Cleavage of N–O Bonds in 1,2,4-Oxadiazolines (1)

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The photochemical cleavage of the N–O bond in 1,2,4-oxadiazolines I to form acetamidines II was found to occur under mild conditions (ordinary light, 3560Å, or 2537Å). The weak N–O bond in 3-methyl-4,5-diphenyl-1,2,4-oxadiazoline (If) was also cleaved by catalytic reduction to give a molecular compound composed of benzyl alcohol and *N*-phenylacetamidine, V.

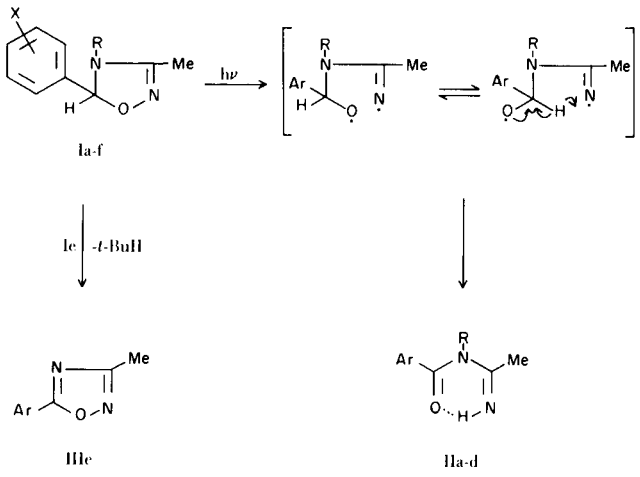
The five membered heterocyclic 1,2,4-oxadiazoline ring may be broken at the weak N–O linkage by photochemical means or neutral catalytic reduction.

The cleavage of a 1,2,4-oxadiazoline to the corresponding substituted amidine (2) with black light (3560Å) (Ia → IIa) was facilitated in more stubborn cases (Ib,c,d → IIb,c,d) by a higher energy source (2537Å). It was not surprising that in the photochemical decomposition of 3-methyl-4-*tert*-butyl-5-*p*-nitrophenyl-1,2,4-oxadiazoline (Ie) isobutane was lost, leaving the 1,2,4-oxadiazole ring (III) intact. Under the more strenuous conditions of the mass spectrometer, the fragmentation pattern included the *tert*-butyl group (m/e 57) as the peak of greatest relative abundance (3). Evidently loss of the *tert*-butyl group is a lower energy transformation photochemically than the ring opening reaction.

Evidence for the structure of the rearranged acetamidine IIa was given in a preliminary report (2). Analytical data are included in the present paper. IR and NMR data for the other rearranged products (IIb,c, and d) confirmed the analogous structures for these compounds, as was earlier assigned to IIa (2).

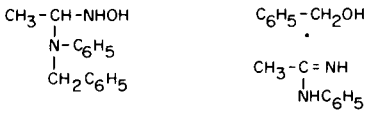
The structure of III was based on the loss of the *tert*-butyl group as shown in the NMR spectrum of the crude reaction product after irradiation of compound Ie. The analytical sample of III gave a parent ion peak (M^+) of 205 in the mass spectrum and the final identification of III was made by comparison of IR and NMR spectra of an authentic sample of the oxadiazole prepared by 1,3-dipolar addition of acetonitrile oxide to *p*-nitrobenzonitrile (4).

A free radical pathway by a chain mechanism for the formation of III was suggested by the fact that with ether or hexane as solvents, a better yield of III (and in shorter time) was obtained than with chloroform or carbon tetrachloride (better radical traps). The *tert*-butyl radical was shown to be a probable link in the chain by identification of *tert*-butyl chloride (25 ± 5% yield) when carbon tetrachloride was used as solvent in a 2½ hour irradiation of Ie with 2537Å light. A yield of 25 ± 5% of III was obtained in the same experiment. These yields were estimated (without isolation) by comparing NMR peak areas of methyl groups in Ie and III and the *tert*-butyl group in Ie and *tert*-butyl chloride.



a. R = $C_2H_5OCH_2CH_2$ X = *p*-NO_2
b. R = $C_2H_5OCH_2CH_2$ X = *m*-NO_2
c. R = $C_2H_5OCH_2CH_2$ X = *p*-OCH_3
d. R = *n*-C_3H_7 X = *p*-NO_2
e. R = *t*-C_4H_9 X = *p*-NO_2
f. R = C_6H_5 X = H

Catalytic reduction of 3-methyl-4,5-diphenyl-1,2,4-oxadiazoline (If) with palladium on carbon cleaved the N–O bond to give a molecular compound V of benzyl alcohol and *N*-phenylacetamidine. Initial cleavage of the carbon to oxygen bond in the ring would have resulted in the formation of the corresponding hydroxylamino derivative IV (or by complete hydrogenolysis, toluene).



IV V

TABLE I

Schiff Bases, ArCH=NR

Compound Ar	R	M.p. °C	ν(C=N) cm⁻¹	NMR ArCH,	Molecular Formula	Analyses Calcd. C	H	N	Found C	H	N
p-$C_6H_4NO_2$	n-C_3H_7	53	1650	8.31		(a)					
m-$C_6H_4NO_2$	-$C_2H_4OC_2H_5$	42	1650	8.21	$C_{11}H_{14}N_2O_3$	59.45	6.30	12.60	59.56	6.30	12.83
p-$C_6H_4OCH_3$	-$C_2H_4OC_2H_5$	(b)	1645	8.18	$C_{12}H_{17}NO_2$	69.56	8.21	6.76	69.70	8.38	6.74
p-C_6H_4-NO_2	-$C_2H_4OC_2H_5$	(c)	1650	8.23	$C_{11}H_{14}N_2O_3$	59.45	6.35	12.60	59.27	6.42	12.52

(a) V. Madan and L. B. Clapp, *J. Am. Chem. Soc.*, 91, 6078 (1969). (b) B.p. 101° (3 mm.). (c) M.p. (55.0-55.5°), analyses, and yield (85%) supplied to us by A. A. Sirotenko and C. Peter Cole, St. John Fisher College, Rochester, New York, private communication.

TABLE II

1,2,4-Oxadiazolines (a)

Compound	M.p. or B.p. (mm.) °C	Yield, %	ν(C=N) cm⁻¹	NMR ArCH	NMR CH_3C=N	Molecular Formula	Analyses Calcd. C	H	N	Found C	H	N
Ia	oil (b)	70	1650	6.16	2.00	$C_{13}H_{17}N_3O_4$	55.90	6.09	15.05	56.00	6.20	14.90
Ib	95 (3)	58	1630	6.16 (c)	2.00	$C_{13}H_{17}N_3O_4$	55.90	6.09	15.05	56.69 (f)	6.23	15.23
Ic	85 (3)	50	1620	6.15 (d)	2.16	$C_{14}H_{20}N_2O_3$	63.63	7.57	10.60	63.93	7.37	10.47
Id	62	80	1625	6.18 (e)	2.00	$C_{12}H_{15}N_3O_3$	57.84	6.02	16.87	58.09	6.07	16.70

(a) Compounds Ie and If are reported in Reference 3. (b) Not distilled. Other IR and NMR data, Reference 3. (c) δ, 7.20-7.46 (m, 4, Ar); 3.10-3.53 (m, 6, CH_2); 1.13 (t, 3, CH_3). (d) δ, 6.88-7.56 (m, 4, Ar); 3.30-3.70 (m, 6, CH_2); 1.30 (t, 3, CH_3); 3.88 (s, 3, OCH_3). (e) δ, 7.66, 8.28 (d, 4, A_2B_2 with J=9 cps); 3.05 (t, 2, NCH_2); 1.4 (m, 2, CH_2); 0.82 (t, 3, CH_3). (f) High carbon on duplicate samples in which H, N analyses were acceptable is not explained. An m/e (279) peak of low relative intensity was observed for both Ib and Ia in the mass spectra.

The same molecular compound of benzyl alcohol and *N*-phenylacetamidine was obtained (in lower yield) when an attempt was made to isolate a product from the catalytic reduction of If in 1,2-dimethoxyethane after one mole of hydrogen had been added.

The three protons on N and O in the molecular compound V appeared in one peak in the NMR spectrum at δ 4.96, and moved 7 cps downfield upon addition of pyridine. This suggests that hydrogen bonding in the molecular compound makes the three protons act as a single functional group. Addition of *N*-phenylacetamidine to the molecular compound broadened the signal but did not shift the center of the signal from δ 4.96. When benzyl alcohol was added to the molecular compound, the signal moved upfield by 11 cps. The relative area due to the CH_2 group increased but remained as a singlet. If the molecular compound had been *N*-phenyl-*N*-benzylacetamidine monohydrate, two different signals for CH_2 would have been observed. A synthetic mixture (1:1) of benzyl alcohol and *N*-phenylacetamidine gave essentially the same NMR spectrum as the molecular compound obtained in the reduction.

The components of the molecular compound were identified by adding picric (or oxalic acid) to yield benzyl alcohol and the picrate (oxalate) of *N*-phenylacetamidine.

EXPERIMENTAL

Melting and boiling points are uncorrected. Analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York, or by Baron Consulting Co., Orange, Connecticut. IR spectra were obtained with a Perkin-Elmer Model 337 Grating Infracord in Nujol mull unless otherwise stated. The NMR spectra were determined in carbon tetrachloride solution with a Varian HA-60 or A-60 instrument and the peak positions are reported in δ values relative to TMS as internal reference. In NMR data, the symbols are br, broad; m, multiplet; s, singlet; and t, triplet. The vpc was carried out using an Aerograph A-90-P gas chromatograph equipped with a ¼″ x 3′ column of 15% Carbowax 20 M on Chromosorb W.

The new Schiff bases (Table I) needed for this work were synthesized by well-known procedures (5). The conversion of Schiff base to 1,2,4-oxadiazolines was made by a modified procedure of Srivastava and Clapp (3) for 1,3-dipolar addition of acetonitrile oxide to Schiff base. The modification was the return to the original method (6) of generating acetonitrile oxide *in situ* in the presence of the Schiff base using a molar ratio of 1.3 nitroethane: 2,6-phenylisocyanate: 1.0 Schiff base. The same work-up as used previously was facilitated by this procedure even though the yields were somewhat lower than obtained in the earlier work (3).

N-*p*-Nitrobenzoyl-*N*-*n*-propylacetamidine (IId).

The oxadiazoline Id (0.400 g.) in 200 ml. of ether was exposed to light (2537Å) in a quartz vessel for 2 hours. The ether was removed and the residue was triturated with petroleum ether (b.p. 40-60°) to remove most of the starting material. Recrystallization of the remaining solid twice from methanol and sublimation at 80° (0.5 mm.) gave 0.250 g., 60%, of the acetamidine IId, m.p. 124°. The IR spectrum, ν cm^{-1}; C=O, 1735; C=N, 1640; NH or OH, 3340 br; NO_2, 1540, 1350. The shielded proton (NMR, Table II) at C5 in Id is replaced by a downfield shift to a broad peak at δ 5.16 (area, 1H) which must be due to =NH. The peak was not shifted by addition of pyridine. The A_2B_2 pattern of protons observed in Id gave way to a sharp singlet δ 8.26 (4H) in IId. A singlet near δ 8.3 is characteristic of aromatic protons in the *p*-nitrobenzoyl group (7). Additional NMR peaks observed were δ 2.06 (s, 3, CH_3–C=N); 3.26 (t, 2, CH_2N); 1.65 (m, 2, CH_2); 1.00 (t, 3, CH_3). The UV absorption data for IId are remarkably similar to those of IIa (2): λ max (methanol), 258 mμ (log ε 4.02). In IIa, λ max (methanol), 259 mμ (log ε 4.16).

When black light (3560Å) was used as the source and the reaction of Id was carried out in carbon tetrachloride solution for two hours, no change could be detected by NMR spectra on the crude product. With methanol as solvent the yield was poor (about 5%). The maximum yield of IId (as well as IIb,c) was obtained with ether as solvent with exposure of 1½-2 hours to light of 2537Å.

Anal. Calcd. for $C_{12}H_{15}N_3O_3 \cdot 1½\ H_2O$: C, 52.18; H, 6.52; N, 15.22. Found: C, 52.59; H, 5.98; N, 15.43.

N-*p*-Nitrobenzoyl-*N*-β-ethoxyethylacetamidine (IIa).

The NMR, UV, and IR spectra of IIa have been described (1). Compound IIa was obtained in quantitative yield from Ia by allowing the viscous oil to stand in ethyl acetate in normal laboratory light for 2 to 3 weeks. The transformation was speeded up (with lower yield, ∿ 30%) by exposure to black light (3560Å). Repeated recrystallization from ethyl acetate or 95% ethanol gave a 70% yield of IIa, m.p. 95-97°, unchanged by sublimation at 87° (0.01 mm.).

Anal. Calcd. for $C_{13}H_{17}N_3O_4 \cdot H_2O$: C, 52.52; H, 6.39; N, 14.14. Found: C, 52.81; H, 6.17; N, 13.90.

The hydrochloride was obtained by passing hydrogen chloride gas into an ether-methylene chloride solution (3:1) of IIa. The salt was filtered and dried *in vacuo*. Recrystallization from absolute ethanol-ether gave the analytical sample, m.p. 123-125°.

Anal. Calcd. for $C_{13}H_{18}ClN_3O_4$: C, 49.45; H, 5.74; N, 13.31. Found: C, 49.32; H, 5.81; N, 13.25.

N-*m*-Nitrobenzoyl-*N*-β-ethoxyethylacetamidine (IIb) and *N*-*p*-methoxybenzoyl-*N*-β-ethoxyethylacetamidine (IIc).

Irradiation of the oxadiazolines Ib and Ic (0.01*M* ethereal solutions) under the influence of 2537Å light for 2 hours gave oils which could not be separated from starting material. The crude products showed carbonyl bands at 1740 (IIb) and 1720 cm^{-1} (IIc) and NH (3350 cm^{-1} br, IIb and IIc). The identifying NMR peaks for ArCH in Ib and Ic at δ 6.15 were replaced by NH at δ 4.34 (IIb) and δ 5.23 (IIc). These chemical shifts were used to estimate the yields of IIb and IIc as 60%.

Photochemical Decomposition of 3-Methyl-4-*tert*-butyl-5-*p*-nitrophenyl-1,2,4-oxadiazoline (Ie).

Five hundred milligrams of 3-methyl-4-*tert*-butyl-5-*p*-nitrophenyl-1,2,4-oxadiazoline (3) in 200 ml. of methanol were exposed to black light (3560Å) for 24 hours. The solution was concentrated and cooled to remove most of the starting material. The residue was recrystallized twice from absolute methanol to give 208 mg., 53%, of 3-methyl-5-*p*-nitrophenyl-1,2,4-oxadiazole, III, m.p. 146.5-147°. The product III, was identical to an authentic sample (4) as shown by IR, NMR, and mass spectra.

Anal. Calcd. for $C_9H_7N_3O_3$: C, 52.67; H, 3.41; N, 20.48. Found: C, 52.61; H, 3.67; N, 20.64.

Twenty milligrams of Ie in carbon tetrachloride were subjected

to 2537Å light in a quartz NMR tube for 2½ hours and then the NMR spectrum was taken. By comparison of the areas under the following peaks an estimated yield of 25 ± 5% of both *tert*-butyl chloride and III was found in the solvent: $(CH_3)_3$ CCl, shift 94 cps; $(CH_3)_3N$-, 78 cps and CH_3, 126 cps in Ie; CH_3 in III, 150 cps.

Catalytic Reduction of 3-methyl-4,5-diphenyl-1,2,4-oxadiazoline (If).

Five hundred milligrams of If (3) were reduced under one atmosphere of hydrogen in 40 ml. of dimethoxyethane with 50 mg. of 5% palladium on charcoal. In 10 hours 1.7 moles of hydrogen were absorbed. The solution was decanted and last traces of the catalyst were removed by filtration through Hyflosupersel. Removal of solvent at room temperature left 263 mg. (52%) of oil that crystallized in ether and pentane, m.p. 45-49°. The yield of the molecular compound of benzyl alcohol and *N*-phenylacetamidine (V) was higher (84%) with ethanol as reduction solvent and the reduction was faster (3 hours) although the apparent hydrogen uptake was only one mole. Evidently the ethanol furnishes hydrogen for the reduction, a phenomenon which has been observed before (8).

The analytical sample was obtained by vacuum sublimation at 38° (0.02 mm.), m.p. 50.0-50.5°.

Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.39; H, 7.44; N, 11.56. Found: C, 74.43; H, 7.58; N, 11.50.

The IR spectra gave a medium absorption (ν, C=N) at 1652 cm^{-1} and a round OH or NH band at 3500-3100 cm^{-1}. The NMR spectra were taken in carbon tetrachloride (7.5% W/V, δ): CH_3–C=N, 1.8 (s); CH_2 (benzylic), 4.46 (s). Three types of signals were observed for the two aromatic (benzylic and phenyl) rings. The five benzylic ring hydrogens and two phenyl hydrogens (*meta*) appeared at 7.16; one phenyl hydrogen (*para*), 7.06; and two (*ortho*) hydrogens at 6.56-6.96. A peak at δ 4.96 (br) with an area representing three protons, moved 7 cps downfield upon addition of pyridine.

Compound V was soluble in both 1.2 *M* hydrochloric acid and 2.5 *M* sodium hydroxide and formed a yellow precipitate in chloroform with an iron III chloride solution.

The picrate of *N*-phenylacetamidine (9) was obtained by mixing a toluene solution of V with a toluene solution of picric acid. The picrate melted at 197-198°. One recrystallization from acetone-hexane gave an analytical sample, m.p. 198-200° but repeated crystallization from the same solvent gave lower melting points, suggesting decomposition. Since four different (all lower) melting points (9,10,11,12) are given in the literature for the picrate, an authentic sample of *N*-phenylacetamidine (9) was prepared. The picrate of the authentic sample did not depress the m.p. 197-198°.

Anal. Calcd. for $C_{14}H_{13}N_5O_7$: C, 46.27; H, 3.60; N, 19.28. Found: C, 46.37; H, 3.49; N, 19.27.

N-Phenylacetamidine was recovered from the picrate prepared from V by removing picric acid on IRA-400 resin from a methanol solution. Evaporation of the methanol gave crude *N*-phenylacetamidine which was recrystallized from ether-cyclohexane four times, m.p. 65-68°. An analytical sample was prepared by sublimation at 42° (0.005 mm.), m.p. 66-68° (Lit. (11) m.p. 68-70°).

Anal. Calcd. for $C_8H_{10}N_2$: C, 71.64; H, 7.46; N, 20.88. Found: C, 71.61; H, 7.57; N, 20.63.

A 5% solution of *N*-phenylacetamidine in carbon tetrachloride gave four bands in the IR at 3525, 3465, 3412, and 3375-3235 (broad) cm^{-1} and ν (C=N), 1665 cm^{-1} (strong). A 10% solution in the same solvent was used for an NMR spectrum (δ) with the following results: five CH protons (aromatic), 7.36-6.50 (m); two NH protons, 5.10 (br); and CH_3, 1.83 (s).

The oxalate salt of *N*-phenylacetamidine was prepared by adding a solution of anhydrous oxalic acid in absolute methanol to a chloroform solution of V. The solvents were removed at room temperature and the oxalate was washed with cold methanol and ether. The oxalate was recrystallized twice from methanol-ether, m.p. 189-190° (Lit. (12), m.p. 179°). The oxalate was analyzed since this melting point also was not in agreement with the literature value.

Anal. Calcd. for $C_{18}H_{22}N_4O_4$: N, 15.63. Found: N, 15.95.

The presence of benzyl alcohol in the methanol-ether washings was confirmed by retention time in a vpc column on Carbowax and by a mixed injection with authentic benzyl alcohol.

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