I from N-(Diethoxyphosphinothioyl)phthalamic Acid and Thionyl Chloride.—A mixture containing 9.61 g. (0.030 mole) of N-(diethoxyphosphinothioyl)phthalamic acid, 2.40 ml. (0.033 mole) of thionyl chloride, and 100 ml. of methylene chloride was heated at reflux overnight. The resulting solution was filtered, the filtrate was evaporated under reduced pressure, and the solid residue was recrystallized from hexane to obtain 8.00 g. (89.0% of theory) of O,O-diethyl phthalimidophosphonothioate.

I from N-(Diethoxyphosphinothioyl)phthalamic Acid and Acetic Anhydride.—A solution containing 6.34 g. (0.020 mole) of N-(diethoxyphosphinothioyl)phthalamic acid, 2.46 g. (0.030 mole) of sodium acetate, and 3.06 g. (0.030 mole) of acetic anhydride in 50 ml. of dimethylformamide was stirred for 4 hr. at 25°. It was then poured into 200 ml. of ice water and after standing for 30 min., the solid was removed by filtration, washed with water, and dried to obtain 5.57 g. (93.1% of theory) of O,O-diethyl phthalimidophosphonothioate.

O,O-Diethyl (Dimethylaminomethylene)phosphoramidothioate.—O,O-Diethyl phosphoramidothioate (16.9 g., 0.10 mole) was added dropwise to a stirred mixture of 8.80 g. (0.20 mole) of a 55.0% mineral oil dispersion of sodium hydride in 300 ml. of dimethylformamide under nitrogen at 3–8°. When the evolution of hydrogen ceased, 36.8 g. (0.20 mole) of saccharic anhydride was added over a 30-min. period at 0–10° and the solution was stirred for 2 hr. at 0–10°. It was then poured into 500 ml. of ice–water and the resulting mixture was extracted with carbon tetrachloride. The organic layer was evaporated under reduced pressure and the 13.5 g. of yellow oil remaining was distilled through a Claisen head still to obtain 8.25 g. (36.8% of theory) of the title compound, b.p. 65–68° (0.3 μ), n^{25}_{D} 1.5140. The substance has an infrared absorption at 1630 cm.$^{-1}$ assigned to C=N stretching[14] and its n.m.r. spectrum contains a triplet at -1.28 ($J = 7.1$ c.p.s.), a doublet at -3.10 ($J = 8.5$ c.p.s.), an octet at -3.96 ($J = 7.1, 8.8$ c.p.s.), and a doublet at -7.95 p.p.m. ($J = 24.6$ c.p.s.) in a 6:6:4:1 ratio.

Anal. Calcd. for $C_7H_{17}N_2O_2PS$: C, 37.5; H, 7.64; N, 12.5. Found: C, 37.4; H, 7.56; N, 12.3.

Diethylphosphinothioic Amide.—Anhydrous ammonia (10.0 g., 0.59 mole) was added as a vapor to a stirred solution of 36.0 g. (0.23 mole) of diethylphosphinothioic chloride in 150 ml. of benzene at 2–10° by means of a dip tube. The addition required 1.3 hr. and the mixture was stirred for another 2 hr. and allowed to warm to 23°. It then was filtered and the insoluble solid was extracted with hot chloroform. Diethylphosphinothioic amide crystallized on cooling the chloroform extract, 25.5 g. (80.8% of theory), m.p. 81–82.5°.

Anal. Calcd. for $C_4H_{12}NPS$: C, 35.0; H, 8.82; N, 10.2. Found: C, 35.3; H, 8.56; N, 10.2.

O,O-Bis(2,2,2-trichloroethyl) Phosphoramidothioate.—Anhydrous ammonia (16.0 g., 0.94 mole) was added as a vapor to a stirred solution of 74.3 g. (0.188 mole) of O,O-bis(2,2,2-trichloroethyl)phosphorochloridothioate in 250 ml. of methylene chloride at −15 to −30° by means of a dip tube. The addition required 20 min. and the mixture was stirred for another 1.5 hr. and allowed to warm to 16°. It was then extracted with water and the organic layer was evaporated under reduced pressure to obtain 92.3 g. of white solid. This was recrystallized from ethylcyclohexane, then aqueous methanol, to obtain 42.4 g. (59.3% theory) of the title compound, m.p. 90–91.5°.

Anal. Calcd. for $C_4H_6Cl_6NO_2PS$: C, 12.8; H, 1.61; Cl, 56.6; N, 3.73. Found: C, 13.3; H, 1.82; Cl, 56.4; N, 3.55.

Diethyl phosphoramidotrithioate was also prepared in this manner, but the colorless oil remaining after evaporation of the methylene chloride was unstable to heat so the crude product was used without further purification. A 99.5% yield of product and 97.3% yield of chloride ion were obtained.

N,N,N′,N′-Tetramethylphosphorothioic Triamide.—N,N,N′,N′-Tetramethylphosphorochloridothioic diamide (160 g., 0.86 mole) was added over a 50-min. period to about 250 ml. of liquid ammonia at −30 to −40° with stirring. The mixture was allowed to stir for 16 hr. at this temperature. The residue obtained after evaporation of the ammonia was diluted with chloroform and the resulting mixture was filtered. Evaporation of the filtrate left a crude product which was washed with hexane and recrystallized from cyclohexane to obtain white crystals, 56 g. (39% of theory), m.p. 58–66° (raised to 64.5–66.5° by further recrystallization). Much of the crude product was shown to be unreacted acid chloride by vapor phase chromatography.

Anal. Calcd. for $C_4H_{14}N_3PS$: N, 25.1. Found: N, 25.0.

Acknowledgment.—O,O-Diethyl phthalimidophosphonothioate was first obtained by Dr. H. Tolkmith of this laboratory during a yet unpublished part of his studies on the nucleophilicity of phosphoramidothionates toward carbon.[17] The authors wish to express their appreciation to Professors J. C. Martin and J. W. Crump for helpful discussions and to H. C. Page for technical assistance.

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Reactions of Dicarboximidophosphonothioate Esters with Nucleophilic Reagents

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Received June 25, 1965

O,O-Diethyl phthalimidophosphonothioate reacts with aniline, isopropylamine, *p*-nitrophenylhydrazine, sodium methoxide, potassium hydroxide, and sodium borohydride by displacement on the carbonyl carbon to produce N-(diethoxyphosphinothioyl)phthalamic acid derivatives, with sodium *p*-chlorophenate by displacement on phosphorus, and with thiourea by displacement on saturated carbon. The alkaline hydrolysis is first order in both hydroxide ion and substrate.

Dicarboximidophosphonothioate esters[1] and the related dicarboximidophosphonates[1-3] contain three different electrophilic centers capable of reaction with nucleophilic reagents: the carbonyl carbon atoms,[4,5] the phosphorus atom,[6,7] and the saturated carbon atoms adjacent to ester oxygen.[6,8] Reaction at a carbonyl carbon atom would result in acylation of the nucleophile and the formation of an N-(dialkoxyphosphinothioyl)amido acid derivative (reaction 1a), while reaction at the phosphorus atom would result in phosphorylation of the nucleophile with the elimination of a dicarboximide (reaction 1b), and reaction at a saturated carbon atom would result in alkylation of the

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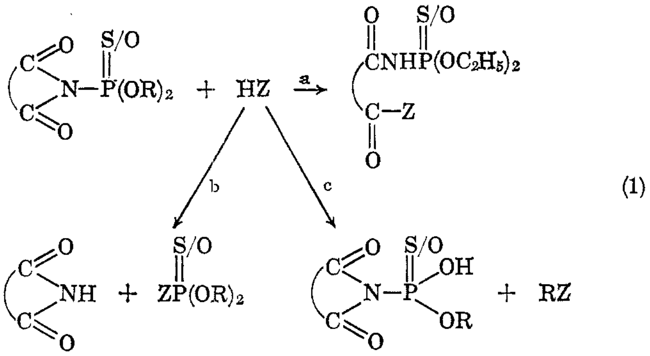
TABLE I

REACTIONS OF O,O-DIETHYL PHTHALIMIDOPHOSPHONOTHIOATE WITH NUCLEOPHILIC REAGENTS

Nucleophilic reagent	pK_{HA}	Product	Yield, %	M.p. or b.p. (mm.), °C.	Formula	Calcd., %			Found, %		
						C	H	N	C	H	N
$NaBH_4$		II, COZ = CH_2OH^a	22	76–78	$C_{12}H_{18}NO_4PS$	47.5	5.98	10.2^b	47.2	5.93	10.0^b
$(C_2H_5O)_2PSNHNa$		II, Z = $NHPS(OC_2H_5)_2{}^a$	85	111.5–113	$C_{16}H_{26}N_2O_6P_2S_2$	41.1	5.60	5.98	40.8	5.44	6.14
KOH	15.7	II, Z = OH^a	97	166–167 dec.	$C_{12}H_{16}NO_5PS$	45.4	5.08	9.76^b	45.2	4.93	9.40^b
CH_3ONa	15.2	II, Z = $OCH_3{}^a$	82	87–89	$C_{13}H_{18}NO_5PS$	47.2	5.48	4.23	47.0	5.44	4.37
i-$C_3H_7NH_2$	10.6	II, Z = NH-i-C_3H_7	83	128–129	$C_{15}H_{23}N_2O_4PS$	50.2	6.47	7.82	50.4	6.55	7.48
p-ClC_6H_4ONa	7.7	p-$ClC_6H_4OPS(OC_2H_5)_2$	57	106–112 $(0.4)^c$							
		Phthalimide^a	70	$232–235^d$							
$C_6H_5NH_2$	4.6	II, Z = NHC_6H_5	82	160–161	$C_{18}H_{21}N_2O_4PS$	55.1	5.39	7.13	55.3	5.61	7.03
p-$O_2NC_6H_4NHNH_2$		II, Z = $NHNHC_6H_4$-NO_2-p	70	170–171 dec.	$C_{18}H_{21}N_4O_6PS$	47.8	4.68	12.2	48.0	4.85	12.2
$(NH_2)_2CS$	−0.96	$C_2H_5SC(NH)NH_2{}^e$	65^e	$186–188^{e,f}$	$C_9H_{11}N_5O_7S^e$			21.0			21.0
		Phthalimide^g	23	230–232							

[a] After acidification. [b] Per cent phosphorus instead of nitrogen. [c] n^{25}_D 1.5222; lit.[15] b.p. 96–102° (0.15 mm.), n^{20}_D 1.5221. [d] Lit.[14] m.p. 238°. [e] Isolated and analyzed as the picrate. [f] Lit.[16] m.p. 188°. [g] After treatment with Dowex 50 acid-form resin.

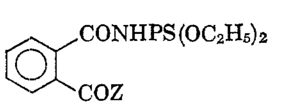


(1)

nucleophile and the formation of an alkyl dicarboximidophosphonothioic acid (reaction 1c).

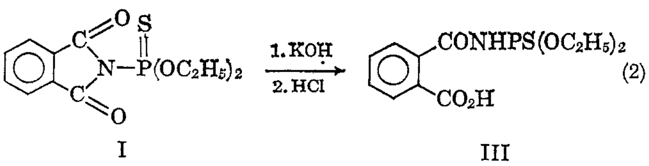
The alkaline hydrolysis of di-n-butyl succinimidophosphonate has been reported to yield dibutyl phosphoramidate and succinic acid[2,3] and must involve displacement on carbonyl carbon. O,O-Diethyl phthalimidophosphonothioate (I)[1] was also found to react with hydroxide ion at that site, but examples of each of these modes of reaction were observed on treatment of I with a variety of nucleophilic reagents.

Almost all of the nucleophilic reagents investigated, including hydroxide ion, methoxide ion, O,O-diethyl phosphoramidothioate anion,[1] aniline, isopropylamine, and p-nitrophenylhydrazine reacted readily with O,O-diethyl phthalimidophosphonothioate (I) to form derivatives (II) of N-(diethoxyphosphinothioyl)phthalamic



II, Z = $OCH_3NHPS(OC_2H_5)_2$, NHC_6H_5, NH-i-C_3H_7, $NHNHC_6H_4NO_2$-p

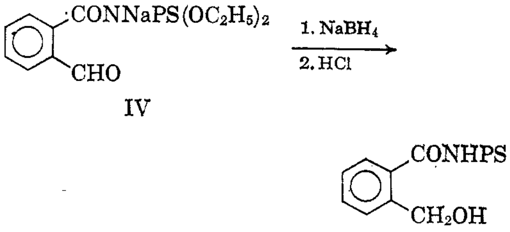
acid (III). The alkaline hydrolysis (reaction 2) is illustrative of these reactions, which involve displacement on the carbonyl carbon atoms of I. Yields of



(2)

I III

70–97% were obtained (Table I). Sodium borohydride apparently also reacted in this way, but the suggested initial product, IV, was reduced further in the reaction medium (reaction 3) and the observed product (Table I) was O,O-diethyl α-hydroxy-o-toluoylphosphoramidothioate (V). Thus, the carbonyl carbon atoms of I appear to be, in general, the most reactive of its electrophilic sites and the compound is principally an acylating agent.



IV

V

(3)

The amido acid derivatives (II) obtained in these reactions are themselves weak acids and are generally soluble in dilute aqueous alkali. Compound II [Z = $NHPS(OC_2H_5)_2$], for example, has pK_a values of 9.06 and 11.35 and the parent acid, III, has pK_a values of 5.27 and 10.57 (in 50% aqueous acetone). Their structures were confirmed by their infrared spectra, which contain two strong carbonyl absorptions, and by their proton n.m.r. spectra, which contain absorptions characteristic[9] of the $PS(OC_2H_5)_2$ group at about −1.35 and −4.25 p.p.m., an aromatic multiplet at about −7.5 p.p.m., and a broad amide hydrogen absorption, as well as the characteristic absorptions of the group represented by Z. Chemically, compound II (Z = NH-i-C_3H_7) was converted to N,N′-diisopropylphthalamide[10] in 68% yield on treatment with excess isopropylamine, and compound III was readily dehydrated to I by a number of reagents,[1] in agreement with the assigned structures.

The kinetics of the alkaline hydrolysis of O,O-diethyl phthalimidophosphonothioate (reaction 2) in 50% aqueous acetone at 25° were investigated briefly and the reaction was found to be first order in both hydroxide ion and substrate in the 9–11.5 pH range. Thus, rough rate measurements were made on reactions carried out keeping the hydroxide ion concentration constant by adding sodium hydroxide at the same rate at which it was consumed. After correction for the hydroxide ion used to satisfy the second ionization constant of the N-(diethoxyphosphinothioyl)phthalamic acid (III) product, the resulting rates of addition of sodium hydroxide were taken as the rates of hydrolysis and were found to give reasonably precise

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TABLE II

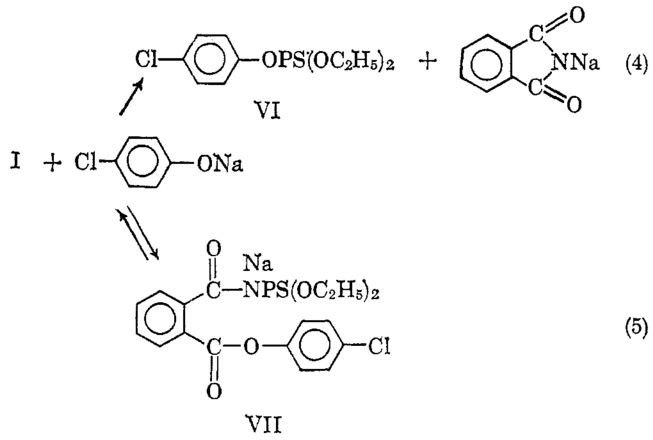
ALKALINE HYDROLYSIS OF O,O-DIETHYL PHTHALIMIDOPHOSPHONOTHIOATE

pH	Equiv. of base[a]	$k \times 10^4$, min.$^{-1}$ [b]
9.00 (± 0.10)	1.03	1.4 (± 0.3)
9.55 (± 0.05)	1.08	12.7 (± 1.7)
10.00 (± 0.02)	1.16	81.0 (± 1.3)
10.50 (± 0.05)	1.36	142 (± 14)
11.00 (± 0.02)	1.66	1250 (± 80)
11.50 (± 0.15)	2.00	3320 (± 250)

[a] Equivalents of base needed to titrate N-(diethoxyphosphinothioyl)phthalamic acid to the indicated pH. [b] In 50% aqueous acetone at 25 ± 1°, average rate constant and range.

pseudo-first-order rate constants (Table II). The logs of these rate constants were further found to be linearly dependent on pH (Figure 1) indicating that the reaction is also first order in hydroxide ion. This kinetic data also confirms the great speed of this reaction under the synthesis conditions of high base concentration. The half-life of I at pH 11.0, for example, is only about 5.5 min. at 25°.

Sodium *p*-chlorophenate reacted more difficultly with I to form O,O-diethyl O-*p*-chlorophenyl phosphorothioate (VI) and sodium phthalimide (reaction 4).



Yields of 57 and 70%, respectively, were obtained (Table I). This apparently anomalous reaction, involving displacement on phosphorus, can be explained by analysis of the equilibrium existing in the reaction medium between the starting materials and the anticipated phthalamic ester derivative VII (reaction 5). Thus, assuming that the basicities toward carbonyl carbon of *p*-chlorophenate ion (pK_{HA} = 7.7) and the amide anion VII [pK_{HA} estimated to be about 9.1 from II, Z = $NHPS(OC_2H_5)_2$] parallel their proton basicities[11,12] and ignoring any proximity effect, the equilibrium of reaction 5 should be almost completely on the side of the less basic *p*-chlorophenate ion and I. Consequently, even though the reaction at carbonyl carbon is probably the faster reaction in this case as it was with the other nucleophilic reagents of similar basicity and polarizability, and equilibrium 5 is probably quickly established, no VII can be isolated. Instead, almost all of the I remains in the solution where it reacts slowly by the less favorable displacement on phosphorus, which is not reversible under these conditions.[1] A similar equilibrium should also exist in the reaction of I with methoxide ion, but not with the neutral nucleophilic reagents, hydroxide ion, or O,O-diethyl phosphoramidothioate anion. In the methoxide ion (pK_{HA} = 15.2) case, however, the equilibrium should lie almost completely on the side of the methyl N-(diethoxyphosphinothioyl)phthalamate anion (analogous to VII) because methoxide ion is by far the strongest base in the system. Correspondingly, II (Z = OCH_3) was obtained in high yield from this reaction (after acidification).

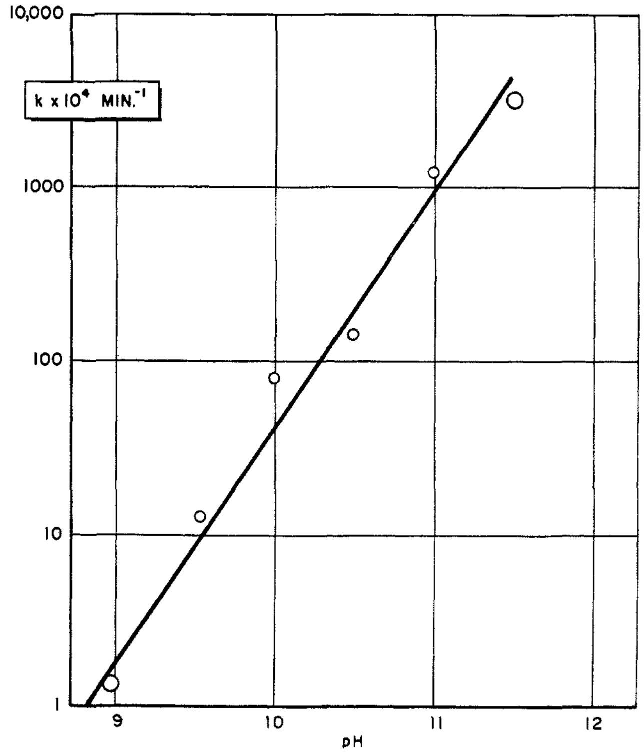
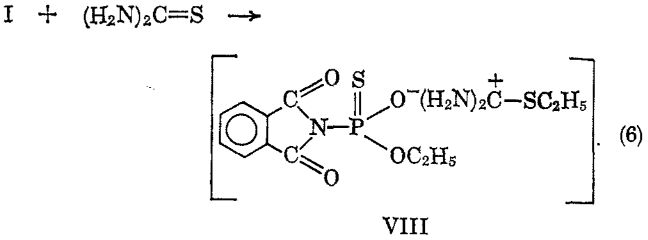


Figure 1.—Hydrolysis of O,O-diethyl phthalimidophosphonothioate.

Thiourea, on the other hand, reacted with I by displacement on saturated carbon to form a salt of S-ethylisothiourea, presumably VIII, in a very slow reaction (reaction 6). Compound VIII was not actually



isolated, but its formation was suggested by the isolation of the S-ethylisothiourea moiety in 65% yield through precipitation with picric acid and by its decomposition to phthalimide on treatment with an acidic ion-exchange resin (Table I). The change in the locus of reaction in this case is explained by the properties of the nucleophilic reagent. Thus, thiourea, which is extremely polarizable but only weakly basic, is predicted to be a very poor nucleophile toward both the carbonyl carbon atoms and the phosphorus atom of I since the relative reactivity of nucleophiles at these sites should depend primarily on the basicity of the nucleophilic reagent.[12,13] It is, however, predicted

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to be a very good nucleophile toward the saturated carbon atoms of I since the relative reactivity of nucleophiles at this site should depend more on polarizability than on basicity.[12] Consequently, with thiourea, alkylation, which is usually the least favored reaction of I with nucleophilic reagents, becomes the predominant reaction.

Experimental Section

N-(Diethoxyphosphinothioyl)phthalamic Acid.—A solution containing 59.8 g. (0.20 mole) of O,O-diethyl phthalimidophosphonothioate and 33.6 g. (0.60 mole) of potassium hydroxide in 500 ml. of 60% aqueous methanol was stirred at 40–50° for 4 hr. It was then cooled and acidified with 200 ml. of 5 *N* hydrochloric acid. The white precipitate that formed was removed by filtration, washed with water and carbon tetrachloride, and dried to obtain 61.3 g. (96.7%) of the title compound, m.p. 166–167° dec. Recrystallization from ethyl acetate did not raise the melting point.

Methyl N-(Diethoxyphosphinothioyl)phthalamate.—A 4 *N* solution of sodium methoxide in methanol, 12.5 ml. (0.050 mole), was added with stirring to a solution of 15.0 g. (0.050 mole) of O,O-diethyl phthalimidophosphonothioate in 175 ml. of tetrahydrofuran. The mixture was stirred at ambient temperatures for 2 hr. during which time there was a slight exotherm and at reflux for 30 min. The solution was cooled to 10° and acidified with 5 *N* hydrochloric acid. The resulting mixture was filtered, the filtrate was evaporated under reduced pressure, and the residue was recrystallized from carbon tetrachloride twice to obtain the title compound as white crystals, 13.6 g. (82.2% of theory), m.p. 87–89°.

O,O-Diethyl (N-Phenylphthalamoyl)phosphoramidothioate.—Aniline (9.31 g., 0.10 mole) was added with stirring to a solution of 15.0 g. (0.050 mole) of O,O-diethyl phthalimidophosphonothioate in 300 ml. of cyclohexane. A precipitate began to form immediately. The mixture was stirred 1 hr. at 25° and 1 hr. at reflux. The solid was removed by filtration and recrystallized from methanol to obtain the white crystalline product, 16.1 g. (82.2%), m.p. 160–160.5°. O,O-Diethyl (N-isopropylphthalamoyl)phoshoramidothioate and N-(diethoxyphosphinothioyl)-phthalamoyl-β-*p*-nitrophenylhydrazide were prepared similarly and recrystallized from carbon tetrachloride and a mixture of carbon tetrachloride and ethanol, respectively.

O,O,O′,O′-Tetraethyl Phthaloyldiphosphoramidothioate.—A 51.2% mineral oil dispersion of sodium hydride, 9.85 g. (0.21 mole), was added in small portions from a solids addition tube to a solution of 29.9 g. (0.10 mole) of O,O-diethyl phthalimidophosphonothioate and 16.9 g. (0.10 mole) of O,O-diethyl phosphoramidothioate in 200 ml. of dimethylformamide with stirring at 0–2° under nitrogen. Stirring was continued for 22 hr. and the solution was then poured into 500 ml. of ice–water. The orange solution obtained was filtered and the filtrate was acidified with 50 ml. of 5 *N* hydrochloric acid. The solid which slowly formed from the resultant oil was removed by filtration, washed with water, and recrystallized from carbon tetrachloride to obtain the title compound as white crystals, 39.3 g. (84.0%), m.p. 111.5–113°.

O,O-Diethyl α-Hydroxy-*o*-toluoylphosphoramidothioate.—A suspension of 1.40 g. (0.037 mole) of sodium borohydride in 75 ml. of 1,2-dimethoxyethane was added over a 2-hr. period to a solution of 5.00 g. (0.0167 mole) of O,O-diethyl phthalimidophosphonothioate in 25 ml. of the same solvent with stirring under nitrogen. An exothermic reaction took place immediately. After stirring 1 hr., the mixture was acidified with dilute hydrochloric acid and evaporated under reduced pressure. The residue was dissolved in methylene chloride and, after extraction with water, the resulting solution was evaporated to obtain a yellow oil. This formed soft, white crystals of the title compound on trituration with hexane, 1.1 g. (22%), m.p. 76–78°. Recrystallization from a mixture of hexane and methylchloroform did not raise the melting point.

O,O-Diethyl O-*p*-Chlorophenyl Phosphorothioate.—A solution of 12.9 g. (0.10 mole) of *p*-chlorophenol in 50 ml. of toluene was added slowly with stirring to a suspension of 3.90 g. (0.10 mole) of sodamide in 150 ml. of toluene. The mixture was heated at reflux for 45 min. and then a solution of 29.9 g. (0.10 mole) of O,O-diethyl phthalimidophosphonothioate in 100 ml. of toluene was added and the mixture was stirred another 3 hr. at reflux. After standing overnight, the mixture was filtered. The insoluble solid was dissolved in water and the resulting strongly basic solution was acidified to obtain phthalimide, 10.3 g. (70.1% of theory), m.p. 232–235° (lit.[14] m.p. 238°). The filtrate was evaporated under reduced pressure and the residual oil was distilled under vacuum to obtain 2.4 g. (19% recovery) of *p*-chlorophenol and 16.0 g. (57.0%) of the title compound, b.p. 106–112° (0.4 mm.), $n^{25}\mathrm{D}$ 1.5222 [lit.[15] b.p. 96–102° (0.15 mm.), $n^{20}\mathrm{D}$ 1.5221]. The same products were obtained when the reaction was carried out in refluxing tetrahydrofuran in the presence of 0.20 mole of *p*-chlorophenol for 3 hr., but 45% of the starting material was recovered unchanged.

S-Ethylisothiourea.—A solution containing 15.0 g. (0.050 mole) of O,O-diethyl phthalimidophosphonothioate and 3.80 g. (0.050 mole) of thiourea in 100 ml. of 1,2-dimethoxyethane was heated at reflux with stirring for 20 hr. The resulting solution was cooled and filtered, and the filtrate was evaporated under reduced pressure to obtain a yellow oil, 20.9 g. A 2.81-g. portion of this oil was dissolved in 25 ml. of hot ethanol and 1.91 g. (0.0075 mole) of 90% picric acid was added. The yellow platelets of S-ethylisothiourea picrate that formed on cooling amounted to 1.45 g. (64.8%), m.p. 186–188° (lit.[16] m.p. 188°). A 5.33-g. portion of the oil was dissolved in methanol and the solution was passed through a Dowex 50 acid column. The methanol was evaporated with heat to obtain an oily solid which, after washing with carbon tetrachloride, left 0.44 g. (23% of theory) of phthalimide, m.p. 230–232° (lit.[14] m.p. 238°).

Hydrolysis Rates.—A Sargent Model D automatic titrator equipped with a time-axis recorder and glass electrode was employed. A 5.00-ml. portion of an acetone solution containing 2.000 g. of O,O-diethyl phthalimidophosphonothioate/100 ml. of solution was added to 95.0 ml. of a 50% aqueous acetone solution at 25 ± 1° under argon and adjusted to the desired pH. The pH was then maintained automatically by adding 0.100 *N* sodium hydroxide (except the pH 11.5 rate in which the solution was 0.200 *N*) and the rate of addition was recorded. A sodium hydroxide titration curve of N-(diethoxyphosphinothioyl)phthalamic acid under these conditions was made to determine the equivalents of base required to adjust this acid to each pH value studied.

Acknowledgment.—The author wishes to express appreciation to Dr. W. B. Crummett for the hydrolysis rate data, to Professors J. C. Martin and J. W. Crump for helpful discussions, and to H. C. Page for technical assistance.

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