Phosphonic Acids. VIII. The Identification of Organophosphorus Acids and Esters by S-*p*-Chlorobenzylthiuronium Derivatives[1,2]

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Received October 1, 1962

S-*p*-Chlorobenzylthiuronium salts, conveniently prepared by reaction of S-*p*-chlorobenzylthiuronium chloride with the monosodium salt of the organophosphorus acid, are useful derivatives for the purification and identification of phosphonic, phosphinic, phosphoric, and phosphorothioic acids and their esters. Organophosphorus esters are first converted to the appropriate monosodium salt by treatment with sodium ethyl mercaptide.

During the course of investigations in organophosphorus chemistry, we often have experienced considerable difficulty in the purification and positive identification of small amounts of certain phosphorus containing acids and especially their esters. Many such substances are hygroscopic liquids which are not readily obtained in an analytically pure form. Thus there was a need for a conveniently prepared crystalline derivative of these phosphorus compounds, preferably one from which the parent substance might be recovered if desired.

The most generally employed derivatives of phosphoric and phosphonic[3] acids have been salts either with heavy metals, such as barium, calcium, lead, or silver, or with nitrogen bases, such as aniline or cyclohexylamine. Although heavy metal salts often provide a convenient means of isolation and purification of the desired organophosphorus acid, the melting point usually is too high to be of value in characterization. In many instances the amine salts provide quite satisfactory derivatives, but in other cases they are not readily crystallized from solution. There have been two reports of the use of S-benzylthiuronium salts as derivatives of organophosphorus acids; namely, for diphenyl and dibenzyl phosphates[4] and for ethyl *m*-chlorophenoxymethylphosphonate.[5] Inasmuch as thiuronium salts have been widely used as derivatives of carboxylic acids,[6] an investigation was made of the general applicability of such salts as derivatives for organophosphorus acids.

It was found that S-*p*-chlorobenzylthiuronium chloride[7] is an excellent reagent for the conversion of monosodium salts of various types of organophosphorus acids into crystalline S-*p*-chlorobenzylthiuronium derivatives. These derivatives show characteristic sharp melting points which differ widely for different substances. Formation of the derivative involves a considerable gain in molecular weight, an advantage when only small amounts of substance are available. By passing an aqueous alcoholic solution of the S-*p*-chlorobenzylthiuronium salt through an acidic ion exchange resin, the free acid is readily recovered.

As described in a preceding paper,[1] treatment of phosphate, phosphonate, and phosphorothioate esters with sodium ethyl mercaptide provides a convenient means of converting them to the corresponding monosodium salts. Thus, preparation of S-*p*-chlorobenzylthiuronium derivatives of such esters involves treatment first with sodium ethyl mercaptide and then with S-*p*-chlorobenzylthiuronium chloride. Examples of S-*p*-chlorobenzylthiuronium derivatives are listed in Table I, and the procedure for their preparation is given in the Experimental.

Experimental

Preparation of S-*p*-Chlorobenzylthiuronium Chloride.—This reagent was obtained in two crystalline modifications,[8] one melting at 201–203°, similar to that reported by Dewey and Sperry[7] to melt at 197°, and the other at 177–178°. A mixture of the two forms melted at 177–178°. After standing for 1 week in a closed container, the melting point of the lower melting material was unchanged, whereas the originally higher melting substance now melted at 177–179°.

In a preparation carried out as described previously,[7] *p*-chlorobenzyl chloride (23.7 g., 0.10 mole) was added to a hot solution of thiourea (7.5 g., 0.10 mole) in 200 ml. of ethanol. The resulting solution was concentrated to 60 ml. and allowed to stand for 2 hr. at ambient temperature whereupon crystals separated. These were collected on a filter and washed with alcohol and then with ether to yield S-*p*-chlorobenzylthiuronium chloride, 11.6 g., 49%, m.p. 177–178°.

Anal. Calcd. for $C_8H_{10}Cl_2N_2S$: C, 40.51; H, 4.25; Cl, 29.89; S, 13.52. Found: C, 40.44; H, 4.58; Cl, 30.03; S, 13.57.

The combined filtrate and washings were concentrated to about 60 ml. and an equal volume of ether added. On standing overnight there separated crystals of the higher melting form of the product, 9.0 g., 38%, m.p. 201–203°.

Anal. Found: C, 40.74; H, 4.18; Cl, 30.04; S, 13.46.

In a more convenient preparation of the reagent, the same quantities of reactants were dissolved in 80 ml. of ethanol and the solution boiled until a white solid began to separate. The mixture was cooled to room temperature and an equal volume of ether added with stirring. The precipitated solid was collected on a filter and washed with ether to give the lower melting form of S-*p*-chlorobenzylthiuronium chloride, 20.3 g., 86%, m.p. 177–178°.

Derivatives from Organophosphorus Acids and Salts.—For the preparation of S-*p*-chlorobenzylthiuronium salts of *n*-octylphosphonic (I), phenylphosphonic (II), and phenylphosphinic (III) acids, the free acid (5 mmoles) was suspended in a minimum amount of water[9] and neutralized to phenolphthalein with *N* sodium hydroxide, whereupon solution took place. The neutralized solution was warmed to about 95°, and a saturated ethanolic solution of the S-*p*-chlorobenzylthiuronium chloride (2.37 g., 10 mmoles) was added. With compounds I and II, the derivative separated immediately, and with III it crystallized

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(1) Paper VII. R. G. Harvey, H. I. Jacobson, and E. V. Jensen, *J. Am. Chem. Soc.*, in press.

(2) This paper is taken from the Ph.D. dissertation of R. G. Harvey, University of Chicago, 1960. It was presented in part before the 139th National Meeting of the American Chemical Society, St. Louis, Mo., 1961.

(3) L. D. Freedman and G. O. Doak, *Chem. Rev.*, **57**, 479 (1957).

(4) J. Baddiley and E. M. Thain, *J. Chem. Soc.*, 246 (1951).

(5) M. H. Maguire and G. Shaw, *ibid.*, 1756 (1955).

(6)(a) J. J. Donleavy, *J. Am. Chem. Soc.*, **58**, 1004 (1936); (b) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 202.

(7) B. T. Dewey and R. B. Sperry, *J. Am. Chem. Soc.*, **61**, 3251 (1939).

(8) S-Benzylthiuronium chloride likewise is reported[6a] to exist in two crystalline forms.

(9) For certain compounds it is advantageous to employ alcohol instead of water as the solvent. In this case sodium chloride will precipitate when the S-*p*-chlorobenzylthiuronium chloride reagent is added, and should be removed before isolation of the derivative.

TABLE I

S-*p*-CHLOROBENZYLTHIURONIUM SALTS

	Phosphorus compound	Derivative[a]	M.p., °C.	Cryst. solvent	C		H		Cl		S	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
I.	$C_8H_{17}PO(OH)_2$	$C_8H_{17}P(OH)O_2Q$	192–193	Ethanol	48.67	48.57	7.15	7.08	8.95	8.86	8.12	7.88
II.	$PhPO(OH)_2$	$PhP(OH)O_2Q$	200–202	Pyridine	46.73	46.76	4.49	4.70	9.85	9.57	8.93	9.44
III.	$PhPHO(OH)$	$PhPHO_2Q$	180–182	Ethanol	49.05	49.04	4.70	4.74	10.35	10.36	9.35	9.33
IV.	$(EtO)_2POSNa$	$(EtO)_2POSQ$	81–82	Ether	38.86	39.41	5.44	5.40	9.56	9.38	17.30	17.16
V.	$(EtO)_3PO$	$(EtO)_2PO_2Q$	160–161	Acetone	40.62	40.71	5.68	5.79	9.88	9.48	9.04	9.17
VI.	$EtPO(OEt)_2$	$EtP(OEt)O_2Q$	166–167	Acetone	42.54	42.41	5.95	6.11	10.47	9.94	9.46	9.65
VII.	$EtSPO(OEt)_2$	$EtSP(OEt)O_2Q$	151–152	Water	38.86	39.34	5.44	5.38	...	...	...	...
VIII.	$PhSPO(OEt)_2$	$PhSP(OEt)O_2Q$	174–176	Water	45.87	46.13	4.81	4.87	...	...	15.31	15.02

[a] Q = $p\text{-}ClC_6H_4CH_2\overset{+}{S}{=}C(NH_2)_2$.

slowly as the reaction mixture stood at room temperature. Recrystallization from the appropriate solvent, indicated in Table I, furnished the analytically pure derivative.

The derivative of sodium O,O-diethylphosphorothioate (IV) was prepared in similar fashion, except that the neutralization step was not necessary.

Derivatives from Organophosphorus Esters.—For the preparation of S-*p*-chlorobenzylthiuronium salts from phosphate (V), phosphonate (VI), or phosphorothioate (VII, VIII) esters, the following procedure is recommended: Sodium ethyl mercaptide is prepared by dissolving sodium (220 mg., 10 mmoles) in a mixture of 10 ml. of ethyl mercaptan and 3 ml. of ethanol. The ester (10 mmoles) is added and the resulting solution heated under reflux for 24 hr. A saturated alcoholic solution of S-*p*-chlorobenzylthiuronium chloride (2.38 g., 10 mmoles) is added and the resulting precipitate of sodium chloride removed by filtration. The solvent is evaporated from the filtrate and the residue crystallized from the appropriate solvent, indicated in Table I.

Recovery of the Free Acid from the Thiuronium Salt.—One gram of the S-*p*-chlorobenzylthiuronium derivative of phenylphosphinic acid (III) was dissolved in 30 ml. of 50% aqueous ethanol and passed through a column of 16 g. of Dowex 50W-X8 resin which previously had been well washed with 50% alcohol. The aqueous alcohol eluate was concentrated to about 10 ml. and extracted with ether. Evaporation of the ether gave phenylphosphinic acid, 264 mg., 64% recovery, m.p. 81–83°.

Reactions of Elemental Phosphorus with Organometallic Compounds

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Received August 10, 1962

The direct synthesis of phenylphosphine from phosphorus was achieved in 25% and 40% yields, respectively, by reaction of white phosphorus with phenylmagnesium bromide and with phenyllithium. *n*-Butylphosphine was prepared in 7 to 9% yields by reactions of phosphorus with *n*-butylmagnesium bromide and with *n*-butyllithium. In these reactions much of the phosphorus was converted to nonmelting, insoluble yellow solids, believed to be organopolyphosphines. Reactions of phenylsodium and tri-*n*-butylaluminum with phosphorus gave organopolyphosphines, exclusive of monomeric phosphines.

The susceptibility of white phosphorus to nucleophilic attack is suggested by its well known reaction with hydroxide ion. Hypophosphite, phosphite, phosphine, and hydrogen are obtained as products, and while the mechanism is complex,[1] the first step would appear to involve a nucleophilic attack by hydroxide on the P_4 tetrahedron.

To test the possibility of obtaining organophosphorus compounds by reaction of phosphorus with organic nucleophiles, we have treated a variety of organometallic compounds with white phosphorus. The results are summarized in Table I. The reactions were carried out by adding the organometallic solution dropwise to a slurry of finely divided white phosphorus (method A), or by adding the phosphorus as 0.1-g. pieces in one portion to the organometallic solution (method B). In all of the experiments the phosphorus reacted completely in one to three hours giving deep red solutions. Hydrolysis of reaction mixtures from experiments with organolithium and organomagnesium compounds gave mixtures of corresponding organophosphines with the primary phosphine generally predominating. Liberation of phosphine or hydrogen during hydrolysis could not be detected by mass spectroscopy.

The highest organophosphine yields were obtained from phenyllithium in ether solution and from phenylmagnesium bromide in refluxing tetrahydrofuran (THF). Butyllithium and butylmagnesium bromide gave butylphosphines in low yields under the conditions studied. In the phenyllithium reactions the order of addition had little effect on yields but with butyllithium and butylmagnesium bromide better yields were obtained using addition method B. The choice of solvent was critical for reactions of phenyllithium and phenylmagnesium bromide. For phenyllithium, ether was far superior to tetrahydrofuran, but for phenylmagnesium bromide refluxing tetrahydrofuran gave substantially better yields. Phenylmagnesium bromide in di-*n*-butyl ether at 100° gave predominately diphenylphosphine but the over-all yield of phosphine was relatively poor.

In the experiments with phenyllithium, ratios of starting materials were varied from one mole of phenyllithium per gram-atom of phosphorus to four moles of phenyllithium per gram-atom of phosphorus. Varying reactant ratios in the range of 1.6:1 to 4:1 had little effect on over-all yields based on phosphorus but some-

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[1] J. R. VanWazer, "Phosphorus and Its Compounds," Interscience Publishers, Inc., New York, N. Y., 1958, p. 356.