

Thermal Reaction of *N*-(1-Azido-2-oxoalkylidene)-*N'*-(*o*-alkenyloxyphenyl)hydrazines; Intramolecular 1,4-Cycloaddition of 1,2,4-Triaza-1,3-diene Intermediates

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Functionalised *C*-azido-hydrazones (1) were prepared by treating the corresponding chloro-hydrazones (2) with sodium azide under phase-transfer conditions. Treatment of the hydrazones (1) with boiling benzene afforded 3,4,4a,5-tetrahydro[1,2,4]triazino[6,1-*c*][1,4]benzoxazines (3). Mechanisms are discussed.

ORGANIC azides are useful intermediates for the construction of nitrogen-containing heterocycles; there is a wide variety of unsaturated functions capable of reacting with the azido-group and/or with the nitrene species derived from it.¹ However, little is known of the thermal chemistry of *C*-azido-hydrazones, although these substrates are easily accessible by nucleophilic substitution of the corresponding *C*-chloro-hydrazones. In continuation of our work on the intramolecular reactions of functionalised azides,² we have synthesised a series of *C*-azido-hydrazones of type (1), and subjected them to thermal reaction. The results reveal a novel pattern of behaviour which opens new perspectives in the application of *C*-azido-hydrazones in heterocyclic syntheses.³

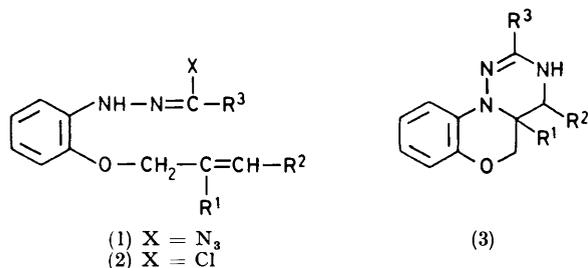
The azido-hydrazones (1a–f) were prepared by treating the corresponding chloro-hydrazones (2a–f) with sodium azide under phase-transfer conditions, *i.e.* in benzene–water in the presence of hexadecyltributylphosphonium bromide (see Table 1). The best yields

TABLE 1

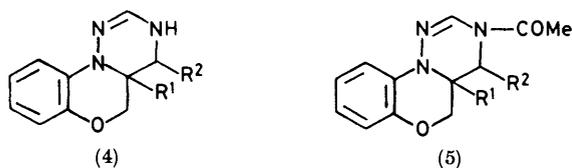
Preparation of *C*-azido-hydrazones (1) ^{a, b}

Compd.	Time (h)	Yield (%)	M.p. (decomp.) (°C)	ν_{\max} . (Nujol)/ cm ⁻¹
(1a)	8 ^c	58	95–96	3 320, 2 150, 1 710
(1b)	7	55	Oil ^d	3 330, 2 140, 1 720
(1c) ^e	5	65	Oil ^d	3 320, 2 150, 1 710
(1d)	8	60	93–95	3 370, 2 140, 1 680
(1e)	3	65	93–95	3 320, 2 150, 1 670
(1f)	5	70	104–105	3 370, 2 130, 1 650

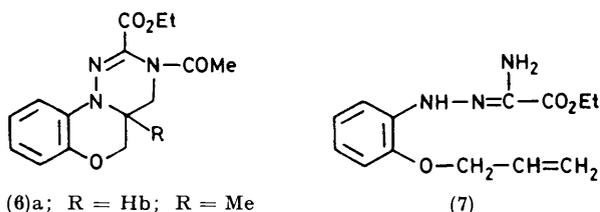
^a All compounds listed gave appropriate n.m.r. spectra. ^b Samples of analytical purity were not obtained because of the thermal labilities. ^c With 3 mol equiv. of sodium azide. ^d Purity *ca.* 95% (n.m.r.). ^e Isomer of *E*-configuration, as shown by the coupling constant of the olefinic protons (16 Hz).



- a; R¹ = R² = H, R³ = CO₂Et
b; R¹ = Me, R² = H, R³ = CO₂Et
c; R¹ = H, R² = Ph, R³ = CO₂Et
d; R¹ = R² = H, R³ = COMe
e; R¹ = Me, R² = H, R³ = COMe
f; R¹ = R² = H, R³ = C(=O)Ph



- a; R¹ = R² = H
b; R¹ = Me, R² = H
c; R¹ = H, R² = Ph



were achieved at 40 °C; at higher temperatures decomposition of the first-formed azido-derivatives began to occur.

In addition to the desired azido-compounds, the reaction gave small quantities of 3,3a-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazines, previously obtained by treating (2) with triethylamine in boiling benzene.⁴ The formation of these products, which arise from an intramolecular 1,3-dipolar cycloaddition of nitrilimine intermediates, is in line with the previously suggested hypothesis⁵ that the nucleophilic substitutions of *C*-chloro-hydrazones proceed through an elimination–addition mechanism involving nitrilimines.

Treatment of the azido-hydrazones (1a–f) with boiling benzene led to the results summarised in Table 2. Compounds (1a–c) underwent a clean reaction, complete within a few hours, and provided 3,4,4a,5-tetrahydro[1,2,4]triazino[6,1-*c*][1,4]benzoxazines (3a–c) in good yield. The product structures were assigned on the basis of elemental analyses, molecular weights, and i.r. and n.m.r. spectra (see Table 3). Critical evidence came from the n.m.r. spectrum of (3b): one proton of the methylene adjacent to nitrogen exhibits, in addition to the geminal coupling, a further coupling (4.5 Hz) which

TABLE 2
Thermal reactions of *C*-azido-hydrazones (1)

Compound	Time (h)	Product	Yield (%)	Isolation procedure ^a
(1a)	3	(3a)	63	A
(1b)	3	(3b)	69	A
(1c)	2	(3c)	79	B
(1d)	20 ^b	(3d)	43	A
(1e)	30 ^b	(3e)	25	A
(1f)	12 ^b	(3f)	35	A

^a A, chromatography on silica gel column with benzene-ethyl acetate (9:1) as eluant; B, crystallization from cyclohexane-benzene. ^b Some starting material was still present in the reaction mixture.

disappears on treatment with D₂O, thus revealing the presence of a CH₂NH grouping.

Chemical evidence in favour of the above structures was obtained from alkaline hydrolysis of the esters (3a—c). The corresponding carboxylic acids were not thermally stable, but readily underwent decarboxylation to give (4a—c). Treatment of (4a—c) and (3a and b) with boiling acetic anhydride afforded the *N*-acetyl derivatives (5a—c) and (6a and b), respectively. Under

the same conditions, no change was observed in (3c), probably because of steric hindrance due to the two substituents near the potential reaction centre. Spectral data for compounds (4a—c), (5a—c), and (6a and b) are given in Table 3. The n.m.r. spectra reveal that the *N*-acetyl group exerts a strong deshielding effect on one proton in the 4-position. This feature is more consistent with the given structures than with the 1-acetyl isomers.

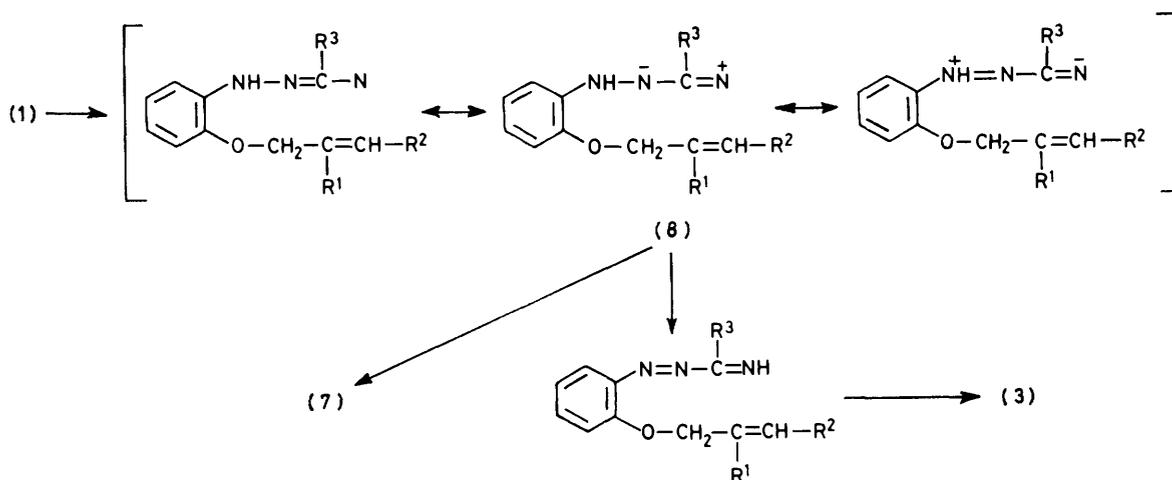
Compounds (1d—f) were more stable than (1a—c). They decomposed during several hours, providing the tricyclic products (3d—f) in modest yield with concomitant formation of uncharacterised material. The close analogy between the spectral properties of (3d—f) and (3a—c) (Table 3) favours the assigned structures. In particular, as in the case of (3b), the n.m.r. spectrum of (3e) indicates coupling between NH and one proton of the adjacent methylene (4.5 Hz).

Compound (1a) was also decomposed in boiling ethanol; in this solvent the reaction gave, together with (3a), a considerable amount of the *C*-amino-hydrazone (7).

TABLE 3
Physical and spectral data of [1,2,4]triazino[6,1-*c*][1,4]benzoxazines (3)—(6)^{a, b}

Compd.	M.p. (°C)	Recryst. solvent	$\nu_{\max.}$ (Nujol)/ cm ⁻¹	δ (<i>J</i> in Hz)	
				$\nu_{\max.}$ (Nujol)/ cm ⁻¹	δ (<i>J</i> in Hz)
(3a)	100	n-Hexane-chloroform	3 380 1 690	C ₆ D ₆ : 1.04 (3 H, t), 2.0—2.5 (2 H, m), 2.6—2.9 (1 H, m), 3.27 and 3.57 (2 H, AB of ABX, <i>J</i> _{AB} 10.5, <i>J</i> _{AX} 9.3, <i>J</i> _{BX} 3.5), 4.11 (2 H, q), 4.9 (1 H, br, s), 6.6—7.1 (3 H, m), 8.0—8.2 (1 H, m)	
(3b)	151	n-Pentane-chloroform	3 380 1 710	CDCl ₃ : 1.20 (3 H, s), 1.39 (3 H, t), 3.10 and 3.23 (2 H, see text, <i>J</i> _{gem} 11), 3.82 and 4.06 (2 H, AB, <i>J</i> 10.5), 4.38 (2 H, q), 5.6 (1 H, br, s), 6.6—7.2 (3 H, m), 7.5—7.8 (1 H, m)	
(3c)	216	Cyclohexane-benzene	3 360 1 690	CDCl ₃ : 1.38 (3 H, t), 3.24 (1 H, ddd, <i>J</i> 9.2, 7.5, and 3.9), 3.7—4.2 (3 H, overlapping m), 4.37 (2 H, q), 5.6 (1 H, br, s), 6.7—7.1 (3 H, m), 7.2—7.5 (5 H, m), 7.6—7.8 (1 H, m)	
(3d)	140	Methanol	3 430 1 680	CDCl ₃ : 2.50 (3 H, s), 2.9—3.6 (3 H, overlapping m), 3.83 and 4.37 (2 H, AB of ABX, <i>J</i> _{AB} 10.5, <i>J</i> _{AX} 9, <i>J</i> _{BX} 3.5), 5.5 (1 H, br, s), 6.7—7.1 (3 H, m), 7.5—7.7 (1 H, m)	
(3e)	184	Di-isopropyl ether-benzene	3 360 1 670	CDCl ₃ : 1.23 (3 H, s), 2.52 (3 H, s), 3.05 and 3.25 (2 H, see text, <i>J</i> _{gem} 11), 3.80 and 4.10 (2 H, AB, <i>J</i> 10.5), 5.7 (1 H, br, s), 6.8—7.2 (3 H, m), 7.6—7.8 (1 H, m)	
(3f)	121	Methanol	3 400 1 640	CDCl ₃ : 3.0—4.0 (4 H, overlapping m), 4.41 (1 H, dd, <i>J</i> 10.5 and 3.5), 5.8 (1 H, br, s), 6.7—7.0 (3 H, m), 7.3—7.6 (4 H, m), 8.1—8.3 (2 H, m)	
(4a)	152	Di-isopropyl ether-acetone	3 330	C ₆ D ₆ : 2.1—2.5 (2 H, m), 2.7—3.1 (3 H, m), 3.50 and 3.66 (2 H, AB of ABX, <i>J</i> _{AB} 10.5, <i>J</i> _{AX} 9.5, <i>J</i> _{BX} 3.5), 6.4 (1 H, br, s), 6.6—7.1 (4 H, overlapping m), 7.8—8.1 (1 H, m)	
(4b)	138	n-Hexane-benzene	3 280	CDCl ₃ : 1.23 (3 H, s), 3.15 (2 H, br, s), 3.88 and 4.03 (2 H, AB, <i>J</i> 10.5), 4.7 (1 H, br, s), 6.7—7.1 (4 H, m), 7.4—7.6 (1 H, m)	
(4c)	155	n-Hexane-acetone	3 260	CD ₃ COCD ₃ : 3.10 (1 H, ddd, <i>J</i> 9, 8, and 4), 3.8—4.0 (2 H, m), 4.20 (1 H, d, <i>J</i> 8), 6.1 (1 H, br, s), 6.5—6.9 (3 H, m), 7.08 (1 H, d, <i>J</i> 4) ^c , 7.3—7.6 (6 H, m)	
(5a)	161	Benzene	1 680	C ₆ D ₆ : 1.49 (3 H, s), 2.0—2.4 (1 H, m), 2.6—2.9 (1 H, m), 3.31 and 3.55 (2 H, AB of ABX, <i>J</i> _{AB} 10.5, <i>J</i> _{AX} 9.5, <i>J</i> _{BX} 3.5), 3.7—4.0 (1 H, m), 6.6—7.2 (4 H, overlapping m), 7.8—8.0 (1 H, m)	
(5b)	128	Di-isopropyl ether-acetone	1 690	CD ₃ COCD ₃ : 1.17 (3 H, s), 2.41 (3 H, s), 2.80 (2 H, br, s), 3.94 and 4.30 (2 H, AB, <i>J</i> 10.5), 6.7—7.0 (3 H, m), 7.4—7.8 (2 H, overlapping m)	
(5c)	175	Di-isopropyl ether-acetone	1 690	CD ₃ COCD ₃ : 2.25 (3 H, s), 3.3—3.6 (1 H, m), 4.1—4.3 (2 H, m), 5.12 (1 H, d, <i>J</i> 8), 6.8—7.1 (3 H, m), 7.3—7.7 (6 H, m), 8.10 (1 H, s)	
(6a)	141	n-Pentane-benzene	1 715 1 690	C ₆ D ₆ : 1.08 (3 H, t), 1.45—1.75 (1 H, m), 1.91 (3 H, s), 2.7—3.6 (3 H, overlapping m), 4.0—4.4 (3 H, overlapping m), 6.6—7.0 (3 H, m), 7.8—8.0 (1 H, m)	
(6b)	129	n-Hexane-ethanol	1 725 1 670	C ₆ D ₆ : 0.78 (3 H, s), 1.10 (3 H, t), 1.73 (1 H, d, <i>J</i> 12), 1.92 (3 H, s), 2.95 and 3.35 (2 H, AB, <i>J</i> 10.5), 4.0—4.4 (3 H, overlapping m), 6.7—7.0 (3 H, m), 7.9—8.1 (1 H, m)	

^a All compounds listed gave appropriate molecular ion peaks in the mass spectra. ^b Elemental analyses are collected in Table 4. ^c Singlet after deuteration of the NH group.



SCHEME

As illustrated in the Scheme, it is reasonable to invoke as the first stage of the formation of compounds (3) the thermally induced loss of nitrogen from the azido-group, giving the transient nitrenes (8). These intermediates, however, are unusual nitrene species in that 1,3- as well as 1,4-dipolar resonance forms can be conceived; thus, they could undergo a prototropic 1,4-shift followed by an intramolecular 1,4-cycloaddition of the 1,2,4-triazole-1,3-diene system to the neighbouring ethylenic function. Such a process resembles the recently reported^{6,7} formation of 1,2,4-triazine derivatives upon treatment of 3-diazopyrazoles (or 3-diazoindazoles) with electron-rich ethylenes. The intermediates (8) are structurally related to the iminonitrenes, which have been shown to be capable of cycloaddition to multiple bonds giving five-membered heterocycles.^{8,9} By analogy, these intermediates could have followed an intramolecular 1,3-cycloaddition pathway leading to fused-ring imidazolines.

One might expect the azido-group of (1) to react as such with the neighbouring ethylenic bond to form a 1,2,3-triazoline intermediate, which subsequently would eliminate nitrogen and afford stable products. However, several points rule against this hypothesis: (i) although intramolecular 1,3-dipolar cycloadditions are well known,¹⁰ they usually occur when favoured by the spatial proximity of the addends, which is not the case for the substrates (1); (ii) as found for vinyl azides,¹¹ the azido-group of (1) should have a low propensity to react as a 1,3-dipole. Support for the latter consideration (ii) was obtained on heating (1a) in the presence of an excess of 2-methyl-1-morpholinopropene; the tricyclic compound (3a) was again the only product and no intermolecular reaction was observed despite the dipolarophilicity of enamines towards azides.¹² On the other hand, since the formation of primary amines from nitrenes *via* hydrogen abstraction from the environment is well documented,¹³ the formation of (7) proves that the azido-hydrazone (1) can really generate the nitrenes (8).

EXPERIMENTAL

M.p.s were taken with a Büchi apparatus. N.m.r. spectra were obtained with a Varian HA-100 instrument, with SiMe_4 as an internal standard. I.r. spectra were recorded with a Perkin-Elmer 377 spectrophotometer. Compounds (2a-c) were prepared according to the literature method.⁴

Preparation of C-Chloro-hydrazone (2d-f).—Compounds (2d-f) were prepared from the appropriate *o*-alkenyloxyanilines according to the procedure described for (2a).⁴ Yields and properties were: (2d), 61%, m.p. 94 °C (from pentane-benzene), ν_{max} (Nujol) 3 270 and 1 670 cm^{-1} ; (2e), 57%, m.p. 96 °C (from ethanol), ν_{max} (Nujol) 3 290 and 1 670 cm^{-1} ; (2f), 52%, m.p. 118 °C (from ethanol), ν_{max} (Nujol) 3 350 and 1 670 cm^{-1} .

Preparation of C-Azido-hydrazone (1a-f).—A solution of the chloro-hydrazone (2) (10 mmol) in benzene (100 ml) was treated with a solution of sodium azide (20 mmol) and hexadecyltributylphosphonium bromide (1 mmol) in water (50 ml). The mixture was heated at 40 °C with vigorous stirring for the time indicated in Table 1. The aqueous layer was removed and the organic solution was washed several times with water and dried (Na_2SO_4). The solvent was evaporated off under reduced pressure and the residue was chromatographed on a silica gel column with benzene-ethyl acetate (9 : 1) as eluant. Yields and properties are collected in Table 1.

Thermal Reaction of C-Azido-hydrazone (1a-f).—A solution of the hydrazone (1) (5 mmol) in dry benzene (250 ml) was refluxed for the time given in Table 2. The solvent was removed under reduced pressure and the residue was worked up as indicated in Table 2. Products, yields, and properties are reported in Tables 2-4.

When the hydrazone (1a) was refluxed in ethanol (5 h), column chromatography of the reaction mixture [silica gel, diethyl ether-light petroleum (1 : 1) as eluant] gave the amino-hydrazone (7) in 37% yield, b.p. 165-170 °C at 0.5 mmHg; ν_{max} (film) 3 430, 3 340, and 1 700 cm^{-1} ; $\delta(\text{CDCl}_3)$ 1.39 (3 H, t), 4.35 (2 H, q), 4.5-4.8 (4 H, overlapping signals), 5.2-5.5 (2 H, m), 5.8-6.2 (1 H, m), 6.7-7.1 (3 H, overlapping signals), and 7.4-7.6 (1 H, m); M^+ 263. Further elution gave (3a) (28%).

Treatment of the Tricyclic Esters (3a-c) with Sodium Hydroxide.—Compound (3a) (0.20 g) was dissolved in

TABLE 4
Elemental analyses

Compd.	Required (%)			Found (%)		
	C	H	N	C	H	N
(3a)	59.8	5.8	16.1	59.6	5.6	15.9
(3b)	61.1	6.2	15.3	60.9	6.4	15.1
(3c)	67.6	5.7	12.5	67.5	5.9	12.3
(3d)	62.3	5.7	18.2	62.1	5.6	18.0
(3e)	63.7	6.2	17.1	63.5	6.0	16.9
(3f)	69.6	5.2	14.3	69.5	5.1	14.1
(4a)	63.5	5.9	22.2	63.3	5.8	22.1
(4b)	65.0	6.5	20.7	64.8	6.4	20.5
(4c)	73.1	6.2	15.0	72.9	6.2	14.9
(5a)	62.3	5.7	18.2	62.5	5.9	18.2
(5b)	63.7	6.2	17.1	63.9	6.3	17.1
(5c)	70.3	5.6	13.7	70.1	5.6	13.6
(6a)	59.4	5.7	13.9	59.5	5.8	13.7
(6b)	60.6	6.0	13.2	60.8	6.2	13.3

methanolic 0.2M-sodium hydroxide (50 ml) and refluxed for 30 min. After cooling, the mixture was acidified with aqueous hydrochloric acid, the solvent was partly removed under reduced pressure, and the residue was treated with water and extracted with chloroform. The organic solution was dried (Na_2SO_4) and evaporated. The residue was taken up in benzene (60 ml) and refluxed for 1 h. After removal of the solvent, treatment with di-isopropyl ether and filtration afforded (4a) (56%); see Tables 3 and 4.

Under the same conditions, (3b) and (3c) gave (4b) and (4c) in 67 and 75% yield, respectively; see Tables 3 and 4.

Treatment of the Tricyclic Products (3a and b) and (4a—c) with Acetic Anhydride.—A solution of (3a) (0.15 g) in acetic anhydride (10 ml) was refluxed for 4 h. The solvent was removed under reduced pressure and the residue was taken up in ether and washed with aqueous sodium hydrogen carbonate. The organic solution was dried (Na_2SO_4) and

evaporated. The residue was treated with di-isopropyl ether and the mixture filtered to afford (6a) in 63% yield; see Tables 3 and 4.

Treatment of (3b) and (4a—c) under the same conditions gave (6b) (45%), (5a) (79%), (5b) (81%), and (5c) (83%), respectively. In the case of (3b), the reaction time was 10 h and the product had to be purified by chromatography on a silica gel column.

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