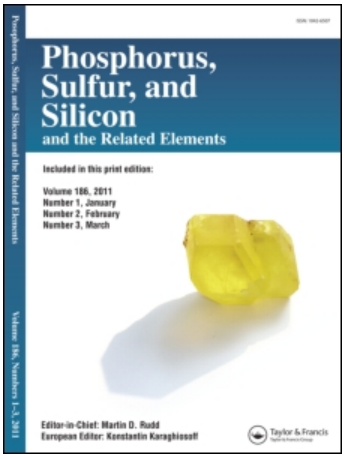

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CHLOROMETHYLATION OF *O,O*-DIETHYL PHOSPHORODITHIOIC ACID USING FORMALDEHYDE AND CHLORINATING REAGENTS

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CHLOROMETHYLATION OF *O,O*-DIETHYL PHOSPHORODITHIOIC ACID USING FORMALDEHYDE AND CHLORINATING REAGENTS

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A chloromethylation of *O,O*-diethyl phosphorodithioic acid (**1**) was effected by a two step procedure. The first step involved the preparation of the hydroxymethyl derivative by reaction of **1** with formaldehyde and hydrogen chloride to give **3**. The hydroxymethyl intermediate **3** was converted to *S*-(chloromethyl) *O,O*-diethyl phosphorodithioate **2** in high yields by using PCl_5 or PCl_3 in combination with $ZnCl_2$ and/or HCl catalyst.

INTRODUCTION

Several methods have been described in the literature for chloromethylating substituted thiols For example, Bohme and co-workers reported the chloromethylation of alkyl and aromatic thiols using formaledehyde and hydrogen chloride, Eq. 1.[1] Dolman *et al.* reported the production of a

$$RSH + CH_2{=}O \xrightarrow{HCl} RSCH_2Cl + (RS)_2CH_2 \quad (1)$$

where R = alkyl or aryl

(hydroxymethyl)thio aromatic by reacting equivalent amounts of the aromatic thiol and formaldehyde in the presence of a catalytic amount of sodium methoxide.[2] The subsequent treatment of the hydroxymethyl derivative with thionyl chloride afforded the corresponding (chloromethyl) thio aromatic, Eq. 2. More recently, several groups of workers have described the preparation of (chloromethyl)thio heteroaromatic compounds by reacting the corresponding thiols with dihalomethanes.[3,4] This method was improved by the

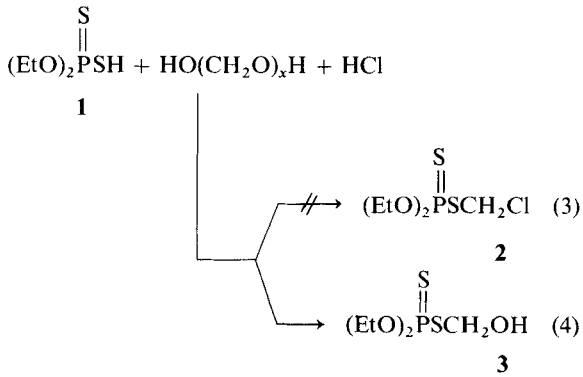
$$ArSH + CH_2{=}O \xrightarrow{NaOCH_3} ArSCH_2OH \xrightarrow{SOCl_2} ArSCH_2Cl \quad (2)$$

use of the phase transfer catalyst, benzyltriethylammonium bromide.[5] The chloromethylation of 2-mercaptobenzothiazole by reaction with formaldehyde to produce the hydroxymethyl intermediate followed by reaction with phosphorus trichloride has been shown to occur at the nitrogen atom[6] and not the sulfhydryl group as originally reported.[7]

The chloromethylation of phosphorodithioic acids which might be expected to be similar to chloromethylating thiols has received little attention in the literature. The only reported method involves reaction of metal salts of phosphorodithioic acids with bromochloromethane.[8] We would like to report a new method of chloromethylation of *O,O*-diethyl phosphorodithioic acid, **1**, to produce *S*-chloromethyl *O,O*-diethyl phosphorodithioate, **2**, where the application of reported methods of chloromethylating thiols have failed.

RESULTS AND DISCUSSION

Many of the literature methods for chloromethylation were found to be unsuccessful when applied to **1**. The reaction of **1** with formaldehyde[9] and



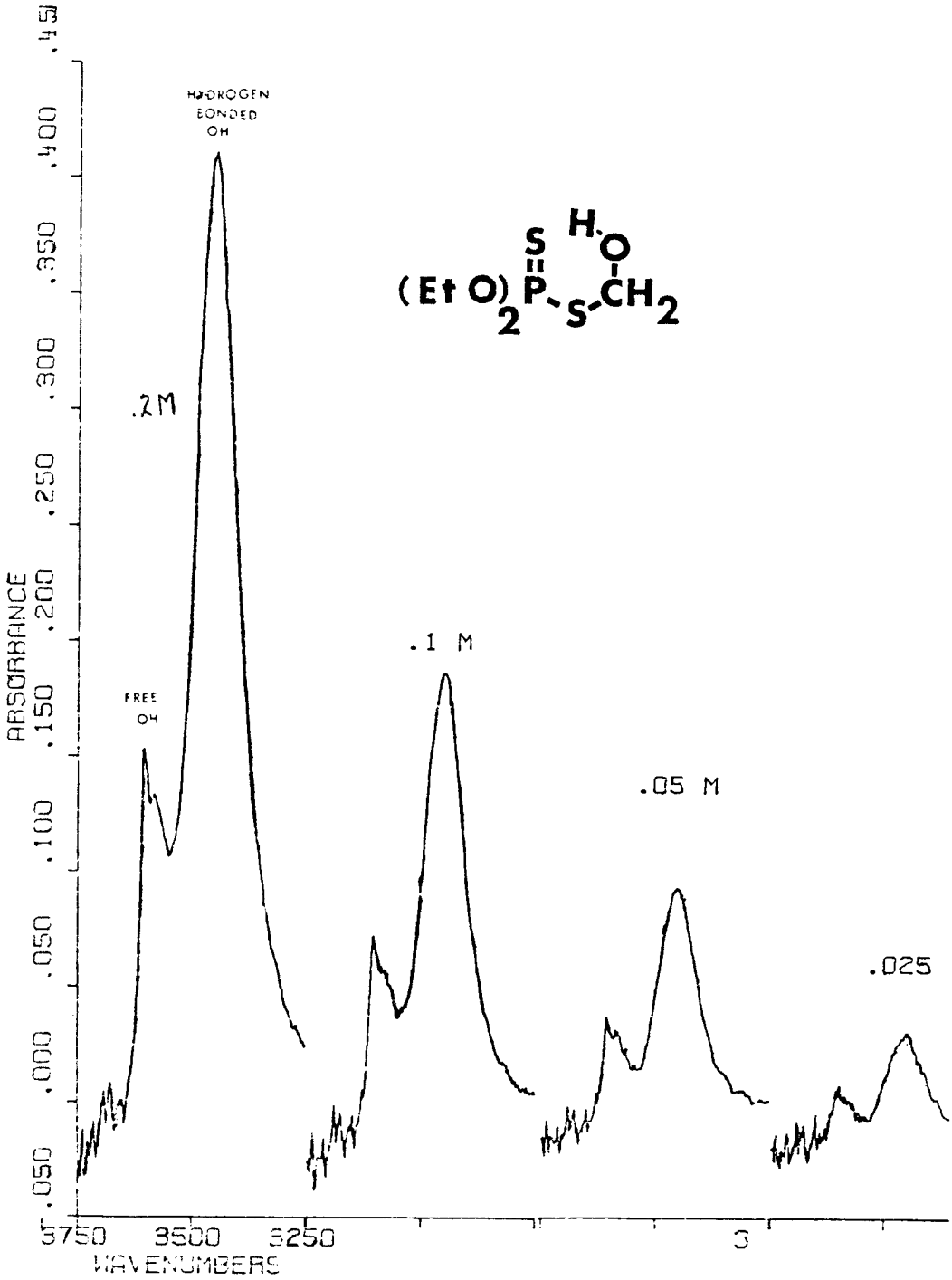


FIGURE 1 Infrared dilution study.

hydrogen chloride did not yield the expected chloromethylated product, **2**, Eq. 3; but instead gave *O,O*-diethyl *S*-(hydroxymethyl) phosphorodithioate, **3**, Eq. 4.[10] The use of anhydrous $ZnCl_2$ to effect chloromethylation of **3** was likewise not successful, resulting in dehydration to *bis*(*O,O*-diethyldithiophosphoromethyl)ether, **4**, in almost quantitative yield, Eq. 5.

$$3 + ZnCl_2 \longrightarrow \underset{\mathbf{4}}{\left[(EtO_2PSCH_2\right]_2O} \quad (5)$$

The structure of the hydroxymethyl derivative, **3**, was difficult to establish because of its instability. Attempts at purifying **3** by vacuum distillation or preparative thick layer chromatography resulted in the reversion to starting dithioic acid, **1**. An infrared study of structure **3** revealed a significant amount of intramolecular hydrogen bonding. The IR spectra are summarized in Figure 1. The ratio of the free-OH absorbance to the hydrogen bonded absorbance remains relatively constant (ca. 0.45) as a sample of **3** is diluted from 0.20 M to 0.025 M indicating a compound that contains a significant amount of intramolecular hydrogen bonding.[11] The structure of **3** was established by converting it to *O,O*-diethyl *S*-(methoxymethyl) phosphorodithiolate, **5**, and *O,O*-diethyl *S*-methyl phosphorodithioate, **6**, in an overall yield of 15% and 67%, respectively, via reaction with diazomethane, Eq. 6. The methoxymethyl derivative, **5**, was also prepared independently by an acid catalyzed reaction of **1** with dimethoxymethane, Eq. 7. The

$$3 + CH_2N_2 \longrightarrow \underset{\mathbf{5}}{(EtO)_2PSCH_2OCH_3} + \underset{\mathbf{6}}{(EtO)_2PSCH_3} \quad (6)$$

spectral properties of **5**, which is easily purified by distillation, were consistent with its structure.

$$1 + (CH_3O)_2CH_2 \xrightarrow[100\%]{H^+} 5 \quad (7)$$

The conversion of **3** to the desired chloromethyl derivative **2** was accomplished in excellent yield by reaction with phosphorus pentachloride in a dry, inert solvent, e.g., diethyl ether (67%); hexane (88%), toluene (96%), or carbon tetrachloride (99%), Eq. 8. Attempts at using $POCl_3$ as the chloromethylating reagent were not successful and resulted only in dehydration of **3** to **4**.

$$3 + PCl_5 \longrightarrow (EtO)_2PSCH_2Cl + POCl_3 + HCl \quad (8)$$

Alternatively, the conversion of **3** to **2** has been achieved by reacting **3** with phosphorus trichloride to produce a mixture of phosphite esters. After several hours, anhydrous $ZnCl_2$ was added to the mixture, Eq. 9. The overall yield of **2** from **3** was

$$3 \xrightarrow{PCl_3} ((EtO)_2PSCH_2O)_nPCl_{3-n} \xrightarrow[HCl]{ZnCl_2} 2$$

where n = 1, 2, and 3 (9)

about 70%. Other Lewis acids used as catalysts, e.g., $SnCl_4 \cdot 5H_2O$ and $SbCl_5$ were not as effective. The conversion of the hydroxymethyl derivative **3** to the acetoxy derivative **7** by reaction with acetyl chloride in the presence of a catalytic amount of $ZnCl_2$ was a high yield reaction (90%), Eq. 10. Further conversion of **7** to **2** was effected by reaction with hydrogen chloride in the presence of anhydrous $ZnCl_2$ in 55% yield.

$$3 + CH_3CCl \xrightarrow[CCl_4]{ZnCl_2} \underset{\mathbf{7}}{(EtO)_2PSCH_2OCCH_3} \xrightarrow[HCl]{ZnCl_2} 2 \quad (10)$$

A generalized mechanism for normal chloromethylation chemistry is shown in Scheme I.[12] The first step involves the addition of RSH to the activated formaldehyde to give $RSCH_2OH$, Eq. 11. Further reaction of $RSCH_2OH$ with HCl would effect chloromethylation by either a SN1 or SN2 type process Eq. (12). The success of the chloromethylation reaction appears to be dependent on the structure of R.

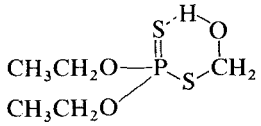
$$RSH + CH_2{=}\overset{+}{O}H \rightleftharpoons RSCH_2OH + H^+ \quad (11)$$

$$RSCH_2OH + HCl \longrightarrow \underset{\mathbf{8}}{RSCH_2\overset{+}{\underset{|}{O}}H} \xrightarrow{Cl^-} RSCH_2Cl + H_2O \quad (12)$$

where R = aryl, alkyl, or $(EtO)_2P(S)$—

Scheme I

When R is phenyl or alkyl the chloromethylation proceeds without difficulty as reported by Bohme; however, when R = $(EtO)_2P(S)$— the reaction does not go beyond the hydroxymethyl intermediate **8**. One possible explanation for such behavior arises from the strong intramolecular hydrogen bonding (4.3 Kcal/mol, from infrared) observed in **3** that would not be present when R = alkyl or phenyl, e.g., **9**.[13] Using PCl_5, PCl_3, or acetyl chloride in the reaction in effect removes the hydrogen bonding in the hydroxymethyl intermediate, **8**, by replacing the hydroxyl group with $OPCl_4$; $OPCl_2$; or $OCOCH_3$ and restores the ability to complete the chloromethylation processes.



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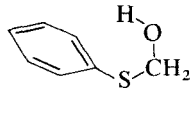

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In summary, chloromethylation of *O,O*-diethyl phosphorodithioic acid, **1**, has been effected in excellent yield by initial conversion of **1** to **3** followed by the reaction of **3** with PCl_5 or PCl_3, along with $ZnCl_2$/HCl catalysts to yield **2**. Alternatively, **3** can be converted to the acetoxymethyl derivative **7** and subsequently converted to **2** in good yield by $ZnCl_2$/HCl.

EXPERIMENTAL

The boiling points are reported uncorrected. Infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer. The ^1H NMR spectra were recorded on a Hitachi Perkin-Elmer R-24B spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded at 70 eV. Gas chromatography was carried out on a Varian 3700 using a 3 meter 8% XE-60 on chrom-W column. The infrared hydrogen bonding studies on **3** were carried out on serial dilutions of a 0.200 M stock solution of **3** in carbon tetrachloride. These spectra were recorded on a Nicolet 7199 Fourier Transform Infared Spectrometer. The samples were contained by a sealed liquid cell. Elemental analyses were carried out by the analytical department at Diamond Shamrock.

O,O - Diethyl S - (hydroxymethyl) phosphorodithioate, **3**. Anhydrous hydrogen chloride was bubbled through a cooled (0°C) ethereal solution (500 mL) of *O-O*-diethyl phosphorodithioic acid, **1**, (45.34 g, 0.243 mole)[7] and paraformaldehyde (7.31 g) for 2–2.5 hours. The ether was then removed by rotary evaporation to give 52.31 g of yellow oil. An ^1H NMR spectrum of this oil showed the desired hydroxymethyl compound in about 98% (mole %) purity. The ^1H NMR and IR supported the proposed structure: ^1H NMR $\delta(CDCl_3)$: 5.13 (2H, d, J = 23 Hz OCH_2S); 4.18 (4H, m, OCH_2); 3.78 (1H, s, OH); 1.37 (6H, t, J = 7Hz. CH_3); IR (*neat*): 3340 (*OH stretching*), 1470, 1440, 1385, 1300, 1160, 1090, 1030, 960, 828, and 795 cm^{-1}. The oil also contained about 2% of *bis(O,O*-diethyldithiophosphoromethyl)ether, **4**; Kugelrohr vacuum distillation caused decomposition. No **2** was detected under these conditions (detectable limits <0.5%).

Reaction of O,O-Diethyl S-(hydroxymethyl) phosphorodithioate, **3**, *with Diazomethane*. An ethereal solution of diazomethane was added to a cooled (0°C) solution of 5.4 g (0.025 mole) of **3** in 200 mL of ether. After 15 minutes, the solution was washed with aqueous Na_2CO_3, water, and then dried over Na_2SO_4. The ether was removed by rotary evaporation to yield 3.3 g of light yellow oil. The ^1H NMR spectrum showed that the oil was 67% *O,O*-diethyl *S*-methyl phosphorodithioate, **6**, and 15.5% *O,O*-diethyl *S*-methoxymethyl) phosphorodithioate, **5**. These components were separated and isolated by preparative liquid chromatography (EM column; Lobar, size B/1 : 1 hexane-CH_2Cl_2/20 mL per min). The spectral characteristics of the isolated components were consistent with those expected for the proposed structures. The spectral characteristics of **5** were identical to those obtained for **5** prepared by another route (see below). TLC (silica gel/1:1 hexane-methylene chloride/I_2; UV) of the two components gave R_f values identical to those of authentic samples of **5** and **6**.

O,O,-Diethyl S-(methoxymethyl) phosphorodithioate, **5**. *O,O*-Diethyl phosphorodithioic acid, **1**, 21.86 g (0.1174 mole) was added to 250 mL of dimethoxymethane (Aldrich Chemical Co., 97%) and the solution sparged with HCl for 1.75 h. The temperature of the solution rose to a maximum of 30°C and was approximately 8°C when the HCl addition was discontinued. The reaction was complete at this point (as determined by an ^1H NMR spectrum taken on a small aliquot). The solvent was removed by rotary evaporation and the residue dissolved in ether. The ether solution was washed twice with 20 mL portions of water, once with 20 mL of 15% Na_2CO_3, and once again with 20 mL of water. The ether solution was dried over anhydrous magnesium sulfate and the solvent removed by rotary evaporation to yield 22.8 g of an amber oil which, upon distillation at 103°C and 0.1 torr, using a 6″ vigreux column gave 17.4 g (64%) of *O,O*-diethyl *S*-(methoxymethyl) phosphorodithioate. ^1H NMR δ ($CDCl_3$): 5.17 (2H, d, J = 20 Hz); 4.23 (4H, m); 3.45 (3H, s); 1.38 (6H, t, J = 7 Hz). IR (neat): 2915, 2882, 1439, 1384, 1302, 1183, 1093, 1020, 957, 830, and 794 cm^{-1}. Anal. Calcd for $C_6H_{15}O_3PS_2$: C, 31.3; H, 6.6. Found: C, 31.1; H, 6.8. No **2** was produced under these conditions.

Bis(O,O-diethyldithiophosphoromethyl)ether, **4**. *O,O*-Diethyl *S*-(hydroxymethyl) phosphorodithioate, **3**, (12 g of 93% purity 0.0516 mole) was dissolved in 180 mL of carbon tetrachloride. Anhydrous zinc chloride (7.56 g, 0.0555 mole) was added and the mixture stirred at room temperature for 4 hours. More $ZnCl_2$ (5.76 g, 0.0423 mole) was added and stirring continued for 25 h. The reaction liquid was decanted from the reaction solids and the solids washed with CCl_4. The CCl_4 washing was added to the reaction liquid. The CCl_4 solution was then washed once with 50 mL of H_2O, once with 50 mL of 15% Na_2CO_3, and again with 50 mL of water. The carbon tetrachloride phase was dried over anhydrous sodium sulfate and the solvent removed by rotary evaporation and vacuum pump to yield 5.9 g of an amber oil, ^1H NMR δ ($CDCl_3$); 5.27 (4H, d, J = 20.4 Hz); 4.23 (8H, m); 1.40 (12H, t); IR (neat): 2941 (CH stretching), 1468, 1437, 1384, 1295, 1235, 1157, 1070, 1005, 957, 903 and 791 cm^{-1}. Anal. Calcd for $C_{10}H_{24}O_5P_2S_4$: C, 29.0; H, 5.8.

Found: C, 27.5; H, 5.5. The purity of the product **4** was 79% by ^{1}H NMR indicating a 43.5% overall yield.

General preparation of S-chloromethyl O,O-diethyl phosphorodithioate, **2**, *using* PCl_5. To a stirred solution of 0.935 g (0.0039 mole) of hydroxymethyl derivative, **3**, in 100 mL of solvent was added 1.08 g (0.0052 mole) of PCl_5 (MC/B). The solution was stirred at room temperature 4 hours. After washing the reaction mixture successively with water and saturated aqueous $NaHCO_3$, the organic layer was dried over Na_2SO_4 and the solvent removed by rotary evaporation and the residue distilled to produce the product as a colorless oil, ^{1}H NMR δ ($CDCl_3$): 4.92 (2H, d, J = 20 Hz, SCH_2); 4.03 (4H, m, OCH_2); 1.40 (6H, t, J = 7 Hz, CH_3); IR (neat): 2940 (CH stretching), 1465, 1435, 1383, 1235, 1160, 1095, 1017, 955, 828, 848, 800, and 727 cm^{-1}; ^{13}C NMR δ ($CDCl_3$): 64.20 (d, J = 5.5 Hz, C-O-P); 47.39 (d, J = 4.9 Hz, C-S-P); 15.55 (d, J = 8.5 Hz, methyl of ethoxy split by phosphorus).

Preparation of 2 using PCl_3 *and* $ZnCl_2/HCl$ *catalysts.* To a stirring solution of 1.00 g (4.63 mmol) of 90% *O,O*-diethyl-*S*-(hydroxymethyl)phosphorodithioate, **3**, in 100 mL of anhydrous diethyl ether was added 0.64 g (4.63 mmol) of PCl_3. After stirring at room temperature 4 hours, 0.01 g (0.07 mmol) of $ZnCl_2$ was added. After 18 hours the reaction mixture was poured into 20 mL of H_2O. The ether layer was separated, dried (Na_2SO_4), and concentrated to give 1.210 g of a colorless oil which assayed 72% **2** by quantitative ^{1}H NMR analysis. A yield of 80% of **2** was obtained.

S-(acetoxymethyl) O,O-diethyl phosphorodithioate, **7**. *O,O*,-Diethyl *S*-(hydroxymethyl) phosphorodithoate, **3**, 17.2 g of 93% purity (0.074 mole), was dissolved in 310 mL of anhydrous ether and 8.7 g (0.111 mole) of acetyl chloride added with stirring, followed by a catalytic amount of $ZnCl_2$ (0.1 g). The reaction mixture was stirred at room temperature for 3 hours. The volatiles were removed by rotary evaporation to yield 20.31 g of oil. The oil was dissolved in ether, washed twice with 20 mL portions of water, once with 20 mL of 5% $NaHCO_3$ solution, and again with 20 mL of water. The ether solution was dried over anhydrous $MgSO_4$ and concentrated by rotary evaporation. The residual oil was dried (10^{-3} torr) to constant weight. A total of 18.95 g of pale yellow oil assaying 90%, **7**, by glc was obtained. Fractional distillation using a 6" Vigreaux column yielded 8.5 g (45% yield) of an oil assaying 98%, **7**, by glc, (bp 100°C/<.1 mm). The spectral data (IR and ^{1}H NMR) were consistent with *S*-(acetoxymethyl) *O,O*-diethyl phosphorodithioate, **7**, ^{1}H NMR δ ($CDCl_3$): 5.4 (2H, d, J = 22 Hz); 4.23 (4H, m); 2.1 (3H, s); 1.40 (6H, t); IR (neat): 2907 (CH stretching), 1754 (C = 0 stretching), 1435, 1414, 1383, 1364, 1312, 1256, 1162, 1096, 1020, 962, 829, and 800 cm^{-1}. Anal. Calcd for $C_7H_{15}O_4PS_2$: C, 32.6; H, 5.9. Found: C, 32.6; H, 6.0.

S-chloromethyl O,O-diethylphosphorodithioate, **2**, *from S-acetoxymethyl O,O-diethyl phosphorodithioate*, **7**. Acetyl chloride (0.5 g, 0.0065 mole) was added to a solution of 0.5 g (0.002 mole) of **3** in 50 mL of ether. Approximately 1 g (0.007 mole) of anhydrous $ZnCl_2$ was added and the mixture stirred 2 hours. Gaseous hydrogen chloride was bubbled through the mixture for 6 hours. The HCl saturated mixture was allowed to stand at room temperature for four days. It was then poured slowly into cold water and the ether solution washed successively with water, saturated $NaHCO_3$ solution, and saturated NaCl solution. The ether extract was dried and the volatiles removed by rotary evaporation to yield 0.37 g of a yellow oil. The oil, assayed by quantitative ^{1}H NMR (external standard method), showed 55% conversion to **2**.

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9. In its polymeric form as paraformaldehyde or *s*-trioxane.
10. Very pure material can be prepared by the indicated reaction, eq. 4., using freshly prepared *O,O*-diethyl phosphorodithioic acid obtained from acidifying freshly recrystallized, commercially available ammonium *O,O*-diethylphosphorodithioate.
11. In a sample which exhibits only intermolecular hydrogen bonding, e.g., ethanol, the ratio of the free OH absorbance to the hydrogen-bonded absorbance changes drastically over the concentration range 0.20 M to 0.025 M.
12. L. I. Belen'kii, Yu. B. Vol'kenshtein, and I. B. Karmanova, *Russ. Chem. Rev.*, **46**, 891 (1977).
13. The intramolecular bonding could also result between the hydroxyl and the oxygen atoms.