Thermal Behaviour of 3-Phenyl-1,2,4-oxadiazol-5-ylhydrazines

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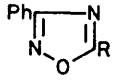
Depending on the substitution on the hydrazine moiety, thermolysis of 3-phenyl-1,2,4-oxadiazol-5-ylhydrazines (1)—(5) gives variable amounts of 1-amino-Δ^2-1,2,4-triazolin-5-ones (13) or (17), Δ^2- or Δ^3-1,2,4-triazolin-5-ones (12), (18), or (19), and the *s*-triazine (20). A possible mechanism accounting for the products and the effects is discussed. A diradical intermediate and a hydrogen transfer from the reaction medium are suggested on the basis of the effect of benzoyl peroxide on the reaction and on the behaviour of the hydrazines (1)—(4) towards catalytic hydrogenation.

Isoxazoles undergo thermal transformations, the first step of which is fission of the N–O bond.[1] Nucleophilic substituents at the 5-position of the isoxazole can be involved in the reaction to afford different heterocycles. Thus, thermal isomerization of isoxazol-5-ylhydrazines has led to 1- and 4-aminopyrazolin-5-ones and tetrahydro-1,2,4-triazin-6-ones *via* the corresponding 2*H*-azirine-2-carbohydrazides.[2] To extend our research on the thermal behaviour of heteroaromatic systems containing an N–O bond, we have now studied the thermolysis of the 1,2,4-oxadiazol-5-ylhydrazines (1)—(5).

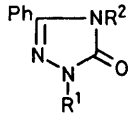


(1) R = NH·NH$_2$
(2) R = NMe·NH$_2$
(3) R = NMe·NHMe
(4) R = NH·NMe$_2$
(5) R = NMe·NMe$_2$
(6) R = NH·NHMe
(7) R = Cl
(8) R = CCl$_3$
(9) R = CH:N·NHMe
(10) R = NMe·N(CHO)Me
(11) R = NHMe

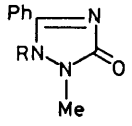
The hydrazines (1)—(4) were conveniently prepared from 5-chloro-3-phenyl-1,2,4-oxadiazole (7)[3] and the appropriate hydrazine. In fact, 3-phenyl-5-trichloromethyl-1,2,4-oxadiazole (8)[4] with methylhydrazine afforded a mixture of isomeric methylhydrazines (2) and (6) and the hydrazone (9). The hydrazine (5) was obtained by treatment of the compound (3) with formic acid to give the formyl derivative (10) which was then reduced by borane–tetrahydrofuran.

The hydrazines (1)—(5), heated in refluxing decalin, gave different products according to the substitution on the hydrazine moiety. Thus the hydrazine (1) gave 3-phenyl-1,2,4-Δ^2-triazolin-5-one (12)[5] and a small amount of 1-amino-3-phenyl-Δ^2-1,2,4-triazolin-5-one (13), which was separated and characterized as its benzylidene derivative (16). Compound (13) was prepared by amination of the triazolinone (12). Its structure followed from the reaction with diazomethane which afforded a mixture of *N*-methyl (14) and *O*-methyl (21) derivatives, deamination of (14) leading to the known methyltriazolinone (15).[6]

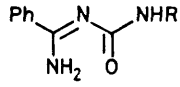
The hydrazines (2) and (3) afforded the 1,2,4-triazolinones (18) or (19),[5] the *s*-triazine (20),[7] and 5-methylamino-3-phenyl-1,2,4-oxadiazole (11).[3] Thermolysis of



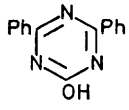
(12) $R^1 = R^2 = H$
(13) $R^1 = NH_2$, $R^2 = H$
(14) $R^1 = NH_2$, $R^2 = Me$
(15) $R^1 = H$, $R^2 = Me$
(16) $R^1 = N{:}CH{\cdot}Ph$, $R^2 = H$
(17) $R^1 = NMe_2$, $R^2 = H$



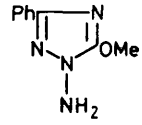
(18) R = H
(19) R = Me



(22) R = NMe$_2$
(23) R = Me



(20)



(21)

the trimethylhydrazine (5) resulted also in formation of the same *s*-triazine (20) in high yield, whereas the dimethylhydrazine (4) gave a mixture of (20) and 1-dimethylamino-Δ^2-1,2,4-triazolin-5-one (17), whose structure was assigned on the basis of spectroscopic evidence (see Experimental section).

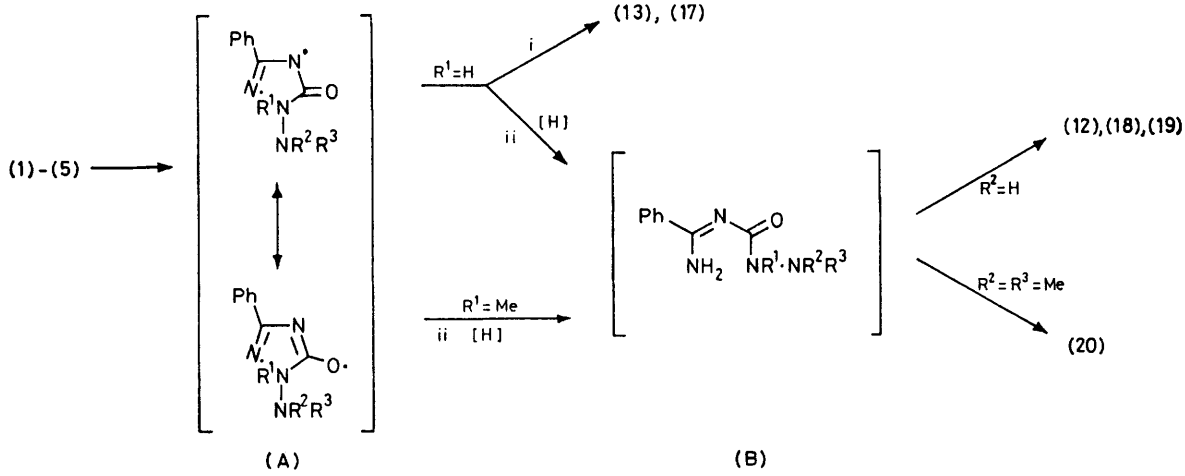
The triazolinone (12) cannot be formed by deamination

of the 1-amino-derivative (13) as the latter was unaffected by refluxing in decalin. Formation of compounds (18) and (19) is indicative of the positions that the αβ-hydrazinic nitrogen atoms of the starting material assume in the products. Compound (11), resulting from the hydrazines (2) and (3) by N–N bond cleavage, is an intermediate in the formation of the *s*-triazine (20) since it afforded the latter product on refluxing in decalin.

On the basis of these results, the thermal behaviour of compounds (1)—(5) can be rationalized as shown in the Scheme. The first step involves the fission of the N–O bond to give the diradical (A). In fact, in the presence of peroxides the reaction was quicker and occurred at lower temperature. Unlike the isoxazole system, the diradical (A) does not give a three-membered ring (in this case a 1*H*-diazirine *) and it shows a low tendency to cyclize to a five-membered ring (pathway i). Thus the expected 1*H*-diazirine rearrangement products (1,2,4,5-tetrazin-3-ones and 4-amino-Δ^2-1,2,4-triazolin-5-ones) were never recovered and the 1-amino-Δ^2-1,2,4-triazolin-ones (13) or (17), which may be formed when $R^1 = H$, were obtained in low yields.

The greater tendency of the diradical (A) is to abstract two hydrogen atoms from the solvent † to give the reduced intermediate (B) (pathways ii). Under the reaction conditions (B) is not stable and if $R^2 = H$ the triazolinones (12), (18), or (19) are obtained. On the contrary, when $R^2 = R^3 = Me$, owing to the impossibility of intramolecular closure, two molecules of (B) afford the *s*-triazine (20), as has been observed for similar compounds.[10]

Support for the presence of the intermediates (B) was obtained by their preparation by hydrogenation of the corresponding 1,2,4-oxadiazol-5-ylhydrazines (1)—(4): even at room temperature [compounds (1)—(3)] or by a short heating [compound (4)], these afford compounds (12), (18), (19), and (20) respectively.



SCHEME

EXPERIMENTAL

I.r. spectra were measured for dispersions in potassium bromide with a Perkin-Elmer 357 spectrometer. ^{1}H N.m.r. spectra (90 MHz) were recorded with a Perkin-Elmer R 32 instrument; chemical shifts are reported in p.p.m. downfield from internal tetramethylsilane. U.v. spectra were measured for solutions in methanol with a Perkin-Elmer 124 spectrophotometer. Silica-gel plates (Merck F_{254}) were used for analytical t.l.c. Extracts were dried over sodium sulphate, and solvents were removed under reduced pressure. Unless otherwise stated, light petroleum refers to the fraction of b.p. 30—50 °C. Hydrogenations were carried out with 10% Pd–charcoal as catalyst.

1,2,4-*Oxadiazol*-5-*ylhydrazines* (1)—(4).—A mixture of 5-chloro-3-phenyl-1,2,4-oxadiazole (7) [3] and the appropriate hydrazine was kept for 1 h at room temperature as indicated in Table 1. Compounds (2)—(4) were recovered by evaporation of the solvents *in vacuo*, whereas compound (1) was collected by filtration after pouring a solution of the compound in dioxan into ice–water. Spectral data are reported in Table 2.

Reaction of 3-*Phenyl*-5-*trichloromethyl*-1,2,4-*oxadiazole* (8) *with Methylhydrazine*.—To methylhydrazine (4.8 g, 0.104 mol) was added 5-trichloromethyloxadiazole (8) [4b] (2.9 g, 0.011 mol) at 0 °C with stirring. The reaction mixture was left at room temperature for 2 h and diluted with water. Extraction with ether afforded an oil which was chromatographed on silica gel [chloroform–methanol (95 : 5 v/v)] yielding 3-*phenyl*-1,2,4-*oxadiazol*-5-*carbaldehyde methylhydrazone* (9) (0.20 g, 9%), m.p. 112 °C (from cyclohexane) (Found: C, 59.7; H, 5.15; N, 27.7. $C_{10}H_{10}N_4O$ requires C, 59.4; H, 5.0; N, 27.7%); $\nu_{max.}$ 3 300 cm^{-1} (NH); δ ($CDCl_3$) 3.03 [d, *J* 4.5 Hz (s with D_2O), NMe], 7.28 (s + broad band which disappears with D_2O, CH and NH), and 7.40—7.55 and 8.05—8.74 (m, C_6H_5). Further elution afforded the methylhydrazine (2) (0.6 g, 29%) and 1-*methyl*-2-(3-*phenyl*-1,2,4-*oxadiazol*-5-*yl*)*hydrazine* (6) (0.25 g, 12%), m.p. 88 °C (from cyclohexane) (Found: C, 56.5; H,

* Only two examples of 1*H*-diazirines have been reported, both of which were obtained by photochemical reactions,[8] and one of which was later disproved.[9]

† By heating the hydrazine (1) in the absence of solvents we obtained similar results but with low yields (1,2,4-triazolin-5-one 30%) and formation of benzonitrile (25%).

TABLE 1

Preparation of 1,2,4-oxadiazol-5-ylhydrazines (1)—(4)

Compound	Molar ratio (7) : hydrazine	Solvent	Yield (%)	M.p./°C	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
(1)	1 : 15	dioxan	90	172 [a]							
(2)	1 : 4	benzene	91	84 [b]	$C_9H_{10}N_4O$	56.6	5.4	29.5	56.8	5.3	29.5
(3)	1 : 2	benzene	84	102 [c]	$C_{10}H_{13}N_4OCl$	50.1	5.2	23.3	49.9	5.4	23.3
(4)	1 : 4	benzene	91	143 [d]	$C_{10}H_{12}N_4O$	59.0	6.0	27.5	58.8	5.9	27.4

[a] From benzene; lit.,[4a] 169—171 °C. [b] From cyclohexane. Compound (2) with benzaldehyde gave a benzal derivative, m.p. 150—151 °C (from cyclohexane) (Found: C, 68.8; H, 4.9; N, 19.95. $C_{16}H_{14}N_4O$ requires C, 69.05; H, 5.1; N, 20.1%). [c] As hydrochloride, recrystallised from methanol–anhydrous ether. [d] From cyclohexane–benzene (1 : 1 v/v).

5.35; N, 29.4. $C_9H_{10}N_4O$ requires C, 56.8; H, 5.3; N, 29.5%). Spectral data are reported in Table 2.

1,1,2-Trimethyl-2-(3-phenyl-1,2,4-oxadiazol-5-yl)hydrazine. (5).—A solution of 1,2-dimethyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)hydrazine (3) (0.02 mol) in formic acid (20 ml) was refluxed for 1 h, cooled, and diluted with water to afford *NN'-dimethyl-N'-(3-phenyl-1,2,4-oxadiazol-5-yl)formohydrazide* (10) (75%), which was crystallized from light

TABLE 2

Spectral data for 1,2,4-oxadiazol-5-ylhydrazines (2)—(6)

Compound	$\nu_{max.}$(NH str.)/ cm^{-1}	δ ($CDCl_3$)
(2)	3 350, 3 300, 3 2800	3.24 (s, NMe), 4.44 (exch., s, NH_2), 7.31—7.50 and 7.90—8.10 (m, C_6H_5)
(3) [a]	3 100—2 000br	2.68 (s, NMe), 3.32 (s, NMe), 6.93 (exch., s, NH_2^+), 7.48—7.65 and 7.85—8.22 (m, C_6H_5) [b]
(4)	3 200	2.67 (s, NMe_2), 6.86 (exch., s, NH), 7.39—7.55 and 7.96—8.11 (m, C_6H_5)
(5)		2.67 (s, NMe_2), 3.16 (s, NMe), 7.30—7.51 and 7.90—8.11 (m, C_6H_5)
(6)	3 390, 3 350, 3 180	2.77 (s, NMe), 4.21br (exch., s, NH), 7.35—7.57 and 7.83—8.12 (m, C_6H_5), 8.32br (exch., s, NH)

[a] As hydrochloride. [b] In $(CD_3)_2SO$.

petroleum (b.p. 40—70 °C), m.p. 74 °C (Found: C, 56.9; H, 5.2; N, 24.3. $C_{11}H_{12}N_4O_2$ requires C, 56.9; H, 5.2; N, 24.1%); $\nu_{max.}$ 1 670 cm^{-1} (CO); δ ($CDCl_3$) 3.12 * and 3.24 (s, NMe), 3.40 (s, NMe), 7.32—7.58 and 7.91—8.12 (m, C_6H_5), and 8.33 (s, CH). Borane–tetrahydrofuran reduction [2b] of the above formyl derivative afforded the *trimethyl-1,2,4-oxadiazolylhydrazine* (5) (51%), m.p. 82—83 °C (from cyclohexane) (Found: C, 60.45; H, 6.6; N, 25.6. $C_{11}H_{14}N_4O$ requires C, 60.5; H, 6.5; N, 25.7%); n.m.r. data of compound (5) are reported in Table 2.

Thermolysis of 1,2,4-Oxadiazol-5-ylhydrazines (1)—(5) *and 5-Methylamino-1,2,4-oxadiazole* (11).—Compounds (1)—(5) and (11) (0.5 g) were refluxed in decalin (20 ml) for the time indicated below. Unless otherwise stated, decalin was removed by eluting the reaction mixture on a silica-gel column with light petroleum.

(a) *3-Phenyl-1,2,4-oxadiazol-5-ylhydrazine* (1). Reaction time 3 h. The solid (0.350 g) was filtered off and identified (i.r., t.l.c.) as 3-phenyl-Δ²-1,2,4-triazolin-5-one (12),[5] contaminated with a small amount of a second compound. Benzaldehyde (1.5 ml) was added to the above mixture in methanol (10 ml) and the solution refluxed for 2 h. The solvent was removed and light petroleum was added to afford solid material which was chromatographed on silica gel (ether as eluant) yielding *1-benzylideneamino-3-phenyl-Δ²-1,2,4-triazolin-5-one* (16) (0.01 g, 1.3%), m.p. 287 °C (from ethanol) (Found: C, 68.1; H, 4.7; N, 20.9. $C_{15}H_{12}N_4O$ requires C, 68.2; H, 4.6; N, 21.2%); $\nu_{max.}$ 3 200—2 500br (NH) and 1 700 cm^{-1} (CO); δ [$(CD_3)_2SO$] 7.42—7.67 and 7.80—8.07 (m, $2C_6H_5$), and 8.78 (s, CH). Elution with methanol afforded the triazolinone (12) (0.3 g, 66%). T.l.c. analysis of the decalin solution showed the presence of small amounts of the *s*-triazine (20) [7] and 5-amino-3-phenyl-1,2,4-oxadiazole.[4a] Compound (12) was also obtained (quantitative yield) by hydrogenation of the hydrazine (1).

(b) *1-Methyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)hydrazine* (2). Reaction time 19 h. Elution with chloroform–methanol (95 : 5 v/v) afforded 5-methylamino-3-phenyl-1,2,4-oxadiazole (11) [3] (22%), the *s*-triazine (20) [7] (18%), and 1-methyl-3-phenyl-Δ³-1,2,4-triazolin-5-one (18) [5] (31%). Compound (18) was also obtained (quantitative yield) by hydrogenation of the methylhydrazine (2).

(c) *1,2-Dimethyl-1-(3-phenyl-1,2,4-oxadiazol-5-yl)hydrazine* (3). Reaction time 24 h. Elution with ether afforded an oil which with light petroleum gave 5-methylamino-3-phenyl-1,2,4-oxadiazole (11) (12%). From the mother-liquor starting material (0.065 g) was recovered. Further elution with chloroform–methanol (85 : 15 v/v) gave the *s*-triazine (20) (26%) and 1,2-dimethyl-3-phenyl-Δ³-1,2,4-triazolin-5-one (19) (26%).[5] Compound (19) was also obtained (quantitative yield) by hydrogenation of the dimethylhydrazine (3).

(d) *1,1-Dimethyl-2-(3-phenyl-1,2,4-oxadiazol-5-yl)hydrazine* (4). Reaction time 5 h. Elution with ether afforded starting material (0.15 g). Further elution with chloroform–methanol (95 : 5 v/v) yielded a mixture of two products which was resolved on Lobar Si 60 (40—63 μm) (Merck) [chloroform–methanol (95 : 5 v/v) as eluant] to give *1-dimethylamino-3-phenyl-Δ²-1,2,4-triazolin-5-one* (17) (0.12 g, 34% based on unrecovered starting material), m.p. 223—225 °C (decomp.) after sublimation at 130 °C and 0.05 mmHg (Found: C, 58.6; H, 5.7; N, 27.15. $C_{10}H_{12}N_4O$ requires C, 58.8; H, 5.9; N, 27.4%); $\nu_{max.}$ 3 200—2 500br (NH) and 1 700 cm^{-1} (CO); $\lambda_{max.}$ 266 nm (log ε 3.97); δ ($CDCl_3$) 2.87 (s, NMe_2), 7.39—7.55 and 7.81—7.96 (m, C_6H_5), 12.82br (exch., s, NH). The second product was the *s*-triazine (20) (0.08 g, 37% based on unrecovered starting material).

(e) *1,1,2-Trimethyl-2-(3-phenyl-1,2,4-oxadiazol-5-yl)hydrazine* (5). Reaction time 40 h. The solid was filtered off and identified as the *s*-triazine (20) (52%). A second crop (total 70%) of the same compound was obtained from the mother-liquors.

(f) *5-Methylamino-3-phenyl-1,2,4-oxadiazole* (11). Operating as above, the *s*-triazine (20) was obtained in 70% yield.

Amination of 3-Phenyl-Δ²-1,2,4-trazolin-5-one (12).—A mixture of the triazolinone (12) (0.60 g, 3.7 mmol) and

* Main branch; branching attributable to a hindered rotation.

hydroxylamine-*O*-sulphonic acid (0.84 g, 7.4 mmol) in 1M-sodium hydroxide (20 ml) was stirred at room temperature for 30 h. Filtration of the neutralized solution afforded starting material (0.36 g). From the ethereal solution, obtained by the continuous extraction (48 h) of the mother-liquors, crude 1-amino-3-phenyl-Δ^2-1,2,4-triazolin-5-one (13) (0.20 g, 76% based on unrecovered starting material) was obtained, m.p. 235—238 °C; $\nu_{max.}$ 3 310, 3 200, 2 960br (NH_2 and NH), and 1 705 cm^{-1} (CO); $\lambda_{max.}$ 268 nm (log ε 4.08). Compound (13) with benzaldehyde gave the benzylideneamino-derivative (16).

Methylation of 1-*Amino*-3-*phenyl*-Δ^2-1,2,4-*triazolin*-5-*one* (13) *with Diazomethane*.—To a solution of the triazolinone (13) (0.12 g, 0.68 mmol) in methanol (5 ml), ethereal diazomethane (0.1 g, 2.0 mmol) was added. Chromatography on silica gel (ether as eluant) gave 1-*amino*-5-*methoxy*-3-*phenyl*-1,2,4-*triazole* (21) (0.055 g, 43%), m.p. 152—154 °C after sublimation at 90 °C and 0.1 mmHg (Found: C, 57.0; H, 5.4; N, 29.4. $C_9H_{10}N_4O$ requires C, 56.8; H, 5.3; N, 29.5%); $\nu_{max.}$ 3 320, 3 240, and 3 210 (NH_2); δ ($CDCl_3$) 4.08 (s, OMe), 4.96 (exch., s, NH_2), and 7.25—7.58 and 7.83—8.01 (m, C_6H_5). Further elution with chloroform–methanol (9 : 1 v/v) afforded 1-*amino*-4-*methyl*-3-*phenyl*-Δ^2-1,2,4-*triazolin*-5-*one* (14) (0.035 g, 27%), m.p. 120—122 °C (from benzene–cyclohexane) (Found: C, 54.0; H, 5.3; N, 28.4. $C_9H_{10}N_4O \cdot 1/2H_2O$ requires C, 54.3; H, 5.6; N, 28.1%); $\nu_{max.}$ 3 280 and 3 210 (NH_2), and 1 710 cm^{-1} (CO); δ ($CDCl_3$) 3.30 (s, NMe), 4.77 (exch., s, NH_2), and 7.29—7.62 (m, C_6H_5).

Deamination of 1-*Amino*-4-*methyl*-3-*phenyl*-Δ^2-1,2,4-*triazolin*-5-*one* (14).—To a solution of the triazolinone (14) (0.03 g, 0.16 mmol) in 6M-hydrochloric acid, sodium nitrite (0.011 g, 0.16 mmol) in the minimum amount of water was added. Extraction (CH_2Cl_2) of the neutralized (NaOH) solution afforded 4-methyl-3-phenyl-Δ^2-1,2,4-triazolin-5-one (15) (0.021 g, 75%), identical (m.p. and i.r. spectrum) with an authentic sample.[6]

4-(α-*Aminobenzylidene*)-1,1-*dimethylsemicarbazide* (22) *and* N-(α-*Aminobenzylidene*)-N′-*methylurea* (23).—Hydrogenation of dimethylhydrazine (4) or methylamine (11) afforded in quantitative yield compounds (22) or (23) respectively, which were crystallized from chloroform–light petroleum. The *semicarbazide* (22) had m.p. 175—177 °C (Found: C, 58.4; H, 6.8; N, 27.2. $C_{10}H_{14}N_4O$ requires C, 58.2; H, 6.8; N, 27.2%); $\nu_{max.}$ 3 330 and 3 170br (NH and NH_2), and 1 610 (CO). The *urea* (23) had m.p. 124—126° (Found: C, 61.0; H, 6.2; N, 23.7. $C_9H_{11}N_3O$ requires C, 61.0; H, 6.3; N, 23.7%); $\nu_{max.}$ 3 420, 3 350, and 3 230br (NH and NH_2), and 1 600 cm^{-1} (CO). On heating the above compounds in refluxing decalin for 20 min, the *s*-triazine (20) was obtained in > 80% yield.

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