[CONTRIBUTION FROM THE STAMFORD RESEARCH LABORATORIES OF THE AMERICAN CYANAMID COMPANY]

The Reaction of O,O-Dialkyl Thiophosphoric Acid Salts with Some α-Haloacyl Derivatives

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Twenty-four new esters of O,O-dialkyl dithiophosphoric and monothiophosphoric acids have been prepared by reaction of an alkali metal salt of the acid with a haloacetonitrile, a haloacetamide, or a haloacetylurea. One of the cyanomethyl esters has been further treated with hydrogen sulfide to produce a thiocarbamylmethyl ester.

Alkali metal or ammonium salts of dithiophosphoric acids are known to react with alkyl halides and acyl halides,[1] splitting out alkali halide or ammonium halide. In the present work, this type of reaction has been extended to cover the preparation of three new series of thiophosphate esters by reaction of an alkali metal salt of an O,O-dialkyl dithio(or monothio-)phosphoric acid with a haloacetonitrile (A), a haloacetamide (B), or a haloacetylurea (C), as shown in the typical equations

$$(RO)_2PSSM + XCH_2CN \longrightarrow (RO)_2PSSCH_2CN + MX \quad (A)$$

$$(RO)_2PSSM + XCH_2CONR'R'' \longrightarrow (RO)_2PSSCH_2CONR'R'' + MX \quad (B)$$

$$(RO)_2PSSM + XCHR'CONHCONHR'' \longrightarrow (RO)_2PSSCHR'CONHCONHR'' + MX \quad (C)$$

Some of these products have been disclosed in a preliminary way in the patent literature,[2,3] but analytical data and, in some cases, yields have not been reported previously.

The cyanoalkyl esters obtained from reaction A were liquids, while the products obtained from reactions B and C were generally solids when the alkyl group R was propyl or smaller and liquids when R was butyl or higher or when the nitrogens carried substituents other than hydrogen. The products were generally stable at room temperature, but several of them decomposed when heated at temperatures above 100° for long periods, hence they could not be purified by distillation.

Animal toxicities were determined on a few of these compounds and the acute oral LD_{50} to mice was found to range from 11 to greater than 800 mg./kg. This indicates that individual compounds of this type may be hazardous and should be handled with caution until animal toxicity tests have shown them to be safe.

Most of the products prepared were esters of dithiophosphoric acid. These were synthesized either by preparing the alkali metal salt *in situ* by treating an O,O-dialkyl dithiophosphoric acid with one equivalent of sodium carbonate, followed by reaction with an α-haloacyl derivative (Procedure I) giving sodium bicarbonate and sodium halide as by-products, or by isolating the sodium or potassium salt of an O,O-dialkyl dithiophosphoric acid and treating it with an α-haloacyl derivative (Procedure II), splitting out sodium or potassium halide.

Two esters of monothiophosphoric acid were prepared by treating potassium O,O-diethyl monothiophosphate[4] with bromoacetonitrile and with chloroacetylurea, respectively. Since Mastin, *et al.*, have indicated the probable existence of resonance in the O,O-diethyl thiol-(or thiono)-phosphate ion, the products from this reaction might be expected to have the structure $(C_2H_5O)_2P(O)OCH_2R'$ or $(C_2H_5O)_2P(S)SCH_2R'$. Infrared data appear to favor the latter structure for these products, indicating that the monothiophosphate esters described here are probably thiol esters.

S-Cyanomethyl O,O-diethyl dithiophosphate was further treated with hydrogen sulfide under pressure to produce the corresponding thioamide, $(RO)_2PSSCH_2CSNH_2$.

The thiophosphate esters described herein have been tested as insecticides, and many of them appear to show interesting properties for this application, although complete data are not yet available.

The thiophosphate esters obtained from the haloacetonitriles, haloacetamides and haloacetylureas are summarized in Table I.

Experimental[5]

Preparation of O,O-Dialkyl Dithiophosphoric Acids and Their Alkali Metal Salts.—Finely ground phosphorus pentasulfide (1 mole) was suspended in benzene or toluene (about 1000 ml.) and the appropriate alcohol (4 moles) was added gradually, with stirring, while the reaction temperature was maintained at 75–80°. Stirring was continued for about 1 hour after completion of the alcohol addition, then the mixture was filtered to remove unreacted phosphorus pentasulfide. The solvent was removed by distillation at 20–30 mm. pressure and the approximate purity of the residual O,O-dialkyl dithiophosphoric acid was determined by titration with standard alkali.

When the sodium or potassium salt of the O,O-dialkyl dithiophosphoric acid was desired, it was not necessary to remove the benzene or toluene from the reaction mixture. Instead the acidity of the solution was determined by alkali titration of an aliquot. An equivalent quantity of sodium or potassium hydroxide was then added with stirring to the reaction mixture, either in the form of pellets or a 50% aqueous alkali solution. It was found helpful to add ethanol (about 200 ml. per mole of salt) before adding the alkali in order to prevent the salt from caking on the sides of the flask. The mixture was then distilled until all the alcohol and water had been removed azeotropically and the sodium or potassium salt was isolated by filtration. The salts were generally rather hygroscopic.

α-Haloacyl Derivatives.—α-Chloro-N-methylacetamide and α-chloro-N,N-dimethylacetamide were prepared by treating chloroacetyl chloride with methylamine and dimethylamine, respectively, in ethylene dichloride using method Ib of Weaver and Whaley[6]; the physical properties

(1) C. J. Romieux and K. D. Ashley, U. S. Patent 2,266,514, issued Dec. 16, 1941.

(2) E. I. Hoegberg, U. S. Patent 2,494,126, issued Jan. 10, 1950.

(3) J. T. Cassaday, E. I. Hoegberg and B. D. Gleissner, U. S. Patents 2,494,283 and 2,494,284, issued Jan. 10, 1950.

(4) Prepared by hydrolysis of O,O-diethylthiophosphoric chloride by the method of T. W. Mastin, G. R. Norman and E. A. Weilmuenster, THIS JOURNAL, **67**, 1662 (1945).

(5) Many of the thiophosphate esters described here are highly toxic to animals.

(6) W. E. Weaver and W. M. Whaley, THIS JOURNAL, **69**, 515 (1947).

TABLE I

ESTERS OF THIOPHOSPHORIC ACIDS $(RO)_2P(=Y)SCH_2R'$

R	Y = S R'	Procedure	Yield, %	M.p., °C.[a]	$n^{25}D$	Empirical formula	Calcd.	Analyses, % Found	Calcd.	Found
Methyl	$CONH_2$	I	41	62–63		$C_4H_{10}NO_3PS_2$	N, 6.52	6.43	S, 29.8	29.8
Methyl	$CONHCONH_2$	II	78	117–118		$C_5H_{11}N_2O_4PS_2$	N, 10.8	10.6	S, 24.8	25.0
Ethyl	CN	I	82		1.5141	$C_6H_{12}NO_2PS_2$	P, 13.8	13.5	S, 28.5	28.3
Ethyl	$CONH_2$	I	89	57–58		$C_6H_{14}NO_3PS_2$	N, 5.76	5.78	S, 26.3	26.7
Ethyl	$CONH(CH_3)$	II	82		1.5292	$C_7H_{16}NO_3PS_2$	N, 5.45	5.26	P, 12.0	11.8
Ethyl	$CONH(C_6H_5)$	II	95	85–87[b]		$C_{12}H_{18}NO_3PS_2$	N, 4.38	4.32	S, 20.0	19.9
Ethyl	$CONH(C_6H_4NO_2\text{-}p)$	II	95	109–110		$C_{12}H_{17}N_2O_5PS_2$	N, 7.68	7.71	S, 17.6	17.8
Ethyl	$CONH(C_6H_4SO_2NH_2\text{-}p)$	I	58	145–146[c]		$C_{12}H_{19}N_2O_5PS_3$	N, 7.03	6.84	S, 24.1	24.2
Ethyl	$CON(CH_3)_2$	II	91		1.5252	$C_8H_{18}NO_3PS_2$	N, 5.16	5.05	S, 23.6	23.4
Ethyl	$CON(C_4H_9\text{-}n)_2$	II	94		1.5026	$C_{14}H_{30}NO_3PS_2$	N, 3.94	3.82	S, 18.0	17.7
Ethyl	$CONHCONH_2$	I	62	93–95		$C_7H_{16}N_2O_4PS_2$	N, 9.78	9.57	S, 22.4	22.4
n-Propyl	$CONH(CH_3)$	II	86		1.5157	$C_9H_{20}NO_3PS_2$	N, 4.91	4.89	P, 10.9	10.8
n-Propyl	$CON(C_2H_5)_2$	II	86		1.5074	$C_{12}H_{26}NO_3PS_2$	N, 4.28	4.12	P, 9.5	9.5
n-Propyl	$CONHCONH_2$	II	89	78–79		$C_9H_{19}N_2O_4PS_2$	N, 8.91	9.10	P, 9.85	9.45
i-Propyl	$CONH_2$	II	95	72–73		$C_8H_{18}NO_3PS_2$	N, 5.17	5.17	S, 23.6	23.8
i-Propyl	$CONH(CH_3)$	II	88		1.5149	$C_9H_{20}NO_3PS_2$	N, 4.9	4.7	P, 10.9	10.7
i-Propyl	$CON(C_2H_5)_2$	II	92		1.5039	$C_{12}H_{26}NO_3PS_2$	N, 4.28	4.20	P, 9.46	9.38
n-Butyl	$CONH_2$	I	92		1.5111	$C_{10}H_{22}NO_3PS_2$	P, 10.3	10.6	S, 21.4	21.5
i-Butyl	$CONH_2$	II	100		1.5182	$C_{10}H_{22}NO_3PS_2$	N, 4.68	4.72	P, 10.3	10.0
n-Amyl	CN	II	79		1.4984	$C_{12}H_{24}NO_2PS_2$	P, 10.0	10.0	S, 20.7	20.7
n-Decyl	$CONHCONH(C_6H_5)$	I	90		1.5222	$C_{29}H_{51}N_2O_4PS_2$	P, 5.28	5.47	S, 10.9	11.5
	Y = O									
Ethyl	CN	II	57	[d]		$C_6H_{12}NO_3PS$	S, 15.3	15.2		
Ethyl	$CONHCONH_2$	II	60	74–75		$C_7H_{17}N_2O_5PS$	P, 11.5	11.3	S, 11.8	11.8

[a] All melting points are uncorrected. [b] Recrystallized from heptane. [c] Recrystallized from ethanol. [d] Liquid which decomposed on prolonged standing.

of the products obtained agreed with those reported by Jacobs, *et al.*, for α-chloro-N-methylacetamide[7,8] and α-chloro-N,N-dimethylacetamide.[7] Other α-haloacyl derivatives were obtained commercially or were prepared by methods reported in the literature.

Reaction of O,O-Dialkyl Thiophosphoric Acid Salts with α-Haloacyl Derivatives. Procedure I.—Anhydrous sodium carbonate (1 mole) was suspended in acetone or methyl isobutyl ketone (600 ml.) and the O,O-dialkyl dithiophosphoric acid (1 mole) was added with stirring at room temperature at such a rate that foaming was easily controlled. The α-haloacyl compound (1 mole) was then added and the mixture stirred at 60–80° for 3 to 10 hours. The sodium bicarbonate and sodium halide were removed by filtration and the filtrate was freed of solvent by distillation on a water-bath under reduced pressure. The residue, which was not heated above 70°, was washed with water and, if a liquid, dried over anhydrous sodium sulfate or magnesium sulfate; if the product was a solid, it was purified by recrystallization from carbon tetrachloride or other suitable solvent.

This procedure was used in treating O,O-dimethyl dithiophosphoric acid with chloroacetamide; O,O-diethyl dithiophosphoric acid with chloroacetonitrile, chloroacetamide, N⁴-chloroacetylsulfanilamide,[9] chloroacetylurea[10] and α-bromoisovalerylurea ("Bromural"); O,O-di-*n*-butyl dithiophosphoric acid with chloroacetamide; and O,O-di-*n*-decyl dithiophosphoric acid with 1-chloroacetyl-3-phenylurea.[11]

Procedure II.—The anhydrous sodium or potassium salt (1 mole) of an O,O-dialkyl dithiophosphoric acid or monothiophosphoric acid was dissolved in acetone (about 1300 ml.) and the α-haloacyl derivative was added. The mixture was allowed to react under reflux for several hours or at room temperature for 24 hours, then filtered. The filtrate was stripped of solvent by distillation under reduced pressure on a water-bath and the residue was washed with water. If the residue was a liquid, it was dried over anhydrous magnesium sulfate, if a solid it was recrystallized.

Procedure II was used in treating potassium O,O-dimethyl dithiophosphate (m. p. 186–187°) with chloroacetylurea; sodium O,O-diethyl dithiophosphate with α-chloroacetanilide[12] and α-chloro-4-nitroacetanilide[13]; potassium O,O-diethyl dithiophosphate with α-chloro-N-methylacetamide, α-chloro-N,N-dimethylacetamide and α-bromo-N,N-di-*n*-butylacetamide[6]; potassium O,O-diethyl monothiophosphate[4] with bromoacetonitrile and chloroacetylurea; potassium O,O-di-*n*-propyl dithiophosphate (m.p. 165°) with α-chloro-N-methylacetamide, α-chloro-N,N-diethylacetamide and chloroacetylurea; potassium O,O-diisopropyl dithiophosphate with chloroacetamide, α-chloro-N-methyl acetamide and α-chloro-N,N-diethylacetamide; potassium O,O-di-isobutyl dithiophosphate with chloroacetamide; and potassium O,O-di-*n*-amyl dithiophosphate (m.p. 152–153°) with chloroacetonitrile.

Reaction of Sodium O,O-Diethyl Dithiophosphate with α-Bromoisovalerylurea.—O,O-Diethyl dithiophosphoric acid (40 g., 0.2 mole) was added slowly with stirring to a suspension of anhydrous sodium carbonate (21.2 g., 0.2 mole) in methyl isobutyl ketone (150 ml.), causing the temperature to rise to 40°. α-Bromoisovalerylurea ("Bromural") (44.6 g., 0.2 mole) was added and the mixture was maintained at 60–70° for 8 hours, then filtered hot through a sintered glass funnel. Methyl isobutyl ketone was removed from the filtrate by distillation under 1 mm. pressure, leaving a viscous, nearly colorless liquid, which gradually crystallized to a sticky solid weighing 66 g. The crude product was recrystallized first from carbon tetrachloride (50 ml.), then twice more from 1:1 (by volume) carbon tetrachloride:hexane, giving 16.7 g. (25%) of colorless crystals, m.p. 96–97°. *Anal.* Calcd. for $C_{10}H_{21}N_2O_4PS_2$: N, 8.53; P, 9.42. Found: N, 8.33; P, 9.19.

(7) W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 145 (1915).

(8) W. A. Jacobs, M. Heidelberger and I. P. Rolf, THIS JOURNAL, **41**, 458 (1919).

(9) W. A. Jacobs and M. Heidelberger, *ibid.*, **39**, 2418 (1917).

(10) I. A. Pearl and W. M. Dehn, *ibid.*, **61**, 1377 (1939).

(11) G. Frerichs, *Arch. Pharm.*, **237**, 321 (1899); *Chem. Centr.*, **70**, II, 419 (1899).

(12) W. A. Jacobs and M. Heidelberger, THIS JOURNAL, **39**, 1439 (1917).

(13) W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 103 (1915).

Reaction of S-Cyanomethyl O,O-Diethyl Dithiophosphate with Hydrogen Sulfide.—S-Cyanomethyl O,O-diethyl dithiophosphate (50 g., 0.22 mole) was heated in an autoclave at 60° for 20 hours with hydrogen sulfide (7.6 g., 0.22 mole) and triethylamine (1 g., 0.01 mole) in toluene (100 ml.). The reaction mixture was then poured into a shallow dish and the toluene was allowed to evaporate, leaving a slurry of yellow crystalline solid in a brown oil. The crystals were separated by filtration; yield 26.3 g. (46%), m.p. 40–45°. An analytical sample was obtained by recrystallizing the yellow crystals first from toluene, then from 1:3 (by volume) toluene–hexane mixture, giving colorless crystals of the thioamide, m.p. 46–47°. *Anal.* Calcd. for $C_6H_{14}NO_2PS_3$: N, 5.41; S, 37.1. Found: N, 5.51; S, 37.2.

Acknowledgment.—The authors are indebted to the staff of the Analytical and Testing Division for the analyses reported herein, to Dr. R. C. Gore and his staff for infrared data and their interpretation, and to Mr. O. Rörsö for carrying out pressure reactions.

STAMFORD, CONN. RECEIVED JULY 26, 1950

[CONTRIBUTION FROM THE CHEMISTRY LABORATORIES OF WITTENBERG COLLEGE AND THE OHIO STATE UNIVERSITY]

Amine Salts of Imidodisulfuric Acid[1]

BY CLAUDE E. BOATMAN AND HARRY H. SISLER[2]

Sixteen amine salts of imidodisulfuric acid have been prepared and characterized. The effect of di-(cyclohexylammonium) imidodisulfate on the surface tension of water has been measured and it was found that there is insufficient lowering of the surface tension of water for the salt to have detergent properties. An explanation has been given for the failure of arylammonium imidodisulfates to be produced by the reaction of arylammonium chloride on trisilver imidodisulfate.

Because of the interesting properties of the metal salts of imidodisulfuric and other nitrogen–sulfur acids[3] and because it was believed that amine salts of this acid might possess detergent properties, it was decided to prepare and investigate a series of substituted ammonium imidodisulfates. No other investigation of these compounds has been reported.

Imidodisulfuric acid forms two series of salts: (a) the so-called "basic" salts with the formula $MN(SO_3M)_2$ and the so-called "neutral" salts with the formula $HN(SO_3)M_2$. Two general methods of preparation of the amine salts were tried in this study: (a) the displacement of ammonia from triammonium imidodisulfate by the amine in liquid ammonia, water or alcohol solution: and (b) the metathesis of the trisilver imidodisulfate with the amine hydrochloride.

$$NH_4N(SO_3NH_4)_2\cdot H_2O + 3RNH_2 \longrightarrow RNH_3N(SO_3H_3NR)_2 + 3NH_3 + H_2O \quad (a)$$

or

$$NH_4N(SO_3NH_4)_2\cdot H_2O + 2RNH_2 \longrightarrow HN(SO_3H_2NR)_2 + 3NH_3 + H_2O$$

$$\underline{AgN(SO_3Ag)_2} + 3RNH_3Cl \longrightarrow RNH_3N(SO_3H_3NR)_2 + \underline{3AgCl} \quad (b)$$

$$\underline{AgN(SO_3Ag)_2} + 3RNH_3Cl \longrightarrow HN(SO_3H_3NR)_2 + \underline{3AgCl} + RNH_2$$

Using method (a) the "neutral" salt was obtained with fifteen out of sixteen amines tried. Octadecylamine yielded the "basic" salt. It was not found possible to obtain a satisfactory preparation of the dimethylammonium or trimethylammonium imidodisulfates.

Dibenzylammonium imidodisulfate was prepared by method (b), but when it was attempted to prepare the *p*-toluidine or aniline salts, the corresponding sulfates were obtained.

Materials.—Triammonium imidodisulfate 1-hydrate was prepared by the method described by Sisler and Audrieth.[4] Trisilver imidodisulfate was prepared from triammonium imidodisulfate and silver nitrate by a modification of the method of Divers and Haga.[5]

Analytical Methods.—The analytical methods used in the characterization of the compounds are given: An ammoniacal solution of the alkylammonium imidodisulfate was treated with a few drops of a 5% barium chloride solution. The imidodisulfate ion produces a flocculent precipitate which is completely soluble in dilute hydrochloric acid. This test serves to distinguish among the sulfamate ion, the imidodisulfate ion and the sulfate ion; the sulfamate ion produces no precipitate, and the precipitate with the sulfate ion is, of course, insoluble in dilute hydrochloric acid.

The quantitative determination of carbon, hydrogen and nitrogen were carried out by micro combustion methods. Many of the nitrogen determinations were checked by the Kjeldahl method.

Sulfur was determined by first hydrolyzing an aqueous solution of the salt with nitrous acid and precipitating the resulting sulfate ion as barium sulfate.

Results.—The preparations and some of the properties of the salts prepared are summarized in Table I.

The failure to obtain arylammonium imidodisulfates by the reaction of trisilver imidodisulfate with the arylammonium chlorides (p-$CH_3C_6H_4NH_3$)Cl and ($C_6H_5NH_3$)Cl is worthy of note. Let us presume that the initial reaction is to form silver chloride in accordance with the equation

$$\underline{AgN(SO_3Ag)_2} + 3Cl^- \longrightarrow N(SO_3)_2^{=} + \underline{3AgCl}$$

The third ionization constant of imidodisulfuric acid as determined by Doyle and Davidson[6] is such as to cause immediate reaction in accordance with the equation

$$N(SO_3)_2^{=} + ArNH_3^+ \longrightarrow HN(SO_3)_2^- + ArNH_2$$

We know further that $HN(SO_3)_2^{=}$ ion is susceptible to acid-catalyzed hydrolysis[2] and so, since sulfate rather than imidodisulfate is found in the solution,

(1) Presented at the Sept., 1950, Meeting of the American Chemical Society.

(2) Department of Chemistry, The Ohio State University, Columbus, Ohio.

(3) Audrieth, Sveda, Sisler and Butler, *Chem. Rev.*, **26**, 49 (1940).

(4) Sisler and Audrieth, "Inorganic Syntheses," Vol. II, McGraw-Hill Book Co., Inc., New York, N. Y., p. 179.

(5) Divers and Haga, *J. Chem. Soc.*, **61**, 974 (1892).

(6) Doyle and Davidson, THIS JOURNAL, **71**, 3491 (1949).