Reaction of Cyclic Phosphoramidites with Disulfides. II. A Novel Synthesis of Ethylene Bis(sulfides) and Bis(dithiocarbamates)

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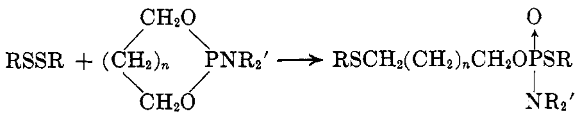
Cyclic phosphoramidites derived from ethylene glycol react with phenyl disulfide, *p*-tolyl disulfide, and benzthiazyl disulfide to form acyclic esters of phosphoramidothioic acid (II, $n = 0$) which are thermally converted to ethylene bis(sulfides) (*e.g.*, VIII). Tetraalkylthiuram disulfides react similarly to form ethylene bis(dithiocarbamates). When the cyclic phosphoramidites are derived from propylene or trimethylene glycol, the resulting phosphoramidothioates (X and II, $n = 1$) are thermally stable and may be molecularly distilled without decomposition at 205° (0.1 μ). A possible mechanism for the thermal decomposition is discussed.

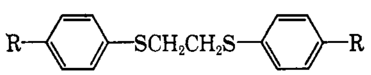
In the previous paper[3] the reaction of nitroaryl disulfides, benzthiazyl disulfide, and tetramethylthiuram disulfide with cyclic phosphoramidites (I) to give acyclic esters of phosphoramidothioic acid (II) was discussed.



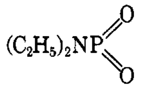
I II

The failure of alkyl disulfides to undergo the reaction up to 115° and the different behavior shown by allyl and benzhydryl disulfide, which were desulfurized by the phosphoramidite (I), prompted us to study other disulfides in order to determine more precisely the scope of the reaction.

It was found that phenyl disulfide and *p*-tolyl disulfide both reacted smoothly with cyclic phosphoramidites to yield acyclic phosphoramidothioates of general structure II (see Table I). Yields were essentially quantitative and all of the products possessed the typical 8.01-μ peak in the infrared associated with the $\geqslant P \rightarrow O$ stretching vibration in a phosphoramidate.[4] On attempted purification of the phosphoramidothioates in Table I, however, it was noted that compounds derived from trimethylene glycol (*i.e.*, $n = 1$) could be molecularly distilled above 200° (0.1 μ) without decomposition while those from ethylene glycol (*i.e.*, $n = 0$, III and IV) decomposed on heating to these elevated temperatures. The products from this thermal degradation of III and IV were readily identified as the known ethylene bis(sulfides) (VIII, R = H and CH_3, respectively); the phosphorus moiety resulting from the decomposition was not identified with certainty but was assumed to be the *meta* phosphoramidate (IX). When the reaction was extended to benzthiazyl disulfide and to several tetraalkylthiuram disulfides, the decomposition of the intermediate phosphoramidothioate [*e.g.*, II, R = $(CH_3)_2NC(S)$, $n = 0$] proved to be so facile in refluxing toluene that the ester was not isolated; the ethylene bis(dithiocarbamate) (see Table II) was obtained directly.



VIII



IX

This marked difference in thermal stability between the ethylene and trimethylene phosphoramidothioates (II, $n = 0$ and $n = 1$, respectively) prompted us to examine the propylene esters (X), some of which had been prepared in our earlier work.[3] While no attempt had been made to distil the benzthiazyl compound (X, R = 2-benzthiazyl, X = piperidino) and the two dimethyldithiocarbamoyl analogs (X, R = $(CH_3)_2NC(S)$, X = piperidino and 4-morpholino) had been obtained as crystalline solids, the phenyl compound (X, R = C_6H_5, X = piperidino) was distilled at 205° (0.1 μ) without decomposition. In this respect then, the propylene compounds (X) are similar to the trimethylene compounds (II, $n = 1$) since both of them appear to be thermally stable.

A mechanism that accounts for these observations involves the quasi four-membered ring transition state shown in XII. The carbon–oxygen bond of the phosphoramidothioate (XI) is weakened by participation of the sulfur in the incipient formation of a sulfonium ion. Analogous three-membered ring sulfonium ions have long been used to explain the reactivity of β-halo sulfides and related compounds.[5] Once the carbon–oxygen bond is weakened, the electronic shifts shown in XII are a reasonable consequence; the main driving force is presumably the greater nucleophilic character of sulfur relative to oxygen and the formation of the resonance-stabilized $\geqslant P \rightarrow O$ bond.[6] The failure of the trimethylene esters (II, $n = 1$) to undergo the thermal rearrangement is understandable because the sulfur would have

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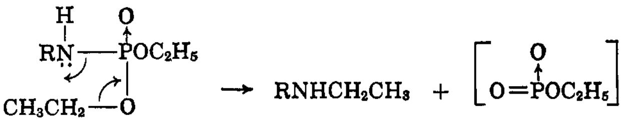
[3] K. Pilgram, D. D. Phillips, and F. Korte, *J. Org. Chem.*, **29**, 1844 (1964).

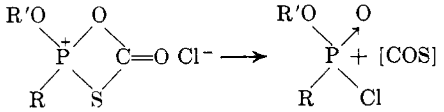
[4] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 258.

(5) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. 2, Chemical Publishing Co., New York, N. Y., 1960, p. 227, *et seq.*

(6) This reaction is formally similar to the alkylation of amines by phosphoric acid esters which is presumed to proceed through the phosphoramidate.[7]



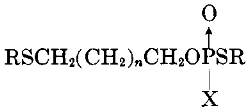
(7) B. P. Lugovkin and B. A. Arbusov, *J. Gen. Chem. USSR*, **22**, 2041 (1952). The reaction of phosgene and phosphonothioic acids has recently been suggested[8] to proceed through a similar four-membered cyclic intermediate.



(8) H. S. Aaaron, R. T. Uyeda, H. F. Frack, and J. I. Miller, *J. Am. Chem. Soc.*, **84**, 617 (1962).

TABLE I

PHOSPHORAMIDOTHIOATES



$RSCH_2(CH_2)_nCH_2O\overset{O}{\overset{\uparrow}{P}}SR$, P–X

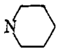
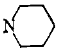
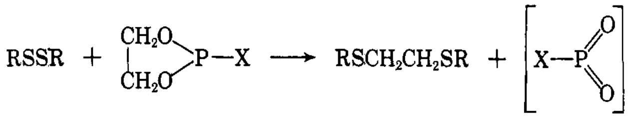
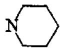
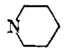
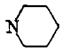
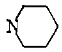
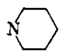
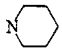
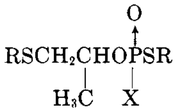
No.	R	X	n	Formula	Yield, %	B.p., °C., at 0.1 μ	Mol. wt. Calcd.	Mol. wt. Found	Nitrogen, % Calcd.	Nitrogen, % Found	Phosphorus, % Calcd.	Phosphorus, % Found	Sulfur, % Calcd.	Sulfur, % Found
III	C_6H_5	$N(C_2H_5)_2$	0	$C_{18}H_{24}NO_2PS_2$	100		381.5		3.67	3.7	8.12	7.5	16.75	16.7
IV	p-$CH_3C_6H_4$	$N(C_2H_5)_2$	0	$C_{20}H_{28}NO_2PS_2$	100		409.6		3.43	3.8	7.59	8.4	15.65	14.5
V	C_6H_5	$N(C_2H_5)_2$	1	$C_{19}H_{26}NO_2PS_2$	96	205	395.5				7.84	8.2	16.00	16.0
VI	C_6H_5		1	$C_{20}H_{26}NO_2PS_2$	98	200	407.5	390			7.62	8.2	15.72	15.8
VII	p-$CH_3C_6H_4$		1	$C_{22}H_{30}NO_2PS_2$	95	205	435.6	413			7.12	7.6		

TABLE II



R	X	M.p., °C., of $RSCH_2CH_2SR$	Lit. m.p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
C_6H_5	$N(C_2H_5)_2$	67–68	65[a] 68.5[b] 69[c] 81[c]	68	$C_{14}H_{14}S_2$			26.00	26.0
p-$CH_3C_6H_4$	$N({}_2CH_5)_2$	81	80[d]	63	$C_{16}H_{18}S_2$			23.35	23.5
$(CH_3)_2NC(S)$		193–194	189[e]	74	$C_8H_{16}N_2S_4$	10.44	9.9	47.75	47.8
$(C_2H_5)_2NC(S)$		93–94		69	$C_{12}H_{24}N_2S_4$	8.65	8.5	39.51	39.0
$(n$-$C_3H_7)_2NC(S)$		112–113		71	$C_{16}H_{32}N_2S_4$	7.37	7.3	33.70	32.9
$(n$-$C_4H_9)_2NC(S)$		68		64	$C_{20}H_{40}N_2S_4$	6.42	5.8	29.39	29.4
$(C_6H_5CH_2)_2NC(S)$		140	137[f]	21	$C_{32}H_{32}N_2S_4$	4.90	4.7	22.35	22.4
2-Benzthiazyl		149–150	144–145[g] 144–146[h]	62	$C_{16}H_{12}N_2S_4$	7.78	7.5	35.55	34.7

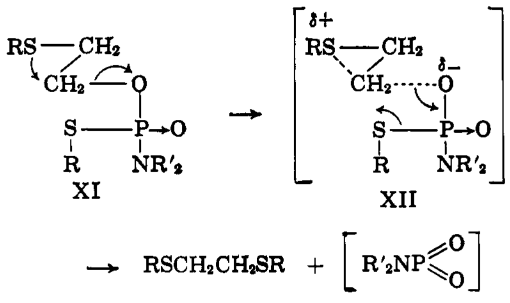
[a] C. W. Blomstrand and F. Ewerlöf, *Ber.*, **4,** 716 (1871). [b] J. Hine and W. H. Brader, Jr., *J. Am. Chem. Soc.*, **75,** 3964 (1953); [c] E. V. Bell and G. M. Bennett, *J. Chem. Soc.*, 3190 (1928). [d] E. Fromm and G. W. Raiziss, *Ann.*, **374,** 98 (1910). [e] A. W. Campbell and P. F. Tryon, *Ind. Eng. Chem.*, **45,** 125 (1953). [f] A. W. Hofmann, *Ber.*, **13,** 1231 (1880). [g] A. Sander, German Patent 811,588 (1951). *Chem. Abstr.*, **48,** 1443 (1954). [h] R. F. Brookes, J. E. Cranham, W. A. Cummings, D. Greenwood, and H. A. Stevenson, *J. Sci. Food Agr.*, **8,** 31 (1957).



$RSCH_2\underset{H_3C}{CH}O\overset{O}{\overset{\uparrow}{P}}SR$, P–X

X

to participate in the reaction through the formation of a four-membered sulfonium ion which is energetically much less favorable. Similarly, it is not surprising that an α-methyl (see X) prevents this thermal rearrangement, as it would provide considerable steric hindrance to the electronic shifts shown in XI → XII → $RSCH_2CH_2SR$.



This interesting insertion reaction provides a convenient synthesis of ethylene bis(sulfides), $RSCH_2CH_2SR$, particularly when the corresponding mercaptan is not readily available for alkylation with ethylene halides. Extension of the reaction to include other cyclic phosphorus compounds and disulfides is under study.

Experimental[9]

Materials.—The cyclic phosphoramidites (I) were prepared from the appropriate glycol and phosphorus trichloride in methylene chloride, followed by treatment with a secondary amine in

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(9) All boiling and melting points are uncorrected; infrared absorption spectra were determined in carbon tetrachloride solution unless specified otherwise. Molecular distillations were carried out in a Rota-Film still, Arthur F. Smith Co., Rochester, N. Y.

ether.[10] 2-Benzthiazyl, phenyl, and *p*-tolyl disulfide were commercial products as were tetramethyl-, tetraethyl-, tetrabutyl-, and tetrabenzylthiuram disulfide; they were used without further purification.

Tetrapropylthiuram disulfide was prepared in 32% yield from dipropylamine, carbon disulfide, and iodine in ethanolic solution following a literature procedure[11] and had m.p. 50–51°.

Anal. Calcd. for $C_{14}H_{28}N_2S_4$: N, 7.95; S, 36.40. Found: N, 7.7; S, 35.6.

Reaction of Phenyl Disulfide with 2-Diethylamino-1,3,2-dioxaphospholane (I, $n = 0$, R′ = C_2H_5).—Phenyl disulfide (16.35 g., 0.075 mole) and 2-diethylamino-1,3,2-dioxaphospholane (12.25 g., 0.075 mole) reacted at room temperature with heat evolution; the temperature was kept below 80° by external cooling. **S-Phenyl O-[2-(phenylthio)ethyl]diethylphosphoramidothioate (III)** was obtained as a colorless viscous liquid, 28.6 g., 100% yield. Thin-layer chromatography showed one compound to be present.

Anal. Calcd. for $C_{18}H_{24}NO_2PS_2$: N, 3.67; P, 8.12; S, 16.75. Found: N, 3.7; P, 7.5; S, 16.7.

The compound was Claisen-distilled at 170–172° (0.05 mm.) to give a 95% yield of a solid complex, m.p. 62–63° (from ether–pentane), which had the same elementary analysis as above but was a mixture of two compounds as shown by thin-layer chromatography. When recrystallized from methanol, the complex was broken and **1,2-bis(phenylthio)ethane (VIII, R = H)** was obtained in 68% yield, m.p. 67–68°.

Oxidation with hydrogen peroxide in acetic acid gave the known **bis(sulfone)**,[12] m.p. 180–181°.

Anal. Calcd. for $C_{14}H_{14}O_4S_2$: S, 20.65. Found: C, 20.6.

When methanol was removed from the mother liquid by heating on the water bath *in vacuo*, a brown resin remained. Attempts to crystallize the latter failed. Treatment with aqueous sodium hydroxide eliminated diethylamine. Analysis was satisfactory for diethyl *m*-phosphoramidate (IX).

Anal. Calcd. for $C_4H_{10}NO_2P$: P, 22.95. Found: P, 22.4.

Reaction of *p*-Tolyl Disulfide with 2-Diethylamino-1,3,2-dioxaphospholane (I, $n = 0$, R′ = C_2H_5).—*p*-Tolyl disulfide (6.15 g., 0.025 mole) and 2-diethylamino-1,3,2-dioxaphospholane (4.08 g., 0.025 mole) reacted at room temperature with heat evolution. The temperature was kept at approximately 80° by external cooling; without cooling, the temperature rose to approximately 130°. There was obtained 10.23 g. (100%) of **S-*p*-tolyl O-[2-(*p*-tolylthio)ethyl]diethylphosphoramidothioate (IV)**, as a colorless viscous liquid; thin-layer chromatography showed the presence of only one compound.

Anal. Calcd. for $C_{20}H_{28}NO_2PS_2$: N, 3.43; P, 7.59; S, 15.65. Found: N, 3.8; P, 8.4; S, 14.5.

The reaction product was heated to 250° over a 15-min. period. On cooling to 120° the red-brown reaction mixture solidified. Dilution with methanol and recrystallization from methanol gave a 63% yield of **1,2-bis(*p*-tolylthio)ethane (VIII, R = CH_3)** as colorless crystals, m.p. 81°. Oxidation with hydrogen peroxide in acetic acid gave the known **bis(sulfone)**,[12-14] m.p. 204–205°, 99% yield.

Anal. Calcd. for $C_{16}H_{18}O_4S_2$: S, 18.95. Found: S, 18.3.

Reaction of Aromatic Disulfides with N,N-Disubstituted 2-Amino-1,3,2-dioxaphosphorinanes.—The results are summarized in Table I. The general procedure is illustrated by the reaction of phenyl disulfide with 2-diethylamino-1,3,2-dioxaphosphorinane.

Phenyl disulfide (43.6 g., 0.2 mole) was cooled to −70° and 2-diethylamino-1,3,2-dioxaphosphorinane (35.4 g., 0.2 mole), at room temperature, was added portionwise with shaking. The reaction temperature rose immediately to 10° where it remained until 75% of the phosphoramidite had been added. The cooling bath was removed and the final 25% of the phosphoramidite was added. The temperature rose to 100° and a colorless liquid resulted. Thin-layer chromatography indicated the presence of only one compound. Distillation at 205° (0.1 μ) afforded 76 g. (96%) of **S-phenyl O-[3-(phenylthio)propyl]diethylphosphoramidothioate (V)** as a colorless oil.

Anal. Calcd. for $C_{19}H_{26}NO_2PS_2$: P, 7.84; S, 16.00. Found: P, 8.2; S, 16.0.

Hydrolysis of V.—The distillate (59.25 g., 0.15 mole) was refluxed for 3 hr. in 100 ml. of 48% hydrobromic acid. After cooling, the upper oily layer was separated and the aqueous layer was extracted with ether. Oil and ether extracts were combined and dried over magnesium sulfate, ether was evaporated, and the residue was distilled to give, as a first fraction, 14.5 g. (88%) of **thiophenol**, b.p. 28° (0.08 mm.), and, as a second fraction, 25 g. (75%) of **3-bromopropyl phenyl sulfide**, b.p. 109° (0.1 mm.).

Anal. Calcd. for $C_9H_{11}BrS$: C, 46.65; H, 4.77; Br, 34.65; S, 13.85. Found: C, 47.5; H, 4.9; Br, 34.3; S, 13.74.

Reaction of 2-Benzthiazyl Disulfide and Tetraalkylthiuram Disulfides with N,N-Disubstituted 2-Amino-1,3,2-dioxaphospholanes.—The results of these reactions are summarized in Table II. The general procedure is illustrated by the reaction of tetramethylthiuram disulfide with 2-piperidino-1,3,2-dioxaphospholane.

To tetramethylthiuram disulfide (12 g., 0.05 mole) in 25 ml. of toluene was added, in three portions, 2-piperidino-1,3,2-dioxaphospholane (8.25 g., 0.05 mole). The internal temperature rose spontaneously to reflux and the tetramethylthiuram disulfide went into solution. After cooling to approximately 100°, **ethylene bis(dimethyldithiocarbamate)** crystallized, yielding 9.92 g. (74%), m.p. 193–194°.

Anal. Calcd. for $C_8H_{16}N_2S_4$: N, 10.44; S, 47.75. Found: N, 9.9; S, 47.8.

Acknowledgment.—The authors are grateful to P. M. Saliman for the microanalyses and to G. E. Pollard for the infrared absorption studies.

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[10] H. J. Lucas, F. W. Mitchell, Jr., and C. N. Scully, *J. Am. Chem. Soc.*, **72**, 5491 (1950).

[11] J. v. Braun, *Ber.*, **35**, 899 (1902).

[12] R. Otto, *ibid.*, **13**, 1272 (1880).

[13] E. Froman and E. Siebert, *ibid.*, **55**, 1014 (1922).

[14] R. Otto, *J. prakt. chem.*, [2]**30**, 354 (1884); **40**, 534 (1889).