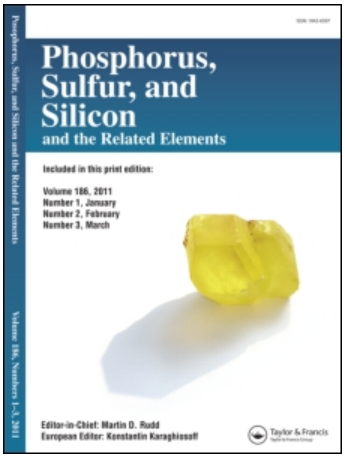

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS AND HYDROLYTIC STABILITY OF SOME NEW PHOSPHONODITHIOITE, PHOSPHONODITHIOATE AND PHOSPHONOTRITHIOATE ESTERS

Sangha Kim[a]; John L. Mimikakis[a]; D. Max Roundhill[a]
[a] Contribution from the Department of Chemistry, Tulane University, New Orleans, LA, U.S.A

To cite this Article Kim, Sangha , Mimikakis, John L. and Roundhill, D. Max(1992) 'SYNTHESIS AND HYDROLYTIC STABILITY OF SOME NEW PHOSPHONODITHIOITE, PHOSPHONODITHIOATE AND PHOSPHONOTRITHIOATE ESTERS', Phosphorus, Sulfur, and Silicon and the Related Elements, 68: 1, 119 — 128
To link to this Article: DOI: 10.1080/10426509208038379
URL: http://dx.doi.org/10.1080/10426509208038379

Phosphorus, Sulfur, and Silicon, 1992, Vol. 68, pp. 119–128
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SYNTHESIS AND HYDROLYTIC STABILITY OF SOME NEW PHOSPHONODITHIOITE, PHOSPHONODITHIOATE AND PHOSPHONOTRITHIOATE ESTERS

SANGHA KIM, JOHN L. MIMIKAKIS and D. MAX ROUNDHILL*
Contribution from the Department of Chemistry, Tulane University, New Orleans, LA 70118, U.S.A.

(Received September 12, 1991; in final form November 14, 1991)

The compounds $RP(SCH_2CH_2CO_2CH_2CH_3)_2$ (R = $(CH_3)_3C$, C_6H_5) have been prepared from $RPCl_2$ and $HSCH_2CH_2CO_2CH_2CH_3$ and base. The compounds react with hydrogen peroxide and with sulfur to give $RP(O)(SCH_2CH_2CO_2CH_2CH_3)_2$ and $RP(S)(SCH_2CH_2CO_2CH_2CH_3)_2$ respectively. The 5-membered ring compound $C_6H_5\overline{P(SCH(CO_2CH_2CH_3)CH(CO_2CH_2CH_3)S)}$ has been synthesized from $C_6H_5PCl_2$ and diethyl-2,3-dimercaptosuccinic acid and base. The compound reacts with hydrogen peroxide and with sulfur to give $C_6H_5\overline{P(O)(SCH(CO_2CH_2CH_3)CH(CO_2CH_2CH_3)S)}$ and $C_6H_5\overline{P(S)(SCH(CO_2CH_2CH_3)CH(CO_2CH_2CH_3)S)}$ respectively. Reacting $C_6H_5PCl_2$ with one equivalent of $HSCH_2CH_2CO_2CH_2CH_3$ and base gives $C_6H_5PCl(SCH_2CH_2CO_2CH_2CH_3)$, which undergoes hydrolysis to give $C_6H_5PH(O)(SCH_2CH_2CO_2CH_2CH_3)$. Except for $C_6H_5\overline{P(SCH(CO_2CH_2CH_3)CH(CO_2CH_2CH_3)S)}$ and $C_6H_5PH(O)(SCH_2CH_2CO_2CH_2CH_3)$, the compounds do not undergo significant hydrolytic cleavage of the P—S bond. The hydrolysis of $C_6H_5\overline{P(SCH(CO_2CH_2CH_3)CH(CO_2CH_2CH_3)S)}$ likely proceeds via $C_6H_5PH(O)(SCH(CO_2CH_2CH_3)CH(CO_2CH_2CH_3)SH)$. The increased hydrolysis rate of $C_6H_5PH(O)(SCH_2CH_2CO_2CH_2CH_3)$ is possibly due to hydrogen bonding between water and the PH(O) functionality.

Key words: Phosphonodithioite; phosphonodithioate; phosphonotrithioate; hydrogen bonding; NMR spectra.

INTRODUCTION

Compounds having phosphorus-sulfur bonds are of interest because of their pharmacological effects on mammalian systems. Two such effects are their toxicity and their function as radioprotectants. A compound which shows high toxicity is *O*-ethyl-S-[2-(diisopropylamino)ethyl] methylphosphonothioate, abbreviated as VX.[1] For radioprotection applications, the compounds *S*-2-(3-aminopropylamino)ethylphosphorothioic acid, abbreviated as ethiofos or WR-2721, has been found to be particularly effective.[2] For each compound, the cleavage of a P—S bond plays an important role. For the compound VX and similar phosphonothioates, oxidative hydrolysis of the P—S bond represents a detoxification route.[1,3] By contrast, the function of WR-2721 as a radioprotective agent involves it becoming dephosphorylated by alkaline phosphatase to the active sulfhydryl protector 2-(3-aminopropylamino)-ethanethiol.[4] In general, however, the hydrolysis of P—S bonds is slow, even under solution conditions of high basicity.[5]

For phosphites, phosphates, and phosphonates which have P—O rather than P—S bonds, the hydrolysis reactions are more rapid.[6] This situation appears to be particularly prevalent for the cyclic analogs, since such alkyl phosphonites are quite

unstable to hydrolytic conditions.[7] This increased instability has been ascribed to the strain induced by the presence of a ring incorporating a 3-coordinate phosphorus.

We have now prepared a series of new phosphonodithioite, phosphonodithioate and phosphonotrithioate esters, including examples which have the analogous cyclic and acyclic structures. These compounds were chosen as a means to evaluate the effect of both the coordination number at phosphorus, and the presence of a ring structure, on the ease of hydrolysis of the P—S bond.

RESULTS AND DISCUSSION

Synthesis

The linear phosphonodithioites have been prepared by reacting *tert*-$(CH_3)_3CPCl_2$ or $C_6H_5PCl_2$ with ethyl-3-mercaptopropanoate. The reactions are carried out in the presence of triethylamine as base, and the products isolated as colorless viscous liquids (Equation 1). The corresponding oxides have been prepared by treating the

$$RPCl_2 + 2\ HSCH_2CH_2CO_2CH_2CH_3 \rightarrow RP(SCH_2CH_2CO_2CH_2CH_3)_2 + 2\ HCl \qquad (1)$$

$$(R = (CH_3)_3C(\mathbf{1}),\quad C_6H_5(\mathbf{3}))$$

tricoordinate compounds with either air or hydrogen peroxide (Equation 2). The linear

$$RP(SCH_2CH_2CO_2CH_2CH_3)_2 + H_2O_2 \rightarrow RP(O)(SCH_2CH_2CO_2CH_2CH_3)_2 + H_2O \qquad (2)$$

$$(R = (CH_3)_3C(\mathbf{2}),\quad C_6H_5(\mathbf{4}))$$

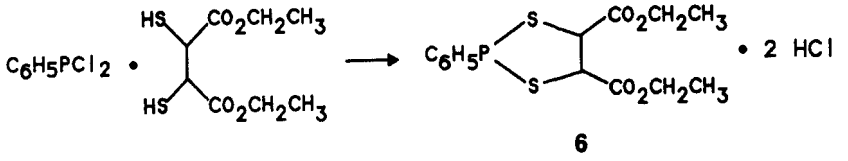
phosphorus sulfide with R = Ph has been obtained by reacting the tricoordinate compound with elemental sulfur (Equation 3).

The cyclic phosphonodithioite **6** has been prepared by reacting $C_6H_5PCl_2$ with

$$\underset{\mathbf{3}}{C_6H_5P(SCH_2CH_2CO_2CH_2CH_3)_2} + 1/8\ S_8 \rightarrow \underset{\mathbf{5}}{C_6H_5P(S)(SCH_2CH_2CO_2CH_2CH_3)_2} \qquad (3)$$

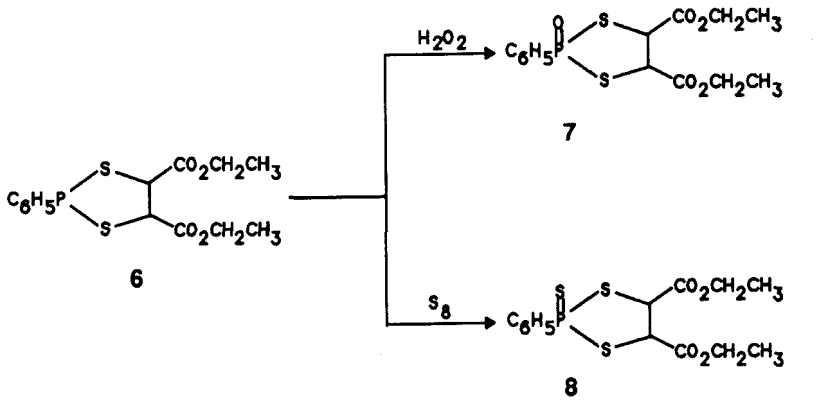
diethyl-2,3-dimercaptosuccinate in the presence of diisopropylethylamine as base (Equation 4). Subsequent reaction of this cyclic product, bis(diethylpropionate)-2-phenyl-1,3,2-dithiaphospholane(**6**), with hydrogen peroxide or sulfur gives the phosphonodithioate (**7**) and phosphonotrithioate (**8**) compounds respectively

(Equation 5). By mass spectrometry these cyclic compounds, like their linear counterparts, have monomeric structures.



(4)

6



(5)

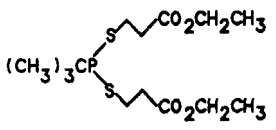
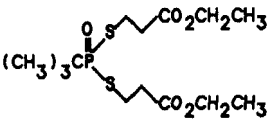
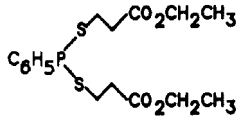
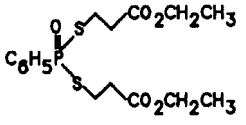
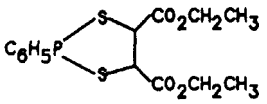
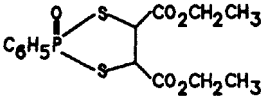
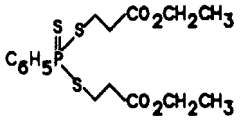
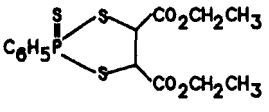
The ^1H NMR spectra show all the expected resonances and multiplicities for the phenyl, *tert*-butyl and ethyl groups. The diastereomeric ring methine hydrogens in the cyclic compounds are observed as a single resonance. The compounds all show a single resonance in the $^{31}P\{^1H\}$ NMR spectrum. These chemical shift values are collected in Table I. The trend in the ^{31}P NMR chemical shifts of the linear chain derivatives having a *P*-phenyl bond follows that observed in the acylic *S*-ethyl derivatives. In each group of compounds the ^{31}P NMR chemical shifts of the phosphonodithioites and the phosphonotrithioates are closely similar, but the chemical shifts of the phosphonodithioates are shifted approximately 25 ppm upfield.[10] For the cyclic derivatives our new complexes also follow the expected trend whereby the ^{31}P NMR chemical shift moves progressively downfield along the phosphonodithioite, phosphonodithioate, and phosphonotrithioate series.[11]

The infrared spectra of the new compounds show expected absorptions due to $\nu(CO)$ in the region of the 1735 cm^{-1}. For the phosphonodithioates there are additional bands due to $\nu(PO)$ in the 1150–1200 cm^{-1} range.

The complete hydrolysis of these compounds involves the cleavage of two separate phosphorus-sulfur bonds. Such a reaction will not involve the simultaneous cleavage of both bonds, but will likely involve a sequential cleavage pathway. A plausible intermediate in the hydrolytic cleavage of P—S bonds in the three-coordinate compounds is a phosphinothioate, RPH(O)SR′. In order to determine whether such compounds are plausible intermediates in the hydrolysis of the three coordinate compounds of type $RP(SR')_2$, we have prepared the compound ethyl propionate phenylphosphinothioate, $C_6H_5PH(O)(SCH_2CH_2CO_2CH_2CH_3)$(**9**). This compound has been synthesized by first reacting $C_6H_5PCl_2$ with an equimolar

TABLE I

^{31}P NMR chemical shift data

	δ		δ
 **1**	114.5	 **2**	83.6
 **3**	78.6	 **4**	53.6
 **6**	45.5	 **7**	65.8
 **5**	81.0	 **8**	83.5

amount of ethyl-3-mercaptopropanoate to give $C_6H_5PCl(SCH_2CH_2CO_2CH_2CH_3)$ (Equation 6). Treating this intermediate compound with

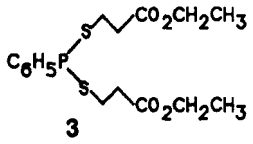
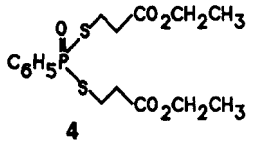
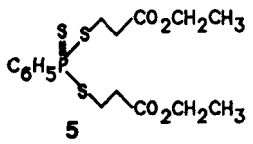
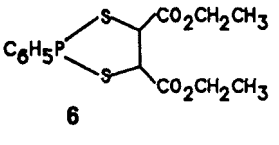
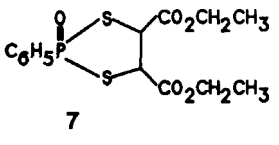
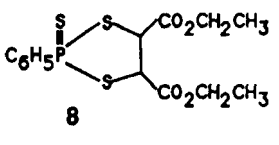
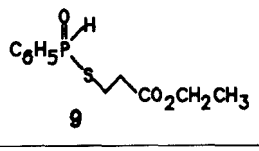
$$C_5H_5PCl_2 + HSCH_2CH_2CO_2CH_2CH_3 \rightarrow C_6H_5PCl(SCH_2CH_2CO_2CH_2CH_3) + HCl \quad (6)$$

water gives the desired compound $C_6H_5PH(O)(SCH_2CH_2CO_2CH_2CH_3)$ (**9**) (Equation 7). The synthesis is carried out in a two-phase reaction mixture containing benzene and

$$C_6H_5PCl(SCH_2CH_2CO_2CH_2CH_3) + H_2O \rightarrow \underset{(\mathbf{9})}{C_6H_5PH(O)(SCH_2CH_2CO_2CH_2CH_3)} + HCl \quad (7)$$

water, and benzene solvent is removed as quickly as possible in order to prevent subsequent cleavage of the P—S bond in **9**.

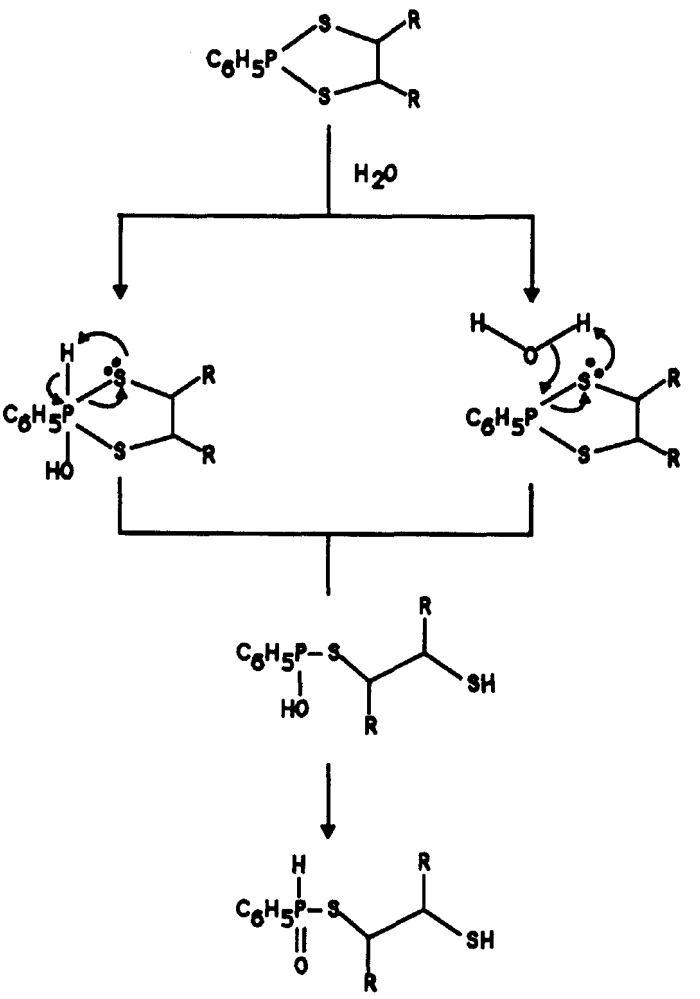
TABLE II
Hydrolysis of cyclic and acylic compounds[a]

Compound	Yield Product
 3	< 10%. $C_6H_5PH(O)OH$
 4	No reaction
 5	No reaction
 6	95%. $C_6H_5PH(O)OH$
 7	< 5%. $C_6H_5P(O)(OH)_2$
 8	No reaction
 9	100%[b]. $C_6H_5PH(O)OH$

a. 15 h. at 50°C in aqueous acetone

b. Reaction complete in 2 h.

The compound is characterized by infrared adsorption bands at 1735 cm^{-1}, 1181 cm^{-1} and 2366 cm^{-1} due to ν(CO), ν(PO), and ν(PH) respectively. The ^{31}P NMR spectrum of the compound is a doublet centered at δ 27.7 ($^1J(PH)$ = 571 Hz). The



SCHEME I

^{1}H NMR spectrum, in addition to other expected resonances and multiplicities, shows a doublet resonance due to PH at δ 7.6 which has a 571 Hz splitting.

Hydrolytic Reactions

The comparative hydrolysis studies show that the linear phosphonodithioite **3**, phosphonodithioate **4** and the phosphonotrithioate **5** show little or no hydrolysis of the P—S bonds after 15 h in aqueous acetone at 50°C. The addition of *cis*-$Co(tren)(OH)(H_2O)^{2+}$ causes no acceleration in the hydrolysis rate, although it is known that cobalt complexes such as this promote the hydrolysis of phosphate esters.[12] By contrast, the cyclic phosphonodithioate $C_6H_5P(SCH(CO_2CH_2CH_3)CH(CO_2CH_2CH_3)S)$ **7** under the same hydrolytic conditions shows 95% conversion to $C_6H_5PH(O)OH$. By contrast, for the acyclic compound

$C_6H_5P(SCH_2CH_2CO_2CH_2CH_3)_2$, the yield of the hydrolysis product is less than 10%. It is clear, therefore, that a parallel exists between the cyclic phosphonodithioites and phosphonates whereby the three coordinate cyclic compounds undergo hydrolytic cleavage more rapidly than their acyclic congeners.[7] We believe that this is the first time that such a direct comparison has been made within a series of such phosphorus sulfur compounds (Table II).

A plausible route for this reaction involves a hydrolytic ring cleavage to give the intermediate $C_6H_5PH(O)(SCH(CO_2CH_2CH_3)CH(CO_2CH_2CH_3)SH)$. Subsequent hydrolysis of this intermediate will lead to a mixture of $C_6H_5PH(O)OH$ and $(CH(SH)(CO_2CH_2CH_3))_2$.

Two pathways for the hydrolytic cleavage of the P—S bond are feasible. These are the attack by water at the tricoordinate phosphorus atom, or the attack by water at one of the sulfur atoms. These alternative routes are shown in Scheme I. Our data do not differentiate between these two pathways. As a test to determine whether the intermediate compound $C_6H_5PH(O)(SCH(CO_2CH_2CH_3)CH(CO_2CH_2CH_3)SH)$ is likely to undergo facile hydrolytic cleavage of the P—S bond, we have synthesized the analogue compound $C_6H_5PH(O)(SCH_2CH_2CO_2CH_2CH_3)$. This compound $C_6H_5PH(O)(SCH_2CH_2CO_2CH_2CH_3)$ shows complete hydrolytic conversion to $C_6H_5PH(O)OH$ after 2 h in aqueous acetone at 50°C (Equation 8). The product compound $C_6H_5PH(O)OH$ is characterized by a resonance in the $^{31}P\{^1H\}$ NMR spectrum at δ 22.8 ($^1J(PH) = 556$ Hz).[13] This experimental

$$C_6H_5PH(O)(SCH_2CH_2CO_2CH_2CH_3) + H_2O \rightarrow C_6H_5PH(O)OH + HSCH_2CH_2CO_2CH_2CH_3 \quad (8)$$

observation correlates with the literature data on the hydrolysis of P—O bonds, where again the most reactive compounds are those which also contain a P—H functionality.[6] Under the neutral conditions of our hydrolytic reaction it is unlikely that $C_6H_5PH(O)(SCH_2CH_2CO_2CH_2CH_3)$ deprotonates to give the hydrolytically unstable anion $C_6H_5P(O)(SCH_2CH_2CO_2CH_2CH_3)^-$. Instead we suggest that the hydrolysis occurs with the uncharged compound, and that the increased yield of hydrolysis product is due to intramolecular association of the water molecule with the PH(O) functionality in $C_6H_5PH(O)(SCH_2CH_2CO_2CH_2CH_3)$, which causes an increased hydrolysis rate. A similar intramolecular association can also occur if the hydrolytic reaction occurs via the 3-coordinate tautomer having the structure $C_6H_5P(OH)S(CH_2CH_2CO_2CH_2CH_3)$.

EXPERIMENTAL

^1H and $^{31}P\{^1H\}$ NMR data were collected on a Bruker AC 200 NMR spectrometer operating at 200 MHz and 81 MHz respectively. Chemical shifts are reported as downfield positive, and referenced against TMS for ^1H, and 85% H_3PO_4 for ^{31}P. The spectra were measured using either $CDCl_3$ or C_6D_6 as solvent. Infrared spectra were measured on a Mattson Cygnus 100 FT-IR spectrometer with the liquid samples pressed between two sodium chloride plates. Mass spectra were measured on a Hewlett-Packard Model 5995 mass spectrometer. Exact mass measurements were made on either a Kratos Concept 1H or a VG70EHF spectrometer. The samples were introduced either as pure liquids or as solutions in benzene. The ionizing source of data collection was electron impact.

Phenyldichlorophosphine (Aldrich Chemical Co.), *tert*-butyldichlorophosphine (Strem Chemicals) and, 3-mercaptopropanoic acid (Evans Chemetics) were used as supplied. 2,3-Dithiosuccinic acid and Diethyl-2,3-dimercaptosuccinate were synthesized according to literature procedures.[8] Triethylamine

(Mallinckrodt) was distilled under nitrogen prior to use. The complex *cis*-Co(tren)(OH)$(H_2O)^{2+}$ was synthesized using the literature procedure.[9] Deuterated NMR solvents (Aldrich Chemical Co.) were dried over potassium carbonate. Other solvents were dried using standard techniques with all distillations being carried out under an atmosphere of nitrogen. Except where noted, all compounds were handled by cannula techniques using a double manifold Schlenk line. All glassware and syringes were oven baked at 150° prior to use.

Ethyl-3-mercaptopropanoate: —$HSCH_2CH_2CO_2CH_2CH_3$. 3-Mercaptopropanoic acid (20.0 mL, 0.226 mol), ethyl alcohol (ca 14 mL) and a catalytic quantity (<1 mL) of sulfuric acid were mixed in a 50 mL round bottom flask, and the mixture refluxed under a nitrogen atmosphere for 8 h. After cooling, the solution was dried over $MgSO_4$, and the filtrate separated. Unreacted ethyl alcohol was removed by distillation under vacuum, and the resulting colorless, viscous liquid extracted into pentane. Evaporation of the pentane gave ethyl-3-mercaptopropanoate as a colorless liquid. Yield 10.5 g (65%). IR (liquid): ν(CO) 1735 cm^{-1}, ν(SH) 2580 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.1 t(CH_3, ^3J(HH) = 7 Hz), δ 1.5 t(SH, ^3J(HH) = 8 Hz), δ 2.5–3.3 m (2 × CH_2), δ 4.0 q(CH_2, ^3J(HH) = 7 Hz).

$(CH_3)_3CP(SCH_2CH_2CO_2CH_2CH_3)_2$(**1**). Into a 25 mL Schlenk flask was placed ethyl 3-mercaptopropanoate (0.59 mL, 5.3 mmol), triethylamine (0.70 mL, 5.0 mmol) and distilled pentane (15 mL). The flask containing the solution was cooled to 0°C. A separate vial was prepared containing *tert*-butyldichlorophosphine (0.38 g, 2.39 mmol) and distilled pentane (5 mL). This pentane solution of *tert*-butyldichlorophosphine from the vial was transferred by syringe into the stirred mixture in the Schlenk flask. Immediate precipitation of triethylamine hydrochloride occurred, and the resulting solution was stirred for 18 h. After this time the solution was filtered, and the precipitate washed with several small aliquots of pentane. The combined filtrate was cooled in a dry ice-acetone bath for 3–4 h, during which time any unreacted ethyl 3-mercaptopropanoate had formed a viscous layer at the bottom of the Schlenk vessel. The supernatant solution containing the product was removed by syringe. This low-temperature extraction procedure with pentane was continued until the final pentane solution containing the product was shown by gc/ms to be free from unreacted ethyl 3-mercaptopropanoate. Removal of the pentane solvent under vacuum gave the compound as a pure colorless liquid. Yield 0.25 g (30%) m/z 354.10822; Calcd for $C_{14}H_{27}O_4PS_2$: m/z 354.10884. IR: ν(CO) 1735 cm^{-1}. ^1H NMR: δ 1.17 d (CH_3, ^3J(PH) = 13 Hz), δ 0.92 t(CH_3, ^3J(HH) = 7 Hz), δ 2.53 t(CH_2, ^3J(HH) = 7 Hz), δ 2.92 dt (SCH_2, ^3J(HH) = 7 Hz, ^3J(PH) = 13 Hz), δ 3.91 q(^3J(HH) = 7 Hz). $^{31}P\{^1H\}$ NMR: δ 114.5

$(CH_3)_3CP(O)(SCH_2CH_2CO_2CH_2CH_3)_2$ (**2**). The compound $(CH_3)_3CP(SCH_2CH_2CO_2CH_2CH_3)_2$ (ca 0.3 mL) was dissolved in acetone (10 mL of 99.5%) in a 25 mL Schlenk flask. To this stirred solution was added hydrogen peroxide (1 drop of 30%), and the resulting solution stirred for an additional 20 m. Removal of the acetone under vacuum gave the product as a colorless oil in quantitative yield. m/z 370.10292; Calcd for $C_{14}H_{27}O_5PS_2$: m/z 370.10376. IR: ν(CO) 1735 cm^{-1}, ν(PO) 1260 cm^{-1}. ^1H NMR: δ 1.26 d (CH_3, ^3J(PH) = 20 Hz), δ 1.25 t(CH_3, ^3J(HH) = 7 Hz), δ 2.77 t(CH_2, ^3J(HH) = 7 Hz), δ 3.17 dt(SCH_2, ^3J(HH) = 7 Hz, ^3J(PH) = 13 Hz), δ 4.14 q(CH_2, ^3J(HH) = 7 Hz).

$C_6H_5P(SCH_2CH_2CO_2CH_2CH_3)_2$ (**3**). To a stirred solution of ethyl-3-mercaptopropanoate (0.36 mL, 3 mmol) and triethylamine (0.41 ml, 3 mmol) in benzene (60 mL) was added dropwise a solution of $C_6H_5PCl_2$ (0.2 mL, 1.5 mmol) in benzene (5 mL) at 0°C. The solution was stirred for 2 h during which time it was allowed to warm to ambient temperature. After stirring for 1 h at ambient temperature the precipitate of triethylamine hydrochloride was filtered and the solution volume reduced under vacuum to 10 mL. The yellow product oil was extracted with pentane (30 mL) and the solution cooled at −78°C. The colorless precipitate which formed was rapidly filtered, and any remaining solvent was evaporated under vacuum to give the product as a colorless liquid. Yield 0.23 g (42%). m/z 374.07562. Calcd for $C_{16}H_{23}O_4PS_2$: m/z 374.07751. IR: ν(CO) 1735 cm^{-1}. ^1H NMR: δ 1.2 t(CH_3, ^3J(HH) = 7 Hz), δ 2.5–3.3 m (2 × CH_2), δ 4.1 q(CH_2, ^3J(HH) = 7 Hz), δ 7.3–7.6 m (C_6H_5). $^{31}P\{^1H\}$ NMR: δ 78.6.

$C_6H_5P(O)(SCH_2CH_2CO_2CH_2CH_3)_2$ (**4**). To a stirred solution of $C_6H_5P(SCH_2CH_2CO_2CH_2CH_3)_2$ (0.2 g, 0.53 mmol) in benzene (20 mL) was added dropwise an aqueous hydrogen peroxide (30%) solution (0.5 mL). After stirring for 5 m the benzene layer was removed and its volume reduced under vacuum to 2 mL. Pentane (10 mL) was added to the pale yellow solution, and the pentane solution extracted and cooled to −78°C. The white precipitate which formed was rapidly filtered, and any remaining solvent evaporated under vacuum to give the product as a colorless liquid. Yield 0.16 g (77.5%). An alternative preparation involves bubbling oxygen through a solution of $C_6H_5P(SCH_2CH_2CO_2CH_2CH_3)_2$ (0.2 g, 0.53 mmol) in benzene (20 mL) for 4 h. The isolation and purification steps were unchanged. m/z 345.03644. Calcd for $C_{14}H_{18}O_4PS_2$: m/z 345.03841. The compound loses a OCH_2CH_3 group even under low energy electron ionization conditions. The exact mass therefore corresponds to the fragment with formula $C_6H_5P(O)(SCH_2CH_2CO_2CH_2CH_3)(SCH_2CH_2CO)$. IR: ν(CO) 1734 cm^{-1}, ν(PO) 1201

cm^{-1}, ^1H NMR ($CDCl_3$): δ 1.2 t(CH_3, $^3J(HH)$ = 7.1 Hz), δ 2.5–3.3 m (2 × CH_2), δ 4.1 q(CH_2, $^3J(HH)$ = 7.1 Hz), δ 7.2–7.9 m (C_6H_5). $^{31}P\{^1H\}$ NMR (C_6D_6): δ 53.6.

$C_6H_5P(S)(SCH_2CH_2CO_2CH_2CH_3)_2$ (**5**). A solution of $C_6H_5P(SCH_2CH_2CO_2CH_2CH_3)_2$ (0.2 g, 0.53 mmol) and sulfur (0.1 g) in benzene (20 mL) was refluxed for 5 h. The yellow solution was filtered and its volume was reduced to 2 mL under vacuum. The yellow solution was extracted with pentane (10 mL), and the pentane solution cooled to 0°C. After 30 m the residual sulfur was extracted. Removal of pentane under vacuum gave the compound as a pale yellow liquid. Yield 0.1 g (47%). m/z 406.04694. Calcd for $C_{16}H_{23}O_4PS_3$: m/z 406.04961. IR: ν(CO) 1735 cm^{-1}. ^1H NMR (C_6D_6): δ 1.0 t (CH_3, $^3J(HH)$ = 7.2 Hz), δ 2.5 dt (CH_2, $^3J(HH)$ = 7.1 Hz, $^4J(PH)$ = 3.1 Hz), δ 3.2 dt (CH_2, $^3J(HH)$ = 7.1 Hz, $^3J(PH)$ = 16.4 Hz), δ 3.8 q(CH_2, $^3J(HH)$ = 7.2 Hz). $^{31}P\{^1H\}$ NMR (C_6D_6): δ 81.0.

$C_6H_5\overline{P(SCH(CO_2CH_2CH_3)CH(CO_2CH_2CH_3)S)}$ (**6**). To a stirred solution of diethyl-2,3-dimercaptosuccinate (0.36 g, 1.5 mmol) and diisopropylethylamine (0.52 mL, 3.0 mmol) in THF (50 mL) was added dropwise a solution of $C_6H_5PCl_2$ (0.2 mL, 1.5 mmol) in THF (5 mL) at 0°C. The solution was stirred for 2 h after which time it was allowed to warm to ambient temperature. After stirring for an additional 1 h, the white precipitate of diisopropylethylamine hydrochloride was filtered, and the solvent removed under vacuum. The yellow oil was extracted with benzene (20 mL), the volume of the solution reduced to 2 mL, and pentane (10 mL) added. Any additional precipitate of diisopropylethylamine hydrochloride was filtered, and the filtrate evaporated to dryness under vacuum to give the compound as a colorless liquid. Yield 0.22 g (43%). m/z 344.03013. Calcd for $C_{14}H_{17}O_4PS_2$: m/z 344.03059. IR: ν(CO) 1735 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.1 t(CH_3, $^3J(HH)$ = 7 Hz), δ 4.1 q(CH_2, $^3J(HH)$ = 7 Hz), δ 4.2 d (CH, $^3J(PH)$ = 1.6 Hz), δ 7.2–7.7 m (C_6H_5). $^{31}P\{^1H\}$ NMR (C_6D_6): δ 45.5.

$C_6H_5\overline{P(O)(SCH(CO_2CH_2CH_3)CH(CO_2CH_2CH_3)S)}$ (**7**). Oxygen was bubbled through a refluxing solution of $C_6H_5\overline{P(SCH(CO_2CH_2CH_3)CH(CO_2CH_2CH_3)S)}$ (0.2 g, 0.58 mmol) in benzene (20 mL) for 8 h. The solvent was removed under vacuum, and the resulting yellow oil extracted with pentane (10 mL). Removal of the pentane solvent under vacuum gave the product as a colorless oil. Yield 0.07 g (33%). m/z 360.01976. Calcd for $C_{14}H_{17}O_5PS_2$: m/z 360.02551. IR: ν(CO) 1735 cm^{-1}, ν(PO) 1262 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.2 t(CH_3, $^3J(HH)$ = 7.2 Hz), δ 4.1 d(CH, $^3J(PH)$ = 6.0 Hz), δ 4.2 q(CH_2, $^3J(HH)$ = 7.2 Hz). $^{31}P\{^1H\}$ NMR (C_6D_6): δ 65.8.

$C_6H_5\overline{P(S)(SCH(CO_2CH_2CH_3)CH(CO_2CH_2CH_3)S)}$ (**8**). A solution containing $C_6H_5\overline{P(SCH(CO_2CH_2CH_3)CH(CO_2CH_2CH_3)S)}$ (0.2 g, 0.58 mmol) and sulfur (0.1 g) in benzene (30 mL) was refluxed for 3 d. Using the same separation and purification procedure as for $C_6H_5P(S)(SCH_2CH_2CO_2CH_2CH_3)_2$ gave the compound as a colorless solid. Yield 0.1 g (46%). m/z 376.00448. Calcd for $C_{14}H_{17}O_4PS_3$: m/z 376.00266. IR: ν(CO) 1735 cm^{-1}. ^1H NMR (C_6D_6): δ 1.3 t(CH_3, $^3J(HH)$ = 7.2 Hz), δ 4.3 q(CH_2, $^3J(HH)$ = 7.2 Hz), δ 4.8 d(CH, $^3J(PH)$ = 12.8 Hz), δ 7.3–8.0 m (C_6H_5). $^{31}P\{^1H\}$ NMR (C_6D_6): δ 83.5.

$C_6H_5PH(O)(SCH_2CH_2CO_2CH_2CH_3)$ (**9**). To a stirred solution of $C_6H_5PCl_2$ (0.27 g, 1.5 mmol) and triethylamine (0.15 g, 1.5 mmol) in benzene (60 mL) was added dropwise a solution of ethyl-3-mercaptopropanoate (0.2 g, 1.5 mmol) in benzene (10 mL) at 0°C. The solution was stirred for 2 h. The triethylamine hydrochloride was filtered, and the solvent removed under vacuum to give $C_6H_5PCl(SCH_2CH_2CO_2CH_2CH_3)$ as a colorless liquid in a yield of approximately 90% as determined by $^{31}P\{^1H\}$ NMR spectroscopy. To a stirred solution of $C_6H_5PCl(SCH_2CH_2CO_2CH_2CH_3)$ (0.2 g, 0.72 mmol) in benzene (20 mL) was added water (0.5 mL) at 0°C. The solution was stirred for 30 m while the solution warmed to ambient temperature. The benzene layer was removed and evaporated to dryness under vacuum to give the compound in approximately 60% yield. m/z 257.03942. Calcd for $C_{11}H_{15}O_3PS$: m/z 257.04013. The compound loses a hydrogen even under low energy electron ionization conditions. The exact mass therefore corresponds to the fragment with formula $C_6H_5P(O)(SCH_2CH_2CO_2CH_2CH_3)$. IR: ν(CO) 1734 cm^{-1}, ν(PH) 2366 cm^{-1}, ν(PO) 1181 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.2 t (CH_3, $^3J(HH)$ = 7.2 Hz), δ 2.6–3.3 m (2 × CH_2), δ 4.1 q(CH_2, $^3J(HH)$ = 7.2 Hz), δ 7.3–8.0 m (C_6H_5), δ 7.6 d(PH, $^1J(PH)$ = 571 Hz). ^{31}P NMR (C_6D_6): δ 27.7 d($^1J(PH)$ = 571 Hz).

Hydrolytic reactions. The hydrolysis studies involved dissolving the compound (ca 0.1 mL) in acetone (4 mL), and adding water (1 mL) to the solution. The solution was then stirred for 15 h with the solution held at 50°C. The product was analyzed by $^{31}P\{^1H\}$ NMR spectroscopy.

ACKNOWLEDGEMENT

We thank the Petroleum Research Fund, administered by the American Chemical Society, and the Center of Bioenvironmental Research, for financial support.

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