Formation of Pyridazino[6,1-*c*][1,4]oxazin-8(7*H*)-ones by Intramolecular Cycloaddition of Azoalkenes

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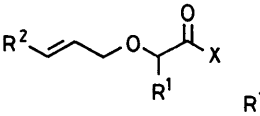
The hydrazides (**3**) and (**4**) of 2-allyloxyalkanoic acids (**1**) and of prop-2-ynyloxyacetic acid have been prepared. These hydrazides have then been converted into the hydrazones (**6**) and (**7**), respectively, by reaction with phenacyl chloride. The azoalkenes have been generated from the hydrazones by reaction with sodium carbonate. The products isolated were the pyridazino-oxazinones (**8**) [from (**6**)] and (**9**) [from (**7**)], formed by spontaneous intramolecular cycloaddition reactions of the azoalkenes. The hydrazones (**6b**) and (**6c**) with asymmetric carbon centres adjacent to the carbonyl groups each gave mixtures of diastereoisomeric oxazines but there was considerable selectivity (6:1) in each case. This is ascribed to steric effects in the transition states. An analogous series of conversions has been carried out with the hydrazones derived from the hydrazides (**3**) and (**4**) and ethyl bromopyruvate. *N*-Acetyl-*N*-allylglycine hydrazide (**11**) has also been prepared. The hydrazones (**13**) formed from this hydrazide and phenacyl chloride was converted by reaction with sodium carbonate into an azoalkene which cyclised to give the pyrazino[1,2-*b*]pyridazin-8-one (**14a**).

We have shown that intramolecular cycloaddition reactions of conjugated azoalkenes, in common with many other intramolecular Diels–Alder reactions, proceed readily when the products are 5,6- or 6,6-fused bicyclic ring systems.[1] In this paper we describe the construction of 6,6-fused ring systems from azoalkenes in which a heteroatom is incorporated into the chain linking the diene and the dienophile. We have also investigated the results of incorporating as asymmetric carbon atom into the chain.

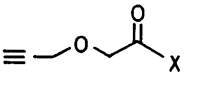
As in the earlier studies,[1,2] we generated the azoalkenes from the hydrazones of halogeno ketones. The choice of the halogeno ketone does not appear to be critical to the success or failure of the intramolecular cycloaddition process and only two, phenacyl chloride and ethyl bromopyruvate, were used in this investigation. Suitable hydrazides with oxygen incorporated into the chain were prepared from the corresponding carboxylic acids or esters. The preparation of the acids was based on the known[3] preparation of allyloxyacetic acid (**1a**) from allyl alcohol and chloroacetic acid. By using the same method, the acids (**1b**), (**1c**), and (**2**), and the ethyl ester of acid (**1d**), were prepared. The hydrazides (**3b**), (**3c**), and (**3d**) were then obtained from the ethyl or methyl esters of the corresponding acids and hydrazine hydrate, but this method proved to be unsatisfactory for compounds (**3a**) and (**4**). These hydrazides were therefore prepared from the corresponding acids by way of the acid chlorides and the t-butoxycarbonylhydrazides, a method first described by Carpino and his co-workers.[4] The hydrazides (**3a**), (**3b**), and (**3c**), which were isolated as oils, were characterised as their hydrazones (**5a**), (**5b**), and (**5c**) by condensation with acetophenone.

The choice of these hydrazides (**3a**)—(**3d**) and (**4**) was made (a) to determine the effect of oxygen in the chain on the intramolecular Diels–Alder reaction, (b) to test the diastereoselectivity of the cycloaddition [with hydrazides (**3b**) and (**3c**)], (c) to determine whether the expected regioselectivity of azoalkene addition to styrenes[5] would be reversed in the intramolecular reaction [with hydrazide (**3d**)], and (d) to test whether an unactivated triple bond would act as a dienophile in this cycloaddition, as in the all-carbon series[1] [with hydrazide (**4**)].

All the hydrazides were condensed with phenacyl chloride. The crystalline hydrazones (**6a**), (**6d**), and (**7**) were isolated and characterised from the corresponding hydrazides (**3a**), (**3d**), and (**4**). Compounds (**6b**) and (**6c**) were obtained as oils and were not fully characterised. The hydrazones were also obtained by reaction of the hydrazides (**3a**) and (**4**) with ethyl bromopyruvate: these were not characterised but were immediately converted into azoalkenes by reaction with sodium carbonate in dichloromethane. The other hydrazones were converted into azoalkenes in the same way. All the azoalkenes reacted *in situ* to give cycloadducts which were isolated and characterised.



X	R^1	R^2
(**1**) OH	a ; H	H
(**3**) $NHNH_2$	b ; Me	H
(**5**) NHN=C(Me)Ph	c ; Ph	H
(**6**) $NHN{=}C(CH_2Cl)Ph$	d ; H	Ph



X
(**2**) OH
(**4**) $NHNH_2$
(**7**) $NHN{=}C(CH_2Cl)Ph$

The product formed from the hydrazone (**6a**) was formulated as the intramolecular Diels–Alder adduct (**8a**). The ^1H n.m.r. spectrum, recorded at 250 MHz, provided the major evidence for the structure and also allowed some deductions

Table 1. ^{1}H N.m.r. spectra of the oxazinones (**8**): chemical shift values[a]

Compound	3ax-H	3eq-H	4ax-H	4eq-H	4a-H	5ax-H	5eq-H	7ax-H	7eq-H
(8a)	2.63	2.86	1.61	2.04	3.79	3.56	4.13	4.31	4.46
(8b)	2.35	2.84	1.44	2.04	3.77	3.55	4.12	4.33	4.55
(8c)	2.59	2.84	1.55	2.02	3.82	3.60	4.13		4.67
(8d)	2.74	2.94	1.72	2.12	3.94	3.64	4.16	4.41	
(8e)	2.69	2.90	1.60	2.04	3.92	3.67	3.92		5.60
(8f)	2.65	2.88	1.68	2.09	4.03	3.80	4.27	5.31	
(8g)	2.81	3.08	2.87		3.97	3.49	3.77	4.29	4.46

[a] Chemical shifts (δ) are recorded for 250 MHz spectra in $CDCl_3$. Hydrogen atoms are labelled as shown for compound (**8a**) in Figure 1.

Table 2. ^{1}H N.m.r. spectra of the oxazinones (**8**): coupling constants

	J (Hz)					
Coupling	(**8a**)	(**8b**)	(**8d**)	(**8e**)	(**8f**)	(**8g**)
3eq–3ax	18.4	19.0	*a*	18.6	18.3	*a*
3eq–4eq	1.3	0.5	*a*	1.1	0.5	
3eq–4ax	6.1	5.3	*a*	6.6	5.3	*a*
3ax–4eq	7.1	7.1	*a*	7.1	7.2	
3ax–4ax	11.9	11.6	*a*	11.9	11.9	11.3
4eq–4ax	14.0	15.8	*a*	*a*	*a*	
4eq–4a	2.7	*a*	*a*	*a*	*a*	
4ax–4a	10.1	12.0	*a*	*a*	*a*	10.6
4a–5eq	3.9	3.8	3.9	4.2	3.7	4.1
4a–5ax	10.4	9.9	10.5	11.6	10.8	10.3
5eq–5ax	11.7	11.1	11.7	13.2	11.1	12.1
5eq–7eq	1.2	0		0		1.2
7eq–7ax	16.8	16.5				16.8

[a] Value not determined.

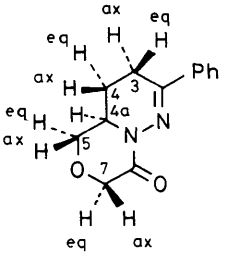


Figure 1.

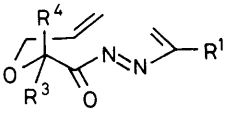
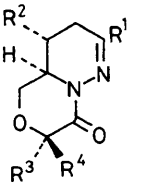


Figure 2.

to be made about the preferred conformation of the molecule. In particular, the two hydrogen atoms attached to C-7 show different chemical shifts (δ 4.13 and 4.31). The higher field signal is a simple doublet but the lower field signal shows an additional coupling (*J* 1.2 Hz) to one of the hydrogen atoms attached to C-5. We have attributed this to a W-type coupling, with the C–H bonds lying in approximately the same plane. The oxazine ring in structure (**8a**) thus has a half-chair conformation with the hydrogen at C-4a (the ring junction) in a pseudo-axial position and the two coupled hydrogens attached to C-5 and C-7 in pseudo-equatorial positions. The n.m.r. spectrum is summarised in Tables 1 and 2, the labelling of the hydrogen atoms being as indicated in Figure 1. By starting with the hydrazide (**3a**) and ethyl bromopyruvate, an analogous cyclo-



	R^1	R^2	R^3	R^4
(**8**) a ;	Ph	H	H	H
b ;	CO_2Et	H	H	H
c ;	Ph	H	H	Me
d ;	Ph	H	Me	H
e ;	Ph	H	H	Ph
f ;	Ph	H	Ph	H
g ;	Ph	Ph	H	H

adduct (**8b**), having an ethoxycarbonyl substituent at C-2, was produced in moderate yield in a one-pot procedure.

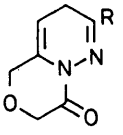
The hydrazones (**6b**) and (**6c**) both gave mixtures of diastereoisomeric oxazinones when they were stirred with sodium carbonate. The cycloadducts derived from compound (**6b**) were obtained as a mixture, the components of which were not separated: the mixture was characterised as such. The n.m.r. spectrum showed the presence of two components, to which the structures (**8c**) and (**8d**) have been assigned, in a ratio of 14:86. These were distinguished by the separate signals for 7-H, each signal being a quartet. The assignment of structure to the isomers is based on the chemical shift values of these signals. The lower field signal is assigned to structure (**8c**) which has a pseudo-equatorial hydrogen at C-7, by analogy with the values for 7eq-H and 7ax-H of compound (**8a**) (Table 1).

The cycloadducts derived from the hydrazone (**6c**) were assigned structures (**8e**) and (**8f**). These compounds were obtained as a mixture in a ratio of 1:6 and the components were then separated by column chromatography. The assignment of structure to the isomers is again based on their n.m.r. spectra, the major isomer (**8f**) having the higher field signal for 7-H (Table 1).

We have suggested that these cycloadditions go by way of *anti* transitions states, the azo group of the diene having the vinyl and carbonyl substituents *trans*.[1] In the cycloadditions leading to the formation of the oxazinones (**8**), this allows the linking chain to adopt a conformation which produces the oxazinone ring as a half chair. The preferential formation of the oxazinones (**8d**) and (**8f**), respectively, can then be ascribed to a steric effect, the substituents at C-7 preferentially adopting a pseudo-equatorial position in the transition state (Figure 2). Diastereoselectivity of this kind has been observed in several other intramolecular Diels–Alder reactions, and it is usually ascribed

to steric effects, although there are also such reactions in which no stereoselectivity has been found.[6]

The hydrazone (**6d**) gave the cycloadduct (**8g**), the structure of which is consistent with the large (10.6 Hz) coupling constant between the hydrogen atoms attached to C-4 and C-4a observed in the n.m.r. spectrum. This cycloaddition thus goes in the same way as those with terminally unsubstituted alkenyl groups, although the regiochemistry is opposite to that expected for an intermolecular addition. As with other intramolecular Diels–Alder reactions, steric effects clearly predominate over electronic effects. Cycloaddition to the triple bond of the intermediates derived from prop-2-ynyl alcohol also took place readily to give the oxazinones (**9a**) and (**9b**). These reactions

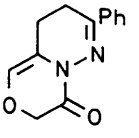


R

(**9**) a; Ph

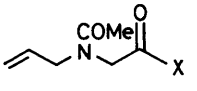
b; CO_2Et

provide further examples[1] of intramolecular addition to unactivated triple bonds. Compound (**9a**) was found to isomerise to the oxazinone (**10**) when treated with trifluoroacetic acid.



(**10**)

One intramolecular reaction was also carried out in which nitrogen, rather than oxygen, was incorporated into the chain. We started from the known[7] ethyl ester of *N*-allylglycine. It was necessary to protect the basic nitrogen in order to avoid complications in subsequent reactions with phenacyl chloride. The compound was therefore acetylated and the hydrazide (**11**) was then prepared in the usual way. As this was an oil, it was characterised as its crystalline hydrazone (**12**). Reaction of the



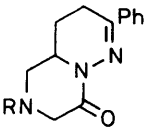
X

(**11**) $NHNH_2$

(**12**) NHN=C(Me)Ph

(**13**) $NHN=C(CH_2Cl)Ph$

hydrazide (**11**) with phenacyl chloride gave the hydrazone (**13**), from which the azoalkene was generated by reaction with sodium carbonate. The cycloadduct (**14a**) was isolated in good yield from the reaction mixture. The ^1H and ^{13}C n.m.r. spectra of this compound proved to be complex because of slow rotation about the C–N bond of the amide: signals were observed from both rotamers. When the ^1H n.m.r. spectrum was recorded at 145 °C in $(CD_3)_2SO$, the signals were simplified and the spectrum closely resembled that of the analogous oxazine (**8a**). The acetyl group was removed from the compound by acid-catalysed hydrolysis to give the pyridazinone (**14b**).



R

(**14**) a; Ac

b; H

Experimental

For general directions see the preceding paper.

Allyloxyacetohydrazide (**3a**).—(a) *Allyloxyacetic acid t-butoxycarbonylhydrazide*. Allyloxyacetic acid[3] was converted into its acid chloride by reaction with thionyl chloride. A solution of t-butyl carbazate (7.85 g, 68.4 mmol) in dry ether (100 ml) was added dropwise over 1 h to a solution of allyloxyacetyl chloride (9.2 g, 68.4 mmol) and pyridine (5.4 g, 68.4 mmol) in dry ether (50 ml). Pyridine hydrochloride was filtered off and the filtrate was evaporated to leave the crude *hydrazide* (14.0 g, 89%), b.p. 100 °C/0.01 mmHg (Found: *m/z* 230.1262. $C_{10}H_{18}N_2O_4$ requires *m/z* 230.1266); $\nu_{max.}$(film) 3 310 (NH), 1 750 and 1 680 cm^{-1} (CO); δ (220 MHz) 1.43 (9 H), 4.02—4.13 (2 H, m), 4.06 (2 H), 5.18—5.37 (2 H, m), 5.78—5.98 (1 H, m), 7.00 (1 H, br), and 8.35 (1 H, br).

(b) *Hydrazide* (**3a**). The t-butoxycarbonylhydrazide (14.0 g, 61 mmol) was dissolved in nitromethane (20 ml) and dry hydrogen chloride was bubbled through the solution for 10 min. It was then diluted with ether (500 ml) and cooled to −20 °C. The precipitated hydrazide hydrochloride was filtered off and neutralised by addition to the minimum amount of saturated aqueous sodium hydrogen carbonate. Continuous extraction of the aqueous solution with dichloromethane for 24 h gave the *hydrazide* (**3a**) (3.88 g, 49%), b.p. 90 °C/0.1 mmHg (Found: N, 21.5; *m/z* 130.0742. $C_5H_{10}N_2O_2$ requires N, 21.5; *m/z* 130.0742); $\nu_{max.}$($CHCl_3$) 3 440, 3 320 (NH), and 1 675 cm^{-1} (CO); δ (220 MHz) 3.90 (2 H, br), 4.01 (2 H, 4.04—4.13 (2 H, m), 5.18—5.38 (2 H, m), 5.77—5.98 (1 H, m), and 7.90 (1 H, br). The compound was further characterised by reaction with acetophenone to give the *hydrazone* (**5a**), m.p. 66—67 °C (from ether) (Found: C, 67.0; H, 6.8; N, 11.9. $C_{13}H_{16}N_2O_2$ requires C, 67.2; H, 6.9; N, 12.1%).

Allyloxypropanohydrazide (**3b**).—(a) *2-Allyloxypropanoic acid* (**1b**). The acid was prepared by the general procedure described by Evans and Owen[3] for the acid (**1a**), using allyl alcohol (120 ml), sodium (13.0 g, 565 mmol), and 2-chloropropanoic acid (30.0 g, 276 mmol). Distillation gave the acid (**1b**) (8.2 g, 22%), b.p. 140 °C/25 mmHg; δ(220 MHz) 1.48 (3 H, d, *J* 7 Hz), 3.92—4.27 (3 H, m), 5.15—5.38 (2 H, m), 5.81—6.02 (1 H, m), and 9.66 (1 H); *dicyclohexylammonium salt*, m.p. 83 °C (from ether) (Found: C, 68.8; H, 10.8; N, 4.5. $C_{18}H_{33}NO_3$ requires C, 69.4; H, 10.7; N, 4.5%).

(b) *Methyl 2-allyloxypropanoate*. The acid (**1b**) and methanol gave the *ester* (59%), which was purified by bulb-to-bulb distillation at 80 °C (oven) and 25 mmHg (Found: C, 57.7; H, 8.5. $C_7H_{12}O_3$ requires C, 58.3; H, 8.4%); $\nu_{max.}$(film) 1 750 cm^{-1} (CO); δ (220 MHz) 1.44 (3 H, d, *J* 7 Hz), 3.77 (3 H), 3.90—4.23 (3 H, m), 5.16—5.38 (2 H, m), and 5.84—6.04 (1 H, m).

(c) *Hydrazide* (**3b**). The methyl ester (7.5 g, 36.4 mmol) and hydrazine hydrate (2.2 g, 43.7 mmol) were heated in de-gassed methanol (50 ml) under N_2 for 18 h. Distillation gave the *hydrazide* (**3b**) (2.9 g, 71%), b.p. 120 °C/1.0 mmHg (Found: N, 19.7. $C_6H_{12}N_2O_2$ requires N, 19.4%); $\nu_{max.}$($CHCl_3$) 3 425, 3 310 (NH), and 1 675 cm^{-1} (CO); δ (220 MHz) 1.41 (3 H, d, *J* 7 Hz), 3.80 (2 H, br), 3.95—4.10 (3 H, m), 5.20—5.37 (2 H, m), 5.80—6.00 (1 H, m), and 7.90 (1 H, br). It was further charcterised as

the *hydrazone* (**5b**) by reaction with acetophenone; m.p. 71—72 °C (from dichloromethane–cyclohexane) (Found: C, 68.1; H, 7.4; N, 11.5. $C_{14}H_{18}N_2O_2$ requires C, 68.3; H, 7.4; N, 11.4%).

Allyoxy(phenyl)acetohydrazide (**3c**).—(a) *Allyloxy(phenyl)-acetic acid* (**1c**). The acid was prepared by the literature method[3] described for compound (**1a**) from α-bromophenyl-acetic acid (12.0 g, 59 mmol), allyl alcohol (150 ml), and sodium (13.0 g, 565 mmol). Distillation gave the acid (8.78 g, 82%), b.p. 140 °C/0.2 mmHg; δ(220 MHz) 4.13 (2 H, d, *J* 6 Hz), 4.97 (1 H), 5.21—5.38 (2 H, m), 5.82—6.05 (1 H, m), 7.25—7.60 (5 H, m), and 10.05 (1 H, br). The acid was not characterised further.

(b) *Methyl allyloxy(phenyl)acetate*. The acid (**1c**) was converted into its methyl ester by reaction with methanol. Bulb-to-bulb distillation gave the ester (89%), which distilled at 90 °C (oven) and 25 mmHg; $\nu_{max.}$(film) 1 750 cm^{-1} (CO); δ (220 MHz) 3.70 (3 H), 4.09 (2 H, d, *J* 7 Hz), 4.97 (1 H), 5.19—5.38 (2 H, m), 5.85—6.06 (1 H, m), and 7.22—7.57 (5 H, m). The ester was not characterised further.

(c) *Hydrazide* (**3c**). The ester (7.50 g, 36.4 mmol) and hydrazine hydrate (2.20 g, 43.7 mmol) in methanol (50 ml) gave, by the method described for compound (**3b**), the hydrazide (**3c**) (6.20 g, 83%), b.p. 100 °C/0.1 mmHg; $\nu_{max.}$(film) 3 420, 3 320 (NH), and 1 670 cm^{-1} (CO); δ (220 MHz) 3.85 (2 H, br), 3.88—4.13 (2 H, m), 4.89 (1 H), 5.20—5.37 (2 H, m), 5.80—6.03 (1 H, m), 7.25—7.65 (5 H, m), and 8.11 (1 H, br). It was characterised by reaction with acetophenone as the *hydrazone* (**5c**), m.p. 85—87 °C (from hexane) (Found: C, 73.9; H, 6.6; N, 9.3. $C_{19}H_{20}N_2O_2$ requires C, 74.0; H, 6.5; N, 9.1%).

(E)-(3-*Phenylallyloxy)acetohydrazide* (**3d**).—(a) *Ethyl* (E)-(3-*phenylallyloxy)acetate*. Cinnamyl alcohol (10.0 g, 75 mmol) in dry tetrahydrofuran (50 ml) was added dropwise to a stirred suspension of sodium hydride (1.80 g, 75 mmol) in tetrahydrofuran (50 ml). When gas evolution had ceased, ethyl bromoacetate (12.5 g, 75 mmol) in tetrahydrofuran (50 ml) was added at a rate such that the reaction mixture was kept gently boiling. The mixture was then heated under reflux for 2 h. The solvent was distilled off and the residue was partitioned between water (200 ml) and ether (200 ml). The aqueous layer was washed with ether (2 × 200 ml) and the combined ethereal extracts were dried and evaporated. Flash chromatography of the residue gave (with ether–light petroleum, 1:4) the *ester* (8.0 g, 49%), b.p. 150 °C/0.1 mmHg (Found: *m/z* 220.1099. $C_{13}H_{16}O_3$ requires *m/z* 220.1099); $\nu_{max.}$(film) 1 750 cm^{-1} (CO); δ (220 MHz) 1.24 (3 H, t, *J* 7 Hz), 4.11 (2 H), 4.15—4.30 (2 H, m), 4.23 (2 H, q, *J* 7 Hz), 6.18—6.37 (1 H, m), 6.59 (1 H, d, *J* 17 Hz), and 7.17—7.41 (5 H, m).

(b) *Hydrazide* (**3d**). The ester (2.1 g, 9.5 mmol) and hydrazine hydrate (0.6 g, 11.5 mmol) in ethanol (25 ml) gave, by the method described for the hydrazide (**3b**), the *hydrazide* (**3d**) (1.9 g, 96%), m.p. 76—79 °C (from dichloromethane–hexane) (Found: C, 63.6; H, 6.8; N, 13.3. $C_{11}H_{14}N_2O_2$ requires C, 64.1; H, 6.8; N, 13.6%); $\nu_{max.}$(KBr) 3 350, 3 310 (NH), and 1 660 cm^{-1} (CO); δ (220 MHz) 3.85 (2 H, br), 4.04 (2 H), 4.16 (2 H, d, *J* 7 Hz), 6.13—6.30 (1 H, m), 6.60 (1 H, d, *J* 17 Hz), 7.22—7.43 (5 H, m), and 7.77 (1 H, br).

Prop-2-ynyloxyacetohydrazide (**4**).—(a) *Prop-2-ynyloxyacetic acid* (**2**). Propynol (50 ml) was added dropwise to a stirred suspension of sodium hydride (24.0 g, 1.0 mmol) in dry tetrahydrofuran (300 ml). When evolution of hydrogen had ceased, chloroacetic acid (90.0 g, 0.95 mmol) in tetrahydrofuran (200 ml) was added dropwise with stirring over 2 h. The mixture was stirred for a further 18 h, quenched with water (500 ml), and acidified to pH 2 with sulphuric acid. The organic product was extracted with ether (3 × 400 ml); the solution was dried and evaporated to leave the *acid* (**2**) (36.6 g 33%), b.p. 120 °C/0.1 mmHg (Found: C, 52.3; H, 5.3. $C_5H_6O_3$ requires C, 52.6; H, 5.3%); δ (220 MHz) 2.53 (1 H, t, *J* 3 Hz), 4.28 (2 H), 4.33 (2 H, d, *J* 3 Hz), and 11.00 (1 H, br).

(b) N′-*t-Butoxycarbonyl(prop-2-ynyloxyacetohydrazide*). The acid (**2**) was converted into its acid chloride by reaction with thionyl chloride. A solution of t-butyl carbazate (26.4 g, 192 mmol) in dichloromethane (100 ml) was added over 1 h to the acid chloride (25.5 g, 192 mmol) and pyridine (15.2 g, 192 mmol) in dichloromethane (100 ml). The solution was washed with saturated aqueous sodium hydrogen carbonate and water, dried, and the solvent evaporated off to leave the *t-butoxy-carbonylhydrazide* (39.3 g, 89%), m.p. 73—75 °C (from dichloro-methane–hexane) (Found: C, 52.4; H, 6.9; N, 12.5. $C_{10}H_{16}N_2O_4$ requires C, 52.6; H, 7.1; N, 12.3%); $\nu_{max.}$(KBr) 3 320, 3 245 (NH), 2 090 (C≡C), 1 725, and 1 670 cm^{-1} (CO); δ (220 MHz) 1.43 (9 H), 2.56 (1 H, t, *J* 3 Hz), 4.18 (2 H), 4.25 (2 H, d, *J* 3 Hz), 7.24 (1 H), and 8.51 (1 H).

(c) *Hydrazide* (**4**). The t-butoxycarbonylhydrazide (39.3 g, 172 mmol) in nitromethane (100 ml) was converted into the hydrazide (**4**) by the method of Carpino *et al.*,[4] as described for the hydrazide (**3a**). Crystallisation gave the *hydrazide* (**4**) (19.0 g, 86%), m.p. 51 °C (from dichloromethane–hexane) (Found: C, 46.9; H, 6.1; N, 22.2. $C_5H_8N_2O_2$ requires C, 46.9; H, 6.3; N, 21.9%); $\nu_{max.}$(KBr) 3 280 (NH), 2 100 (C≡C), and 1 670 cm^{-1} (CO); δ (220 MHz), 2.69 (1 H, t, *J* 3 Hz), 3.90 (2 H, br), 4.10 (2 H), 4.25 (2 H, d, *J* 3 Hz), and 7.90 (1 H, br); *m/z* 128 (M^+) and 69 (base).

N-*Acetyl*-N-*allylglycine Hydrazide* (**11**).—(a) N-*Allylglycine ethyl ester*. This compound was prepared (48%) from allylamine and ethyl bromoacetate as described by Speziale and Jaworski;[7] $\nu_{max.}$(film) 3 320 (NH) and 1 735 cm^{-1} (CO); δ (220 MHz) 1.25 (3 H, t, *J* 7 Hz), 1.67 (1 H), 3.15—3.30 (2 H, m), 3.36 (2 H), 4.16 (2 H, q, *J* 7 Hz), 4.98—5.31 (2 H, m), and 5.60—6.11 (1 H, m).

(b) N-*Acetyl*-N-*allylglycine ethyl ester*. The ester (8.4 g, 64. mmol) was acetylated by heating with acetic anhydride (12 ml) under reflux for 0.5 h. This gave the *title compound*, b.p. 120 °C/0.1 mmHg (Found: N, 7.65; *m/z* 185.1045. $C_9H_{15}NO_3$ requires N, 7.6; *m/z* 185.1052); $\nu_{max.}$(film) 1 745 and 1 650 cm^{-1} (CO); δ (220 MHz) (mixture of rotamers) 1.27—1.41 (3 H, m), 2.14 and 2.30 (together, 3 H), 4.07—4.14 (2 H, m), 4.17 (2 H), 4.21—4.38 (2 H, m), 5.20—5.38 (2 H, m), and 5.76—6.02 (1 H, m).

(c) *Hydrazide* (**11**). The *N*-Acetyl ester (2.0 g, 11.0 mmol) and hydrazine hydrate (0.65 g, 13.0 mmol) in ethanol (15 ml) gave, by the method described for the hydrazide (**3b**), the hydrazide (**11**) (1.84 g, 100%) as a viscous oil, which was distilled at 200 °C (oven) and 0.1 mmHg; $\nu_{max.}$($CHCl_3$) 3 420, 3 320 (NH), and 1 670 cm^{-1} (CO); δ (220 MHz) 2.07 (3 H), 3.85 (2 H, br), 3.93 (2 H), 4.01 (2 H, d, *J* 7.3 Hz), 5.06—5.26 (2 H, m), 5.69—5.88 (1 H, m), and 8.65 (1 H, br). Condensation with acetophenone gave the *hydrazone* (**12**), m.p. 106 °C (from ether) (Found: C, 66.2; H, 7.3; N, 15.3 $C_{15}H_{19}N_3O_2$ requires C, 65.9; H, 7.0; N, 15.4%).

Reaction of Hydrazides with Phenacyl Chloride: General Procedure.—The hydrazide was dissolved in the minimum amount of ethanol. Phenacyl chloride (1 equiv.) was added and the mixture was warmed briefly to dissolve the ketone. It was then cooled, HCl (1—2 drops) was added, and the solution was stirred for 0.5—2 h, during which time the hydrazone was precipitated. The solid was filtered off and recrystallised. The following were characterised:

(a) *Allyloxyacetylhydrazone* (**6a**). The hydrazide (**3a**) (1.64 g, 12.6 mmol) and phenacyl chloride (1.95 g, 12.6 mmol) gave the *hydrazone* (**6a**) (3.10 g, 92%), m.p. 98—99 °C (from ethanol) (Found: C, 58.6; H, 5.7; N, 10.45. $C_{13}H_{15}ClN_2O_2$ requires C, 58.5; H, 5.6; N, 10.5%); $\nu_{max.}$(KBr) 3 190 (NH) and 1 695 cm^{-1} (CO); δ (220 MHz) (mixture of *syn* and *anti* isomers) 4.05—4.21

(2 H, m), 4.18 and 4.52 (together, 2 H), 4.41 and 4.61 (together, 2 H), 5.15—5.43 (2 H, m), 5.80—6.05 (1 H, m), 7.30—7.50 (3 H, m), 7.64—7.84 (2 H, m), and 9.90 (1 H).

(b) 3-*Phenylallyloxyacetylhydrazone* (**6d**). The hydrazide (**3d**) (1.03 g, 5.0 mmol) and phenacyl chloride (0.77 g, 5.0 mmol) gave the *hydrazone* (**6d**) (0.81 g, 48%), m.p. 126 °C (from ethanol) (Found: C, 66.2; H, 5.6; N, 7.95. $C_{19}H_{19}ClN_2O_2$ requires C, 66.5; H, 5.6; N, 8.2%); $\nu_{max.}$(KBr) 3 120 (NH) and 1 720 cm^{-1} (CO); δ (200 MHz) 4.01 (2 H, d, *J* 7 Hz), 4.06 (2 H), 4.51 (2 H), 5.80—6.00 (1 H, m), 6.38 (1 H, d, *J* 17 Hz), 7.18—7.55 (10 H, m), and 9.55 (1 H).

(c) *Prop-2-ynyloxyacetylhydrazone* (**7**). The hydrazide (**4**) (1.02 g, 8.0 mmol) and phenacyl chloride (1.21 g, 8.0 mmol) gave the *hydrazone* (**7**) 1.74 g, 83%), m.p. 105—106 °C (from ethanol) (Found: C, 59.2; H, 5.0; N, 10.5. $C_{13}H_{13}ClN_2O_2$ requires C, 59.0; H, 4.9; N, 10.6%); $\nu_{max.}$(KBr) 3 190 (NH), 2 095 (C≡C), and 1 680 cm^{-1} (CO); δ (220 MHz) (mixture of *syn* and *anti* isomers) 1.38—1.57 (1 H, m), 3.99—4.12 (2 H, m), 4.25—4.78 (4 H, m), 7.20—7.90 (5 H, m), and 8.40 and 9.44 (together, 1 H).

(d) *N-(Acetyl-N-allylaminoacetylhydrazone* (**13**). The hydrazide (**11**) (0.52 g, 3.0 mmol) and phenacyl chloride (0.46 g, 3.0 mmol) gave the *hydrazone* (**13**) (0.60 g, 65%), m.p. 129—130 °C (from ethanol) (Found: C, 58.6; H, 5.9; N, 13.6. $C_{15}H_{18}ClN_3O_2$ requires C, 58.5; H, 5.9; N, 13.7%); $\nu_{max.}$(KBr) 3 190 (NH), 1 675, and 1 645 cm^{-1} (CO); δ (220 MHz) (mixture of *syn* and *anti* isomers) 2.10 and 2.28 (together, 3 H), 4.02—4.20 (2 H, m), 4.53—4.61 (2 H, m), 4.64 (2 H), 5.12—5.31 (2 H, m), 5.70—5.95 (1 H, m), 7.33—7.40 (3 H, m), 7.69—7.85 (2 H, m), and 10.60 and 10.90 (together, 1 H).

2-*Phenyl* 3,4,4a,5-*tetrahydropyridazino*[6,1-c][1,4]*oxazin*-8(7H)-*one* (**8a**).—The hydrazone (**6a**) (2.0 g, 7.5 mmol) in dichloromethane (500 ml) was stirred with anhydrous sodium carbonate (3 g) for 24 h. The reaction mixture was filtered and the filtrate was evaporated to leave the *oxazinone* (**8a**) (1.43 g, 82%), m.p. 201—204 °C (from dichloromethane–ether) (Found: C, 67.6; H, 6.1; N, 12.1. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.1; N, 12.2%); $\nu_{max.}$(KBr) 1 670 cm^{-1} (CO); n.m.r. data are given in the Tables.

Ethyl 3,4,4a,5,7,8-*Hexahydro*-8-*oxopyridazino*[6,1-c][1,4]-*oxazine*-2-*carboxylate* (**8b**).—The hydrazide (**3a**) (1.10 g, 8.5 mmol) was added to a solution of ethyl 3-bromo-2-oxopropanoate (1.56 g, 8.5 mmol) in ether (10 ml) and the reaction mixture was stirred for 2 h. The ether was then evaporated off and the residue was re-dissolved in dichloromethane (200 ml). The solution was stirred for 24 h with sodium carbonate (5 g). Flash chromatography (with ethyl acetate) gave the *oxazinone* (**8b**) (0.65 g, 34%), m.p. 109 °C (from ethanol–ether) (Found: C, 52.8; H, 5.9; N, 12.3. $C_{12}H_{14}N_2O_4$ requires C, 53.1; H, 6.2; N, 12.4%); $\nu_{max.}$(KBr) 1 730 and 1 680 cm^{-1} (CO); δ (250 MHz) 1.31 (3 H, t *J* 7 Hz, OCH_2Me) and 4.24—4.41 (2 H, m, OCH_2Me); for other signals see the Tables.

cis- *and* trans-7-*Methyl*-2-*phenyl*-3,4,4a,5-*tetrahydropyridazino*[6,1-c][1,4]*oxazin*-8(7H)-*one* (**8c**) *and* (**8d**).—A solution of the hydrazide (**3b**) (0.48 g, 3.3 mmol), phenacyl chloride (0.52 g, 3.3 mmol), and HCl (1 drop) in ethanol (5 ml) was stirred for 2 h. The solvent was then distilled off to leave an oil, which was re-dissolved in dichloromethane (150 ml). Sodium carbonate (2 g) was added and the mixture was stirred for 48 h. The solids were filtered off through Celite and the filtrate was evaporated to leave a solid. Crystallisation gave the *oxazinones* (**8c**) and (**8d**) as a mixture (0.42 g, 52%), m.p. 189—193 °C (from dichloromethane–ether) (Found: C, 68.8; H, 6.7; N, 11.2. $C_{14}H_{16}N_2O_2$ requires C, 68.8; H, 6.6; N, 11.5%); $\nu_{max.}$(KBr) 1 670 cm^{-1} (CO); δ (250 MHz) 1.60 (3 H, d, *J* 6.8 Hz, 7-Me of both isomer), 4.41 [0.86 H, q, *J* 6.8 Hz, 7ax-H of (**8d**)], 4.67 [0.41 H, q, *J* 6.8 Hz, 7eq-H of (**8c**)], 7.27—7.43 (3 H, m), and 7.86—7.90 (2 H, m); other signals are given in the Tables.

cis- *and* trans-2,7-*Diphenyl*-3,4,4a,5-*tetrahydropyridazino*-[6,1-c][1,4]*oxazin*-8(7H)-*one* (**8e**) *and* (**8f**).—A solution of the hydrazide (**3c**) (1.08 g, 5.2 mmol), phenacyl chloride (0.78 g, 5.0 mmol), and HCl (1 drop) in methanol (5 ml) was stirred for 2 h. The solvent was evaporated off and the residue, an oil, was re-dissolved in dichloromethane (300 ml). The solution was stirred for 48 h with sodium carbonate (3 g). The solids were filtered off through Celite and the solvent was evaporated off from the filtrate to leave a solid, which consisted of a mixture of isomers (**8e**) and (**8f**) in a ratio of 1:6, as estimated by n.m.r. from the ratio of the 7ax and 7eq singlets. Crystallisation gave the diastereoisomers as a mixture (0.52 g, 33%). Flash chromatography of this mixture gave (with ether) the cis-*oxazinone* (**8e**) (50 mg), m.p. 183—184.5 °C (from dichloromethane–ether) as the less polar component (Found: C, 74.0; H, 5.9; N, 9.1. $C_{19}H_{18}N_2O_2$ requires C, 74.5; H, 5.9; N, 9.15%); $\nu_{max.}$(KBr) 1 670 cm^{-1}; for n.m.r. data see the Tables.

Further elution with ether gave the trans-*oxazinone* (**8f**) (420 mg), m.p. 219—220 °C (decomp.) (from dichloromethane–ether) (Found: C, 74.3; H, 5.8; N, 9.4%); $\nu_{max.}$(KBr) 1 665 cm^{-1} (CO); for n.m.r. data see the Tables.

2,4-*Diphenyl*-3,4,4a,5-*tetrahydropyridazino*[6,1-c][1,4]-*oxazin*-8(7H)-*one* (**8g**).—The hydrazone (**6d**) (0.55 g, 1.60 mmol) was stirred in dichloromethane (200 ml) with sodium carbonate (2 g) for 48 h. The solids were filtered off through Celite and the filtrate was evaporated to leave the crude oxazinone. Crystallisation gave the *oxazinone* (**8g**) (0.25 g, 51%), m.p. 218 °C (from dichloromethane–ether) (Found: C, 74.8; H, 6.15; N, 9.2. $C_{19}H_{18}N_2O_2$ requires C, 74.5; H, 5.9; N, 9.15%); $\nu_{max.}$(KBr) 1 675 cm^{-1} (CO); for n.m.r. data see the Tables.

3,5-*Dihydro*-2-*phenylpyridazino*[6,1-c][1,4]*oxazin*-8(7H)-*one* (**9a**).—A solution of the hydrazone (**7a**) (1.5 g, 5.7 mmol) in dichloromethane (300 ml) was stirred with sodium carbonate (3 g) for 48 h. The solids were filtered off through Celite and the filtrate was evaporated to leave an amorphous solid. Flash chromatography (with ethyl acetate–light petroleum, 3:2) gave the oxazinone (**9a**), m.p. 133—136 °C (from ethyl acetate–light petroleum) (Found: C, 68.3; H, 5.3; N, 12.35. $C_{13}H_{12}N_2O_2$ requires C, 68.4; H, 5.3; N, 12.3%); $\nu_{max.}$(KBr) 1 690 cm^{-1} (CO); δ (250 MHz) 3.33 (2 H, d, 3-H), 4.33 (2 H, d, 5-H), 4.45 (2 H, 7-H), 4.99 (1 H, tt, 4-H), 7.40—7.45 (3 H, m), and 7.81—7.86 (2 H, m); $J_{3,4}$ 3.6 and $J_{4,5}$ 1.2 Hz; δ(^{13}C) 23.18 (C-3), 66.58 (C-5), 69.39 (C-7), 97.98 (C-4), 126.22, 128.24, 130.42, and 135.47 (Ph), 130.30 (C-4a), 150.18 (C-2), and 171.83 (C-8).

Ethyl 3,5,7,8-*Tetrahydro*-8-*oxopyridazino*[6,1-c][1,4]-*oxazine*-2-*carboxylate* (**9b**).—A solution of ethyl 3-bromo-2-oxopropanoate (1.1 g, 5.6 mmol) in ether (5 ml) containing HCl (1 drop) was stirred with the hydrazide (**4**) (0.64 g, 5.0 mmol) for 1 h. The ether was then evaporated off to leave an amorphous solid, which was immediately re-dissolved in dichloromethane (200 ml). This solution was stirred with sodium carbonate (2 g) for 24 h, and the solids were then filtered off through Celite. The filtrate was evaporated to dryness and the residue was subjected to flash chromatography which gave (with ethyl acetate) the *oxazinone* (**9b**) (0.34 g, 31%), m.p. 115—119 °C (from ethyl acetate–hexane) (Found: C, 53.6; H, 5.4; N, 12.2. $C_{10}H_{12}N_2O_4$ requires C, 53.6; H, 5.4; N, 12.5%); δ (220 MHz) 1.36 (3 H, t, *J* 7 Hz), 3.20 (2 H, d, br, *J* 4.8 Hz, 3-H), 4.30—4.33 (2 H, m, 5-H), 4.35 (2 H, q, *J* 7 Hz), 4.44 (2 H, 7-H), and 4.92 (1 H, t, *J* 4.8 Hz, showing further splitting, 4-H).

6-*Acetyl*-3,4,4a,5,6,7-*hexahydro*-2-*phenylpyrazino*[1,2-b]-*pyridazin*-8-*one* (**14a**).—A solution of the hydrazone (**13**) (0.71 g, 2.3 mmol) in dichloromethane (175 ml) was stirred with sodium carbonate (2 g) for 24 h. The solid was filtered off and the filtrate was evaporated to dryness to leave a solid. Crystallisation gave the *pyrazinone* (**14a**) (0.45 g, 72%), m.p. 200—202 °C (from dichloromethane–ether) (Found: *m/z* 271.1333. $C_{15}H_{17}N_3O_2$ requires *m/z* 271.1321); $\nu_{max.}$(KBr) 1 675 and 1 660 cm^{-1} (CO); δ (250 MHz) [$(CD_3)_2SO$, 145 °C] 1.50—1.69 (1 H, m, 4ax-H), 2.03 (3 H), 2.09—2.23 (1 H, m, 4eq-H), 2.50—2.87 (2 H, m 3ax- and 3eq-H), 3.14 (1 H, dd, *J* 13.3 and 11.5 Hz, 5ax-H), 3.62—3.76 (1 H, m, 4a-H), 3.98 (1 H, d, *J* 17.5 Hz, 7ax-H), 4.30 (1 H, d, br, *J* 13.3 Hz, 5eq-H), 4.49 (1 H, dd, *J* 17.5 and 1.2 Hz, 7eq-H), 7.29—7.41 (3 H, m), and 7.70—7.76 (2 H, m).

3,4,4a,5,6,7-*Hexahydro*-2-*phenylpyrazino*[1,2b]*pyridazin*-8-*one* (**14b**).—The pyridazinone (**14a**) (0.20 g, 0.80 mmol) was heated in a mixture of ethanol (10 ml) and conc. HCl (10 ml) at 78 °C for 2 h. The solution was neutralised with aqueous KOH and it was then subjected to continuous extraction with dichloromethane. This gave the *pyrazinone* (**14b**) (0.16 g, 86%), m.p. 225—230 °C (from dichloromethane–ether) (Found: C, 68.3; H, 6.5; N, 18.4. $C_{13}H_{15}N_3O$ requires C, 68.1; H, 6.6; N, 18.3%); $\nu_{max.}$(KBr) 3 280 (NH) and 1 650 cm^{-1} (CO); δ (250 MHz) 1.61—173 (1 H, m, 4ax-H), 1.78 (1 H, NH), 2.03—2.11 (1 H, m, 4eq-H), 2.53—2.68 (1 H, m, 3ax-H), 2.77—2.88 (2 H, m, 3eq- and 5ax-H), 3.32—3.37 (1 H, m, 5eq-H), 3.57—3.64 (1 H, m, 4a-H), 3.64—3.83 (2 H, m, 7ax- and 7eq-H), 7.25—7.43 (3 H, m), and 7.71—7.85 (2 H, m).

Acid-catalysed Rearrangement of the Oxazinone (**9a**).—A solution of the oxazinone (**9a**) (0.11 g, 0.5 mmol) in trifluoroacetic acid (15 ml) was kept at 20 °C for 18 h. The solvent was distilled off to leave an oil. Layer chromatography (silica; ethyl acetate) gave 3,4-*dihydro*-2-*phenylpyridazino*[6,1-c][1,4]*oxazin*-8(7H)-*one* (**10**) (50 mg, 54%) as an oil (Found: *m/z* 228.0896. $C_{13}H_{12}N_2O_2$ requires *m/z* 228.0899); δ (250 MHz) 2.58 (2 H, td, *J* 6.1 and 0.5 Hz, 4-H), 2.84 (2 H, t, *J* 6.1 Hz, 3-H), 4.60 (2 H, 7-H), 6.18 (1 H, t, *J* 0.5 Hz, 5-H), 7.38—7.47 (3 H, m), and 7.80—7.90 (2 H, m); δ(^{13}C) 18.00 (C-4), 23.55 (C-3), 68.54 (C-7), 115.34 (C-4a), 126.09, 126.77, 128.32, and 129.82 (Ph), 136.26 (C-5), 151.74 (C-2), and 160.68 (C-8).

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