[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Investigation of Some Substituted 1,3,4-Thiadiazoles

BY C. AINSWORTH

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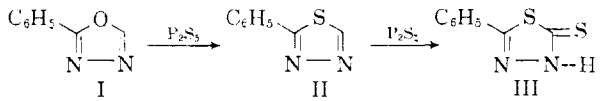
Phosphorus pentasulfide has been found to bring about the sulfurization of 2-phenyl-1,3,4-thiadiazole (II) to the thione III. Some related compounds were likewise sulfurated under conditions where sulfur was not effective. Potassium 3-benzoylthiocarbazate (IV) was ring closed with concentrated sulfuric acid at 0° to give III, and at 50° to give the disulfide V. The hydrolytic cleavage of V in base has been studied and evidence for the presence of the sulfenic acid intermediate VI is presented.

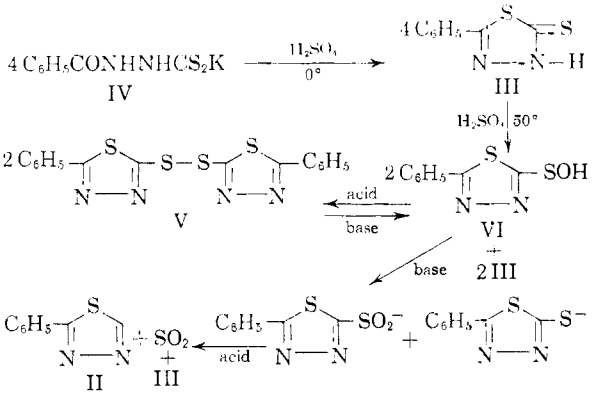
During the attempted conversion of 2-phenyl-1,3,4-oxadiazole[1] (I) to 2-phenyl-1,3,4-thiadiazole (II) using phosphorus pentasulfide, it was found that 2-phenyl-Δ^2-1,3,4-thiadiazoline-5-thione[2] (III) was also formed. Further, the reaction of compound II with sublimed phosphorus pentasulfide yielded III.



However, when sulfur was substituted for phosphorus pentasulfide in the above examples, no reaction took place.[3] Similarly, treatment of the *p*-chloro analog of I with phosphorus pentasulfide yielded a mixture of the corresponding *p*-chloro analogs of II and III. The ring-opened hydrolysis product of I, namely, 1-benzoyl-2-formylhydrazine, was treated with phosphorus pentasulfide and gave a mixture of compounds II and III. As another example, benzothiazole and phosphorus pentasulfide gave a small yield of 2-mercaptobenzothiazole, and again sulfur was not effective in bringing about this conversion.

With attention thus focused on compound III it was of interest to investigate an independent method of synthesis. Young and Wood[4] have reported the preparation of III from thiobenzoic acid hydrazide and carbon disulfide, and Sandstrom[5] has obtained it as a product from the reaction of potassium thiobenzoylthioglycolate with ethyl dithiocarbazate. Hoggarth[6] has reported that potassium 3-benzoyldithiocarbazate (IV) with either dilute mineral acid or sirupy phosphoric acid failed to cyclize to give III. However, when we attempted this reaction using concentrated sulfuric acid at 0°, compound III, m.p. 215°, was obtained in fair yield. On the other hand, reaction of either III or IV with concentrated sulfuric acid at 50° yielded a new compound melting at 163°. When this material was treated with 1 *N* sodium hydroxide it dissolved slowly, and on acidification of the resulting solution sulfur dioxide was evolved and two solids were obtained. These proved to be compounds II and III.

The compound melting at 163° is formulated as the disulfide V, and the following transformations are proposed.



It seems likely that the concentrated sulfuric acid first brings about the cyclization of IV to III (or its tautomeric thiol) and that the latter is oxidized with the warm acid to the intermediate sulfenic acid[7] VI before conversion to V. That the sulfuric acid itself is the oxidizing agent and does not require atmospheric oxygen was shown by performing the reaction in a nitrogen atmosphere. The disulfide V was obtained by an alternative method[8] from III by oxidation with iodine.

Attention was then directed to the base-catalyzed fission of V. The hydrolytic cleavage of a disulfide in base was discovered by Schiller and Otto.[9] Fromm[10] first proposed a sulfenic acid as an intermediate in the intramolecular oxidation–reduction reaction. Apparently the sulfenic acid intermediate VI disproportionates in basic solution to give the thiol and the sulfinate. The latter, in this example, loses sulfur dioxide on acidification to give II.

The ultraviolet absorption curves shown in Fig. 1 confirm these proposals. The spectrum of V (curve A) was shifted in base (curve B) and this shift was reversible if the solution was acidified almost immediately (curve C). Although the sulfenic acid VI was not isolable, its ultraviolet spectrum was obtained by difference. The absorption maxima at about 250 and 375 mμ both have log

(1) C. Ainsworth, THIS JOURNAL, **77**, 1148 (1955).

(2) The infrared spectrum of III obtained in chloroform shows an intense and narrow band at 2.94 μ for free NH and a broad underlying absorption between 3.0 and 3.6 μ for hydrogen bonded NH, supporting the thiono tautomer rather than the thiol form; *cf.* C. Ainsworth, *ibid.*, **78**, 4475 (1956).

(3) N. Lozac'k and co-workers, *e.g.*, *Bull. soc. chim. France*, 1130 (1956), have reported a number of sulfuration reactions where multisulfur containing ring compounds were obtained using sulfur or phosphorus pentasulfide at high temperature.

(4) R. W. Young and K. H. Wood, THIS JOURNAL, **77**, 400 (1955).

(5) J. Sandstrom, *Arkiv Kemi*, **4**, 297 (1952); [*C. A.*, **47**, 9271 (1953)].

(6) E. Hoggarth, *J. Chem. Soc.*, 4811 (1952).

(7) See J. A. Barltrop and K. J. Morgan, *ibid.*, 4245 (1956), for a recent report on sulfenic acids and an interesting proposal concerning their dismutation.

(8) The author is grateful to a referee for some references and helpful suggestions regarding compound V.

(9) R. Schiller and R. Otto, *Ber.*, **9**, 1637 (1876).

(10) E. Fromm, *ibid.*, **41**, 3397 (1908).

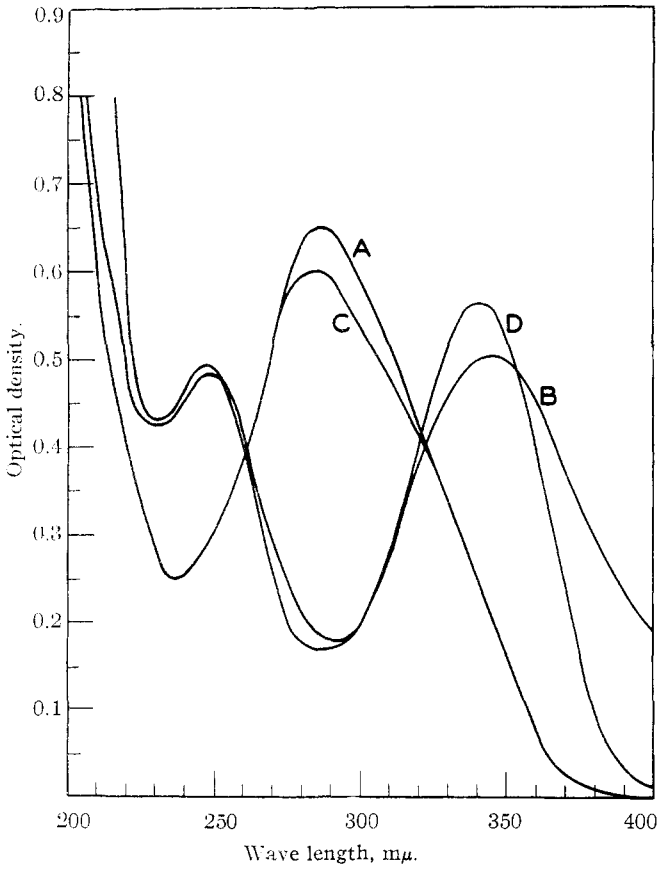


Fig. 1.—Ultraviolet absorption spectra obtained in methyl alcohol for 3.3 ml. of compound V at 0.01 mg./ml. (curve A); A + 30 λ of 3.3 *N* potassium hydroxide (curve B); B + 100 λ of 2.0 *N* hydrochloric acid (curve C); A + 30 λ of 3.3 *N* potassium hydroxide after standing at room temperature overnight (curve D).

a_M values of about 4.0. After standing for a few hours, a basic solution of V (curve D) on acidification did not give a spectrum characteristic of V, but rather it showed two absorption bands approximately corresponding to the composite of compounds II and III. In fact, an equimolar synthetic system of compounds II and III in the mole ratio of 1:3 was found to have an ultraviolet spectrum identical with D. This is in agreement with the stoichiometry suggested in the equations above.

Acknowledgments.—The microanalyses were performed by W. L. Brown, H. L. Hunter and G. M. Maciak. The physical studies were conducted by H. E. Boaz and L. G. Howard.

Experimental[11]

2-Phenyl-1,3,4-oxadiazole and Phosphorus Pentasulfide.—A mixture of 14.6 g. (0.1 mole) of 2-phenyl-1,3,4-oxadiazole,[1] 22.2 g. (0.1 mole) of sublimed phosphorus pentasulfide[12] and 100 ml. of dry xylene was heated overnight under reflux. Water was added cautiously, and the aqueous layer was extracted twice with 100 ml. of ether. The combined organic layers were extracted with three 50-ml. portions of 1 *N* sodium hydroxide. After cooling, the basic extract was acidified with dilute hydrochloric acid, and the resulting solid was collected, washed with water, and air-dried. The product was recrystallized from acetic acid or ethyl alcohol, and 5 g. (26% yield) of 2-phenyl-Δ^2-1,3,4-thiadiazoline-5-thione (III) was obtained, m.p. 215° (lit.[5] m.p. 215–216°); λ_{max} 250 mμ, log ε 3.93, inflection at 278 mμ; λ_{max} 336 mμ, log ε 4.16.

Anal. Calcd. for $C_8H_6N_2S_2$: C, 49.46; H, 3.11; S, 33.01. Found: C, 49.45; H, 3.45; S, 33.07.

The organic extracts that had been washed with base were dried with anhydrous magnesium sulfate and then concentrated by heating on a steam-bath under reduced pressure. The residue was distilled, and 6 g. (37% yield) of 2-phenyl-1,3,4-thiadiazole (II) was obtained as a pale yellow oil, b.p. 115–118° (0.1 mm.). It solidified on standing, m.p. 40° (lit.[13] m.p. 42°); λ_{max} 266 mμ, log ε 4.10.

Anal. Calcd. for $C_8H_6N_2S$: C, 59.23; H, 3.73; S, 19.77. Found: C, 59.69; H, 4.03; S, 19.92.

1-Benzoyl-2-formylhydrazine and Phosphorus Pentasulfide.—A mixture of 14 g. (0.085 mole) of 1-benzoyl-2-formylhydrazine,[14] 22 g. (0.1 mole) of phosphorus pentasulfide[15] and 300 ml. of xylene was heated under reflux for 7 days. The mixture was treated in the same manner as that described above for 2-phenyl-1,3,4-oxadiazole and phosphorus pentasulfide. The yields of compounds II and III were 5 (37%) and 2.5 g. (15%), respectively.

2-Phenyl-1,3,4-thiadiazole and Phosphorus Pentasulfide.—A mixture of 5 g. (0.03 mole) of 2-phenyl-1,3,4-thiadiazole, 6.6 g. (0.03 mole) of phosphorus pentasulfide and 100 ml. of dry xylene was heated under reflux for 2 days. The reaction mixture was treated essentially the same as that described above for 2-phenyl-1,3,4-oxadiazole and phosphorus pentasulfide. In this way 2 g. of starting material II was recovered, and 3 g. of 2-phenyl-Δ^2-1,3,4-thiadiazoline-5-thione (III) was obtained, m.p. 214–215°, m.m.p. 215°.

Benzothiazole and Phosphorus Pentasulfide.—A mixture of 6.8 g. (0.05 mole) of benzothiazole,[16] 11 g. of phosphorus pentasulfide[15] and 200 ml. of xylene was heated under reflux for 20 hours. The hot xylene was decanted and washed with 1 *N* sodium hydroxide. After evaporation of the xylene 4.5 g. of starting material remained. The basic extract was acidified and 0.1 g. (1.2% yield) of 2-mercaptobenzothiazole was obtained, m.p. 180°, m.m.p. 180°.

2-(4-Chlorophenyl)-1,3,4-oxadiazole and Phosphorus Pentasulfide.—A mixture of 9 g. (0.05 mole) of 2-(4-chlorophenyl)-1,3,4-oxadiazole,[1] 11 g. (0.05 mole) of phosphorus pentasulfide and 200 ml. of dry xylene was heated under reflux for 3 days. After cooling, the xylene was decanted and 1 *N* sodium hydroxide was added to the residue until the mixture was basic. This mixture was extracted with ether, and the ether was combined with xylene. The ether–xylene solution was washed with water and dried with magnesium sulfate. Following evaporation of the solvents the solid that remained was recrystallized from benzene–petroleum ether, and 5 g. (51% yield) of 2-(4-chlorophenyl)-1,3,4-thiadiazole was obtained as needles, m.p. 106–107°.

Anal. Calcd. for $C_8H_5ClN_2S$: C, 48.86; H, 2.56; S, 16.31. Found: C, 48.80; H, 2.66; S, 16.21.

The basic extract was acidified and 3 g. (26% yield) of 2-(4-chlorophenyl)-Δ^2-1,3,4-thiadiazoline-5-thione was obtained, m.p. 205–206°.

Anal. Calcd. for $C_8H_5ClN_2S_2$: C, 42.01; H, 2.20; S, 28.04. Found: C, 41.91; H, 2.28; S, 27.88.

Potassium 3-Benzoyldithiocarbazate and Sulfuric Acid.—(a) About 5.5 g. (0.025 mole) of freshly prepared potassium 3-benzoyldithiocarbazate[16] was added slowly with stirring to 40 ml. of cold concentrated sulfuric acid. The temperature was maintained near 10° during the addition. After standing for 0.5 hour the mixture was added to 150 ml. of ice-water, and the solid that separated was collected and washed with cold water. The product was recrystallized from acetic acid, and 2 g. (42% yield) of 2-phenyl-Δ^2-1,3,4-thiadiazoline-5-thione (III) was obtained, m.p. 215°.

(11) The melting points were determined with a Fisher–Johns assembly. The ultraviolet data were obtained in methyl alcohol.

(12) Supplied by Victor Chemical Works, Chicago, Ill.

(13) M. Ohta, R. Hagewora and Y. Mizushima, *J. Pharm. Soc. Japan*, **73**, 701 (1953); [*C. A.*, **48**, 7005 (1954)].

(14) E. Muller and W. Kreutzmann, *Ann.*, **512**, 264 (1934).

(15) Supplied by Eastman Kodak Co., Rochester, N. Y.

(16) M. Busch and M. Starke, *J. prakt. Chem.*, **93**, 49 (1916).

(b) To about 200 ml. of concentrated sulfuric acid was added 22 g. (0.1 mole) of freshly prepared potassium 3-benzoyldithiocarbazate. The temperature rose rapidly to about 50°. After standing at room temperature for 4 hours the mixture was added to 1 l. of ice-water, and the solid that separated was collected and washed with cold water. The crude product weighed 10 g. and was recrystallized from acetic acid or ethyl alcohol to give 6 g. (31% yield) of bis-(2-phenyl-1,3,4-thiadiazole-5) disulfide (V), m.p. 163°; λ_{max} 286 mμ, log ε 4.40; mol. wt., 406 (cryoscopic).

Anal. Calcd. for $C_{16}H_{10}N_4S_4$: C, 49.71; H, 2.61; N, 14.50. Found: C, 49.53; H, 2.53; N, 14.44.

Compound V also was prepared from a sample of 2-phenyl-Δ^2-1,3,4-thiadiazoline-5-thione (III) and concentrated sulfuric acid heated at 50° for two minutes. A sample of III was dissolved in 1 *N* sodium hydroxide solution and was treated with iodoform reagent. The solid that separated was identified as compound V.

(c) Air was bubbled for 1 hour into a mixture of 10 g. of potassium 3-benzoyldithiocarbazate and 100 ml. of concentrated sulfuric acid warmed at 40°. The mixture was poured into ice-water and the resulting solid was collected and washed with water. The solid was treated with 100 ml. of saturated sodium carbonate solution and then was filtered. The insoluble material was recrystallized from ethyl acetate–petroleum ether and 2 g. (23% yield) of V was obtained. The sodium carbonate extract was neutralized with concentrated hydrochloric acid and 0.2 g. of III was obtained.

When the reaction was repeated using a nitrogen atmosphere in place of air the yields of the two products were the same.

Basic Cleavage of Bis-(2-phenyl-1,3,4-thiadiazole-5) Disulfide (V).—About 2 g. (0.005 mole) of bis-(2-phenyl-1,3,4-thiadiazole-5) disulfide and 20 ml. of 1 *N* sodium hydroxide was warmed on a steam-bath for 1 hour during which time it dissolved and formed a yellow colored solution. Hydrochloric acid was added until the solution was acidic and sulfur dioxide was evolved. The solution was made basic and was extracted with ethyl acetate. The ethyl acetate was evaporated and the residue was shown by infrared analysis to be 2-phenyl-1,3,4-thiadiazole. The basic layer was made acidic with hydrochloric acid and the solid that separated was identified as 2-phenyl-Δ^2-1,3,4-thiadiazoline-5-thione (III). The yields were almost quantitative.

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[CONTRIBUTION NO. 2306 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

Nuclear Magnetic Resonance Spectra. Nitrogen Inversion Rates of N-Substituted Aziridines (Ethylenimines)[1]

BY ALBERT T. BOTTINI[2] AND JOHN D. ROBERTS

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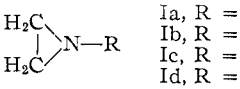
The nuclear magnetic resonance spectra of various cyclic imines ranging in ring size from three to six have been examined. The spectra of N-substituted aziridine (ethylenimine) derivatives were found to be strongly temperature dependent as would be expected if the nitrogen atoms and attached groups do not lie in a plane and inversion occurs rather slowly. It has been possible to evaluate some factors which affect the inversion rates of non-planar nitrogen atoms in cyclic imines. As would be expected, attachment of unsaturated groups to non-planar nitrogen increases the inversion rate as the result of conjugation with the nitrogen unshared electron pairs. The rates are also increased by bulky groups whether attached to nitrogen or to the carbons of the imine ring. Substitution of alkyl groups for one hydrogen or for two *cis*-hydrogens attached to carbon appears to make the molecules assume preferred configurations with the N-substituent *trans* to the ring substituent(s). The inversion rates most probably are decreased in hydroxylic solvents because of stabilization of the separate configurations by hydrogen bonding between the solvent and the imino nitrogen. The data so far obtained indicate that substituted aziridines with molecular asymmetry due to trivalent nitrogen are likely only to be resolvable into reasonably stable optical antipodes at temperatures below −50°. The nitrogen inversion rates of N-substituted azetidines (trimethylenimines) and larger-ring imines appear to be too great to be measurable by nuclear magnetic resonance techniques at temperatures above −77°.

Introduction

Considerable effort has been expended in attempts to resolve substances into optical isomers which would owe their asymmetry solely to nonplanar trivalent nitrogen.[3] Failure to obtain such compounds in optically active forms indicates that the molecules of the type NRR′R″ readily undergo optical inversion.

In 1939, several groups of workers[4] postulated independently that suitably substituted aziridines (ethylenimines) might be favorably constituted to permit existence of stable, optically active antipodes. This idea was given support by Kincaid and Henriques[5] through calculations of the magnitude of the energy barrier for inversion of the nitrogen in 1-methylaziridine (Ia). With the aid



Ia, R = CH_3–		Ie, R = C_6H_{11}–
Ib, R = C_2H_5–		If, R = t-C_4H_9–
Ic, R = $C_6H_5CH_2$–		Ig, R = C_6H_5–
Id, R = $C_6H_5CH_2CH_2$–		Ih, R = H–

of Wall and Glockler's expression for the potential energy of ammonia,[6] they first estimated an activation energy (ΔE) of 38 kcal./mole for inversion of Ia. Since the same method gave 11 kcal./mole for the barrier height in ammonia, as compared to the "more reasonable" value of 8 kcal./mole, Kincaid and Henriques reduced their estimated ΔE for Ia to 25 kcal./mole. They noted that resolution would be practically impossible unless the above rate constant for inversion is less than 10^{-5} sec.$^{-1}$. From the Arrhenius equation (1) and assumption of a normal preexponential factor of 10^{13}, ΔE must be greater than 25 kcal./mole if the rate constant for inversion is to be less than 10^{-5} sec.$^{-1}$ at room temperature.

$$k' = 10^{13}\, e^{-\Delta E/RT} \qquad (1)$$

(1) Supported in part by the Office of Naval Research.

(2) National Science Foundation Predoctoral Fellow, 1954–1957.

(3) (a) R. L. Shriner, R. Adams and C. S. Marvel in H. Gilman, "Organic Chemistry, An Advanced Treatise," John Wiley and Sons, Inc., New York, N. Y., second edition, 1943, Vol. I, pp. 402–413; (b) V. Prelog and P. Wieland, *Helv. Chim. Acta*, **27**, 1127 (1944).

(4) (a) R. Adams and T. L. Cairns, THIS JOURNAL, **61**, 2464 (1939); (b) P. Maitland, *Ann. Rept. Chem. Soc. London*, **36**, 239 (1939); (c) J. Meisenheimer and L.-H. Chou, *Ann.*, **539**, 70 (1939); (d) J. D. C. Mole and E. E. Turner, *Chemistry & Industry*, **17**, 582 (1939).

(5) J. F. Kincaid and F. C. Henriques, Jr., THIS JOURNAL, **62**, 1474 (1940).

(6) F. T. Wall and G. Glockler, *J. Chem. Phys.*, **5**, 314 (1937).