}N_3O$ requires C, 62.15; H, 7.80; N, 21.75%); $\nu_{max.}$ 2 240, 1 150, and 1 040 cm^{-1}; *m/z* (%); 193 (M^+, 10), 164 (100), and 153 (14).

2-(2-*Methoxycarbonylethyl*)-3-*ethyl*-3-*methyl*-4- *and* -5-*methoxycarbonylisoxazolidine* (15) *and* (16) (R^1 = Me, R^2 = Et, X = CO_2Me).—This was obtained as a pale yellow oily mixture (82%) of regio- and stereo-isomers (Found: C, 55.3; H, 8.15; N, 5.35. $C_{12}H_{21}NO_5$ requires C, 55.60; H, 8.15; N, 5.40%); $\nu_{max.}$ 1 750, 1 200, and 1 050 cm^{-1}; *m/z* (%), 259 (M^+, 12), 230 (100), and 186 (17).

Reaction of O-*Allylsalicylaldehyde Oxime with Acrylonitrile.*—A solution of *O*-allylsalicylaldehyde oxime (5 g, 2.83 × 10^{-2} mol) and acrylonitrile (2.25 g, 4.24 × 10^{-2} mol) in pyridine (50 ml) was heated at 80 °C for 2 d. The residue, after removal of pyridine under reduced pressure, was poured into 5% aqueous hydrochloric acid (220 ml) and CH_2Cl_2 (250 ml). The aqueous layer was extracted with CH_2Cl_2 (3 × 200 ml), washed with water (3 × 200 ml), and dried ($MgSO_4$). After evaporation of solvent under reduced pressure, the crude product (5.56 g, 79%) was chromatographed (p.t.l.c.; ether–pentane, 4 : 1) to give 1-*cyanoethyl*-1,3a,4,9b-*tetrahydro*-3H-*isoxazolo*[3,4-d]*benzo*[b]*pyran* (31b) (3.34 g, 53.4%), colourless rods, m.p. 118—119 °C (Found: C, 67.9; H, 6.15; N, 12.25. $C_{13}H_{14}N_2O_2$ requires C, 67.80; H, 6.15; N, 12.15%), $\nu_{max.}$ 2 245 (CN), 1 610, 1 590, 1 490, and 1 450 (aromatic ring) cm^{-1}; δ 7.18, 6.92 (m, 4 H, C_6H_4), 4.18, 3.74 (dd, 4 H, 2 × CH_2), 4.07 (d, 1 H, J_{AB} 4.7 Hz, H_A), 3.0 (m, 1 H, H_B), 3.2, 2.66 (m, 4 H, CH_2CH_2); *m/z* (%) 230 (M^+, 28), 190 (16), and 145 (100), *and* 2-(2-*cyanoethyl*)-3-(*o*-*allyloxyphenyl*)-5-*cyanoisoxazolidine* (32a) (2.21 g, 27.7%) as a pale yellow oil, which comprised an approximately 1 : 1 mixture of *E*- and *Z*-isomers together with minor amounts of the other stereoisomeric regioisomers (Found: C, 67.9; H, 6.05; N, 14.6. $C_{16}H_{17}N_3O_2$ requires C, 67.80; H, 6.05; N, 14.85%); $\nu_{max.}$ 2 240, 1 200, and 1 060 cm^{-1}; *m/z* (%) 283 (M^+, 41), 243 (49), 198 (75), and 41 (100); δ (*Z*-isomer), 7.59—6.87 (m, 4 H, C_6H_4), 6.10, 5.35 (m, 3 H, CH=CH_2), 4.88 (q, 1 H, 5-H), 4.58 (m, 2 H, OCH_2), 4.22 (m, 1 H, 3-H), 3.10, 2.7 (m, 4 H, CH_2CH_2), 2.92 and 2.5 (m, 2 H, 4-H); δ (*E*-isomer), 7.48—6.87 (m, 4 H, C_6H_4), 6.06, 5.36 (m, 3 H, CH=CH_2), 4.79 (q, 1 H, 5-H), 4.60 (m, 2 H, OCH_2), 4.22 (m, 1 H, 3-H), 3.06 and 2.68 (m, 6 H, CH_2CH_2 and 2 × 4-H).

Reaction of O-*Allylsalicylaldehyde Oxime with Methyl Acrylate.*—A solution of *O*-allylsalicylaldehyde oxime (5 g, 2.83 × 10^{-2} mol) and methyl acrylate (3.64 g, 4.24 × 10^{-2}) in pyridine (50 ml) was heated at 80 °C for 2.5 d. The residue, after removal of pyridine under reduced pressure, was poured into 5% aqueous hydrochloric acid (200 ml) and CH_2Cl_2 (250 ml). The aqueous layer was extracted with CH_2Cl_2 (3 × 200 ml), washed with water (3 × 200 ml), and dried ($MgSO_4$). After evaporation of solvent under reduced pressure, the crude product (6.95 g, 82%) was chromatographed (p.t.l.c.; ether–pentane, 2 : 3) to give 1-(2-methoxycarbonylethyl)-1,3a,4,9b-tetrahydro-3*H*-isoxazolo[3,4-*d*]benzo[*b*]pyran (31c) (3.96 g, 46.5%) as a pale yellow oil (Found: C, 63.65; H, 6.5; N, 5.25. $C_{14}H_{17}NO_4$ requires C, 63.85; H, 6.50; N, 5.25%); $\nu_{max.}$ 1 735, 1 200, and 1 060 cm^{-1}; δ, 7.2, 6.94 (m, 4 H, C_6H_4), 4.24, 3.8 (dd, 4 H, 2 × CH_2), 4.1 (d, 1 H, J_{AB} 3.9 Hz, H_A), 3.67 (s, 3 H, OMe), 3.09 (m, 1 H, H_B), 3.2, 2.66 (m, 4 H, CH_2CH_2); *m/z* (%) 263 (M^+, 24), 190 (20) and 145 (100); and 2-(2-methoxycarbonylethyl)-3-(*o*-allyloxyphenyl)-5-methoxycarbonylisoxazolidine (32b) (2.99 g, 35.2%), a mixture of stereoisomers, as a pale yellow oil (Found: C, 61.95; H, 6.7; N, 4.25. $C_{18}H_{23}NO_4$ requires C, 61.60; H, 6.65; N, 4.00%); $\nu_{max.}$ 1 735, 1 200, and 1 050 cm^{-1}; *m/z* (%), 349 (M^+, 89), 290 (21), 276 (65), 175 (59), and 145 (100); δ (major isomer) 7.58—6.8 (m, 4 H, C_6H_4), 6.05, 5.36 (m, 3 H, $CHCH_2$), 4.6 (m, 3 H, OCH_2 and 5-H), 4.45 (t, 1 H, 3-H), 3.78, 3.67 (2 × s, 6 H, OMe), 3.15, 2.76 (m, 4 H, CH_2CH_2), 2.86 and 2.52 (m, 2 H, 2 × 4-H).

Reaction between Acetone Oxime and N-*Phenylmaleimide.*—(*a*) Acetone oxime (0.5 g, 6.9 mmol) and *N*-phenylmaleimide (1.18 g, 6.9 mmol) were dissolved in acetonitrile (40 ml). The solution was purged with argon for 20 min and then boiled under reflux for 3 d. Evaporation of the solvent left an orange viscous oil (1.45 g) the n.m.r. spectrum of which showed it to contain the 2 : 1 adduct (33) (*ca.* 60%). The crude mixture was dissolved in chloroform and ether added to afford (33) as colourless prisms, m.p. 193—194 °C (Found: C, 65.55; H, 5.0; N, 9.85. $C_{23}H_{21}N_3O_5$ requires C, 65.86; H, 5.05; N, 10.00%); $\nu_{max.}$ (KBr), 1 780, 1 710, 1 590, and 1 490 cm^{-1}; δ 7.53—7.25 (m, 10 H, ArH), 5.01 (d, 1 H, J_{AB} 8.09 Hz, H_A), 4.22 (dd, 1 H, *J* 8.09 and 5.88 Hz, H_C), 3.67 (d, 1 H, H_B), 3.12 (m, 2 H, H_D), 1.64 (s, 3 H, Me), and 1.39 (s, 3 H, Me); *m/z* (%), 419 (M^+, 6), 173 (100), 145 (6), 129 (17), 117 (12), 103 (6), and 91 (8).

(*b*) The above reaction was repeated using *N*-phenylmaleimide (2.37 g, 13.8 mmol) and work-up as before gave an orange froth (2.80 g) the n.m.r. spectrum of which indicated a mixture of (33) (60%) and unchanged *N*-phenylmaleimide.

Reaction between Acetone Oxime, N-*Phenylmaleimide, and Methyl Acrylate.*—(*a*) Acetone oxime (18 mg, 0.25 mmol), methyl acrylate (22 mg, 0.25 mmol), and *N*-phenylmaleimide (43 mg, 0.25 mmol) were dissolved in [$^2H_3$]acetonitrile (0.5 ml) in an n.m.r. tube which was then sealed and heated at 80 °C

Table 8. Atomic co-ordinates for non-hydrogen atoms (the e.s.d.s refer to the last digit)

Atom	*X*	*Y*	*Z*
C(1)	0.330 23(16)	0.863 1(3)	0.228 94(19)
C(2)	0.358 56(17)	0.736 2(3)	0.172 49(22)
C(3)	0.438 59(19)	0.618 2(3)	0.240 2(3)
C(4)	0.489 55(18)	0.627 5(4)	0.363 5(3)
C(5)	0.460 97(18)	0.751 1(4)	0.420 48(23)
C(6)	0.381 67(18)	0.869 9(3)	0.354 42(21)
C(7)	0.245 92(16)	0.996 9(3)	0.155 33(19)
C(8)	0.279 00(19)	1.194 7(3)	0.165 78(22)
C(9)	0.190 32(18)	1.297 5(3)	0.164 41(20)
C(10)	0.099 39(17)	0.855 9(3)	0.154 36(19)
C(11)	0.019 50(17)	0.880 9(3)	0.191 54(21)
C(12)	0.063 10(18)	0.901 5(3)	0.321 76(22)
C(13)	0.218 30(18)	1.378 4(3)	0.282 80(21)
N(1)	0.172 39(12)	1.006 39(24)	0.198 86(15)
N(2)	0.096 56(19)	0.919 9(3)	0.422 46(20)
N(3)	0.237 76(18)	1.442 8(3)	0.372 31(21)
O	0.111 89(11)	1.164 78(21)	0.133 68(13)

for 2 d. The ^{1}H n.m.r. spectrum after this time showed the presence of acetone (50%) and (34) (30%, see below).

(*b*) Acetone oxime (0.73 g, 10 mmol), methyl acrylate (0.86 g, 10 mmol), and *N*-phenylmaleimide (3.46 g, 20 mmol) were dissolved in acetonitrile (40 ml) and the solution purged with argon for 20 min and then boiled under reflux for 4 h. Evaporation of the solvent afforded an orange gum (5 g) the n.m.r. spectrum of which showed it to consist of (33) and (34) (ratio 57 : 43) (*ca.* 60%) and unchanged *N*-phenylmaleimide (*ca.* 40%). The crude gum was dissolved in chloroform and ether added to induce crystallisation whereupon (33) (0.55 g, 11%) separated as colourless prisms, m.p. 193—194 °C (see above). Preparative t.l.c. (ether) of a sample (500 mg) of the residue from the crystallisation afforded (34) (18 mg, 4% recovery), m.p. 128—130 °C, as colourless needles from chloroform (Found: C, 61.5; H, 6.35; N, 8.5. $C_{17}H_{20}N_2O_5$ requires C, 61.45; H, 6.05; N, 8.45%), $\nu_{max.}$ (KBr), 1 780, 1 730, 1 705, 1 590, and 1 490 cm^{-1}; δ 7.51—7.24 (m, 5 H, ArH), 4.84 (d, 1 H, J_{AB} 7.35 Hz, H_A), 3.64 (s, 3 H, CO_2Me), 3.22 (d, 1 H, H_B), 2.95 (m, 2 H, NCH_2), 2.67 (m, 2 H, CH_2CO_2Me), 1.31 (s, 3 H, Me), and 1.25 (s, 3 H, Me); *m/z* (%), 322 (M^+, 44), 318 (20), 317 (100), 259 (49), 173 (12), 170 (14), 142 (12), 119 (17), 112 (16), and 91 (12).

X-*Ray Analysis of* 2-(2-*Cyanoethyl*)-cis-5-*cyano*-3-*phenylisoxazolidine* (23; R = Ph, X = CN).—*Crystal data.* $C_{13}H_{13}N_2O$, M = 213.26, monoclinic, space group $P2_1/c$, a = 15.090 (7), b = 7.414(2), c = 12.721(5) Å, β = 119.77(3)°, U = 1235.37 Å^3, D_m = 1.17 g cm^{-3}, Z = 4, D_c = 1.147 g cm^{-3}, μ = (Mo-K_α) = 0.81 cm^{-1}.

Data collection conditions. Crystal size 0.35 × 0.30 × 0.20 mm, temperature 20 °C, take-off angle 3°, scan speed 2° min^{-1} in 2 θ, background 10% of total scan on both sides, scan width (1.4 + 0.692 tan θ)°, 2 θ limits 3.0—45.0°.

Precession and Weissenberg photographs were used to determine the space group and approximate cell dimensions. A crystal suitable for data collection was mounted in a Lindemann tube and accurate cell dimensions were determined by least-squares refinement of 34 accurately centred reflections (2θ = 26.5—35.3°, λ(Mo-K_α) = 0.709 26 Å). Data were collected using a Picker FACS-I automatic four-circle diffractometer with a graphite monochromator and a scintillation counter with pulse height discrimination. Symmetrical θ—2θ scans were used, whilst stationary-crystal, standing-counter background counts were taken for 10% of the scan time at each scan limit. The background corrected intensity and associated error of each reflection was determined by the peak profile method of Gabe and Grant (1977.)[20] The intensity values of two standards, measured every 70 reflections, were found to vary, ±4% from the mean, during data collection. The data set was scaled appropriately using the five-point smoothing procedure of Gabe *et al.*[21] Intensities (3° ⩽ 2θ ⩽ 45) were measured for 1 605 independent reflections, of which 1 161 were classed observed [$I \geqslant 2.3\ \sigma(I)$]. Lorentz and polarisation corrections have been made, however, no absorption correction has been applied in view of the low absorption coefficient (0.81 cm^{-1}).

Table 9. Bond parameters

(a) Distances (Å)

C(1)–C(2)	1.374(4)	C(9)–O	1.436(3)
C(2)–C(3)	1.390(3)	O–N(1)	1.466(2)
C(3)–C(4)	1.369(5)	N(1)–C(7)	1.467(4)
C(4)–C(5)	1.316(5)	C(9)–C(13)	1.475(4)
C(5)–C(6)	1.384(3)	C(13)–N(3)	1.131(4)
C(6)–C(1)	1.387(3)	N(1)–C(10)	1.470(3)
C(1)–C(7)	1.515(3)	C(10)–C(11)	1.509(4)
C(7)–C(8)	1.534(3)	C(11)–C(12)	1.455(4)
C(8)–C(9)	1.533(4)	C(12)–N(2)	1.128(4)

(b) Angles (°)

C(1)–C(2)–C(3)	120.5(2)	C(8)–C(9)–O	105.0(2)
C(2)–C(3)–C(4)	117.7(3)	C(9)–O–N(1)	101.4(1)
C(3)–C(4)–C(5)	123.1(2)	O–N(1)–C(7)	101.6(2)
C(4)–C(5)–C(6)	119.6(3)	O–N(1)–C(10)	104.7(1)
C(5)–C(6)–C(1)	119.8(3)	C(7)–N(1)–C(10)	112.4(2)
C(6)–C(1)–C(2)	119.0(2)	C(13)–C(9)–C(8)	112.6(2)
C(2)–C(1)–C(7)	120.6(2)	C(13)–C(9)–O	109.6(2)
C(6)–C(1)–C(7)	120.4(2)	N(1)–C(10)–C(11)	110.4(2)
C(1)–C(7)–C(8)	115.8(2)	C(10)–C(11)–C(12)	112.9(2)
C(1)–C(7)–N(1)	111.0(2)	C(11)–C(12)–N(2)	179.1(3)
N(1)–C(7)–C(8)	101.3(2)	C(9)–C(13)–N–3	178.4(5)
C(7)–C(8)–C(9)	103.3(2)		

Structure Solution and Refinement.—The structure was solved using MULTAN. The tangent refinement solution with best agreement factors was used to phase an *E*-map which revealed all the non-hydrogen atoms of the molecule. These atoms were assigned isotropic temperature factors and allowed to refine until there was no further improvement in the agreement (R = 0.125). At this stage the hydrogen atoms of the molecule were included in refinement, fixed in their calculated positions, with isotropic temperature factors derived from those of their parent carbon atoms. After three cycles of refinement the agreement remained constant at R = 0.083. After these cycles the co-ordinates of the hydrogen atoms were also allowed to refine resulting in further improvement in the agreement.

The final agreement factors converged at R = 0.034 [$R = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$] and R_w = 0.031 [$R_w = (\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2)^{\frac{1}{2}}$] for 207 variables, as a result of Gausse-Seidel block-diagonal least-squares refinement with anisotropic temperature factors for all non-hydrogen atoms and isotropic temperature factors for all hydrogen atoms. Analysis of the data set as a function of sin θ/λ and Miller indices indicated that unit weights provide the best basis for refinement. Atomic scattering factors including anomalous dispersion corrections were taken from International Tables for *X*-ray Crystallography (1974).[22] Atomic co-ordinates for non-hydrogen atoms are listed in Table 8. A table of bond distances and angles is presented in Table 9. Final positional parameters and thermal parameters for all atoms, mean

planes data and structure factor listings have been deposited as a Supplementary publication [SUP. No. 23752 (14 pp.)].* The computer programs used here are those belonging to 'The NSERC PDP-8e crystal structure system.' [21]

Acknowledgements

We thank Allen and Hanburys Ltd., Queen's University and the S.E.R.C. for support.

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* For details of the Supplementary publications scheme, see Instructions for Authors (1984), *J. Chem. Soc., Perkin Trans. 1*, 1984, Issue 1.

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Received 27th May 1983; ***Paper*** 3/857