5,2,4,6-triazatriphosphorine].—A solution of allylamine (17.1 g., 0.3 mole) and triethylamine (30 g., 0.3 mole) in diethyl ether (200 ml.) was added dropwise over 3 hr. to a stirred solution of hexachlorocyclotriphosphonitrile (104 g., 0.3 mole) in diethyl ether (500 ml.). After completion of the addition, the mixture was stirred at 25° for 24 hr. The white precipitate of triethylamine hydrochloride (49.8 g.) was washed with ether and the combined filtrates were evaporated to leave a colorless oil. The oil was then vacuum distilled. Unchanged hexachlorocyclotriphosphonitrile (10.2 g.) sublimed initially and contaminated the distillate. A second distillation yielded impure fractions of V, 50 g., b.p. 115–130° (0.5 mm.), $n^{25}D$ 1.5480. Vapor phase chromatography on a silicone column at 175 and 225° indicated that these mixtures contained I (1–6%), V (~93%), two di(allylamino) tetrachlorocyclotriphosphonitrile isomers (1–4%), and a tri(allylamino)-trichlorocyclotriphosphonitrile trimer (0.3–1.8%). These latter three compounds were identified on the basis of retention times only. A pure sample of V was isolated by vapor phase chromatography.

Anal. Calcd. for $C_3H_6Cl_5N_4P_3$: C, 9.77; H, 1.63; Cl, 48.13; N, 15.21; P, 25.25; mol. wt., 368.3. Found: C, 9.95; H, 1.99; Cl, 48.33; N, 15.12; P, 24.59; mol. wt. (by vapor pressure lowering), 377.

Higher boiling fractions (43.5 g.), b.p. 120–150° (0.5 mm.), $n^{25}D$ 1.5480, were also isolated, in which the chlorine analysis was lower (43–46%). These fractions presumably contained mixtures of products with a higher number of allylamino groups. The total yield of V from this reaction was estimated to be more than 50% based on I.

Polymerization of II. A. Solution Reactions.—Mixtures of II (1 g.), benzene (2 ml.), and azobisisobutyronitrile, benzoyl peroxide, or *t*-butylperoxy pivalate (0.04 g.) were degassed and sealed in a nitrogen atmosphere in thick-walled glass tubes. The tubes were then heated at 60° for 4 days. No solid had precipitated after this time, and evaporation of the solvent yielded a semicrystalline mixture of II and low molecular weight oligomers.

B. Bulk Reactions.—Compound II was mixed with 2 wt. % 2,5-dimethyl-2,5-di-*t*-butylperoxy-*n*-hexane (Lupersol 101) and the mixture was degassed and sealed under nitrogen in glass tubes. After 48 hr. at 130°, or after 17 hr. at 158°, the product was a hard, insoluble glass which did not melt below 300°. Similarly, when 2 wt. % di-*t*-butyl peroxide was used as a catalyst, the material formed a cross-linked, amber-colored glass after 17 hr. at 128° and after 2 hr. at 170°.

Anal. Found: C, 40.40; H, 6.52; N, 25.77; P, 20.46.

Thermogravimetric analysis of a powdered polymer of II, using a 10°/min. temperature increase in air, showed no weight loss at 250°, 1% weight loss at 300°, 10% weight loss at 400°, 30% weight loss at 500°, and 34% weight loss at 600°. The total weight loss at 1000° varied from 65 to 85%.

Acknowledgment.—We thank Dr. W. M. Thomas for his interest and suggestions, Dr. R. Feinland for the gas chromatographic separations, and Mrs. R. Marcus for technical assistance.

Synthesis of ω-(Aminooxy)alkanethiols[1,2]

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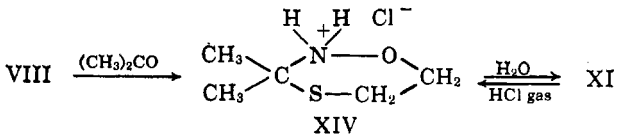
As part of our program on the synthesis of antiradiation drugs we set out to prepare two short-chain aminooxyalkanethiols, $H_2NO(CH_2)_nSH$ (n = 2 or 3). Previous attempts to prepare β-aminooxyethyl mercaptan by the alkaline hydrolysis of S-[β-(phthalimidooxy)-ethyl]isothiuronium bromide[3] or the acid hydrolysis of sodium S-[β-(phthalimidooxy)ethyl] thiosulfate[3] failed, phthalic acid being the only recognizable product. Thus we turned to S-[ω-(phthalimidooxy)alkyl] thiolacetates as precursors for the required compounds since acid hydrolysis would readily liberate the aminooxy[4] and thiol groups simultaneously and in the last step.

Two routes seemed feasible to prepare S-[ω-(phthalimidooxy)alkyl] thiolacetates. The reaction of β-(phthalimidooxy)ethyl bromide[3] with sodium thiolacetate furnished a number of unidentifiable products while the reaction of N-hydroxyphthalimide with ω-bromoalkyl thiolacetates afforded these essential intermediates. The reaction of 1,2-dibromoethane and 1,3-dibromopropane with sodium thiolacetate furnished the required ω-bromoalkyl thiolacetates. Reaction of β-bromoethyl thiolacetate with N-hydroxyphthalimide yielded a mixture of the required S-[β-(phthalimidooxy)-ethyl] thiolacetate (V) and N-acetoxyphthalimide,[5] which were separated by fractional crystallization. However, when N-hydroxyphthalimide was treated with γ-bromopropyl thiolacetate, the required product VI was isolated and no N-acetoxyphthalimide could be found in the reaction mixture.

Acid hydrolysis of V and VI (n = 2 and 3) produced the corresponding aminooxythiols which were isolated as their hydrochlorides (VIII and IX, respectively) and characterized by analysis and their n.m.r. spectra. Table I presents a summary of the n.m.r. spectra of the compounds described in this work.

Condensation of β-(aminooxy)ethyl mercaptan hydrochloride with acetone furnished a product assigned the cyclic structure XIV, also prepared when β-(isopropylideneaminooxy)ethyl mercaptan was treated with hydrogen chloride in dry ether. The salt was hydrolyzed in water to the oximinothiol XI, which was



XIV

synthesized independently from the corresponding bromide X, with sodium hydrosulfide. The infrared spectrum of XI showed a weak broad band for SH (2550 in liquid film, 2430 cm.$^{-1}$ in $CHCl_3$) as well as the

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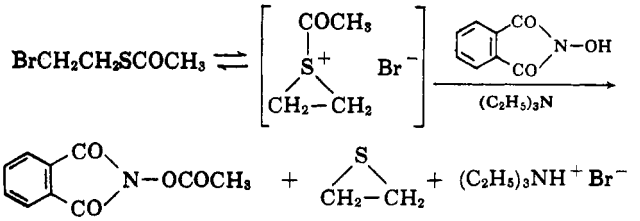
(2) This project was sponsored by the office of the Surgeon General, U. S. Army Medical Research and Development Command (Contract DA-49-193-MD-2047), whose generous support is gratefully acknowledged.

(3) L. Bauer and K. S. Suresh, *J. Org. Chem.*, **28**, 1604 (1963).

(4) L. Bauer, A. Shoeb, and V. C. Agwada, *ibid.*, **27**, 3153 (1962).

(5) The formation of this product could easily be explained if S-acetylepisulfonium bromide is considered as a logical reactive intermediate in the reaction. Such an intermediate has been postulated in another reaction by H. Böhme and H. D. Stachel [*Ann.*, **606**, 75 (1957)]. Such a mechanism



would demand the formation of ethylene sulfide. When the aqueous mother liquors of our reaction were extracted exhaustively with toluene and the first 10% of that solution was distilled, it was shown that ethylene sulfide was present (infrared and n.m.r. spectra). It was further shown that under similar reaction conditions, N-hydroxyphthalimide was not acetylated by *n*-butyl thiolacetate nor by 1,2-bis(acetylmercapto)ethane.

TABLE I

No.	Compd.	Chemical shift (δ), p.p.m. Assignments: -SH	$(CH_3)_2C=$	C-CH_2-C	CH_3CO	C-CH_2-S	C-CH_2Br	CCH_2ON	Arene
I	$BrCH_2CH_2SCOCH_3$[a]				2.31	3.33	3.33		
II	$CH_3COSCH_2CH_2SCOCH_3$[a]				2.26	2.98			
III	$BrCH_2CH_2CH_2SCOCH_3$[a]			2.08	2.28	2.97	3.40		
IV	o-$C_6H_4(CO)_2NOCOCH_3$				2.35				4.60
V	o-$C_6H_4(CO)_2NO(CH_2)_2SCOCH_3$[a]				2.28	3.20[c]		4.20	4.57
VI	o-$C_6H_4(CO)_2NO(CH_2)_3SCOCH_3$[a]			2.03	2.30	3.10		4.20	4.59
VII	$BrCH_2CH_2ONH_3^+Cl^-$[b]						3.60	4.33	
VIII	$HSCH_2CH_2ONH_3^+Cl^-$[b]					2.88[c]		4.27	
IX	$HSCH_2CH_2CH_2ONH_3^+Cl^-$[b]			2.05		2.65		4.21	
X	$(CH_3)_2C=NOCH_2CH_2Br$[a]		1.83				3.46	4.18	
XI	$(CH_3)_2C=NOCH_2CH_2SH$[a]	1.41[d]	1.82			2.70[c,d]		4.02	
XII	$[(CH_3)_2C=NOCH_2CH_2]_2S$[a]		1.80			2.75[c]		4.08	
XIII	$(CH_3)_2C=NO(CH_2)_2SCSOC_2H_5$[a]		1.82			3.35[c]		4.17	

[a] In $CDCl_3$ with tetramethylsilane as internal standard. [b] In D_2O with sodium 3-(trimethylsilyl)-1-propanesulfonate as internal standard. [c] $J_{SCH_2-CH_2O}$ = 6.4–6.9 c.p.s. [d] J_{SH-CH_2} = 8.3 c.p.s.

C=N band (at 1640 cm.$^{-1}$ in liquid film or in $CHCl_3$) and the SH triplet [δ 1.41 in $CDCl_3$; 1.95 in $(CD_3)_2SO$] in its n.m.r. spectrum. The n.m.r. spectrum of the cyclic salt in $(CD_3)_2SO$ showed four signals (in p.p.m. from TMS), a sharp singlet at 1.80, two triplets at 2.96 and 4.18 (J = 6.6 c.p.s.), and a relatively sharp but broad band at 9.38 in the ratio of 3:1:1:1, corresponding to the $(CH_3)_2C$, CH_2S, CH_2O, and NH_2 resonances; the signal for an SH proton was absent.

The oxime thiol XI was also converted to the corresponding sulfide XII. Another synthesis of XI was possible when the oxime bromide X was converted first to the xanthate ester XIII which in turn was hydrolyzed by base.

Experimental[6]

S-(β-Bromoethyl) Thiolacetate.—To a stirred suspension of sodium hydride (53% in mineral oil; 24 g., 0.5 mole) in tetrahydrofuran (500 ml.) was added dropwise redistilled thiolacetic acid (38 g., 0.5 mole). After the salt was formed, 1,2-dibromoethane (188 g., 1 mole) was added and the mixture was stirred first at 25° for 8 hr., then at the reflux for 2 hr. Salts were filtered off and the filtrate was distilled to yield the product (86 g., 47%), b.p. 55–57° (0.2 mm.).

Anal. Calcd. for C_4H_7BrOS: C, 26.24; H, 3.85. Found: C, 26.45; H, 3.81.

A part of the residue in the flask solidified. This crystallized from ethanol as a colorless solid, m.p. 73–74°. This was identified as the diacetyl derivative of 1,2-ethanedithiol, lit.[7] m.p. 68.2–69.8°.

S-(γ-Bromopropyl) Thiolacetate.—This was prepared from 1,3-dibromopropane (in 21% yield) as described above for the ethyl analog. It was a colorless oil, b.p. 64–65° (1.5 mm.).

Anal. Calcd. for C_5H_9BrOS: C, 30.46; H, 4.60. Found: C, 30.55; H, 4.73.

Reaction of N-Hydroxyphthalimide with S-(β-Bromoethyl) Thiolacetate.—A solution of the bromo compound (18.3 g.; 0.1 mole), N-hydroxyphthalimide (16.3 g., 0.1 mole), and triethylamine (10.1 g., 0.1 mole) in N,N-dimethylformamide (100 ml.) was set aside at 25° for 17 hr. Triethylammonium bromide was filtered off and the filtrate was diluted with 200 ml. of water and the solid was filtered off. The solid was triturated with ethanol at room temperature and filtered to give N-acetoxyphthalimide, 8.1 g. (40%), m.p. and m.m.p. 191–192° (from ethanol), lit.[8] m.p. 183–185°.

Anal. Calcd. for $C_{10}H_7NO_4$: C, 58.53; H, 3.43; N, 6.82. Found: C, 58.75; H, 3.46; N, 6.71.

The original ethanolic filtrate from the N-acetoxyphthalimide was chilled to −20° when S-[β-(phthalimidooxy)ethyl] thiolacetate (2.65 g., 10%) precipitated which crystallized from petroleum ether (b.p. 40°). It melted at 85–86°.

Anal. Calcd. for $C_{12}H_{11}NO_4S$: C, 54.32; H, 4.17; N, 5.28. Found: C, 54.27; H, 4.35; N, 5.35.

S-[γ-(Phthalimidooxy)propyl] Thiolacetate.—S-(γ-Bromopropyl) thiolacetate (3.7 g., 0.019 mole) was treated with N-hydroxyphthalimide (1.63 g., 0.01 mole) as described for the ethyl analog. The product (0.98 g., 35%) precipitated from aqueous N,N-dimethylformamide solution and crystallized from ethanol, m.p. 76–77°.

Anal. Calcd. for $C_{13}H_{13}NO_4S$: C, 55.89; H, 4.69; N, 5.01. Found: C, 56.02; H, 4.65; N, 5.10.

β-(Aminooxy)ethylmercaptan Hydrochloride.—A solution of S-(β-phthalimidooxyethyl) thiolacetate (5 g., 0.018 mole) in acetic acid (13.5 ml.) containing concentrated hydrochloric acid (7.5 ml.) was heated under reflux for 15 min. On cooling in an ice–water bath, phthalic acid precipitated and was filtered off. The filtrate was evaporated *in vacuo* and the residue was crystallized from ethanol–ether, 1.26 g., (52%), m.p. 70–71°.

Anal. Calcd. for C_2H_8ClNOS: C, 18.53; H, 6.22; N, 10.80. Found: C, 18.69; H, 6.16; N, 10.69.

γ-(Aminooxy)propyl Mercaptan Hydrochloride.—S-(γ-Phthalimidooxypropyl) thiolacetate (5 g., 0.018 mole) was hydrolyzed as the ethyl analog to give the salt, 0.43 g. (17%), m.p. 114–115°.

Anal. Calcd. for $C_3H_{10}ClNOS$: C, 25.08; H, 7.01; N, 9.75. Found: C, 25.30; H, 7.01; N, 9.46.

β-(Aminooxy)ethyl Bromide Hydrochloride.—This salt was formed in preference to the hydrobromide described previously.[3] β-(Phthalimidooxy)ethyl bromide (10 g., 0.037 mole) was hydrolyzed as described for the preparation of β-(aminooxy)ethyl mercaptan hydrochloride. The salt was obtained, 3 g. (46%), m.p. 173–174° (from ethanol–ether).

Anal. Calcd. for $C_2H_7BrClNO$: C, 13.61; H, 3.99; N, 7.93. Found: C, 13.81; H, 4.11; N, 8.01.

β-(Isopropylideneaminooxy)ethyl Bromide.—To a cold aqueous solution of β-(aminooxy)ethyl bromide hydrochloride (5.0 g., 0.028 mole) in 10 ml. of water and 2.2 g. of acetone (0.08 mole) was added a solution of sodium hydroxide (1.3 g. in 2 ml. of water). On stirring for 5 min., the oil which had separated was extracted into chloroform. Distillation afforded a colorless liquid, 3 g. (59%), b.p. 57–58° (9 mm.).

Anal. Calcd. for $C_5H_{10}BrNO$: C, 33.35; H, 5.59; N, 7.77. Found: C, 33.63; H, 5.51; N, 7.75.

β-(Isopropylideneaminooxy)ethyl Mercaptan.—An ethanol solution of sodium ethoxide (2.3 g. of sodium in 100 ml.) was saturated with dry hydrogen sulfide. β-(Isopropylideneaminooxy)-ethyl bromide (18 g.) was added and the mixture was stirred for 8 hr., while an atmosphere of hydrogen sulfide was maintained. The mixture was filtered and filtrate was distilled to give the thiol, 5 g. (38%), b.p. 45–46° (0.3 mm.).

Anal. Calcd. for $C_5H_{11}NOS$: C, 45.08; H, 8.32; N, 10.51. Found: C, 45.34; H, 8.38; N, 10.55.

(6) All boiling and melting points are uncorrected. Melting points were determined on a Mel-Temp apparatus. Analyses were performed by Dr. Kurt Eder, Geneva, Switzerland, and Micro-Tech Laboratories, Inc., Skokie, Ill. Infrared spectra were obtained using a Beckman IR-4 or Perkin-Elmer Model 337 recording spectrophotometer. The Varian A-60 spectrometer was used to produce the n.m.r. spectra.

(7) S. Mathias, *Univ. São Paulo, Fac. filosof., cienc. e letras, Bol., Quim.* **14**, No. 1, 75 (1942); *Chem. Abstr.*, **40**, 2793 (1946).

(8) W. R. Orndorff and D. S. Pratt, *Am. Chem. J.*, **47**, 89 (1912).

β-(Isopropylideneaminooxy)ethyl Sulfide.—To a solution of sodium ethoxide (0.092 g. of sodium) in ethanol (50 ml.) was added β-(isopropylideneaminooxy)ethyl bromide (7.2 g.) and β-(isopropylideneaminooxy)ethyl mercaptan (5.32 g.). The mixture was refluxed for 2 hr. in an atmosphere of N_2, then filtered, and distilled. The product (2.5 g., 27%) boiled at 104–105° (2 mm.).

Anal. Calcd. for $C_{10}H_{20}N_2O_2S$: C, 51.70; H, 8.67; N, 12.05. Found: C, 51.74; H, 8.80; N, 11.56.

Ethyl S-(β-Isopropylideneaminooxy)ethyl Xanthate.—A solution of β-(isopropylideneaminooxy)ethyl bromide (22.5 g.) and ethyl potassium xanthate (20 g.) in ethanol (250 ml.) was boiled for 3 hr. Salts were filtered off and the filtrate was distilled to give a pale yellow liquid, 13 g. (47%), b.p. 120–121° (0.5 mm.).

Anal. Calcd. for $C_8H_{15}NO_2S_2$: C, 43.43; H, 6.83; N, 6.32. Found: C, 43.86; H, 6.94; N, 6.60.

This xanthate (2 g.) was dissolved in sodium hydroxide (5 g. in 10 ml. of water and 10 ml. of ethanol) solution at 100° for 1.5 hr. (N_2 atmosphere). The cold solution was extracted with chloroform and distillation of the extract gave the mercaptan (1.0 g.) identified by its boiling point and infrared and n.m.r. spectra.

3,3-Dimethyl-1-oxa-2-aza-4-thiacyclohexane Hydrochloride (XIV).—When β-(aminooxy)ethyl mercaptan hydrochloride (VIII) was crystallized from acetone, the salt, m.p. 145–146°, was obtained which was crystallized from ethanol.

Anal. Calcd. for $C_5H_{12}ClNOS$: C, 35.39; H, 7.12; N, 8.25. Found: C, 35.15; H, 6.92; N, 8.11.

The same product was obtained when a stream of hydrogen chloride gas was led through a dry ether solution of XI.

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Configurational Relationships among Sulfinyl Amino Acids

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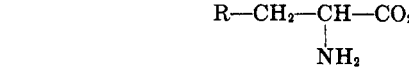
Numerous naturally occurring sulfoxides have been isolated in recent years.[2] Among these are isothiocyanate sulfoxides and sulfinyl amino acids. The sulfur atom is an asymmetric center in these compounds and consequently they exist in isomeric forms which vary in biological activity. This Note reports the results of an optical rotatory dispersion (O.R.D.) study of some sulfinyl amino acids and the significance of these results with regard to the relative and absolute configurations of these molecules.

The O.R.D. and ultraviolet parameters for several sulfinyl amino acids are listed in Table I. The alkyl sulfinyl amino acids show a low wave-length ultraviolet absorption, appearing as a shoulder, centered at 208–212 mμ which is in good agreement with the absorption maximum of saturated sulfoxides, reported[3] to be near 210 mμ in aqueous solution. This absorption band is presumably due to an $n \rightarrow \pi^*$ transition.[3] The O.R.D. data for the alkyl sulfinyl amino acids show a positive Cotton effect for the dextrorotatory isomers while the levorotatory isomers show a negative Cotton effect centered at slightly higher wave lengths. These Cotton effects are apparently associated with the powerfully rotating sulfoxide chromophore present in these amino acids. The O.R.D. and ultraviolet data for the isomeric 3-(*n*-propylsulfinyl)alanines are presented in Figure 1.

TABLE I

SOME PROPERTIES[a] OF OPTICALLY ACTIVE



R	Absorption λ_{max}, mμ	Cotton effect: Amplitude[b] $[\phi] \times 10^{-4}$	Cotton effect: Estimated midpoint, mμ
(+)-CH₃–S(=O)–	210 (sh)[c]	+2.85	209
(−)-CH₃–S(=O)–	210 (sh)	−1.76	216
(+)-CH₃CH₂CH₂–S(=O)–	212 (sh)	+2.77	212
(−)-CH₃CH₂CH₂–S(=O)–	212 (sh)	−2.34	218
(+)-CH₃–S(=O)–CH₂–	208 (sh)	+1.01	207
(−)-CH₃–S(=O)–CH₂–	208 (sh)	−0.78	213

[a] All samples were run in distilled water. [b] Since optical purities are unknown, these are minimum values. [c] sh = shoulder.

The molecular amplitudes of the Cotton effects for the isomeric 3-(*n*-propylsulfinyl)alanines and the 3-(methylsulfinyl)alanines are quite similar, that of the dextrorotatory isomer being greater in both cases. The amplitudes of the isomeric 4-(methylsulfinyl)-α-amino-*n*-butyric acids are much smaller, apparently owing to insertion of another methylene group between the amino acid and sulfoxide chromophores. However, the positive isomer again has a larger amplitude than the negative one. That each series of alkyl sulfinyl amino acids has a more highly rotating positive isomer can be explained as being due to the presence of an L-amino acid residue. The amino acids reported in this study were originally derived from either L-cysteine or L-methionine. It has been shown[4] that L-amino acids give rise to a positive Cotton effect in the 190–215-mμ region. The amplitudes of the Cotton effects for aliphatic amino acids are not large[5] in comparison with the amplitudes of the sulfinyl amino acids. The Cotton effects observed in this study are probably a combination of both the sulfoxide and amino acid chromophores with the sulfoxide group determining the sign of the Cotton effect and the sign of rotation at the sodium line. Interaction of the two chromophores is suggested by the lower amplitude Cotton effects observed

(1) A laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) (a) H. A. Jones, "Onions and Their Allies," Interscience Publishers, Inc., New York, N. Y., 1963; (b) A. I. Virtanen, *Angew. Chem.*, **74**, 374 (1962), and references cited therein.

(3) H. H. Jaffe and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962.

(4) (a) I. P. Dirkx and F. L. J. Sixma, *Rec. trav. chim.*, **83**, 522 (1964); (b) W. Gaffield, *Chem. Ind.* (London), 1460 (1964).

(5) The amplitudes [φ] of the low wave-length Cotton effects for α-amino-*n*-butyric acid and norleucine are 3800 and 4600, respectively, measured in aqueous solution. These Cotton effects are centered near 200–203 mμ.