[CONTRIBUTION FROM THE BEN MAY LABORATORY FOR CANCER RESEARCH, UNIVERSITY OF CHICAGO, CHICAGO 37, ILL.]

Phosphonic Acids. VI. The Reaction of Trivalent Phosphorus Esters with Organic Disulfides[1,2]

BY RONALD G. HARVEY, HERBERT I. JACOBSON AND ELWOOD V. JENSEN

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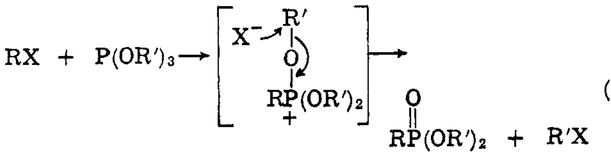
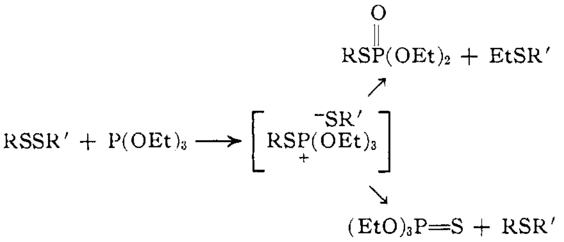
Organic disulfides react smoothly with triethyl phosphite (or dimethyl phenylphosphonite) in the presence of a free radical inhibitor to yield a thioether and an O,O,S-trisubstituted phosphorothioate (or analogous phosphonothioate) ester. Symmetrical aryl disulfides are more reactive than alkyl disulfides, and with the unsymmetrical disulfides studied the transformation takes place exothermically at room temperature. Benzoyl disulfide is unique in that it yields the O,O,O-phosphorothioate ester and benzoyl sulfide. In all cases the products are consistent with an ionic mechanism involving nucleophilic attack of trivalent phosphorus on the polarizable disulfide linkage with alkylation of the mercaptide anion displaced. Cleavage of unsymmetrical disulfides takes place in the direction to eliminate the more stable mercaptide anion.

One of the classical phenomena of organophosphorus chemistry is the Michaelis–Arbuzov reaction[3] of a trialkyl phosphite with an alkyl halide to form the dialkyl ester of a phosphonic acid and a new alkyl halide (eq. 1, X = Cl, Br, I). This transformation is believed to proceed by nucleophilic attack of the trivalent phosphorus atom on the polarized carbon–halogen linkage to displace a halide ion which then is alkylated by reaction at one of the alkoxy groups of the phosphonium intermediate. Attack of the displaced anion on the alkoxy linkage is facilitated by the tendency of the phosphorus atom to withdraw electrons by expanding its valency shell, and the driving force for the over-all process is furnished by conversion of the trigonal trivalent phosphorus with p^3-bonding to the more stable tetrahedral phosphorus atom with sp^3-bonding.

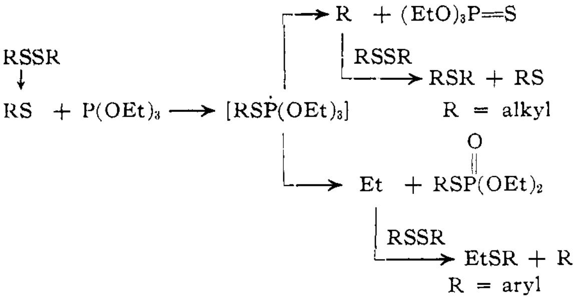


$$RX + P(OR')_3 \longrightarrow \left[\begin{array}{c} X^- \;\; R' \\ | \\ O \\ | \\ R\underset{+}{P}(OR')_2 \end{array}\right] \longrightarrow R\overset{O}{\overset{\|}{P}}(OR')_2 + R'X \qquad (1)$$

More recently it has been demonstrated that analogous reactions take place between trivalent phosphorus esters and a variety of substances with polarized or easily polarizable linkages subject to nucleophilic displacement of an anionic species. Transformations which appear to involve the same type of reaction sequence occur when trivalent phosphorus esters interact with acyl halides[3] or anhydrides,[4] molecular chlorine,[5] bromine[6] or iodine,[7] alkyl sulfonate esters,[8] Mannich base salts,[9] sulfenyl[10] and sulfonyl[11] halides, alkyl thiocyanates[12] and hypochlorites,[13] chlorinated amines[14] and propiolactone.[15] There is also a related type of process in which the negative charge, rather than appearing on a displaced anion, is transferred through a conjugated system to another location in the molecule where alkylation by reaction with the $\equiv\overset{+}{P}-O-R$ group takes place. Such reactions have been observed with trialkyl phosphites and acrolein,[16] cinnamic acid,[17] chloranil[18] and benzoquinone.[19]



$$RSSR' + P(OEt)_3 \longrightarrow \left[\begin{array}{c} {}^-SR' \\ RS\underset{+}{P}(OEt)_3 \end{array}\right] \begin{array}{l} \nearrow RS\overset{O}{\overset{\|}{P}}(OEt)_2 + EtSR' \qquad (2a) \\ \\ \searrow (EtO)_3P{=}S + RSR' \qquad (2b) \end{array}$$



$$\begin{array}{ll} & \rightarrow R + (EtO)_3P{=}S \\ RSSR & \quad \xrightarrow{RSSR} RSR + RS \qquad (3a) \\ \downarrow & \quad\quad R = \text{alkyl} \\ RS + P(OEt)_3 \longrightarrow [RS\dot{P}(OEt)_3] & \\ & \rightarrow Et + RS\overset{O}{\overset{\|}{P}}(OEt)_2 \qquad (3b) \\ & \quad \xrightarrow{RSSR} EtSR + RS \\ & \quad\quad R = \text{aryl} \end{array}$$

It was previously reported from this Laboratory that ethyl disulfide reacts with boiling triethyl phosphite to yield ethyl sulfide and O,O,S-triethyl phosphorothioate.[20] It was proposed that this transformation represents another example of Arbuzov-type valency expansion reaction of phosphorus in which nucleophilic attack of the phosphite on the easily polarizable disulfide linkage displaces a mercaptide ion which then is alkylated to produce the thioether (eq. 2a, R = R′ = Et). Subsequently, Poshkus and Herweh[11c] reported that phenyl disulfide reacts with triethyl phosphite in boiling benzene to give analogous products (eq. 2a, R = R′ = Ph), while Michalski and Wieczorkowski[21] found that acetyl disulfide and triethyl phosphite yield O,O,O-triethyl phosphorothioate and acetyl sulfide (eq. 2b, R = R′ = Ac), suggesting that in this case the displaced

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[1] Paper V: R. G. Harvey, T. C. Myers, H. I. Jacobson and E. V. Jensen, *J. Am. Chem. Soc.*, **79**, 2612 (1957).

[2] This paper is taken from the Ph.D. dissertation of R. G. Harvey, University of Chicago, 1960, and was presented in part before the 139th National Meeting of the American Chemical Society, St. Louis, Mo., March, 1961. The authors gratefully acknowledge support by a grant from the National Institutes of Health, U. S. Public Health Service (RG-3053).

[3] (a) G. M. Kosolapoff, "Organophosphorus Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1950, Ch. 7; (b) P. C. Crofts, *Quart. Rev.* (London), **12**, 341 (1958).

[4] G. Kamai and V. A. Kukhtin, *Dokl. Akad. Nauk SSSR*, **102**, 283 (1955).

[5] H. McCombie, B. Saunders and G. Stacey, *J. Chem. Soc.*, 380 (1945).

[6] W. Gerrard and G. J. Jeacocke, *ibid.*, 3647 (1954).

[7] J. P. Forsman and D. Lipkin, *J. Am. Chem. Soc.*, **75**, 3145 (1953).

[8] T. C. Myers, S. Preis and E. V. Jensen, *ibid.*, **76**, 4172 (1954).

[9] T. C. Myers, R. G. Harvey and E. V. Jensen, *ibid.*, **77**, 3101 (1955).

[10] D. C. Morrison, *ibid.*, **77**, 181 (1955).

[11] (a) E. E. Gilbert and C. J. McGough, U. S. Patents 2,690,450 (1954), 2,690,451 (1954); (b) F. W. Hoffmann, T. R. Moore and B. Kagan, *J. Am. Chem. Soc.*, **78**, 6413 (1956); (c) A. C. Poshkus and J. E. Herweh, *ibid.*, **79**, 4245 (1957).

[12] J. Michalski and J. Wieczorkowski, *Bull. acad. polon. sci., Classe III*, **4**, 279 (1956); *Chem. Abstr.*, **51**, 4266 (1957).

[13] K. A. Petrov and G. A. Sokol'skii, *Zhur. Obshchei Khim.*, **26**, 3377 (1956).

[14] K. A. Petrov and G. A. Sokol'skii, *ibid.*, **26**, 3378 (1956).

[15] R. L. McConnell and H. W. Coover, Jr., *J. Am. Chem. Soc.*, **78**, 4453 (1956).

[16] G. Kamai and V. A. Kukhtin, *Dokl. Akad. Nauk SSSR*, **112**, 868 (1957).

[17] G. Kamai and V. A. Kukhtin, *Tr. Kazansk. Khim.-Tekhnol. Inst.*, **23**, 133 (1957).

[18] F. Ramirez and S. Dershowitz, *J. Am. Chem. Soc.*, **81**, 587 (1959).

[19] F. Ramirez, E. H. Chen and S. Dershowitz, *ibid.*, **81**, 4338 (1959).

[20] H. I. Jacobson, R. G. Harvey and E. V. Jensen, *ibid.*, **77**, 6064 (1955).

[21] J. Michalski and J. Wieczorkowski, *Bull. acad. polon. sci., Classe III*, **5**, 917 (1957); *Chem. Abstr.*, **52**, 6157 (1958).

TABLE I

REACTION OF TRIETHYL PHOSPHITE AND DIMETHYL PHENYLPHOSPHONITE WITH ORGANIC DISULFIDES

Reactants				Products (% yield)	
Disulfide symmetrical R = R′ =		Phosphorus reagent	Solvent	Phosphorothioate	Sulfide
Et		$PhP(OMe)_2$	None	$PhPO(OMe)SEt$ (82)	$EtSMe$ (72)
Et[a]		$P(OEt)_3$	Excess phosphite	$EtSPO(OEt)_2$ (77[b])	$EtSEt$ (95[b])
n-Pr		$P(OEt)_3$	Excess phosphite	$PrSPO(OEt)_2$ (68[b])	$PrSEt$(66,[b] 77)
n-Pr		$P(OEt)_3$	None	$PrSPO(OEt)_2$ (36)	$PrSEt$ (31)
Ph		$P(OEt)_3$	Benzene	$PhSPO(OEt)_2$ (70)	$PhSEt$ (75)
p-$MeOC_6H_4$		$P(OEt)_3$	Benzene	$MeOC_6H_4SPO(OEt)_2$ (80)	$MeOC_6H_4SEt$ (79)
DNP[c]		$P(OEt)_3$	Xylene	. . .	$(NO_2)_2C_6H_3SEt$ (77)
Bz		$P(OEt)_3$	Benzene	$(EtO)_3PS$ (92)	$BzSBz$ (84)
Unsymmetrical R =	R′ =				
Me	CCl_3	$P(OEt)_3$	None	$MeSPO(OEt)_2$ (80)	(CCl_3SEt)[d] (68)
Me	Ph	$P(OEt)_3$	None	$MeSPO(OEt)_2$ (71)	$PhSEt$ (86)
Ph	DNP[c]	$P(OEt)_3$	Xylene	$PhSPO(OEt)_2$ (50)	$(NO_2)_2C_6H_3SEt$ (95)
Ph	C_6Cl_5	$P(OEt)_3$	Ether	$PhSPO(OEt)_2$ (92)	C_6Cl_5SEt (100)

[a] Reaction described in ref. 20. [b] Reaction run without added hydroquinone. [c] DNP = 2,4-dinitrophenyl. [d] Product unstable decomposing to thiophosgene; yield based on thiophosgene derivative.

anion cleaves the acyl–sulfur bond rather than an alkoxy linkage in the intermediate.

Observations by Walling and Rabinowitz[22,23] that, in the presence of appropriate initiators, trialkyl phosphites can undergo a free radical chain reaction with alkyl disulfides to yield an O,O,O-trialkyl phosphorothioate ester and an alkyl sulfide (eq. 3a) raised some question concerning the interpretation of the foregoing phenomena as ionic valency expansion reactions of the Arbuzov type. The reactions with ethyl and phenyl disulfides do not provide conclusive evidence for the ionic mechanism, since the products are not incompatible with the radical mechanism. With ethyl disulfide (where R = R′ = Et) the same thioether would be produced by either mechanism, and the O,O,S-triethyl phosphorothioate obtained might arise by isomerization of initially formed O,O,O-triethyl phosphorothioate, a transformation known[24] to take place at elevated temperature. Phenyl disulfide would give the same products by either mechanism, since, because of the strength of the aryl–sulfur bond, an ethyl rather than an aryl radical would be eliminated from the radical intermediate (eq. 3b). When Walling and Rabinowitz[23] carried out the reaction of *n*-butyl disulfide with triethyl phosphite in the presence of hydroquinone to block the free radical process, they did obtain ethyl butyl sulfide as predicted by the ionic mechanism, but the yield was rather low, and some ethyl and butyl sulfides were formed as well. Thus, the exact status of the ionic reaction of organic disulfides with trivalent phosphorus esters remained in some doubt.

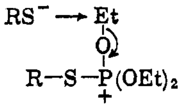
To gain further insight into the processes in question, an investigation has been made of the reaction of triethyl phosphite with a variety of symmetrical and unsymmetrical organic disulfides. The products obtained, as well as the influence of the organic substituents on the reactivity and direction of cleavage of the disulfide linkage, provide consistent evidence that trialkyl phosphites can react efficiently with organic disulfides by an ionic mechanism, and that this phenomenon represents an extension of the *valency expansion* reaction of the Michaelis–Arbuzov type.

Results and Discussion

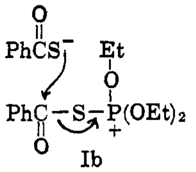
Studies of the interaction of organic disulfides with triethyl phosphite and related phosphorus reagents are summarized in Table I. To minimize competition from free radical processes, these reactions, unless otherwise indicated, were carried out in subdued light in a nitrogen atmosphere in the presence of 2 mole % of hydroquinone. In certain instances positive identification of the phosphorothioate ester was accomplished by conversion to the corresponding S-*p*-chlorobenzylthiuronium salt by the procedure described in a separate paper.[25]

The results obtained provide evidence that triethyl phosphite and related trivalent phosphorus esters react readily with organic disulfides by an ionic mechanism analogous to that of the Michaelis–Arbuzov reaction. The reaction of triethyl phosphite with *n*-propyl disulfide proceeds with comparable facility in the presence or absence of hydroquinone to yield in either case the mixed thioether which *is predicted by the ionic but not the radical mechanism.* The reaction of dimethyl phenylphosphonite with ethyl disulfide follows an analogous course to form the mixed thioether and the S-ethyl phosphonothioate. Triphenyl phosphite appears to be unreactive with disulfides just as it is with alkyl halides.[3]

The reactions of triethyl phosphite with symmetrical aryl disulfides do not delineate the type of mechanism since the same products would be expected from either the ionic or radical process. In agreement with Poshkus and Herweh,[11c] symmetrical aryl disulfides were found to react in a shorter time at a substantially lower temperature than do alkyl disulfides. This greater reactivity of aryl disulfides is not due to any effect of the aromatic solvent employed, since *n*-propyl disulfide was found to react only very slowly with triethyl phosphite in refluxing xylene.



Ia



Ib

The formation of O,O,S-trialkyl phosphorothioates by the mechanism of eq. 2a implies that the displaced mercaptide anion attacks the phosphonium cation selectively at a carbon–oxygen rather than a carbon–sulfur linkage (Ia). Such behavior is similar to that of phosphorothioate esters, which are cleaved preferentially at an alkoxy linkage, both by sodium mercap-

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[22] C. Walling and R. Rabinowitz, *J. Am. Chem. Soc.*, **79**, 5326 (1957).

[23] C. Walling and R. Rabinowitz, *ibid.*, **81**, 1243 (1959).

[24] W. G. Emmett and H. O. Jones, *J. Chem. Soc.*, **99**, 713 (1911).

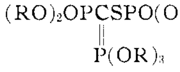
[25] R. G. Harvey and E. V. Jensen, *J. Org. Chem.*, **28**, 470 (1963).

tides[25,26] and by lithium chloride.[27] In the case of benzoyl disulfide, which like the previously reported[21] acetyl disulfide reacts exothermically with triethyl phosphite at room temperature, the products are the O,O,O-phosphorothioate ester and benzoyl sulfide (eq. 2b, R = R′ = Bz), suggesting that the acyl–sulfur linkage in the intermediate Ib is more susceptible to cleavage by the mercaptide ion than is the alkoxy bond.

Unsymmetrical substitution of the disulfide group results in a striking enhancement of reactivity. The four examples listed in Table I, which include unsymmetrical dialkyl, aryl-alkyl and diaryl disulfides, all undergo exothermic reaction with triethyl phosphite at room temperature. In all these experiments, with the exception of the phenyl pentachlorophenyl disulfide reaction which was carried out in ether solution, the reaction mixtures were later heated to ensure completion of conversion, but this precaution probably is unnecessary.

From the reaction of triethyl phosphite with an unsymmetrical disulfide, two different sets of products might be produced, depending on which way the disulfide linkage is cleaved. In all cases studied, only one set of products could be detected; namely, that predicted by eq. 2a when the anion eliminated is that of the more acidic mercaptan. It would appear that trichloromethyl and phenyl mercaptides are displaced in preference to methyl, whereas 2,4-dinitrophenyl and pentachlorophenyl mercaptides are eliminated rather than phenyl. Unfortunately the influence on disulfide cleavage of an electron-donating aryl substituent was not evaluated, since all attempts to prepare phenyl *p*-anisyl disulfide for study led to a mixture of *p*-anisyl disulfide and phenyl disulfide.

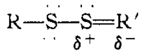
In the reaction of methyl trichloromethyl disulfide with triethyl phosphite, the thioether produced (EtSCCl$_3$) is unstable and decomposes to yield ethyl chloride and thiophosgene. The latter substance was identified by conversion to thiocarbanilide by treatment with two equivalents of aniline. Subsequent to the completion of these experiments, it was reported by Birum[28] that alkyl trichloromethyl disulfides react with excess triethyl phosphite to yield an O,O,S-trialkyl phosphorothioate ester and thiophosgene; the latter substance reacts further with three moles of phosphite to yield an alkyl halide and a compound formulated as



$$(\mathrm{RO})_2\mathrm{OP}\underset{\underset{\mathrm{P(OR)_3}}{\|}}{\mathrm{C}}\mathrm{SPO(OR)_2}.$$

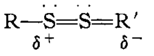
Although in the present experiment using equimolar quantities of reagents none of the latter substance was detected, our conclusions as to the general course of the reaction and the direction of cleavage of the disulfide linkage appear to be in agreement with those of Birum.

The preferential scission of the unsymmetrical disulfide bond and the striking differences in reactivity observed among the various types of organic disulfides have certain implications in regard to the mechanism of the over-all transformation. If the reaction were to proceed by direct nucleophilic displacement on one of the sulfur atoms, the direction of cleavage should depend on which sulfur atom is attacked by the phosphite, and this in turn should be determined by the polarization of the unsymmetrical disulfide bond. The simplest consideration would predict that the sulfur atom adjacent to the more electron-withdrawing substituent (R′) should be the more electropositive (II), since measurements[29] of ultraviolet spectra indicate that structures of type III are not of importance, at least in the ground state. Support for this conclusion is provided by



$$\mathrm{R{-}\overset{..}{\underset{..}{S}}{-}\overset{..}{\underset{\delta^+}{S}}{=}\underset{\delta^-}{R'}}$$

II



$$\mathrm{R{-}\overset{..}{\underset{\delta^+}{S}}{=}\overset{..}{S}{=}\underset{\delta^-}{R'}}$$

III

observations that *electrophilic* reagents, such as sulfenyl halides[30] and peracids,[31] attack the sulfur atom remote from the electron-withdrawing substituent. But this is the same sulfur atom which becomes attached to the *nucleophilic* phosphorus atom in the reaction with triethyl phosphite, and similar results have been observed with other nucleophilic reagents, including sodium diethyl phosphonate,[26] sodium bis-(phenylsulfonyl)-methane[32] and a variety of simple nucleophiles,[33,34] such as cyanide, iodide, mercaptide, thiocyanate, etc. It would appear either that nucleophiles attack the same sulfur atom in an unsymmetrical disulfide as do electrophiles or else that the process involves the formation of a transition intermediate, so that, no matter which sulfur atom is attacked initially, the more stable mercaptide ion is preferentially ejected.

Although the stability of the anion may determine which mercaptide is displaced, mercaptide elimination does not appear to control the rate of the over-all transformation. The greatly increased reactivity of unsymmetrical disulfides is not consistent with either the elimination of the mercaptide ion or its attack on an alkoxy linkage as being rate determining. For example, methyl phenyl disulfide reacts with triethyl phosphite at a much lower temperature than does phenyl disulfide, yet in each case the ion displaced is thiophenoxide which cleaves an ethoxy linkage to form ethyl phenyl sulfide. It is suggested that the rate-limiting step is the initial attack of the phosphite on the disulfide, and that unsymmetrical substitution facilitates this attack by effecting polarization, or at least easy polarizability, of the disulfide linkage. With symmetrical disulfides the relative reactivities (benzoyl > aryl > alkyl) lie in the order predicted by the expected effects of these substituents on the polarizability of the disulfide bond.

Experimental

Materials.—Triethyl phosphite, hereafter abbreviated TEP, (Virginia–Carolina Co.) was redistilled before use. Dimethyl phenylphosphonite,[35] b.p. 101° (17 mm.), n^{25}D 1.5278, was prepared by the reaction of dichlorophenylphosphine with two equivalents of methanol and dimethylaniline at 0°.

The unsymmetrical disulfides studied were prepared by the reaction of the appropriate sulfenyl chloride and mercaptan as described in detail later in this section. Of the symmetrical disulfides, benzoyl disulfide (K and K Laboratories) and phenyl and 2,4-dinitrophenyl disulfides (Eastman Kodak Co.) were used as supplied, whereas ethyl and *n*-propyl disulfides (Eastman) were redistilled before use. Pentachlorophenyl disulfide,[36] m.p. 235–236° from benzene, used for the preparation of phenyl pentachlorophenyl disulfide, was prepared in 90% yield by the oxidation of a neutralized aqueous solution of pentachlorothiophenol (obtained from K and K Laboratories and recrystallized from benzene with filtration) with 30% hydrogen peroxide. *p*-Anisyl disulfide,[37] m.p. 37–38°, was obtained in 69% yield when Merck zinc dust was employed for the reduction of *p*-methoxybenzenesulfonyl chloride according to the procedure de-

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(26) R. G. Harvey, H. I. Jacobson and E. V. Jensen, *J. Am. Chem. Soc.*, **85**, 1623 (1963).

(27) J. Lecocq and A. R. Todd, *J. Chem. Soc.*, 2381 (1954).

(28) (a) G. H. Birum, Abstracts of the 137th National Meeting of the American Chemical Society, Cleveland, O., April, 1960, p. 32-O; (b) G. H. Birum, British Patent 871,695 (1961).

(29) E. Campaigne, J. Tsurugi and W. W. Meyer, *J. Org. Chem.*, **26**, 2486 (1961).

(30) C. G. Moore and M. Porter, *J. Chem. Soc.*, 2890 (1958).

(31) G. Leandri and A. Tundo, *Ann. chim.* (Rome), **44**, 74 (1954).

(32) G. Leandri and A. Tundo, *ibid.*, **44**, 512 (1954).

(33) A. J. Parker and N. Kharasch, *J. Am. Chem. Soc.*, **82**, 3071 (1960).

(34) R. G. Hiskey and F. I. Carroll, *ibid.*, **83**, 4644 (1961).

(35) (a) A. E. Arbuzov, *Zhur. Obshchei Khim.*, **4**, 898 (1934); (b) H. J. Harwood and D. W. Grisley, Jr., *J. Am. Chem. Soc.*, **82**, 423 (1960).

(36) W. Tadros and E. Saad, *J. Chem. Soc.*, 1155 (1954).

(37) A. Vinkler and F. Klivenyi, *Acta Chim. Acad. Sci. Hung.*, **5**, 159 (1954).

scribed in ref. 38 for the preparation of thiophenol. Reduction of *p*-methoxybenzenesulfonyl chloride by the same procedure using Mallinckrodt zinc dust gave a 73% yield of *p*-methoxythiophenol,[39] b.p. 64° (0.4 mm.), n^{25}D 1.5822, reacting with 2,4-dinitrofluorobenzene in the presence of sodium ethoxide to form *p*-methoxyphenyl 2,4-dinitrophenyl sulfide, m.p. 116–117°.

Reaction of Ethyl Disulfide with Dimethyl Phenylphosphonite.—A mixture of ethyl disulfide (11.5 g., 0.094 mole), dimethyl phenylphosphonite (16.0 g., 0.094 mole) and hydroquinone (220 mg., 2.0 mmoles) was heated under reflux for 9 hours. Then the pressure was gradually reduced to 8 mm., whereupon 6.5 g. of volatile material was evolved and collected in a cold trap. Redistillation of this substance through a 24-in. tantalum spiral wire column yielded methyl ethyl sulfide, 5.2 g., 72%, b.p. 64.6°, n^{25}D 1.4366; reported[40] b.p. 66.7°, n^{25}D 1.4374. When treated with mercuric chloride, this product formed a crystalline adduct, m.p. 101–102°; reported[41] m.p. of $CH_3SC_2H_5{\cdot}HgCl_2$, 101–102°.

The remainder of the reaction mixture was distilled at reduced pressure through a 30-in. Fenske column to yield O-methyl S-ethyl phenylphosphonothioate, 16.3 g., 82%, b.p. 117° (0.6 mm.), n^{25}D 1.5520. Redistillation of a portion of this material through a Podbielniak whirling band column furnished the analytical sample, b.p. 112° (2.2 mm.), n^{25}D 1.5532, with characteristic infrared absorption at 1002, 1033, 1186, 1230 and 1437 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{13}O_2PS$: C, 50.00; H, 6.06; P, 14.33; S, 14.83. Found: C, 50.13; H, 6.29; P, 14.07; S, 13.99.

Reaction of *n*-Propyl Disulfide with TEP. (a) **In the Absence of Hydroquinone.**—A mixture of *n*-propyl disulfide (30 g., 0.20 mole) and TEP (99 g. 0.60 mole) was slowly distilled at atmospheric pressure through a 30-in. Fenske column over the course of 17 hours, during which time there was collected 52 g. of distillate boiling in the range 143–151°. To remove TEP, this distillate was shaken overnight with aqueous sodium hydroxide, after which the phosphite odor no longer was detectable. The thioether was extracted with several portions of ether which were combined, dried over sodium sulfate and distilled through a Fenske column to yield ethyl *n*-propyl sulfide, 13.5 g., 66%, b.p. 116°, n^{25}D 1.4411; reported[42] b.p. 115–117°. Identification was confirmed by reaction with equal molar quantities of ethyl iodide and mercuric iodide to form the complex sulfonium salt[43] $(n\text{-PrSEt}_2)^+(\text{HgI}_3)^-$, m.p. 90.5–91° from acetone–ethanol; reported[44] m.p. 88–89°; not depressed by mixture with an authentic sample of the complex obtained from equal molar quantities of ethyl sulfide, propyl iodide and mercuric iodide. A complex obtained similarly from *n*-propyl sulfide, ethyl iodide and mercuric iodide was found to melt at 73.5–74°, showing definitely that the thioether obtained from the reaction of TEP with *n*-propyl disulfide is not *n*-propyl sulfide.

The residual portion of the original reaction mixture was distilled through the Fenske column at reduced pressure yielding 39.4 g. of distillate, boiling from 110° (20 mm.) to 95° (3 mm.) and containing the remainder of the excess TEP; followed by a fraction, 38.5 g., boiling from 95° (3 mm.) to 94° (1.2 mm.). Redistillation of the latter fraction through a Podbielniak whirling band column yielded O,O-diethyl S-*n*-propyl phosphorothioate, 28.7 g., 68%, b.p. 90° (1.2 mm.), n^{25}D 1.4560; ν_{liq} 1020, 1163 and 1252 cm.$^{-1}$.

(b) **In the Presence of Hydroquinone.**—A mixture of *n*-propyl disulfide (30 g., 0.20 mole), TEP (99 g., 0.60 mole) and hydroquinone (440 mg., 4.0 mmoles) was slowly distilled through a 24-in. tantalum spiral wire column with high reflux ratio. During a period of 9 hours there was collected practically pure ethyl *n*-propyl sulfide, 16.0 g., 77%, b.p. 116°, n^{25}D 1.4410. However, the residual material in the still-pot decomposed to a black tar before any pure products could be recovered.

A similar experiment was carried out using equimolar quantities of reagents. A mixture of *n*-propyl disulfide (37.6 g., 0.25 mole), TEP (41.5 g., 0.25 mole) and hydroquinone (550 mg., 5.0 mmoles) was heated under reflux for 9 hours and then distilled through a 4-in. Vigreux column. The first fraction, 28.3 g., boiling from 33° (19 mm.) to 55° (12 mm.), was redistilled through a 30-in. Fenske column to yield ethyl *n*-propyl sulfide, 8.0 g., 31% b.p. 116°, n^{25}D 1.4420. After intermediate fractions, 26.0 g., boiling from 50° (3 mm.) to 67 (0.3 mm.), there was collected O,O-diethyl S-*n*-propyl phosphorothioate, 19.3 g., 36%, b.p. 70° (0.3 mm.), n^{25}D 1.4562.

When 100 ml. of xylene was employed as a solvent for the foregoing quantities of reactants, only a 12.5% conversion to ethyl *n*-propyl sulfide took place during 9 hours heating under reflux.

Reaction of Phenyl Disulfide with TEP.—When TEP (16.6 g., 0.10 mole) was added to a solution of phenyl disulfide (21.8 g., 0.10 mole) and hydroquinone (220 mg., 2.0 mmoles) in 40 ml. of benzene, no visible reaction occurred. The mixture was heated under reflux for 2.5 hours, and then the solvent was evaporated at aspirator pressure. A one-tenth aliquot portion of the residue was chromatographed on 200 g. of Florisil prepared in pentane. With pentane there was eluted phenyl ethyl sulfide, 1.05 g., 75%, n^{25}D 1.5652, reported[39] $n^{22.5}$D 1.5662, identified by oxidation with 30% hydrogen peroxide to phenyl ethyl sulfone, m.p. 41–42°, reported[45] m.p. 41–42°. Elution with methylene chloride gave an intermediate fraction (1.02 g.) of lower refractive index (1.5002), and finally with methylene chloride–ether (3:1) there was obtained O,O-diethyl S-phenyl phosphorothioate, 1.71 g., 70%, n^{25}D 1.5213, reported[46] n^{20}D 1.5248, identified by conversion to the S-*p*-chlorobenzylthiuronium salt of O-ethyl S-phenyl phosphorothioate,[25] m.p. 174–176° not depressed by admixture with an analyzed sample of this derivative. The phosphorothioate showed characteristic infrared absorption at 1025, 1166 and 1259 cm.$^{-1}$.

Reaction of *p*-Anisyl Disulfide with TEP.—The reaction of *p*-anisyl disulfide (6.96 g., 0.025 mole) with TEP (4.15 g., 0.025 mole) in 10 ml. of benzene containing 55 mg. of hydroquinone was carried out as described for phenyl disulfide to yield, on Florisil chromatography, *p*-anisyl ethyl sulfide, 3.34 g., 79%, n^{25}D 1.5580, and O,O-diethyl S-*p*-anisyl phosphorothioate, 5.60 g., 80%, n^{25}D 1.5296.

Anal. Calcd. for $C_9H_{12}OS$: C, 64.24; H, 7.19; S, 19.05. Found: C, 64.07; H, 7.15; S, 18.91. Calcd. for $C_{11}H_{17}OPS$: C, 47.80; H, 6.20; S, 11.61. Found: C, 47.74; H, 6.80; S, 11.26.

Reaction of 2,4-Dinitrophenyl Disulfide with TEP.—A solution of hydroquinone (44 mg., 0.4 mmole) in TEP (3.32 g., 0.02 mole) was added to a suspension of 2,4-dinitrophenyl disulfide (7.96 g., 0.02 mole) in 20 ml. of xylene. When no visible reaction occurred, the mixture was heated under reflux for 2.5 hours, whereupon most of the solid dissolved and the reaction mixture turned dark. Filtration of the cooled reaction mixture yielded 0.88 g. of unreacted disulfide.

The xylene was evaporated from the reaction mixture at reduced pressure and the viscous residue allowed to stand overnight, whereupon it partially crystallized. Trituration with pentane left a solid (5.08 g.) of which a 1.10-g. portion was dissolved in ethanol, leaving a 94-mg. residue of 2,4-dinitrophenyl disulfide. The hot ethanol solution was decolorized with charcoal and filtered. On cooling, the filtrate deposited yellow needles of 2,4-dinitrophenyl ethyl sulfide, 0.76 g., 77%, m.p. 113–114°, reported[47] m.p. 115°, not depressed by admixture with an analyzed sample of this sulfide obtained from the reaction of TEP with phenyl 2,4-dinitrophenyl disulfide.

Evaporation of the pentane washings of the original reaction product left a reddish brown semisolid residue. Chromatography of a 1.0-g. portion of this material on 30 g. of Florisil yielded only 30 mg. of an impure material (m.p. 209–211°) for which no meaningful analysis could be obtained.

Attempts to synthesize the expected product, O,O-diethyl S-2,4-dinitrophenyl phosphorothioate, by the reaction of sodium O,O-diethyl phosphorothioate with 2,4-dinitrochlorobenzene in acetone or with 2,4-dinitrofluorobenzene in boiling tetrahydrofuran gave 2,4-dinitrophenyl sulfide, m.p. 194–196°, and, presumably, tetraethyl thiopyrophosphate. This behavior no doubt is analogous to the reaction of 2,4-dinitrofluorobenzene with sodium alkyl phosphates.[48]

Reaction of Benzoyl Disulfide with TEP.—When TEP (16.6 g., 0.10 mole) was added to a suspension of benzoyl disulfide (27.4 g., 0.10 mole) in 50 ml. of dry benzene containing hydroquinone (220 mg., 2 mmoles), an exothermic reaction ensued. As the temperature rose to about 60°, the disulfide rapidly dissolved. The reaction mixture was then heated under reflux for 2.5 hours, after which the solvent was evaporated under reduced pressure. The residual oil was distilled through a short Vigreux column to yield O,O,O-triethyl phosphorothioate, 18.7 g., 92%, b.p. 62° (1.3 mm.), n^{30}D 1.4454; reported[49] b.p. 88.5° (8 mm.), n^{20}D 1.4480. The product showed characteristic infrared absorption at 1033 and 1168 cm.$^{-1}$ and no significant absorption in the region from 1190 to 1360 cm.$^{-1}$ indicating the absence of the $P{=}O$ group. Redistillation of a portion of this product through a Podbielniak whirling band column yielded the analytical sample, n^{30}D 1.4448.

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(38) R. Adams and C. Marvel in "Organic Syntheses," Coll. Vol. I, H. Gilman and A. H. Blatt, ed., John Wiley and Sons, Inc., New York, N. Y., 2nd Ed., 1941, p. 504.

(39) F. Taboury, *Ann. chim. phys.*, [8] **15**, 5 (1908).

(40) W. E. Haines, R. V. Helm, C. W. Bailey and J. S. Ball, *J. Phys. Chem.*, **58**, 270 (1954).

(41) E. H. Thierry, *J. Chem. Soc.*, **127**, 2756 (1925).

(42) D. Strömholm, *Chem. Ber.*, **33**, 823 (1900).

(43) H. J. Cavell and S. Sugden, *J. Chem. Soc.*, 2572 (1930).

(44) P. C. Ray and P. C. Guha, *ibid.*, **115**, 1148 (1919).

(45) R. Otto, *Chem. Ber.*, **18**, 154 (1885).

(46) J. Michalski, J. Wieczorkowski, J. Wasiak and B. Pliszka, *Roczniki Chem.*, **33**, 247 (1959); *Chem. Abstr.*, **53**, 17884 (1959).

(47) R. W. Bost, J. O. Turner and R. D. Norton, *J. Am. Chem. Soc.*, **54**, 1985 (1932).

(48) R. Wittmann, *Angew. Chem.*, **74**, 214 (1962).

(49) B. A. Arbuzov and V. S. Vinogradova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 459 (1947).

Anal. Calcd. for $C_6H_{15}O_3PS$: C, 36.35; H, 7.63. Found: C, 36.25; H, 7.61.

The distillation residue was a viscous oil which, on standing in the cold room, crystallized to yield a solid, m.p. 40–44°. Recrystallization from ether gave benzoyl sulfide, 21.0 g., 87%, m.p. 47–48°, reported[50] m.p. 48°.

Anal. Calcd. for $C_{14}H_{10}O_2S$: C, 69.40; H, 4.16. Found: C, 68.61; H, 4.38.

Reaction of Methyl Trichloromethyl Disulfide with TEP.—After a preliminary experiment had indicated that TEP and methyl trichloromethyl disulfide interact vigorously and exothermically at room temperature, TEP (33.3 g., 0.20 mole) was added gradually during 30 minutes to a stirred mixture of methyl trichloromethyl disulfide (39.5 g., 0.20 mole) and hydroquinone (440 mg., 4.0 mmoles) held at 0°, whereupon an orange color formed. Stirring was continued at 0° for 30 minutes longer, and then the reaction mixture was warmed gradually over a period of 2 hours to a temperature of 90°. During this time the reaction mixture became red, and a volatile substance was evolved which was collected in a cold trap as a bright red liquid (13 ml.). This material was shown to be thiophosgene by reaction of a 1-ml. portion with 10 ml. of aniline in 25 ml. of ether at 0° to give aniline hydrochloride, 3.32 g., m.p. 197°, and thiocarbanilide, 2.36 g., m.p. 153–154° (lit.[51] 154°), from ethanol.

Anal. Calcd. for $C_{13}H_{12}N_2S$: C, 68.39; H, 5.30; N, 12.28; S, 14.05. Found: C, 68.20; H, 5.57; N, 12.31; S, 14.03.

A 20-g. portion of the main reaction mixture (57.6 g.) was distilled at reduced pressure through a short Vigreux column to give a forerun, 4.6 g., b.p. 37–64° (4 mm.), $n^{28}\mathrm{D}$ 1.5442, containing unreacted disulfide, followed by the main product, O,O-diethyl S-methyl phosphorothioate, 8.84 g., 69%, b.p. 89° (4 mm.), $n^{28}\mathrm{D}$ 1.4566; ν_{liq} 1028, 1166, 1254 cm.$^{-1}$; reported[52] b.p. 127.5–128° (26 mm.), $n^{20}\mathrm{D}$ 1.4607.

Anal. Calcd. for $C_5H_{13}O_3PS$: C, 32.60; H, 7.11; P, 16.81; S, 17.41. Found: C, 32.55; H, 7.19; P, 15.93; S, 17.95.

Chromatography on Florisil of a 2.7-g. portion of the 5.4 g. of residue in the distillation flask afforded in the ether eluate an additional 0.72 g. of O,O-diethyl S-methyl phosphorothioate, $n^{25}\mathrm{D}$ 1.4582, bringing the total yield to 80%. In acetone there was eluted a brownish liquid of undetermined structure, 0.80 g. equivalent to 4.6 g. total yield, $n^{25}\mathrm{D}$ 1.4676.

Anal. Found: C, 39.01; H, 7.15; P, 13.62; S, 10.90.

Reaction of Methyl Phenyl Disulfide with TEP.—When methyl phenyl disulfide (15.6 g., 0.10 mole) was added to TEP (16.6 g., 0.10 mole) containing hydroquinone (220 mg., 2.0 mmoles) the reaction mixture warmed spontaneously until the flask became too hot to touch. The reaction mixture was heated under reflux for 9 hours and then distilled through a 4-in. Vigreux column at reduced pressure. First there was collected crude ethyl phenyl sulfide, 11.9 g., 86%, b.p. 60° (1 mm.), $n^{25}\mathrm{D}$ 1.5446, which on redistillation through a Podbielniak whirling band column yielded the analytical sample, b.p. 189°, $n^{25}\mathrm{D}$ 1.5624, m.p. of sulfone 41°; reported[53] b.p. 200°, $n^{22.5}\mathrm{D}$ 1.5662,[39] m.p. of sulfone[45] 41–42°.

Anal. Calcd. for $C_8H_{10}S$: C, 69.51; H, 7.30; S, 23.20. Found: C, 69.49; H, 7.41; S, 23.01.

Continued distillation of the reaction mixture yielded a fraction, 14.9 g., b.p. 62° (1 mm.) to 76° (0.8 mm.), $n^{28}\mathrm{D}$ 1.4700, which on redistillation gave O,O-diethyl S-methyl phosphorothioate,[52] 13.0 g., 71%, b.p. 62° (0.3 mm.), $n^{30}\mathrm{D}$ 1.4570; ν_{liq} 1020, 1163, 1255 cm.$^{-1}$.

Anal. Calcd. for $C_5H_{13}O_3PS$: C, 32.60; H, 7.11; P, 16.82; S, 17.41. Found: C, 33.24; H, 7.41; P, 15.95; S, 16.67.

Reaction of Phenyl 2,4-Dinitrophenyl Disulfide with TEP.—When TEP (4.15 g., 0.025 mole) containing hydroquinone (55 mg., 0.5 mmole) was added to phenyl 2,4-dinitrophenyl disulfide (7.70 g., 0.025 mole) in 10 ml. of xylene, heat was evolved and the reaction flask became too hot to touch. The reaction mixture was maintained at reflux temperature for 2.5 hours, and then the solvent was evaporated at reduced pressure. The dark, semisolid residue, which possessed no detectable odor of TEP, was triturated with several portions of ether leaving yellow crystals of 2,4-dinitrophenyl ethyl sulfide, 4.30 g., 75%, m.p. 112–114°, recrystallized from ethanol to yield the analytical sample, m.p. 114.4–115.2°, reported[47] m.p. 115°.

Anal. Calcd. for $C_8H_8N_2O_4S$: C, 42.10; H, 3.53; N, 12.28; S, 14.05. Found: C, 42.39; H, 3.73; N, 12.31; S, 13.86.

Concentration of the ether solution gave a viscous oil (7.60 g.) from which yellow crystals separated. These were recrystallized from cyclohexane yielding an additional 0.22 g. of 2,4-dinitrophenyl ethyl sulfide. The combined filtrates were concentrated and chromatographed on 30 g. of Florisil prepared in pentane. Elution with cyclohexane gave an additional 0.92 g. of the sulfide, bringing the total yield of 2,4-dinitrophenyl ethyl sulfide to 95%.

The methylene chloride eluates were evaporated and 6.14 g. of the liquid residue (7.38 g.) was distilled through a Podbielniak whirling band column to yield O,O-diethyl S-phenyl phosphorothioate,[46] 2.55 g., 50%, b.p. 95° (1.5 mm.), $n^{25}\mathrm{D}$ 1.5059, showing an infrared spectrum similar to that of the product obtained from the reaction of phenyl disulfide with TEP. Some decomposition occurred during the distillation so that the analytical data for the distillate were not satisfactory. The phosphorothioate was identified by conversion to the S-*p*-chlorobenzylthiuronium salt of O-ethyl S-phenyl phosphorothioate, m.p. 174–176°.

Anal. Calcd. for $C_{16}H_{20}ClN_2O_3PS_2$: C, 45.87; H, 4.81; S, 15.31. Found: C, 46.13; H, 4.87; S, 15.02.

Reaction of Phenyl Pentachlorophenyl Disulfide with TEP.—When TEP (460 mg., 2.77 mmoles) was added to a solution of phenyl pentachlorophenyl disulfide (1.08 g., 2.77 mmoles) and hydroquinone (6 mg., 0.02 mmole) in 10 ml. of dry ether, the yellow color of the solution disappeared and the ether began to boil. The reaction mixture was maintained under reflux for 15 minutes and then allowed to stand overnight at room temperature. The ether was evaporated, leaving an oily liquid from which there separated, in two crops, white needles of pentachlorophenyl ethyl sulfide, 358 mg., 41%, m.p. 51–52°, reported[36] m.p. 42–44°.

Anal. Calcd. for $C_8H_5Cl_5S$: C, 30.95; H, 1.62; Cl, 57.10; S, 10.32. Found: C, 30.88; H, 1.75; Cl, 57.40; S, 10.40.

The remainder of the reaction product was chromatographed on 30 g. of Florisil. Elution with pentane yielded an additional amount of pentachlorophenyl ethyl sulfide, 514 mg., 60%, m.p. 51–52°, bringing the total yield of thioether to the theoretical. Elution of the column with methylene chloride gave O,O-diethyl S-phenyl phosphorothioate,[46] 616 mg., 92%, $n^{25}\mathrm{D}$ 1.5254; ν_{liq} 1024, 1168, 1260 cm.$^{-1}$; characterized by conversion to the S-*p*-chlorobenzylthiuronium salt[25] of O-ethyl S-phenyl phosphorothioate, m.p. 174–176°.

Methyl Trichloromethyl Disulfide.—Trichloromethanesulfenyl chloride (Eastman Kodak Co., 186 g., 1.0 mole) was added to methyl mercaptan (100 g., 2.08 moles) at such a rate that the mercaptan refluxed steadily with the stirred reaction mixture cooled in an ice–water-bath. The addition required 1 hour, after which stirring was continued for 15 minutes at 0° and then for an additional hour with the reaction mixture maintained at reflux by means of a warm water-bath. Distillation of the reaction mixture at reduced pressure gave crude methyl trichloromethyl disulfide, 185 g., b.p. 78–100° (40 mm.), which was shaken with 5% aqueous sodium bicarbonate, dried over magnesium sulfate and stored in the dark in the presence of a trace of hydroquinone. An 80-g. portion of this product was redistilled through a 30-inch Fenske column, giving an orange-colored forerun, 19 g., b.p. 70° (42 mm.), $n^{28}\mathrm{D}$ 1.5946, followed by methyl trichloromethyl disulfide, 58 g., 69%, b.p. 101° (40 mm.), $n^{28}\mathrm{D}$ 1.5668; reported[54] b.p. 77–78° (13 mm.), $n^{15}\mathrm{D}$ 1.575. The product appeared to be contaminated with hydrochloric acid, which was removed by distilling ether from the disulfide until the distillate no longer tested acid with indicator paper, yielding a product with $n^{25}\mathrm{D}$ 1.5724.

Anal. Calcd. for $C_2H_3Cl_3S_2$: C, 12.16; H, 1.53; Cl, 53.84; S, 32.46. Found: C, 12.92; H, 1.80; Cl, 53.33; S, 32.17.

Methyl Phenyl Disulfide.—Methanesulfenyl chloride,[55] b.p. 31° (150 mm.), was prepared by bubbling chlorine into methyl disulfide at −20° until one molar equivalent had been absorbed. This sulfenyl chloride (25 g., 0.30 mole) was added over a period of 1 hour to a stirred solution of thiophenol (33 g., 0.30 mole) in 100 ml. of dry ether at −10° in a nitrogen atmosphere. After addition was complete, stirring was continued for 40 minutes as the reaction mixture was allowed to warm to ambient temperature. The ether was evaporated and the residue distilled at reduced pressure to yield methyl phenyl disulfide, 24 g., b.p. 96° (10 mm.). An ether solution of this product was shaken with 5% aqueous sodium bicarbonate, dried with sodium sulfate and redistilled to yield pure methyl phenyl disulfide, 19.5 g., 42%, b.p. 96° (7 mm.), $n^{25}\mathrm{D}$ 1.6162.

Anal. Calcd. for $C_7H_8S_2$: C, 53.80; H, 5.16; S, 41.05. Found: C, 53.61; H, 5.17; S, 41.43.

Phenyl 2,4-Dinitrophenyl Disulfide.—A solution of 2,4-dinitrobenzenesulfenyl chloride[56] was prepared by bubbling chlorine into a suspension of 2,4-dinitrophenyl disulfide (50 g., 0.125 mole) in

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(50) H. Adkins and Q. E. Thompson, *J. Am. Chem. Soc.*, **71**, 2242 (1949).

(51) B. Pawlewski, *Chem. Ber.*, **37**, 158 (1904).

(52) M. I. Kabachnik, S. T. Ioffe and T. A. Mastryukova, *Zhur. Obshchei Khim.*, **25**, 684 (1955).

(53) O. Stadler, *Chem. Ber.*, **17**, 2075 (1884).

(54) H. J. Backer and E. Westerhuis, *Rec. trav. chim.*, **21**, 1065 (1952).

(55) H. Brintzinger, K. Pfannstiel, H. Koddebusch and K. E. Kling, *Chem. Ber.*, **83**, 87 (1950).

(56) M. H. Hubacher in "Organic Syntheses," Coll. Vol. II, A. H. Blatt, ed., John Wiley and Sons, Inc., New York, N. Y., 2nd Ed., 1943, p. 455.

300 ml. of nitrobenzene at 120° for 3.5 hours until the disulfide dissolved completely. A stream of dry nitrogen was passed through the resulting bright red solution for 1 hour to remove unreacted chlorine. The solution was stirred at 100° while thiophenol (27.5 g., 0.25 mole) was added in portions over the period of 15 minutes. Dry nitrogen was bubbled through the hot stirred reaction mixture until the effluent gas no longer was acidic. The solvent was evaporated at reduced pressure and the residual product recrystallized from alcohol to yield phenyl 2,4-dinitrophenyl disulfide, 62 g., 80%, m.p. 86–87°, reported[57] m.p. 86–87°.

Phenyl Pentachlorophenyl Disulfide.—When chlorine was bubbled into a suspension of pentachlorophenyl disulfide (8.24 g., 0.015 mole) in 100 ml. of refluxing carbon tetrachloride for 1.5 hours, no reaction was observed. Fuming sulfuric acid (3 drops) was added as a catalyst,[58] whereupon the disulfide dissolved within 10 minutes. The solution was maintained at reflux for another 10 minutes and then allowed to cool. A 5-ml. test portion of the reaction mixture was removed and evaporated, leaving yellow needles of what presumably was pentachlorobenzenesulfenyl chloride, m.p. 99–101°. To the remainder of the reaction mixture a solution of thiophenol (3.08 g., 0.028 mole) in 10 ml. of carbon tetrachloride was added with stirring over a period of 20 minutes. The solvent was evaporated under reduced pressure and the residue triturated with ether, leaving recovered pentachlorophenyl disulfide, 5.43 g., 65%, m.p. 233–235°. The ether extract was concentrated to yield yellow cubes of phenyl pentachlorophenyl disulfide, 2.26 g., 21%, m.p. 93–94°.

Anal. Calcd. for $C_{12}H_5Cl_5S_2$: C, 36.90; H, 1.29; S, 16.42. Found: C, 36.60; H, 1.52; S, 16.42.

An attempt to prepare phenyl pentachlorophenyl disulfide by the reaction of benzenesulfenyl chloride[59] with pentachlorothiophenol gave only the symmetrical products, phenyl disulfide and pentachlorophenyl disulfide in 67 and 96% yields, respectively. Similarly, the attempted preparation of phenyl *p*-anisyl disulfide, either by reaction of benzenesulfenyl chloride with *p*-methoxythiophenol or of *p*-methoxybenzenesulfenyl chloride with thiophenol, yielded only the corresponding symmetrical disulfides.

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(57) I. Danielsson, J. E. Christian and G. L. Jenkins, *J. Am. Pharm Assoc., Sci. Ed.*, **36**, 261 (1947).

(58) N. Kharasch, G. I. Gleason and C. M. Buess, *J. Am. Chem. Soc.*, **72**, 1796 (1950).

(59) W. E. Truce, H. E. Hill and M. M. Boudakian, *ibid.*, **78**, 2760 (1956).

[CONTRIBUTION FROM THE BEN MAY LABORATORY FOR CANCER RESEARCH, UNIVERSITY OF CHICAGO, CHICAGO 37, ILL.]

Phosphonic Acids. VII. The Reaction of Sodium Diethyl Phosphonate with Organic Disulfides[1,2]

BY RONALD G. HARVEY, HERBERT I. JACOBSON AND ELWOOD V. JENSEN

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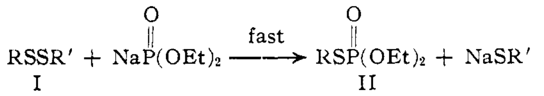
Sodium diethyl phosphonate in tetrahydrofuran solution reacts rapidly with organic disulfides to produce a phosphorothioate ester and a sodium mercaptide. From ethyl disulfide and β-acetamidoethyl disulfide the respective products are O,O,S-triethyl phosphorothioate and O,O-diethyl S-β-acetamidoethyl phosphorothioate. Reaction with phenyl ethyl disulfide takes place in one direction only to form O,O,S-triethyl phosphorothioate and sodium thiophenoxide. Unless separated immediately, the phosphorothioate and sodium mercaptide produced interact further to form a sodium dialkyl phosphorothioate and a thioether. Sodium ethyl mercaptide is an effective reagent for the monodealkylation of phosphate, phosphonate and phosphorothioate esters; with the latter substances a carbon–oxygen bond is cleaved in preference to a simple carbon–sulfur bond.

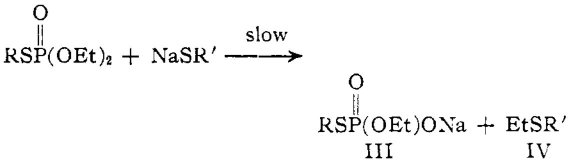
In the previous paper,[1] evidence was presented that the reaction of trialkyl phosphites with organic disulfides takes place through an ionic mechanism of the same valency expansion type by which trivalent phosphorus esters react with a large variety of chemical groupings susceptible to nucleophilic displacement. It seemed of interest to inquire whether another type of nucleophilic phosphorus reagent, sodium diethyl phosphonate, can likewise cleave the disulfide linkage with the establishment of a sulfur to phosphorus bond. It was found that the reaction of disulfides with sodium diethyl phosphonate, described independently by Michalski and co-workers,[3] takes place extremely rapidly at low temperature and provides a convenient synthesis of phosphorothioate esters.

Results and Discussion

When a solution of sodium diethyl phosphonate in tetrahydrofuran is added to a tetrahydrofuran solution of ethyl disulfide at 0°, there is an instantaneous precipitation of sodium ethyl mercaptide (eq. 1). If this solid is separated within a few minutes, distillation of the supernatant solution affords O,O,S-triethyl phosphorothioate (IIa) in 74% yield. If the reaction products are allowed to remain in contact, a secondary reaction takes place (eq. 2) and eventually the precipitate consists entirely of sodium O,S-diethyl phosphorothioate (IIIa).



$$\underset{\text{I}}{\mathrm{RSSR'}} + \mathrm{Na\overset{O}{\overset{\|}{P}}(OEt)_2} \xrightarrow{\text{fast}} \underset{\text{II}}{\mathrm{RS\overset{O}{\overset{\|}{P}}(OEt)_2}} + \mathrm{NaSR'} \quad (1)$$



$$\mathrm{RS\overset{O}{\overset{\|}{P}}(OEt)_2} + \mathrm{NaSR'} \xrightarrow{\text{slow}} \underset{\text{III}}{\mathrm{RS\overset{O}{\overset{\|}{P}}(OEt)ONa}} + \underset{\text{IV}}{\mathrm{EtSR'}} \quad (2)$$

a, $R = R' = C_2H_5$

b, $R = R' = CH_3CONHC_2H_4$

c, $R = C_2H_5$, $R' = C_6H_5$

$(CH_3CONHC_2H_4)_2S$ V

In similar fashion, β-acetamidoethyl disulfide (Ib) reacts instantaneously with sodium diethyl phosphonate in tetrahydrofuran at room temperature or below to give a 44% yield of O,O-diethyl S-(β-acetamidoethyl)-phosphorothioate[4] (IIb). On prolonged contact a secondary reaction takes place, but in this case the only substance which could be isolated from the rather intractable reaction mixture was a 14% yield of β-acetamidoethyl sulfide (V).

With the unsymmetrical compound, ethyl phenyl disulfide (Ic), reaction with sodium diethyl phosphonate was found to take place in one direction only to give a 71% yield of O,O,S-triethyl phosphorothioate (IIc = IIa) and a precipitate from which there was obtained a 65% yield of thiophenol. No products resulting from cleavage of the disulfide linkage in the opposite direction

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(1) Paper VI, R. G. Harvey, H. I. Jacobson and E. V. Jensen, *J. Am. Chem. Soc.*, **85**, 1618 (1963).

(2) This paper is taken from the Ph.D. dissertation of R. G. Harvey, University of Chicago, 1960, and was presented in part before the 134th National Meeting of the American Chemical Society, Chicago, Ill., 1958. The investigation was supported in part by a grant from the National Institutes of Health, U. S. Public Health Service (RG-3053).

(3) J. Michalski, J. Wieczorkowski, J. Wasiak and B. Pliszka, *Roczniki Chem.*, **33**, 247 (1959); *Chem. Abstr.*, **53**, 17884 (1959).

(4) This product is the phosphorothioate ester of N-acetylcysteamine, a substance which possesses the structure of the reactive portion of coenzyme-A, and which will substitute for the complete coenzyme in certain enzymatic reactions. Preliminary tests indicate that IIb is a moderately toxic substance in mice (LD_{50} 23 mg./kg.) causing convulsions and labored respiration.