amount of water present) during the titration. Therefore, all titrations were carried out at 0.005 M concentrations. The pK_a point was always in the desired flat portion of the titration curve. The e.m.f. at half neutralization was taken as one-half the calculated stoichiometric end point. As mentioned above, the latter was always very close to the observed inflection point, and resulted in a maximum error of e.m.f. values of about 5 mv. Runs were carried out in duplicate. Repeat determinations were always within 10 mv. and generally within 5 mv. The collected Δe.m.f. values at half neutralization (ΔHNP values, referred to N,N'-diphenylguanidine) are given in Table III. A plot of these ΔHNP values vs. literature $pK_{a(H_2O)}$ values for several of these bases (diphenylguanidine, triethylamine, pyridine, acetamide, and urea) indicated a straight-line relationship, and so the $pK_{a(H_2O)}$ values for the series of N,N-disubstituted amides are interpolated from this line (Tables I and III).

The least-squares calculation of $pK_{a(H_2O)}$ vs. ΔHNP was $pK_{a(H_2O)} = 10.10 - 0.0118\Delta HNP$, with a standard deviation of 33 mv. This is appreciably different in slope from the equation calculated from Streuli's reported data for these compounds, of $pK_{a(H_2O)} = 10.10 - 0.0152\Delta HNP$.[12] On the other hand, our equation based on amides, ureas, and amines is quite close to Streuli's equation reported for amines and for N,N-disubstituted amides ($pK_{a(H_2O)} = 10.12 - 0.0129\Delta HNP_{(CH_3NO_2)}$).

Reaction of Cyclic Phosphoramidites with Disulfides.   I.   A Novel Synthesis of Phosphoramidothioates

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N,N-Disubstituted cyclic esters of phosphoramidous acid react readily with aromatic disulfides, tetraalkylthiuram disulfides, and certain heterocyclic disulfides to give derivatives of phosphoramidothioic acid in which the ring of the phosphoramidite has been opened. Benzhydryl and allyl disulfide are desulfurized by cyclic phosphoramidites without ring opening to give *sym*-tetraphenylethane and allyl sulfide, respectively. Simple aliphatic disulfides are not reactive towards cyclic phosphoramidites at the temperature of refluxing toluene. Alkyl aryl disulfides are cleaved by preferential attachment of the alkylthio moiety to phosphorus. A mechanistic rationalization of these experimental facts is presented.

The chemistry of cyclic esters of phosphoramidous acid (I) has received only scant attention; Arbuzov found that they react abnormally with alkyl halides to form poorly defined products although they add sulfur normally[3] and apparently undergo a typical Arbuzov reaction with cyanogen bromide to give phosphoramidocyanidates (II).[4] Their brief chemistry has recently been reviewed.[5,6]
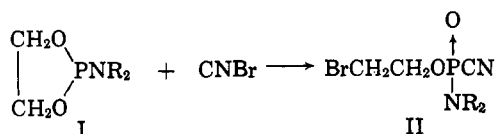
We were interested in reactions of disulfides with cyclic phosphoramidites; they have not been studied although the reaction of trialkyl and triaryl phosphites with disulfides has been investigated extensively[7–11] and reviewed recently.[5,12] These latter reactions are mainly ionic and supposedly proceed by a Michaelis–

Arbuzov mechanism. Since cyclic phosphoramidites are more nucleophilic than trialkyl phosphites, reaction with disulfides seemed a distinct possibility. This has been shown to be the case as discussed in more detail below.

At least two possible courses can be envisioned for the reaction of a cyclic phosphoramidite with a disulfide: Michaelis–Arbuzov rearrangement with cleavage of the phospholane ring to form the phosphoramidothioic ester (III), or desulfurization, with no ring cleavage, to form the corresponding sulfide (IV) and cyclic phosphoramidothionate (V). We have found that both reactions
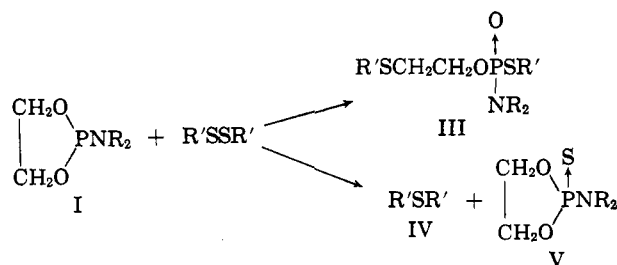
do occur, the path being determined by the nature of the disulfide reactant. For example, when an N,N-disubstituted cyclic phosphoramidite of general structure I [R = C_2H_5, $-(CH_2)_5-$, $-(CH_2)_2O(CH_2)_2-$] is mixed with an aromatic disulfide, a vigorously exothermic reaction occurs and an acyclic phosphoramidothiolate (III, R' = aryl) is formed in almost quantitative yield. Tetramethylthiuram disulfide reacts analogously with cyclic phosphoramidites derived from propylene glycol (VI) to give mixed anhydrosulfides

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(3) A. E. Arbuzov and V. M. Zoroastrova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk.* 789 (1952).

(4) G. Schrader, German Patent 949,650; *Chem. Abstr.*, **51**, 12,957 (1957).

(5) J. I. G. Cadogan, *Quart. Rev.* (London), **16**, 208 (1962).

(6) R. S. Edmundson, *Chem. Ind.* (London), 1770 (1962).

(7) H. I. Jacobson, R. G. Harvey, and E. V. Jensen, *J. Am. Chem. Soc.*, **77**, 6064 (1955).

(8) A. C. Poshkus and J. E. Herweh, *ibid.*, **79**, 4245 (1957).

(9) J. Michalski and J. Wieczorkowski, *Bull. Acad. polon. Sci. Classe III*, **5**, 917 (1957); *Chem. Abstr.*, **52**, 6157 (1958).

(10) K. Pilgram, Ph.D. thesis, Universtät Würzburg, 1959.

(11) R. L. McConnell, U. S. Patent 2,865,960; *Chem. Abstr.*, **53**, 12,181 (1959).

(12) A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 621 (1959).

(VII).[13] Only one heterocyclic disulfide, 2-benzthiazolyl disulfide, has been investigated; it reacted with a cyclic phosphoramidite (VI, X = CH_2) to form the product analogous to VII.


VI

VII
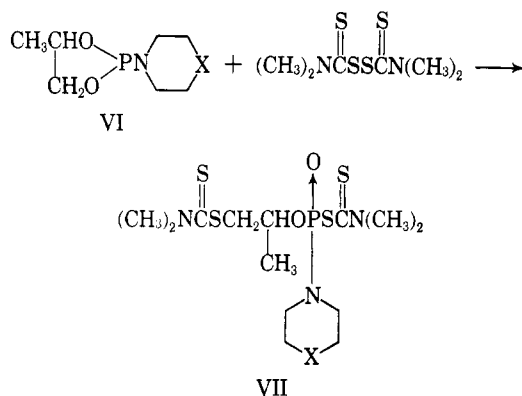
Allyl disulfide reacted with a cyclic phosphoramidite (I, R = C_2H_5) at room temperature, but with only slight exothermicity; the products were those of desulfurization, i.e., allyl sulfide (IV, R' = allyl) and the cyclic phosphoramidothionate (V, R = C_2H_5). In this respect the reaction is similar to the desulfurization of allyl disulfide with triphenyl phosphine.[15]

Benzhydryl disulfide did not react with the cyclic phosphoramidite (I, R = C_2H_5) until the reaction temperature reached 150°. At this point a vigorous reaction ensued with the formation of sym-tetraphenylethane and, presumably, the cyclic phosphoramidothionate (V, R = C_2H_5), although the presence of the latter was not definitely established. The appearance of a transitory blue color during the course of the reaction as well as the nature of the products isolated strongly suggest a radical mechanism for this particular transformation

Simple alkyl disulfides, such as ethyl disulfide, do not react with cyclic phosphoramidites when heated to reflux in toluene solution. Benzhydryl disulfide is similarly unreactive in refluxing toluene and the strenuous conditions referred to above (150°, no solvent) had to be employed before any reaction took place.

In seeking a rationalization for the observation that alkyl disulfides are unreactive towards cyclic phosphoramidites in refluxing toluene while allyl disulfide is desulfurized by the same reagent under mild conditions, we were struck by the similarity of these results and those of Moore and Trego.[16] These workers found that alkyl disulfides are stable to the reaction of tri-

(13) This is in contrast to the reaction between tetramethylthiuram disulfide and ethyl propylene phosphite which we have found to take the following course.
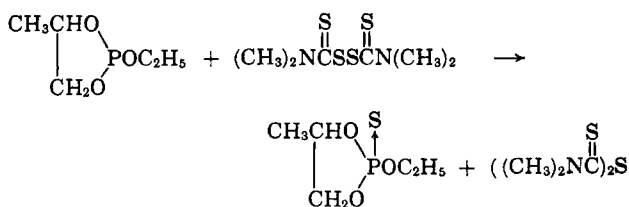

The desulfurization of tetramethylthiuram disulfide also occurs when it is heated with triphenyl phosphine.[14]

(14) A. Schonberg, Ber., **68**, 163 (1935).

(15) F. Challenger and D. Greenwood, J. Chem. Soc., 26 (1950).

(16) C. G. Moore and B. R. Trego, Tetrahedron **18**, 205 (1962); J. Chem. Soc., 4205 (1962).

phenyl phosphine at 140°, whereas allylic disulfides are smoothly desulfurized at 80°. The SNi' mechanism proposed by these authors[16] seems applicable to the reaction discussed herein, and in the absence of supporting kinetic data, provides a convenient rationalization for our results. For example, allyl disulfide and
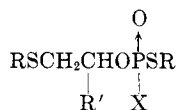

R' = allyl

VIIa

R'SCH₂CH=CH₂ +
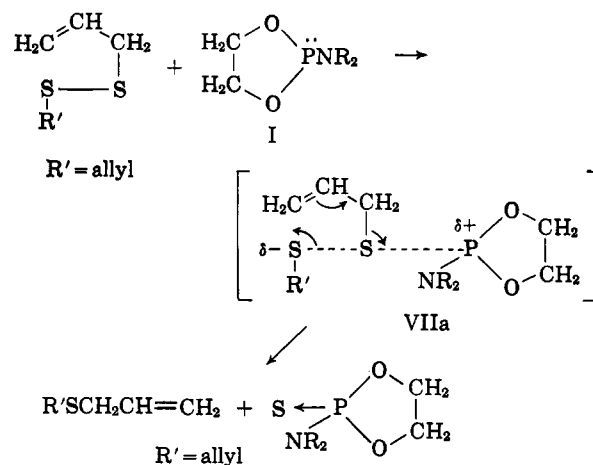
R' = allyl

the cyclic phosphoramidite (I, R = C_2H_5) are assumed to react by way of the transition state VIIa which can uniquely collapse to the products by the series of electronic shifts shown. A simple alkyl disulfide, lacking the unsaturation of the allyl group, would have to undergo an energetically much less favorable SN2 attack of RS^- on a saturated carbon atom to form the same type of products, and it is consequently not surprising that an alkyl disulfide does not react with a cyclic phosphoramidite under mild conditions. The fact that triphenylphosphine requires a temperature of 80° to desulfurize allyl disulfide,[16] whereas the cyclic phosphoramidite (I, R = C_2H_5) partially desulfurizes allyl disulfide at room temperature, can be ascribed to the greater nucleophilicity of I in which the electron density about the phosphorus atom is increased by electron release from nitrogen.

The reaction of an aryl disulfide with a cyclic phosphoramidite to form phosphoramidothioate III may be regarded as a typical Michaelis-Arbuzov reaction.

III
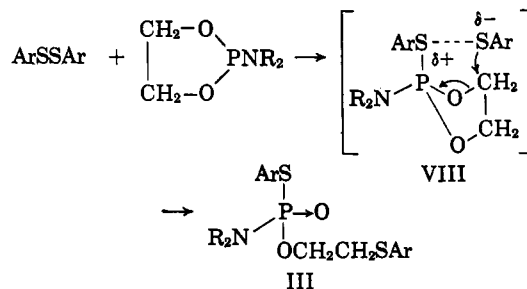
In the transition state VIII it is probable that stabilization of the negative charge on sulfur is necessary before the electronic shifts shown in VIII can occur to give III (see discussion above). Such stabilization is provided by delocalization of the charge throughout the aromatic ring or, as in the case of the tetraalkylthiuram disulfides

which also undergo this reaction, by the $R_2N\overset{\overset{S}{\|}}{C}-$ group. In order to establish the importance of this stabilization, we examined the reaction between the unsym-

## TABLE I

PHOSPHORAMIDOTHIOATES[a]

$$RSCH_2CHO\overset{O}{\underset{\underset{X}{R'}}{\overset{\uparrow}{P}}}SR$$

R	R'	X	Formula	Yield, %	B.p. (μ) or m.p., °C.	Nitrogen Calcd.	Nitrogen Found	Phosphorus Calcd.	Phosphorus Found	Sulfur Calcd.	Sulfur Found
Phenyl	CH₃	Piperidino	$C_{20}H_{26}NO_2PS_2$	87	205 (0.1)	3.44	3.14	7.61	7.8	15.73	15.8
4-Nitrophenyl	H	Diethylamino	$C_{18}H_{22}N_3O_6PS_2$	100	b	8.88	8.9	6.56	6.7	13.55	13.8
4-Nitro-o-tolyl	H	Diethylamino	$C_{20}H_{26}N_3O_6PS_2$	100	b	8.41	8.1	6.21	6.5	12.72	12.7
6-Nitro-o-tolyl	H	Diethylamino	$C_{20}H_{26}N_3O_6PS_2$	100	66–67	8.41	8.7	6.21	6.3		
6-Nitro-o-tolyl	H	Piperidino	$C_{21}H_{26}N_3O_6PS_2$	100	b	8.22	8.1	6.07	6.4	12.55	12.6
3-Nitro-o-tolyl	H	Diethylamino	$C_{20}H_{26}N_3O_6PS_2$	100	82–83	8.41	8.6	6.21	6.7	12.72	12.9
3-Nitro-o-tolyl	H	Piperidino	$C_{21}H_{26}N_3O_6PS_2$	100	b	8.22	7.9	6.07	6.1	12.55	11.8
5-Nitro-o-tolyl	H	Diethylamino	$C_{20}H_{26}N_3O_6PS_2$	100	b	8.41	7.8	6.21	6.3	12.72	12.9
2-Methoxy-4-nitrophenyl	H	Diethylamino	$C_{20}H_{26}N_3O_8PS_2$	100	b	7.91	7.4	5.84	6.2		
2-Benzthiazolyl	CH₃	Piperidino	$C_{22}H_{24}N_3O_2PS_4$	100	b			5.95	6.0	24.6	23.8
Dimethyldithiocarbamoyl	CH₃	Piperidino	$C_{14}H_{28}N_3O_2PS_4$	25	91–92, 110–111			7.22	7.3	29.9	31.5
Dimethyldithiocarbamoyl	CH₃	4-Morpholino	$C_{13}H_{26}N_3O_3PS_4$	30	120–121	9.75	9.6	7.18	7.5	29.7	30.4

[a] All products showed characteristic $\geqslant$P→O absorptions in the infrared in the region of 7.8–8.0 μ. [b] Undistillable oil; thin-layer chromatography showed the presence of one component.

TABLE II

BIS(ARYL) DISULFIDES, RSSR

R	Formula	Yield, %	M.p., °C.	Nitrogen Calcd.	Nitrogen Found	Sulfur Calcd.	Sulfur Found
6-Nitro-o-tolyl	$C_{14}H_{12}N_2O_4S_2$	78	149	8.33	8.3	19.05	19.1
3-Nitro-o-tolyl	$C_{14}H_{12}N_2O_4S_2$	78.5	121	8.33	8.2	19.05	19.2
5-Nitro-o-tolyl	$C_{14}H_{12}N_2O_4S_2$	81	151	8.33	7.7	19.05	18.8
2-Methoxy-4-nitrophenyl	$C_{14}H_{12}N_2O_6S_2$	67.5	188.5	7.61	7.4	17.40	17.2

metrical disulfide IX and the phosphoramidite X. The reaction was much more exothermic than any of the diaryl disulfide examples (see Table I) and proceeded with exclusive formation of XI.[17] The absence of the
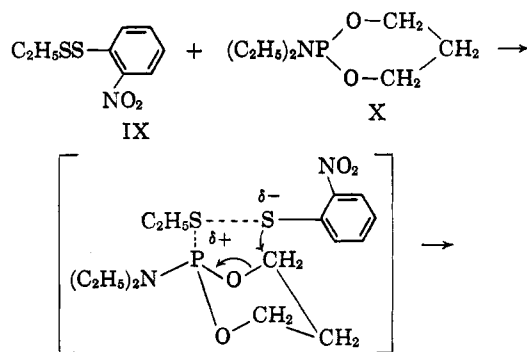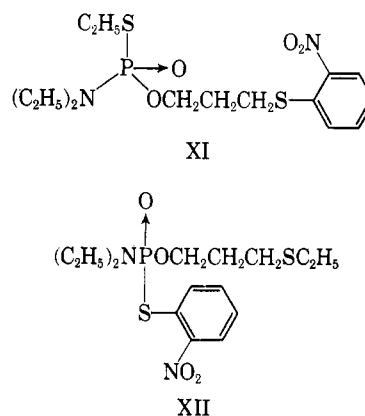

other product (XII) that would result from incipient formation of $C_2H_5S^-$ in the transition state, we regard as supporting evidence for the postulated mechanism.[18a]

This facile reaction between cyclic phosphoramidites and suitably constituted disulfides represents a convenient preparative method for phosphoramidothioates of structures III and VII. The thermal behavior of compounds of this type is described in the accompanying paper.[18b]

Experimental

All melting and boiling points are uncorrected. Infrared absorption spectra were determined in carbon tetrachloride solution on a Beckman IR-4 double beam instrument.

XI

XII

Materials.—Phenyl disulfide, tetramethylthiuram disulfide, and allyl disulfide were commercial products and were used without further purification. p-Nitrophenyl disulfide[19] and benzhydryl disulfide[20] were each prepared according to a literature procedure. The new disulfides listed in Table II were prepared by introducing ammonia into a suspension of the corresponding thiocyanate in ethanol following a known procedure.[21] Ethyl propylene phosphite, 2-diethylamino-1,3,2-dioxaphospholane, 2-piperidino-1,3,2-dioxaphospholane, and 2-piperidino-4-methyl-1,3,2-dioxaphospholane were prepared as previously described.[22] The latter procedure was also used to prepare the

(17) The structure of XI was proven by hydrolysis experiments, details of which may be found in the Experimental section.

(18) (a) Since the completion of this work, similar results have been reported for the reaction between triethyl phosphite and unsymmetrical disulfides by R. G. Harvey, H. I. Jacobson, and E. V. Jensen [J. Am. Chem. Soc., **85**, 1618 (1963)]. These authors ascribe the difference in reactivities to a different ease of polarization in unsymmetrical disulfides. (b) K. Pilgram, D. D. Phillips, and F. Korte, J. Org. Chem., **29**, 1848 (1964).

(19) T. Zincke and S. Lenhardt, Ann., **400**, 2 (1913).

(20) H. Staudinger and H. Freudenberger, Ber., **61**, 1576 (1928).

(21) K. Brand and H. W. Leyerzapf, ibid., **70**, 288 (1937).

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

new 2-(4-morpholino)-4-methyl-1,3,2-dioxaphospholane, b.p. 77° (0.08 mm.), n^{20}D 1.4897, 29% yield.

Reaction of Cyclic Phosphoramidites with Disulfides.—The results from the reaction of cyclic phosphoramidites with disulfides are summarized in Table I. The general procedures are illustrated by the reaction of 2-piperidino-4-methyl-1,3,2-dioxaphospholane with phenyl disulfide and by the reaction of 2-(4-morpholino)-4-methyl-1,3,2-dioxaphospholane with tetramethylthiuram disulfide.

S-Phenyl O-(2-Phenylthio-1-methylethyl)piperidinophosphono-thioate.—A mixture of 2-piperidino-4-methyl-1,3,2-dioxaphospholane (18.9 g., 0.10 mole) and phenyl disulfide (21.8 g., 0.10 mole) in a 100-ml. flask fitted with a thermometer and magnetic stirrer was gradually heated to 40° at which point an exothermic reaction occurred and the internal temperature rose rapidly to approximately 175°. The resultant light yellow viscous oil was molecularly distilled to give 35.5 g. (87.3%) of the phosphoramido-thioate as a colorless viscous liquid, b.p. 205° (0.1 μ), n^{25}D 1.5873, and 5 g. of a light yellow residue; the latter was identical with the distilled product as shown by thin-layer chromatograms.

O-[2-(Dimethylthiocarbamoylthio)-1-methylethyl]morpholino-phosphonothioate Anhydrosulfide with Dimethyldithiocarbamic Acid (VII, X = O).—To a stirred suspension of tetramethyl-thiuram disulfide (12.0 g., 0.05 mole) in toluene (25ᐧ ml.) was added, at room temperature, 2-(4-morpholino)-4-methyl-1,3,2-dioxaphospholane (9.55 g., 0.05 mole) in two portions. A clear solution resulted and the internal temperature rose immediately to approximately 75°. After the reaction mixture had stood overnight at room temperature, colorless crystals separated. Filtration afforded 5.5 g. (30.1%) of the desired product, m.p. 120–121° (from ethanol).

Reaction of 2-Diethylamino-1,3,2-dioxaphospholane with Benz-hydryl Disulfide. A. Without Solvent.—A mixture of 2-di-ethylamino-1,3,2-dioxaphospholane (9.78 g., 0.06 mole) and benzhydryl disulfide (11.94 g., 0.03 mole) in a 50-ml. flask fitted with a magnetic stirrer and thermometer was gradually heated under a nitrogen atmosphere. When the temperature of the initially colorless solution reached 100°, a blue color appeared. When the temperature reached 140°, an exothermic reaction occurred and the internal temperature rose to reflux (250°). The dark blue color disappeared and, on cooling to 120°, the reaction mixture solidified. After cooling to room temperature, 100 ml. of ether was added to the red-brown reaction product, and the solid was filtered and recrystallized from 200 ml. of toluene. There was obtained 5.5 g. (54.8%) of sym-tetraphenyl-ethane, m.p. 217°.

Anal. Calcd. for $C_{26}H_{22}$: C, 93.4; H, 6.6. Found: C, 92.9; H, 6.7.

The residual oil from the mother liquors (6 g.) was not investigated.

B. With Toluene as Solvent.—The same amounts of reactants as used in the preceding experiment were dissolved in toluene (50 ml.) and refluxed under a nitrogen atmosphere for 2 hr. (internal temperature 145–148°). After this time the starting materials were largely recovered.

Reaction of 2-Diethylamino-1,3,2-dioxaphospholane with Allyl Disulfide.—2-Diethylamino-1,3,2-dioxaphospholane (12.3 g., 0.076 mole) was treated with 11.0 g. (0.076 mole) of allyl disulfide

at 24°. The temperature rose to 39° within 10 min. The mixture then was heated to 80° for 4 hr. and molecularly distilled to give 11.0 g. (78%) of **O,O-ethylene diethylphosphoramidothio-nate (V, R = C_2H_5)** as a mobile yellow oil, b.p. 100° (0.1 μ), n^{25}D 1.5042.

Anal. Calcd. for $C_6H_{14}NO_2PS$: P, 15.9; S, 16.4. Found: P, 15.1; S, 16.4.

Allyl sulfide (7.0 g., 82%) was recovered from the cold trap and was identified by comparison of its infrared absorption spectrum with an authentic specimen.

Reaction of Ethyl Propylene Phosphite with Tetramethylthi-uram Disulfide.[13]—Tetramethylthiuram disulfide (24.0 g., 0.1 mole) dispersed in 50 ml. of toluene was treated at 22° with 15.0 g. (0.10 mole) of ethyl propylene phosphite. The temperature rose within 10 min. to about 45° and the tetramethylthiuram disulfide slowly dissolved to give a yellow-green solution. The solution then was heated under reflux for 2 hr. and allowed to stand overnight. The yellow crystals that separated (10 g.) were filtered. On cooling in Dry Ice–acetone, the mother liquors afforded a second crop of 6 g.; the total yield of tetramethyl-thiuram sulfide was 77%, m.p. 110°.

The solvent was removed from the mother liquors and the residue was molecularly distilled to give 18.0 g. (99%) of O-ethyl O,O-propylene phosphorothionate, b.p. 100° (0.1 μ), n^{25}D 1.4746.

Anal. Calcd. for $C_5H_{13}O_3PS$: S, 17.6. Found: S, 17.8.

Reaction of 2-Diethylamino-1,3,2-dioxaphosphorinane (X) with Ethyl o-Nitrophenyl Disulfide (IX).—Ethyl o-nitrophenyl disulfide[23] (21.5 g., 0.1 mole) was cooled to −70°, and 17.7 g. (0.1 mole) of 2-diethylamino-1,3,2-dioxaphosphorinane at 22° was added in one portion. The temperature rose to approximately 10° and remained there for about 10 min. The resultant viscous yellow oil was molecularly distilled to give 37.5 g. (95.7%) of **S-ethyl O-[3-(o-nitrophenyl)propyl]diethylphosphor-amidothioate (XI)**, b.p. 205° (0.1 μ), n^{25}D 1.5720. The product was initially a red oil, but it became yellow on standing overnight. Thin-layer chromatography showed the presence of only one component, but attempts to crystallize the distillate failed.

Anal. Calcd. for $C_{15}H_{25}N_2O_2PS_2$: N, 7.15; P, 7.91; mol. wt., 392.5. Found: N, 7.0; P, 8.0; mol. wt. (ebullioscopic in benzene), 394.

To confirm the structure of the phosphoramidothioate (XI), 22.0 g. (0.056 mole) of XI was heated with 200 ml. of 48% hydrobromic acid. After 2 hr. at 100–110°, 3.2 g. (92%) of **ethyl mercaptan** had condensed in the Dry Ice trap. The aqueous solution was extracted extensively with ether and with methylene chloride. The combined extracts were dried over magnesium sulfate, the solvents were removed *in vacuo*, and the yellow residue was crystallized from ethanol to give 11.5 g. (75%) of **3-bromopropyl o-nitrophenyl sulfide** as yellow crystals, m.p. 37–38°.

Anal. Calcd. for $C_9H_{10}BrNO_2S$: N, 5.07; S, 11.6. Found: N, 5.1; S, 11.3.

(23) J. F. Harris, Jr., U. S. Patent 2,962,417 (1960).