The Reaction of Benzenephosphonous Esters With Sulfenyl Chlorides[1]

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A previous report[2] described the reaction of trialkyl phosphites with sulfenyl chlorides to form tertiary phosphorothioates, $(RO)_2PO(SR')$.[3,4] This reaction has now been extended to include the interaction of esters of benzenephosphonous acid with alkyl sulfenyl chlorides. The products are thiophosphonates, and the reaction may be represented as:

$$C_6H_5P(OR)_2 + R'SCl \longrightarrow C_6H_5PO(OR)(SR') + RCl$$

The thiophosphonates are colorless high-boiling liquids of unpleasant odors. The action of methanesulfenyl chloride,[5,6] ethanesulfenyl chloride,[7] and *beta*-chloroethanesulfenyl chloride[8] on diethyl benzenephosphonite was examined and also the reaction of methanesulfenyl chloride with (unisolated) di(*beta*-chloroethyl) benzenephosphonite. The products were unsymmetrical esters if the alkyl groups of the reactants were different. They were employed in cancer chemotherapy studies.

EXPERIMENTAL

The sulfenyl halides were prepared in chloroform or in benzene-petroleum ether solution, and were kept below 0° (usually −30°) until used. They were added dropwise to the phosphonous ester solution at −30 to 0°, the orange color of the sulfenyl chloride being discharged.

As an example, the synthesis of S-methyl-O-(*beta*-chloroethyl) benzene-thiophosphonate is given. In other preparations, the isolated phosphonous ester was employed and equimolar amounts of reactants were used.

A solution of 27.2 ml. (0.20 mole) of phenyl dichlorophosphine in 50 ml. of benzene was added dropwise, with stirring, to a solution of 28 ml. (0.42 mole) of ethylene chlorohydrin and 33.5 ml. (0.42 mole) of pyridine in 500 ml. of an equi-volume mixture of benzene and petroleum ether, cooled to 0° in an ice-bath. All reagents were anhydrous and freshly distilled. The mixture was left 2 hours in the bath and 6 hours at room temperature, and then was filtered. The filter cake was washed 3 times with the mixed solvent. The combined filtrates were cooled to 0° and then were treated dropwise with methanesulfenyl chloride solution which had been made one hour before. This was prepared from 9.7 ml. (0.11 mole) of dimethyl disulfide and 9 ml. (0.11 mole) of sulfuryl chloride in benzene-petroleum ether solution. The excess sulfenyl halide was employed to allow for the excess of reactants in the crude phosphonous ester. After $^1/_2$ hour, the solution was washed with water, dilute sodium carbonate solution and twice by water. The solvents were removed at 70 mm. and the residue was fractionated under 2 mm. pressure. Thus 48 g. of an oil were obtained (95.8% yield). This was redistilled for analysis, b.p. 148–152° at 3 mm.

TABLE I

PROPERTIES OF THIOPHOSPHONATES $C_6H_5PO(OR)(SR')$

R	R′	Yield, %	C, Calc'd	C, Found	H, Calc'd	H, Found	d^{25}_0	B.P., °C.	MM.
Ethyl	Ethyl	88.7	52.17	52.22	6.52	6.58	1.1473	145–146	5
Ethyl	Methyl	71.3[a]	50.00	50.16	6.02	5.98	1.1728	125–135	3
Ethyl	*beta*-Chloroethyl	76.8	45.37	45.02	5.29	5.21	1.2378	138–141	1–2
beta-Chloroethyl	Methyl	95.8	43.11	42.78	4.79	4.93	1.2940	148–152	3

[a] Reaction carried out at 5–10°.

The four esters which were prepared are listed in Table I, together with physical constants and analyses.

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(2) Morrison, *J. Am. Chem. Soc.*, **77**, 181 (1955).

(3) Gilbert and McGough, U. S. Patent No. 2,690,450.

(4) Gilbert and McGough, U. S. Patent No. 2,690,451.

(5) Schneider, *Ber.*, **84**, 911 (1951).

(6) Brintzinger, Pfannstiel, Koddebusch, and Kling, *Ber.*, **83**, 87 (1950).

(7) Brintzinger and Langheck, *Ber.*, **86**, 557 (1953).

(8) Fuson, Price, Bauman, Bullitt Jr., Hatchard, and Maynert, *J. Org. Chem.*, **11**, 471 (1946).

Basic Zinc Double Salts of O,O-Dialkyl Phosphorodithioic Acids

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In the course of preparing a series of zinc O,O-di-*n*-alkyl phosphorodithioates by metathesis between the corresponding sodium salts and zinc chloride in aqueous solution, a new and unusual type of basic zinc salt was isolated as a by-product from the preparation of zinc O,O-di-*n*-butyl phosphorodithioate. We should like to report some properties of two members of this new class of compounds.

Elemental analyses and non-aqueous acid-base titration data satisfied the requirements of a basic

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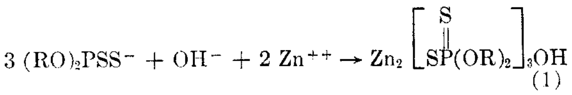
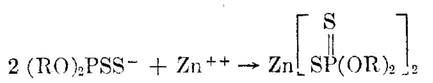
zinc double salt having the composition represented by the formula, $Zn_2[\overset{S}{\overset{\|}{S}}P(OC_4H_9)_2]_3OH$. Titration with perchloric acid in acetonitrile-dioxane solution gave a neutral equivalent equal to the molecular weight and presumably corresponds to the titration of the basic hydroxyl group. Titration with tetrabutylammonium hydroxide gave a neutral equivalent of one-third the molecular weight and corresponds to the reaction of the three phosphorodithioate ions with a stronger base than zinc hydroxide. Subsequent preparation of the isopropyl homologue indicated that such salts may be generally obtained from O,O-dialkyl phosphorodithioic acids. The formation of basic zinc double salts of the type described is not entirely unexpected. Abegg[2] lists, among others, such inorganic basic zinc salts as $Zn_2(OH)_3NO_2$ and $Zn_2(OH)_2SO_4$.

Formation of the basic zinc double salts appears to depend on the presence of excess hydroxyl ion during the reaction of zinc ion with the phosphorodithioate ion. Indeed, either the normal zinc salts or the basic zinc double salts may be prepared with the exclusion of the other by selecting the proper molar ratios of phosphorodithioate ion, zinc ion and hydroxyl ion consistent with their respective formulas. The stoichiometry of equation (1) gives the basic zinc double salt and that of equation (2) gives the normal salt.



$$3\,(RO)_2PSS^- + OH^- + 2\,Zn^{++} \rightarrow Zn_2\left[\overset{S}{\overset{\|}{S}}P(OR)_2\right]_3OH \qquad (1)$$



$$2\,(RO)_2PSS^- + Zn^{++} \rightarrow Zn\left[\overset{S}{\overset{\|}{S}}P(OR)_2\right]_2 \qquad (2)$$

A characteristic of these basic zinc double salts is their insolubility in methanol. The normal salts are very soluble in methanol at room temperature. Both series of salts are soluble in hexane. The basic zinc salts melt considerably higher than the corresponding normal salts: zinc O,O-di-*n*-butyl phosphorodithioate is a liquid at 25° whereas the basic zinc double salt melts at 150–153°; zinc O,O-diisopropyl phosphorodithioate melts about 53° lower than the basic salt.

Acknowledgments. We are indebted to Dr. John E. Lancaster for the preparation of the infrared spectra and to Messrs. R. P. Smith and G. A. Clarke, under whose direction the elemental analyses and non-aqueous titrations were performed.

EXPERIMENTAL[3]

O,O-Di-n-butyl phosphorodithioic acid. A. Crude acid. Two moles (150 g.) of 1-butanol were heated to 75° and, with agitation, 111 g. (0.5 mole) of phosphorus pentasulfide was added as rapidly as the concomitant foaming and exothermic reaction permitted. The temperature rose to the maximum of 96°. The reaction mixture was heated on the steam-bath for 90 minutes, after which time it was treated with 25 g. each of charcoal (Darco) and filter aid and filtered. Titration with standard alkali indicated a purity of 90%. This procedure is an improvement over that reported by Mastin, Norman, and Weilmuenster.[4] The increased control of the reaction results in a superior product.

B. Ammonium salt. One mole (269 g.) of the crude acid was dissolved in 500 ml. of hexane and was treated with an excess of dry ammonia admitted beneath the surface of the stirred solution. A 74% yield (191.5 g.) of air-dried ammonium O,O-di-*n*-butyl phosphorodithioate was obtained. The product was recrystallized from 400 ml. of benzene; 179 g. was recovered as white platelets.

Anal. Calc'd for $C_8H_{22}NO_2PS_2$: N, 5.41; P, 11.96; S, 24.75. Found: N, 5.33; P, 12.0; S, 25.6.

C. Purified acid. The recrystallized salt (90.5 g., 0.35 mole) was dissolved in 150 ml. of water containing 50 g. of ice in a separatory-funnel and a mixture of 28 g. (0.27 mole) of 96% sulfuric acid and 75 g. of ice was added. After vigorous shaking the organic and aqueous phases were allowed to separate and the lower product layer was drained off and stored over 30 g. of anhydrous sodium sulfate. The yield of purified O,O-di-*n*-butyl phosphorodithioic acid was 72.0 g. (85.3%); its purity, by titration, was 99.6%. Calc'd for $C_8H_{19}O_2PS_2$: Neut. Equiv., 242.3. Found: 243.5.

Zinc O,O-di-n-butyl phosphorodithioate. One mole (269 g.) of crude O,O-di-*n*-butyl phosphorodithioic acid was dissolved in a solution of 45 g. (1.1 moles) of sodium hydroxide in 400 ml. of water. The solution was adjusted to *p*H 9.5 with an additional 4 g. of sodium hydroxide. In order to remove an insoluble, oily contaminant the solution was treated with 25 g. of Darco and 20 g. of filter aid and filtered. Zinc chloride (68 g., 0.5 mole) in 40 ml. of water was added to the filtered solution and the resulting mixture was heated at 75° for about 10 minutes. The hot product was separated from the supernatant aqueous phase, stripped of residual water, and filtered through a layer of filter aid in a steam-jacketed filter funnel. The yield, before the final filtration, was 233 g. (90.0%); the final product was semi-solid.

Anal. Calc'd for $C_{16}H_{36}O_4P_2S_4Zn$: P, 11.31; S, 23.40; Zn, 11.93. Found: P, 11.1; S, 21.9; Zn, 12.3.

Although the analysis is fair for a preparation of this sort it was evident that the product was not homogeneous and, after standing for five weeks, it had separated into a pale, yellow liquid phase and a white, crystalline solid phase, the latter comprising 15–20% of the whole. The two phases were separated by centrifugation and the liquid phase was shown to be the desired zinc salt by elemental analysis, and by its lack of basicity.

Anal. Calc'd for $C_{16}H_{36}O_4P_2S_4Zn$: P, 11.31; S, 23.40; Zn, 11.93. Found: P, 11.3; S, 24.3; Zn, 11.8.

Basic zinc double salt of O,O-di-n-butyl phosphorodithioic acid. A. By-product from preparation of zinc O,O-di-n-butyl phosphorodithioate. The crystalline solid phase from the preceding preparation was very soluble in diethyl ether, soluble in hexane, and practically insoluble in methanol. The centrifuged material was washed repeatedly with cold methanol and recrystallized from hexane giving large, white, friable crystals; m.p. 150–153°. The neutral equivalent of the product as an acid was determined by titration of a sample in pyridine with 0.1 *N* tetrabutyl ammonium hydroxide in benzene-methanol solution;[5] its neutral equivalent

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[2] Abegg, *Handbuch der Anorganischen Chemie,* S. Hirzel, Leipzig, 1905, Vol. 2^2, pp. 405–407.

[3] Melting points are not corrected.

[4] Mastin, Norman, and Weilmuenster, *J. Am. Chem. Soc.,* **67,** 1662 (1945).

[5] Cundiff and Markunas, *Abstracts, American Chemical Society Meeting,* Minneapolis, Minnesota, September 11–16, 1955, p. 12B.

as a base was determined by titration of a sample in acetonitrile with 0.1 *N* perchloric acid in dioxane using the conventional techniques discussed by Fritz.[6] The titration data and elemental analyses are in excellent agreement with the values required for a basic zinc double salt.

Anal. Calc'd for $C_{24}H_{55}O_7P_3S_6Zn_2$: P, 10.66; S, 22.07; Zn, 15.00; Neut. Equiv. (as a base), 872; Neut. Equiv. (as an acid), 291. Found: P, 10.7; S, 22.2; Zn, 15.1; Neut. Equiv. (as a base), 880; Neut. Equiv. (as an acid), 295.

This composition was substantiated further by synthesis, using the stoichiometric ratios of phosphorodithioic acid: $Zn^{++}:OH^{-} = 3:2:4$ as required by the proposed formula.

B. Synthesis. Purified O,O-di-*n*-butyl phosphorodithioic acid (24.4 g., 0.1 mole) was added to a solution of 5.5 g. (0.133 mole) of 97% sodium hydroxide in 200 ml. of water containing 50 g. of ice. A very small amount of insoluble oil was removed by filtration of the solution through filter aid. A solution of 9.1 g. (0.067 mole) of zinc chloride in 50 ml. of water was added slowly with manual stirring. The solid crystalline basic zinc double salt began to form immediately; there was no evidence of the liquid normal salt. The yield of air-dried product was 26.0 g. (89.5%). It was identical with the by-product material described previously.

Zinc O,O-diisopropyl phosphorodithioate. A solution of 15.2 g. (0.06 mole) of potassium O,O-diisopropyl phosphorodithioate[7] in 200 ml. of water was treated with 15.0 ml. of 2 *M* zinc chloride solution giving an 86.5% yield (12.7 g.) of crystalline product, m.p. 147–148°.

Anal. Calc'd for $C_{12}H_{28}O_4P_2S_4Zn$: P, 12.60; S, 26.07; Zn, 13.29; Neut. Equiv. (as an acid), 246. Found: P, 12.6; S, 25.9; Zn, 13.9; Neut. Equiv. (as an acid), 253.

No basicity was indicated by titration with perchloric acid.

Basic zinc double salt of O,O-diisopropyl phosphorodithioic acid. A solution of 15.2 g. (0.06 mole) of potassium O,O-diisopropyl phosphorodithioate in 200 ml. of water containing 0.02 mole of sodium hydroxide was treated with 20 ml. of 2 *M* zinc chloride solution. A 13.5 g. (86.0%) yield of crystalline solid was obtained. After recrystallization from cyclohexane it melted at 204–206°.

Anal. Calc'd for $C_{18}H_{43}O_7P_3S_6Zn_2$: P, 11.80; S, 24.42; Zn, 16.59; Neut. Equiv. (as a base), 788; Neut. Equiv. (as an acid), 263. Found: P, 11.7; S, 25.0; Zn, 17.0; Neut. Equiv. (as a base), 798; Neut. Equiv. (as an acid), 281.

Infrared spectra. The infrared absorption spectra of the normal zinc salts were compared with those of basic zinc double salts using a Perkin-Elmer Model 21 double-beam Infrared Spectrophotometer. The two series of salts, examined as Nujol mulls, exhibited essentially the same spectra, with minor exceptions. The normal salts show a shoulder at 1025 cm.$^{-1}$ on the side of the very strong P—O band at 980 cm.$^{-1}$.[8] The normal salts have a medium strong band at 785 cm.$^{-1}$ that the basic salts lack. A band at 1110 cm.$^{-1}$ in the basic salts is lowered 5 cm.$^{-1}$ in the normal salts, and a band at 665 cm.$^{-1}$ in the basic salts is not present in the normal salts. No O—H stretching frequency was observed in the spectrum of the basic salt.

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[6] Fritz, *Acid-Base Titrations in Non-aqueous Solvents*, G. F. Smith Chemical Company, Columbus, Ohio, 1952, p. 9 ff.

[7] Hoegberg and Cassaday, *J. Am. Chem. Soc.*, **73**, 557 (1951).

[8] Gore, *Faraday Society Discussion*, No. **9**, 138 (1950), discusses the infrared absorption spectra of phosphorothioic acid derivatives.

The Synthesis of N-(2-oxoalkyl)-N-methylamides[1] from Sarcosine and Acyl Chlorides in Ethyl Acetate

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The synthesis of some high molecular weight acyl sarcosines was approached by applying the direct amino acid acylation procedure of Ronwin,[2] in which a heterogeneous mixture of amino acid and a solution of the acyl chloride in anhydrous ethyl acetate is heated at reflux temperature. The reactions of myristoyl and palmitoyl chlorides with sarcosine progressed slowly under these conditions, and reflux time was extended to 48 hours. The products from these two reactions (2:1 excess of acyl chloride) proved to be N-(2-oxoalkyl)-N-methylamides instead of acylated sarcosines.

$$2\mathrm{RCOCl} + \mathrm{CH_3NHCH_2COOH} \xrightarrow[\text{ethyl acetate}]{\text{48 hr. reflux in}} \mathrm{RCON(CH_3)CH_2COR}$$

$$\mathrm{R} = \mathrm{C_{13}H_{27}};\ \mathrm{C_{15}H_{31}}$$

A similar reaction of sarcosine, to form N-acetonyl-N-methylacetamide, has been reported.[3] This was the basis for determining that an azlactone is not necessarily an intermediate in the conversion of α-amino acids to "acylamido ketones" in basic solution, as had been proposed previously.[4] The synthesis of the amide compounds from sarcosine, reported here, (a) furnishes additional evidence in this respect, (b) extends the reaction to include high molecular weight acylating agents, and (c) is the first instance, to the authors' knowledge, of the formation of these compounds from an N-alkyl-α-amino acid in the absence of a basic solvent such as pyridine.

EXPERIMENTAL

N-(2-oxopentadecyl)-N-methylmyristamide (I). Sarcosine, 4.46 g. (0.05 mole), and a solution of 24.6 g. (0.10 mole) of myristoyl chloride in 80 ml. of anhydrous ethyl acetate were heated at reflux temperature for 48 hours. The reaction mixture was cooled, filtered, and the filtrate was evaporated to a crystalline residue with a stream of dry air. Recrystallizations from acetone, carbon tetrachloride, and ethanol gave a product melting at 72–73°;[5] further purification from ethyl acetate and from acetone gave I, melting sharply at 75°; 2.91 g. (12.5%); the compound was soluble in concen-

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[1] Nomenclature as amides according to *Chem. Abstr.*, **39**, 5876 (1945); This type of compound is frequently referred to in the literature as an *acylamido ketone.*

[2] Ronwin, *J. Org. Chem.*, **18**, 127, 1546 (1953).

[3] Wiley, *Science*, **111**, 259 (1950); Wiley and Borum, *J. Am. Chem. Soc.*, **72**, 1626 (1950).

[4] Dakin and West, *J. Biol. Chem.*, **78**, 91, 745 (1928); Cleland and Niemann, *J. Am. Chem. Soc.*, **71**, 841 (1949).

[5] All melting points are uncorrected.