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

The Synthesis of Parathion and Some Closely Related Compounds

BY JOHN H. FLETCHER, J. C. HAMILTON, I. HECHENBLEIKNER, E. I. HOEGBERG, BEATRICE J. SERTL AND J. T. CASSADAY

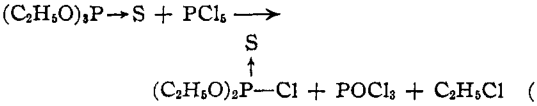
In a previous note[1] we have described a method for the preparation of the important insecticidal compound O,O-diethyl O-*p*-nitrophenyl thiophosphate which is now called "parathion." The method was based upon the synthesis used by Schrader[2] who first prepared the compound and designated it "E-605." We now wish to report further work on the synthesis of parathion and a few of its close relatives.

In the German process[2] for making E-605 phosphorus trichloride[3] (PCl_3) reacts with sulfur to give thiophosphoric trichloride ($PSCl_3$). The latter compound is treated with sodium ethoxide to form O,O-diethyl chlorothiophosphate ($(C_2H_5O)_2PSCl$) which then reacts with sodium *p*-nitrophenoxide to produce parathion. Although the Germans implied[2] that very high yields were obtained by this series of reactions, we considered it worth while to investigate other possible routes of synthesis.

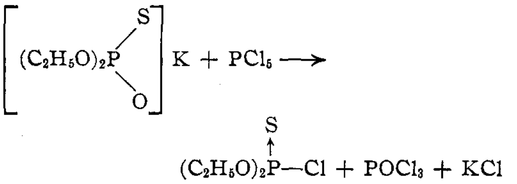
Several other methods of preparing parathion have been proposed by Schrader,[4] and we had tried some of them independently before his publication reached us. In general our observations confirmed those of Schrader, but we did not make a thorough investigation of any of his syntheses because a fundamentally different approach was found.

It had become apparent from our work on the preferred German process for E-605 that the reaction between O,O-diethyl chlorothiophosphate and sodium *p*-nitrophenoxide was straightforward and might be effected in good yield under a variety of reaction conditions. This led us to an investigation of other methods for preparing the intermediate acid chloride.

The literature contains several references to O,O-dialkyl or O,O-diaryl chlorothiophosphates. As early as 1861 Carius[5] reported that the following reactions took place, but he gave no experimental details.



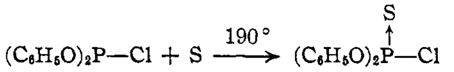
$$(C_2H_5O)_3P\rightarrow S + PCl_5 \longrightarrow (C_2H_5O)_2\overset{\overset{S}{\uparrow}}{P}-Cl + POCl_3 + C_2H_5Cl \quad (1)$$



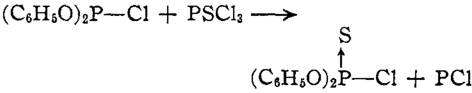
$$\left[(C_2H_5O)_2P\begin{smallmatrix}S\\O\end{smallmatrix}\right]K + PCl_5 \longrightarrow (C_2H_5O)_2\overset{\overset{S}{\uparrow}}{P}-Cl + POCl_3 + KCl \quad (2)$$

The only other mention of O,O-diethyl chlorothiophosphate is by Mastin and co-workers[6] who prepared it in 24% yield by the reaction of ethanol with thiophosphoric trichloride in the presence of pyridine. Delépine[7] used the method of Carius (Reaction 1) to prepare O,O-dimethyl chlorothiophosphate starting with O,O,O-trimethyl thiophosphate, but none of the other simple dialkyl compounds have been reported.

O,O-Diphenyl chlorothiophosphate was first obtained by Anschütz and Emery[8] who heated diphenyl chlorophosphite with sulfur. The addition of sulfur to various phosphites has since been studied by other investigators and found to be a rather general reaction which is markedly influenced by groups attached to the phosphorus atom. Among this work is that of Gottlieb[9] who found that thiophosphoric trichloride gave up its sulfur to certain phosphites.



$$(C_6H_5O)_2P-Cl + S \xrightarrow{190°} (C_6H_5O)_2\overset{\overset{S}{\uparrow}}{P}-Cl \quad (3)$$



$$(C_6H_5O)_2P-Cl + PSCl_3 \longrightarrow (C_6H_5O)_2\overset{\overset{S}{\uparrow}}{P}-Cl + PCl_3 \quad (4)$$

It will be noted that in all of the above methods for obtaining esters of monochlorothiophosphoric acid the source of phosphorus is phosphorus trichloride. We wish to describe a general method for preparing these diester-acid chlorides which does not start with a phosphorus halide but rather with phosphorus pentasulfide.

The reaction between phosphorus pentasulfide (probably existing as P_4S_{10} but assumed for the purposes of this paper to be P_2S_5) and alcohols leading to dialkyl dithiophosphoric acids has been known for a long time. Carius[10] examined the reaction using ethanol and found that, contrary to earlier claims by Kekulé, ethyl mercaptan was not formed; instead, he postulated the reaction

$$5C_2H_5OH + P_2S_5 \longrightarrow (C_2H_5O)_2PSOH + (C_2H_5O)_2PSSC_2H_5 + 2H_2S \quad (5)$$

---

[1] Fletcher, Hamilton, Hechenbleikner, Hoegberg, Sertl and Cassaday, THIS JOURNAL, **70**, 3943 (1948).

[2] Thurston, FIAT Final Report No. 949, October 14, 1946 (PB-60890).

[3] The nomenclature used for phosphorus compounds in this paper is based on a proposed system which has been tentatively agreed upon by the Organophosphorus Advisory Nomenclature Committee of the American Chemical Society (September, 1949).

[4] Coates, Topley, *et al.*, BIOS Final Report No. 1808, Item 22 (1947).

[5] Carius, *Ann.*, **119**, 289 (1861).

[6] Mastin, Norman and Weilmuenster, THIS JOURNAL, **67**, 1662 (1945).

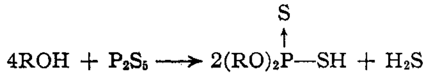
[7] Delépine, *Bull. soc. chim.*, [4] **11**, 576 (1912).

[8] Anschütz and Emery, *Ann.*, **253**, 105 (1889).

[9] Gottlieb, THIS JOURNAL, **54**, 748 (1932).

[10] Carius, *Ann.*, **112**, 190 (1859).

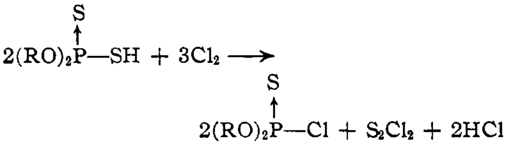
Subsequent work by various investigators[6,11,12,13] has shown that the principal reaction of phosphorus pentasulfide with either alcohols or phenols may be written



$$\mathrm{4ROH + P_2S_5 \longrightarrow 2(RO)_2\overset{\overset{S}{\uparrow}}{P}{-}SH + H_2S} \quad (6)$$

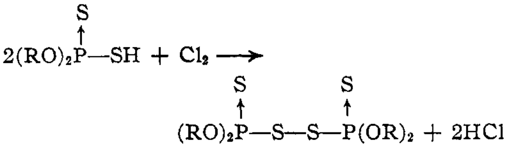
This reaction is also described in more or less detail in a number of patents among which are two[14,15] which give directions for the preparation of O,O-diethyl dithiophosphoric acid. We found it most convenient to suspend phosphorus pentasulfide in an inert solvent, heat to the appropriate reaction temperature, and then add the alcohol gradually. After completion of the reaction the solution was titrated to determine the amount of dithiophosphoric acid produced. Yields in repeated experiments were consistently 80–85%.

One of us (I.H.) discovered that chlorination of O,O-dialkyl or O,O-diaryl dithiophosphoric acids produces the corresponding esters of monochlorothiophosphoric acid in good yield.

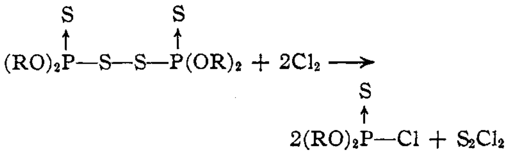


$$\mathrm{2(RO)_2\overset{\overset{S}{\uparrow}}{P}{-}SH + 3Cl_2 \longrightarrow 2(RO)_2\overset{\overset{S}{\uparrow}}{P}{-}Cl + S_2Cl_2 + 2HCl} \quad (7)$$

It was first thought that the reaction of chlorine with O,O-dialkyl or O,O-diaryl dithiophosphoric acids might proceed stepwise



$$\mathrm{2(RO)_2\overset{\overset{S}{\uparrow}}{P}{-}SH + Cl_2 \longrightarrow (RO)_2\overset{\overset{S}{\uparrow}}{P}{-}S{-}S{-}\overset{\overset{S}{\uparrow}}{P}(OR)_2 + 2HCl} \quad (8)$$



$$\mathrm{(RO)_2\overset{\overset{S}{\uparrow}}{P}{-}S{-}S{-}\overset{\overset{S}{\uparrow}}{P}(OR)_2 + 2Cl_2 \longrightarrow 2(RO)_2\overset{\overset{S}{\uparrow}}{P}{-}Cl + S_2Cl_2} \quad (9)$$

Osborne[16] reports having carried out Reaction 8 but does not mention isolation or identification of the product. However, we have evidence that the chlorination when conducted as described below is not so simple, as indicated by Reactions 8 and 9. Work is in progress to elucidate further the mechanism of this interesting reaction.

Chlorinations were carried out by allowing chlorine to vaporize into a solution of the dithiophosphoric acid in an inert solvent or into the acid without added solvent at or near room temperature. Yields varying from 53 to 64% (based on P_2S_5) were obtained in the chlorination of several O,O-dialkyl dithiophosphoric acids, the usual procedure being to prepare the dithiophosphoric acid in benzene and to chlorinate directly the solution of crude acid. The amount of chlorine used was the theoretical quantity as indicated by Reaction 7 based on an assumed yield of 85% of O,O-dialkyl dithiophosphoric acid from Reaction 6. Absorption of chlorine was rapid and mildly exothermic. Although the products of Reaction 7 can be separated fairly well by fractional distillation of the reaction mixture, the preferred procedure was to decompose the by-product sulfur monochloride by hydrolysis with water. Free sulfur and hydrochloric acid are formed in this decomposition. The dialkyl chlorothiophosphates are quite stable to water and aqueous solutions at ordinary temperatures over a considerable range of *p*H. It was found that adding the reaction mixture, after chlorination had been completed, to water at 20–40° produced a crude product which was satisfactory for distillation. A simple distillation with no special attention to fractionation then produced high quality O,O-dialkyl chlorothiophosphate. By this procedure six O,O-dialkyl chlorothiophosphates from methyl through butyl were prepared.

O,O-Diphenyl dithiophosphoric acid was prepared by heating phenol with phosphorus pentasulfide. The product was chlorinated in a manner similar to that used for the O,O-dialkyl dithiophosphoric acids to give O,O-diphenyl chlorothiophosphate. It thus appears that the chlorination reaction may be general for O,O-dialkyl and O,O-diaryl dithiophosphoric acids.

In our earlier note[1] we indicated that substitution of ethanol or water for chlorobenzene as a solvent for the reaction between O,O-diethyl chlorothiophosphate and sodium *p*-nitrophenoxide made possible the use of much shorter reaction times. Since then Toy[17] has reported that small amounts of tertiary aliphatic amines catalyze this reaction in chlorobenzene. We have found that no such catalyst is needed if acetone or methyl ethyl ketone is used as the solvent, the reaction being essentially complete in three to five hours. Nearly quantitative yields of high grade parathion were easily obtained in these solvents without distilling the product.

The other chlorothiophosphates described herein also reacted readily with sodium *p*-nitrophenoxide in acetone or methyl ethyl ketone to give the corresponding *p*-nitrophenyl esters in high yield. The latter were further purified either by distillation or low-temperature recrystallization with the exception of O,O-di-*n*-butyl O-*p*-nitrophenyl thiophosphate which showed signs of decomposition on one attempt at distillation and which gave a satisfactory analysis without distillation.

---

[11] Pistschimuka, *J. prakt. Chem.*, [2] **84**, 746 (1911); *J. Russ. Phys.-Chem. Soc.*, **44**, 1406 (1912); **56**, 11 (1925).

[12] Cambi, *Chimica e industria (Italy)*, **26**, 97 (1944).

[13] Malatesta and Pizzotti, *ibid.*, **27**, 6 (1945).

[14] Buchanan, U. S. Patent 1,868,192 (July 19, 1932).

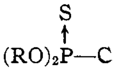
[15] Christmann, U. S. Patent 1,893,018 (January 3, 1933).

[16] Osborne, U. S. Patent 2,343,831 (March 7, 1944).

[17] Toy, U. S. Patent 2,471,464 (May 31, 1949).

TABLE I

O,O-DIALKYL CHLOROTHIOPHOSPHATES



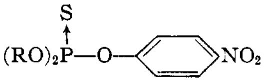
$(RO)_2\overset{\overset{S}{\uparrow}}{P}—Cl$

R	Yield, %[a]	B. p. °C.	Mm.	$n^{25}D$	Phosphorus Calcd.	Phosphorus Found	Sulfur Calcd.	Sulfur Found
					Analyses, %			
CH_3	53	70–72	20	1.4795	19.3	19.4	20.0	19.5
C_2H_5	59	94–96[b]	20	1.4685[b]	16.4	16.3	..	..
n-C_3H_7	58	70–75	1	1.4672	14.3	14.3	14.8	14.7
i-C_3H_7	55	56–59	1	1.4601	14.3	14.2	14.8	15.0
n-C_4H_9	64	95–98	0.7	1.4670	12.7	12.5	13.1	13.1
i-C_4H_9	62	76–82	0.5	1.4624	12.7	12.6	13.1	13.0

Based on phosphorus pentasulfide. [b] These data are in good agreement with b. p. and nD reported previously.[1]

TABLE II

O-p-NITROPHENYL THIOPHOSPHATE ESTERS



R	Solvent[a]	Yield, %	B. p. °C.	Mm.	$n^{25}D$	Analyses, % Calcd.	Found	Calcd.	Found
CH_3[b]	A	73[c]	M. p. 37–38[d]			P, 11.8	11.8	S, 12.2	12.1
C_2H_5	A	96	(Not distilled)[e]		1.5367				
n-C_3H_7	B	86	164	0.5	1.5259	P, 9.70	9.72	N, 4.39	4.25
i-C_3H_7	A	68[c]	M. p. 56–57[f]			P, 9.70	9.70	C, 45.13 H, 5.68	44.91 5.60
n-C_4H_9	B	89	(Not distilled)[g]		1.5195	P, 8.92	8.94	S, 9.23	9.30
i-C_4H_9	B	82	167–175	0.4	1.5155	P, 8.92	8.92	N, 4.03	3.90
C_6H_5	B	30[c]	M. p. 64–65[h]			P, 8.00	7.79	S, 8.28	8.60

[a] A = acetone; B = methyl ethyl ketone. [b] Acid chloride added gradually because reaction is mildly exothermic. [c] No effort was made to recover product from mother liquors. [d] From methanol, cooled in Dry Ice–acetone. [e] Distillation of parathion has been reported previously.[1] [f] From petroleum ether, cooled in Dry Ice–acetone. [g] Attempted distillation gave evidence of decomposition, so the undistilled material was washed with dilute sodium carbonate and heated at <1 mm. to give a satisfactory product. [h] From ethanol.

Experimental[18]

General Procedure for O,O-Dialkyl Chlorothiophosphates.—One-half mole of powdered phosphorus pentasulfide was suspended in 150 cc. of benzene and the mixture heated to 65–80°. Two moles of the appropriate alcohol was added over a period of one and one-half to two and one-half hours with enough heating to hold the reaction mixture at reflux. Refluxing was continued for two hours during which the reaction temperature rose to 90–100°. The mixture was then cooled to 25° and 91 g. (1.28 moles) of chlorine was allowed to vaporize and enter below the surface of the liquid. The temperature during chlorination was held at 25–30° by controlling the rate of introduction of chlorine and by intermittent application of an ice-bath. The time required for adding the chlorine was one and one-quarter to one and one-half hours. The chlorination mixture was stirred for fifteen or twenty minutes to complete the reaction; it was then added over a period of thirty or forty-five minutes to 350 cc. of water in order to destroy sulfur chlorides. During this time good stirring was maintained and ice was added when necessary to keep the hydrolysis mixture at 25–35°. Sulfur separated sometimes as a curdy solid, sometimes as a sticky ball. After stirring for a short time to ensure complete hydrolysis, the mixture was filtered through a Hyflo mat (filtration was very slow without filter aid), and the organic layer in the filtrate was separated and dried with Drierite. The product was then isolated by filtering and distilling. Experimental data are given in Table I.

O,O-Diphenyl Chlorothiophosphate.—A mixture of 376 g. (4.0 moles) of phenol and 222 g. (1.0 mole) of powdered phosphorus pentasulfide was heated and stirred at 130–140° for two hours. The dark colored reaction mixture was cooled and recrystallized from 500 cc. of 1:1 benzene-hexane to give 410 g. (73% yield) of O,O-diphenyl dithiophosphoric acid, m. p. 58–62°. A small portion was recrystallized again from the same solvent giving white crystals, m. p. 62.5–63.5°. The melting point has previously been reported[12] as 61°.

Two hundred and eighty-two grams (1.0 mole) of the O,O-diphenyl dithiophosphoric acid prepared above was dissolved in 500 cc. of benzene, and 110 g. (1.55 moles) of chlorine was passed in with stirring. During the chlorination the reaction temperature was held at 15–25° with an ice-bath. After all the chlorine had been added (two hours) the mixture was stirred for a few minutes more and then hydrolyzed by adding it slowly with good stirring to 500 cc. of water. The temperature of the hydrolysis mixture was kept at 25–35° by adding ice from time to time. The organic layer was separated, filtered, and stripped of solvent. The crude product thus obtained was recrystallized from acetone to give 175 g. (61% yield) of O,O-diphenyl chlorothiophosphate, m. p. 68–71°. Melting points in the range of 63–68° have been reported previously.[8,19]

General Procedure for p-Nitrophenyl Thiophosphates.—A mixture of equimolar quantities (usually 0.2 mole) of the appropriate O,O-dialkyl chlorothiophosphate, p-nitrophenol, and anhydrous sodium carbonate in acetone or methyl ethyl ketone (500–1,000 cc. per mole) was stirred and heated at reflux for three to five hours. After cooling to room temperature the reaction mixture was filtered to remove sodium chloride and sodium bicarbonate, and the filtrate was concentrated at water pump vacuum to remove solvent. The residue, depending upon the nature of the product, was purified by crystallization or vacuum distillation.

Parathion of good quality (purity $\not< 95\%$) was obtained by dissolving the above residue in benzene, washing with

---

(18) Warning: Parathion and its homologs are highly toxic and readily absorbed through the skin.

(19) (a) Autenrieth and Hildebrand, *Ber.*, **31**, 1094 (1898); (b) Ephraim, *ibid.*, **44**, 631 (1911); (c) Strecker and Grossman, *ibid.*, **49**, 63 (1916); (d) Autenrieth and Meyer, *ibid.*, **58B**, 840 (1925).

dilute sodium carbonate and with water, drying, and concentrating again at reduced pressure. Heating (oil-bath at 110°) at 1 mm. served to remove traces of unreacted O,O-diethyl chlorothiophosphate. Experimental data are given in Table II.

Acknowledgments.—The authors wish to express their appreciation for the interest and helpful suggestions of Dr. J. T. Thurston in this work. Analyses were performed by members of the Microanalytical and Macroanalytical Laboratories.

Summary

A new method for the preparation of O,O-dialkyl or O,O-diaryl chlorothiophosphates has been applied to the synthesis of seven such compounds (four of which are new) including O,O-diethyl chlorothiophosphate, an intermediate for parathion. The method involves the chlorination of O,O-dialkyl or O,O-diaryl dithiophosphoric acids which are prepared from phosphorus pentasulfide and alcohols or phenols. Yields of the chlorothiophosphates, based on phosphorus pentasulfide, varied from 44 to 64%.

It was found that the reaction between O,O-diethyl chlorothiophosphate and sodium *p*-nitrophenoxide to form parathion, when carried out in acetone or methyl ethyl ketone, goes essentially to completion in three to five hours at reflux temperature. Sodium *p*-nitrophenoxide was conveniently formed *in situ* by using equivalent quantities of *p*-nitrophenol and sodium carbonate. Six O-*p*-nitrophenyl thiophosphate esters of the parathion type, not previously characterized, were prepared in high yield by this method.

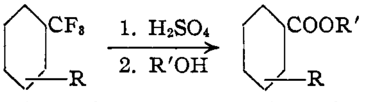
STAMFORD, CONN. RECEIVED NOVEMBER 2, 1949

[JOINT CONTRIBUTION FROM THE J. I. HOLCOMB RESEARCH LABORATORIES AND THE CHEMISTRY DEPARTMENT OF BUTLER UNIVERSITY]

Some Reactions of the Trifluoromethyl Group in the Benzotrifluoride Series. II. Alcoholysis[1]

BY GENE M. LE FAVE[2] AND PAUL G. SCHEURER[3]

It was recently found in this Laboratory that the trifluoromethyl (CF_3^-) group in benzotrifluoride and several ring-substituted members of its series will undergo reaction with approximately 100% sulfuric acid and upon subsequent hydrolysis will result in good yields of the corresponding benzoic acids.[4] While carrying out a study of the mechanism of this reaction,[5] it occurred to us that pouring the reaction product of 100% sulfuric acid and benzotrifluoride into a suitable alcohol would provide the corresponding benzoic ester if the rigorous operative conditions of the reaction, *i. e.*, the presence of hydrogen fluoride, fuming sulfuric acid, and the use of relatively elevated temperatures, did not preclude alcoholysis by causing excessive rearrangement and/or dehydration of the alcohol. Such a result would not be unique as a number of years ago Jacobsen successfully subjected benzotrichloride to ethanolysis in the presence of zinc chloride.[6]



This method proved reasonably successful and in order to ascertain its applicability, the esters listed in Table I were prepared. To obtain good yields it was necessary to permit the alcoholysis to proceed for at least fifteen minutes to one hour, depending on the nature of the alcohol. An excess of alcohol was employed with careful heating and agitation sufficient to remove most of the free hydrogen fluoride.

As expected, an attempt to prepare the benzyl and *t*-butyl esters failed; the benzyl alcohol was polymerized, while with the *t*-butyl alcohol an odor strongly suggestive of an ester was noted when the reaction product of the alcoholysis was poured into cold water. However, we succeeded only in isolating benzoic acid and several unidentified products.[7]

By way of analogy, benzotrichloride under essentially similar conditions, gave *n*-propyl benzoate upon alcoholysis with *n*-propanol. Although it *appears* to undergo alcoholysis at a slower rate than benzotrifluoride, it is, in general, a much smoother reaction.

It would be premature at this time to discuss the mechanism of this reaction,[5] since the nature of the reactants complicates experimental studies. In any case, there is most certainly a close relationship to the partial hydrolysis of benzotrichloride in the presence of various acidic catalysts such as iron(III) chloride and a limited amount of water resulting in the formation benzoyl chloride,[8] hence it seems justifiable to consider the formation

---

(1) Presented before the Organic Division of the American Chemical Society, 116th Meeting, Atlantic City, N. J., September, 1949.

(2) J. I. Holcomb Research Fellow, 1948–1950.

(3) Present address: The Graduate School, The Ohio State University, Columbus, Ohio.

(4) Le Fave, THIS JOURNAL, **71**, 4148 (1949).

(5) Mechanism studies are being conducted and will be reported later.

(6) Jacobsen, German Patent, 11,494; *Friedländer*, **1**, 24.

(7) Rapid hydrolysis or perhaps "complex ionization" [Newman, Kuivila and Garrett, THIS JOURNAL, **67**, 704 (1945)] might account for our failure to isolate the ester, although dehydration of the alcohol is the more probable explanation.

(8) See, for example, Davies and Dick, *J. Chem. Soc.*, 2208 (1932).