THE CONDENSATION OF PHOSPHONOTHIOIC AND PHOSPHONIC DICHLORIDES WITH *o*-DIAMINES[1]

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Received June 8, 1965

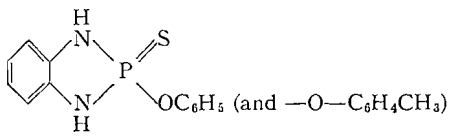
ABSTRACT

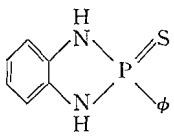
A series of 2,3-dihydro-1*H*-1,3,2-benzodiazaphosphole 2-sulfides and 2-oxides have been prepared, most commonly by the condensation of a diamine with a phosphonothioic or phosphonic dichloride in a refluxing inert solvent. The phosphonothioic dichlorides react more slowly than the corresponding phosphonic dichlorides, and phenylenediamines containing electron-donating substituents are more reactive than those containing electron-withdrawing substituents. The diazaphosphole 2-oxides undergo hydrolysis or alcoholysis of only one of the amide groups under mild conditions. The 2-sulfides are much more resistant to hydrolysis than the 2-oxides. The 2-sulfides are converted to the *N*-methyl derivatives by dimethyl sulfate and alkali. The 2-oxides are hydrolyzed under these conditions. The 2-sulfides are invariably lower melting and more soluble in nonpolar solvents than their 2-oxide analogues.

INTRODUCTION

In a previous paper (1) the reaction of phosphonic dichlorides with *o*-diamines has been found to give high yields of 1,3,2-diazaphosphole 2-oxides. The analogous 1,3,2-diazaphosphole 2-sulfides would be of interest as antimetabolites, not only because the sulfur atom would affect the physiological properties but also because the solubility and hydrolytic stability might be more favorable.

The only 1,3,2-diazaphosphole 2-sulfides previously reported were 2,3-dihydro-2-phenoxy-1*H*-1,3,2-benzodiazaphosphole 2-sulfide (2) and its 2-tolyloxy analogue (3) prepared by Autenrieth and his co-workers and the 2-phenyl compound synthesized by Wagner (4).





The present work was therefore undertaken to develop a general method of synthesis of the 1,3,2-benzodiazaphosphole 2-sulfides and by the preparation of a number of representative compounds to establish the factors influencing both their formation and stability.

EXPERIMENTAL

Reagents

Ethylphosphonous dichloride (5) was converted to ethylphosphonothionic dichloride, b.p. 178.6° at 760 mm (lit. b.p. 80–82° at 50 mm (6)). Ethylphosphonic dichloride, b.p. 177–179° (lit. b.p. 171–175° (7)), was prepared by the method of Kinnear and Perren (8).

4,N-Dimethyl-2-nitroaniline

This type of *N*-methyl amine has been conventionally prepared from the corresponding chloronitro compound and methylamine in a sealed tube. The following procedure at atmospheric pressure is more convenient for a larger scale synthesis. A solution of 4-chloro-3-nitrotoluene (34.3 g, 0.2 mole), ethanol (100 ml), 40% aqueous methylamine (40 g), and pyridine (20 ml added to provide a homogeneous reaction) was heated to incipient boiling (4 days). Each day methylamine (20 ml of 20% ethanolic solution) was added to compensate for any losses. After 4 days the excess amine and ethanol were removed by distillation. The oil phase was

[1]*Presented in part at the 139th National Meeting of the American Chemical Society, Chicago, Illinois, September 1961.*

separated from the residue and washed with three 200 ml portions of water; 30 ml of hexane was added to the semisolid mass, and the product was collected by filtration. Recrystallization from hexane gave 4,*N*-dimethyl-2-nitroaniline (15.5 g, 46%), m.p. 84.5–86° (lit. m.p. 84–85° (9)).

o-Phenylenediamines

In addition to the commercially available compounds, a number of diamines were prepared by reduction of the corresponding nitroanilines. The reduction of 4-ethoxy-2-nitroaniline is given as a typical example. Tin was added in small portions to a suspension of 4-ethoxy-2-nitroaniline (46 g, 0.25 mole) in 25% hydrochloric acid (400 ml) kept at 50°. When addition of a drop of the reaction mixture to aqueous sodium hydroxide gave no orange color, the reduction was judged complete (60 g of tin added). The solution was kept below 50° while being made alkaline and then filtered. The filtrate was extracted with seven 200 ml portions of benzene, and the combined extracts after filtration were saturated with dry hydrogen chloride to precipitate 4-ethoxy-*o*-phenylenediamine dihydrochloride. The dihydrochloride darkened above 230° and decomposed completely above 340°. Titration of a sample to the phenolphthalein endpoint gave 223.2 as a molecular weight (calcd. for $C_8H_{14}Cl_2N_2O$, 225.1). When free amines were desired, the benzene solutions were diluted with pentane and cooled to give crystals. If the parent nitro compounds were not commercially available they were synthesized from their chloronitro analogues by the method of Ashton and Suschitzky (10) unless otherwise indicated in Table I.

TABLE I

Melting points of *o*-diamines (or dihydrochlorides) obtained by reducing 2-nitroanilines

2-Nitroaniline	M.p. diamine		M.p. diaminedihydrochloride	
	Lit.	Found	Lit.	Found
4-Ethoxy	—	—	—	340 decomp.
4-Methoxy	—	—	188 decomp. (11)	222–225 decomp.
4-Trifluoromethyl	58 (12)	54.5–56	—	—
3,5-Dimethyl	77–78 (13)	76–78	—	—
N-Methyl[a]	—	—	191 (14)	193–194
4,*N*-Dimethyl	43–44 (9)	42.5–44	—	—
N-(*n*-Butyl)	35 (10)	35.8–36.2	—	—
N-Cyclohexyl	51 (10)	53–54.5	—	—
4-Methoxy-*N*-methyl[b]	78.3–78.8 (15)	74–76	—	—
(*N*,*N*′-Dimethyl-*o*-phenylenediamine)[c]	31.5 (16)	32–33	—	—

[a]Synthesis analagous to preparation of 4,*N*-dimethyl-2-nitroaniline described here.
[b]From methylation of the sulfonamide (14).
[c]This diamine prepared (16) by methylation of *N*,*N*′-di-*p*-toluenesulfonyl-*o*-phenylenediamide (17).

Condensation of a Phosphonothioic Dichloride with an o-Diamine in the Presence of a Tertiary Amine

Phenylphosphonothioic dichloride (5.28 g, 0.025 mole) in toluene (10 ml) was added dropwise with stirring to 4-carbomethoxy-*o*-phenylenediamine (4.15 g, 0.025 mole) in toluene (200 ml). The reaction mixture was maintained at 60° during the addition and for 15 min thereafter. Triethylamine (5.5 g, 0.054 mole) in toluene (10 ml) was added, and the mixture was refluxed for 2 h, cooled, and filtered. A solution of the precipitate in chloroform (15 ml) was poured into 150 ml of boiling toluene. Chloroform was distilled from this mixture while toluene was added to keep the volume at 150 ml. Filtration of the hot toluene solution removed triethylamine hydrochloride, and evaporation of the filtrate to 50 ml and cooling to 5° gave a semisolid precipitate. The decanted mother liquor when evaporated to 25 ml and cooled to −80° gave more product. Recrystallization of these solids from chloroform gave pure 5-carbomethoxy-2,3-dihydro-2-phenyl-1*H*-1,3,2-benzodiazaphosphole 2-sulfide.

Synthesis of Diazaphosphole 2-Sulfides and 2-Oxides in a Refluxing Solvent

The procedure for the reaction of a phosphonic dichloride with a diamine in bromobenzene was described in a previous paper (1). In using phosphonothioic dichlorides, several minor modifications were employed. Passing the exit gases through a cadmium acetate solution permitted measurement of the hydrogen sulfide evolved (max. yield 2%). With reactions which proceeded with difficulty, *o*-dichlorobenzene was often used as a solvent because of its higher boiling point. Some of the diazaphosphole 2-sulfides were quite soluble in aromatic solvents and it was necessary to reduce the volume of the reaction mixture and (or) add pentane to precipitate the product. The details are given in Tables II and III.

The melting point of every diazaphosphole 2-sulfide is lower than that of its 2-oxide analogue. When both amidic nitrogens are replaced by methyl groups a large decrease in melting point is observed for the 2-oxide structure, a small change for the 2-sulfide. These data reflect the weak hydrogen-bonding tendency of sulfur as compared to oxygen. As expected, this also leads to higher solubility in non-polar solvents for the 2-sulfides

as compared to the 2-oxides. Also, in both series the *N*-alkyl derivatives are more soluble in non-polar solvents. Both series of compounds are soluble in polar solvents such as methanol and ethanol but as traces of acid or base catalyze solvolysis, these solvents are seldom useful.

Hydrolysis of 2,3-Dihydro-2-phenyl-1H-1,3,2-benzodiazaphosphole 2-Oxide

When this benzodiazaphosphole 2-oxide (4.6 g, 0.02 mole) was added to 1 *N* sodium hydroxide (20 ml) at room temperature, an exothermic reaction occurred (the temperature rising to 38°) and the benzodiazaphosphole dissolved while a sodium salt precipitated. After cooling to 20°, the reaction mixture was filtered and the precipitate washed with absolute alcohol (three 5 ml portions) and dried. Additional product was obtained by partially evaporating the mother liquor and chilling. The sodium salt (2 g) was placed in water (20 ml) and acidification with 1 *N* hydrochloric acid to pH 5 gave 2-aminoanilido-phenylphosphonic acid (1.32 g), m.p. 240–247° decomp.

Anal. Calcd. for $C_{12}H_{13}N_2O_2P$: C, 58.06; H, 5.28; N, 11.29. Found: C, 57.56; H, 5.35; N, 11.38.

This product dissolved in aqueous sodium hydroxide and could be precipitated from the alkaline solution by careful acidification. It also dissolved in aqueous hydrochloric acid but underwent hydrolysis and could not be recovered by addition of alkali. When an aqueous acid solution of the 2-aminoanilidophenylphosphonic acid was boiled to remove most of the liquid, cooling produced the *o*-phenylenediamine salt of phenylphosphonic acid; m.p. 224–228°. This salt has been incorrectly reported as the amide (1).

Anal. Calcd. as 2-aminoanilido-phenylphosphonic acid, $C_{12}H_{13}N_2O_2P$: N, 11.29. Anal. Calcd. as the salt of *o*-phenylenediamine and phenylphosphonic acid, $C_{12}H_{15}N_2O_3P$: N, 11.05. Found (1): N, 11.02.

The salt was synthesized independently by heating to 80° a solution of phenylphosphonic acid (1.58 g, 0.01 mole) and *o*-phenylenediamine (1.08 g, 0.01 mole) in water (10 ml) and then cooling. The precipitate was collected, washed with alcohol, and dried, m.p. 226–230°. Its infrared spectrum was identical to that of the hydrolysis product described above.

Alcoholysis of 2,3-Dihydro-2-phenyl-1H-1,3,2-benzodiazaphosphole 2-Oxide

Dry hydrogen chloride was bubbled into a suspension of 2,3-dihydro-2-phenyl-1*H*-1,3,2-benzodiazaphosphole 2-oxide (1.15 g, 0.005 mole) in 10 ml of methanol until the solid dissolved. The mixture was heated just to boiling, cooled to room temperature, and made slightly alkaline with 1 *N* sodium hydroxide, and water was added to precipitate *O*-methyl-2-aminoanilido-phenylphosphonate (1.0 g, 76%), m.p. 149–150° (from methanol–water).

Anal. Calcd. for $C_{13}H_{15}N_2O_2P$: C, 59.53; H, 5.77; N, 10.68. Found: C, 59.49; H, 5.79; N, 10.59.

The same product was isolated when the diazaphosphole (2.3 g) in methanol (10 ml) was heated with sodium methoxide (0.1 g).

Hydrolysis of 2,3-Dihydro-2-phenyl-1H-1,3,2-benzodiazaphosphole 2-Sulfide

The 2-sulfide apparently does not react with 1 *N* sodium hydroxide at room temperature but slowly dissolves when the mixture is heated to 70°. Hydrogen sulfide is evolved when this solution is made acid.

Hydrolysis of 1,3-Dimethyl-2,3-dihydro-2-phenyl-1H-1,3,2-benzodiazaphosphole 2-Oxides and 2-Sulfides

The 2-oxide was recovered in 60% yield from a solution of 1 *N* sodium hydroxide refluxed for 1 min, but no recovery was possible after 3 min of refluxing. In contrast, the 2-sulfide in 1 *N* sodium hydroxide was recovered in 80% yield after 5 min of refluxing.

Methylation of 1-Methyl-2,3-dihydro-2-phenyl-1H-1,3,2-benzodiazaphosphole 2-Sulfide

Sodium hydroxide (6 ml, 25%) was added to the benzodiazaphosphole 2-sulfide (0.52 g, 0.002 mole) in dimethyl sulfate (1.3 g, 0.001 mole), and the mixture was stirred rapidly for 1 h at room temperature. The viscous liquid which separated from the reaction mixture was recrystallized twice from methanol–water to give a crude product, m.p. 91–92° (4.9 g, 89%). Recrystallization from *n*-hexane gave pure 1,3-dimethyl-2,3-dihydro-2-phenyl-1*H*-1,3,2-benzodiazaphosphole 2-sulfide, m.p. 100.5–101.5°, which did not depress the m.p. of an authentic sample obtained from *N,N'*-dimethyl-*o*-phenylenediamine and phenylphosphonothioic dichloride. The infrared spectra of the two samples were identical.

Methylation of 2,3-Dihydro-2-phenyl-1H-1,3,2-benzodiazaphosphole 2-Sulfide

Using identical quantities of materials to those above except for acetone (5 ml) and solid sodium hydroxide (ca. 0.4 g), this 2-sulfide was converted to the dimethyl derivative in 87% yield. The acetone was removed by distillation, and water (10 ml) was added to isolate the crude product.

Methylation of 2,3-Dihydro-2-ethyl-1H-1,3,2-benzodiazaphosphole 2-Sulfide

By the dimethylation procedure, this diazaphosphole produced 1,3-dimethyl-2,3-dihydro-2-ethyl-1*H*-1,3,2-benzodiazaphosphole 2-sulfide (88%), m.p. 70–71° from methanol–water.

Anal. Calcd. for $C_{10}H_{15}N_2PS$: C, 53.07; H, 6.68; N, 12.38. Found: C, 52.32; H, 6.91; N, 12.42.

Methylation of 1,2-Diphenyl-2,3-dihydro-1H-1,3,2-benzodiazaphosphole 2-Sulfide

By the monomethylation procedure, this diazaphosphole produced 1-methyl-2,3-diphenyl-2,3-dihydro-1*H*-1,3,2-benzodiazaphosphole 2-sulfide (93%), m.p. 115–116° from *n*-hexane.

Anal. Calcd. for $C_9H_{17}N_2PS$: C, 67.83; H, 5.09; N, 8.33. Found: C, 68.00; H, 5.12; N, 8.32.

TABLE II

Benzodiazaphosphole 2-sulfide syntheses

Diamine	Yield (%)[a]	Half-life (h)[b]	M.p. (°C)	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
With phenylphosphonothioic dichloride									
o-Phenylenediamine	83[c]	17	152–153.5[d]			11.38			11.41
4-Methyl-*o*-phenylenediamine	71[e]	—	128–130[f]	59.98	5.03	10.76	59.61	5.03	10.82
4-Chloro-*o*-phenylenediamine	40[c]	—	114.5–116[g]	51.34	3.59	9.98	51.43	3.66	10.04
4-Methoxy-*o*-phenylenediamine.2HCl	99[c]	5	186–188[h]	56.53	4.74	10.14	56.39	4.66	10.31
4-Ethoxy-*o*-phenylenediamine.2HCl	63[i]	1.5	113–114[j]	57.88	5.21	9.65	58.29	5.16	9.69
4-Carbomethoxy-*o*-phenylenediamine	41[k]	—	219–222[d]	55.25	4.31	9.27	55.36	4.37	9.34
4-Nitro-*o*-phenylenediamine	24[l]	—	230–231.5[m]	49.48	3.43	14.43	49.74	3.53	14.42
4-Trifluoromethyl-*o*-phenylenediamine	89[e]	13	140–145[n]	49.68	3.27	8.91	49.63	3.16	8.81
3,5-Dimethyl-*o*-phenylenediamine	73[p]	1.5	208–210[j]	61.30	5.51	10.21	61.11	5.47	10.09
4,5-Dimethyl-*o*-phenylenediamine.2HCl	34[c]	—	198–199[j]	61.30	5.51	10.21	61.43	5.50	10.21
4,5-Dichloro-*o*-phenylenediamine	48[q]	2.8	184–186[r]	45.73	2.83	8.89	45.52	2.91	8.87
3-Nitro-5-chloro-*o*-phenylenediamine	49[p]	2.7	234–236[h]	44.22	2.78	12.90	44.05	2.77	12.78
N-Methyl-*o*-phenylenediamine	75[s]	1.2	114–115[t]	59.98	5.03	10.77	59.78	4.94	10.78
4,*N*-Dimethyl-*o*-phenylenediamine	72[e]	1.7	113–114.5[u]	61.30	5.51	10.21	61.06	5.48	10.32
4-Methoxy-*N*-methyl-*o*-phenylenediamine	79[c]	1.5	161.5–162.5[v]	57.92	5.21	9.65	57.58	5.17	9.75
N,*N*′-Dimethyl-*o*-phenylenediamine	71[e]	1.7	101–102[w]	61.30	5.51	10.21	61.38	5.53	10.23
N-(*n*-Butyl)-*o*-phenylenediamine.2HCl	45[e]	3	110.5–111.5[w]	63.55	6.33	9.26	63.77	6.45	9.44

TABLE II (*Concluded*)

Diamine	Yield (%)[a]	Half-life (h)[b]	M.p. (°C)	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
N-Cyclohexyl-*o*-phenylenediamine.HCl	68[e]	4	158.5–159.5[z]	65.83	6.45	8.53	65.59	6.48	8.39
N-Phenyl-*o*-phenylenediamine	80[p]	0.2	188–189[d]	67.06	4.69	8.69	66.91	4.82	8.58
2,3-Diaminonaphthalene	6[y]	—	223–227[z]	64.85	4.42	9.46	64.97	4.49	9.52
1,2-Diaminonaphthalene.2HCl	63[i]	~10	180–181[aa]	64.85	4.42	9.46	65.00	4.48	9.55
2,3-Diaminopyridine	76[p]	2	234–236[bb]	53.43	4.08	16.99	53.83	4.41	16.94
With ethylphosphonothioic dichloride									
o-Phenylenediamine	84[e]	0.3	135.5–137[cc]	48.47	5.59	14.13	48.14	5.54	14.12
N-Methyl-*o*-phenylenediamine.2HCl	67[e]	3.7	92–93[g]	50.92	6.17	13.20	50.59	6.09	13.30

[a] Crude product suitable for most purposes.
[b] Approximate, for reagents were mixed at room temperature then heated to reflux. Also, the boiling points of the solvents used determine the temperature at which the reaction was run so that all of the figures are not comparable. Where an amine salt is the reagent, the half-life listed is for 50% evolution of hydrogen chloride beyond that calculated for the amine salt decomposition.
[c] In refluxing bromobenzene.
[d] From $CHCl_3$, dried in vacuum.
[e] In refluxing bromobenzene, pentane added to precipitate the product.
[f] From trichloroethylene.
[g] From CCl_4, then heptane.
[h] From a $CHCl_3$ solution passed through alumina.
[i] In refluxing bromobenzene, the reaction mixture reduced in volume, CCl_4 added to precipitate the product.
[j] From $CHCl_3$–CCl_4.
[k] In refluxing toluene containing triethylamine, see experimental section.
[l] In refluxing xylene–dioxane (1:2) containing tri-*n*-propylamine. The solvent was distilled, and the residue was dissolved in C_2H_5OH and poured into H_2O to precipitate the product.
[m] From C_2H_5OH–H_2O, then $CHCl_3$–CCl_4, then C_2H_5OH–H_2O.
[n] Recrystallized from chlorobenzene–CCl_4.
[p] In refluxing *o*-dichlorobenzene.
[q] In refluxing bromobenzene. The entire reaction mixture (0.0125 mole) was chromatographed on alumina (60 g), and eluted with $CHCl_3$; then CCl_4 was added to the eluent to produce crystals.
[r] Chromatographed on alumina from $CHCl_3$ solution, eluted with $CHCl_3$–CCl_4 (1:1).
[s] In refluxing bromobenzene. The product (0.05 mole) was adsorbed on alumina and eluted with CCl_4, then precipitated by adding hexane.
[t] From CCl_4.
[u] Chromatographed on alumina and eluted with $CHCl_3$; CCl_4 added to precipitate the product.
[v] A benzene solution passed through alumina, then cooled to give crystals from $CHCl_3$–CCl_4.
[w] A $CHCl_3$ solution chromatographed on alumina. The product was eluted with CCl_4, the volume of the eluent was reduced, and pentane was added.
[x] A CCl_4 solution chromatographed on alumina. The product was eluted with CCl_4, the eluent was reduced in volume, and hexane was added.
[y] In refluxing CCl_4 containing triethylamine. The product isolation was similar to that given in experimental section except that a $CHCl_3$ solution of the crude product was poured into ether to precipitate triethylamine hydrochloride.
[z] Recrystallized from benzene.
[aa] From $CHCl_3$–CCl_4, then benzene, then again from $CHCl_3$–CCl_4.
[bb] Chromatographed on alumina and eluted with dioxane.
[cc] A $CHCl_3$ solution passed through alumina; the eluent was evaporated and CCl_4 was added.

TABLE III

Benzodiazaphosphole 2-oxide syntheses

Diamine	Yield (%)[a]	Half-life (h)[b]	M.p. (°C)	Calcd.			Found		
				C	H	N	C	H	N
With phenylphosphonic dichloride									
4-Methoxy-*o*-phenylenediamine.2HCl	97[c]	0.15	227.5–229[d]	60.00	5.03	10.77	59.98	4.98	10.71
4-Ethoxy-*o*-phenylenediamine.2HCl	77[e]	0.9	189–190.5[f]	61.31	5.51	10.21	61.47	5.38	10.23
4-Trifluoromethyl-*o*-phenylenediamine	100[g]	1.2	154–157[h]	52.38	3.38	9.40	52.09	3.50	9.00
3,5-Dimethyl-*o*-phenylenediamine	98[c]	0.08	311–313[i]	65.11	5.85	10.85	64.88	5.76	10.89
4,5-Dimethyl-*o*-phenylenediamine.2HCl	98[g]	0.4	322–324[d]	65.11	5.85	10.85	64.98	5.76	10.84
4,5-Dichloro-*o*-phenylenediamine	95[c]	0.06	300–301[j]	48.18	3.03	9.37	48.06	3.11	9.37
3-Nitro-5-chloro-*o*-phenylenediamine	91[k]	0.04	283–286[l]	46.54	2.93	13.57	46.46	3.20	13.87
N-Methyl-*o*-phenylenediamine.2HCl	98[c]	0.25	263–265[m]	63.93	5.36	11.46	64.05	5.49	11.43
4,*N*-Dimethyl-*o*-phenylenediamine	93[g]	0.06	196–197[n]	65.11	5.84	10.85	64.79	5.86	10.74
4-Methoxy-*N*-phenyl-*o*-phenylenediamine.2HCl	96[c]	0.3	213–214.5[p]	61.31	5.51	10.21	61.08	5.53	10.14

TABLE III (*Concluded*)

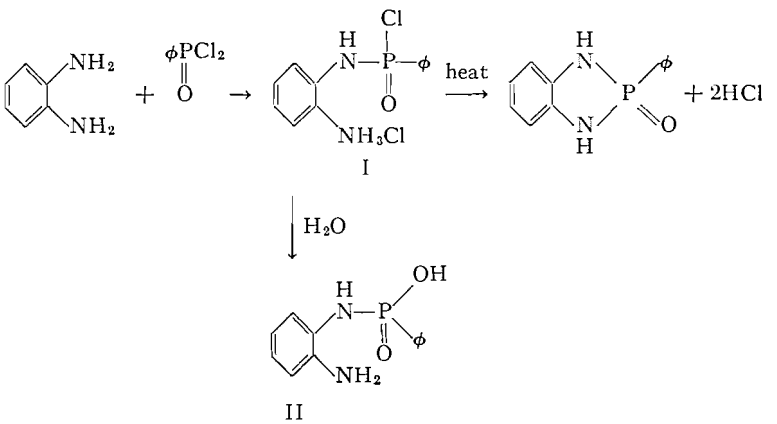
Diamine	Yield (%)[a]	Half-life (h)[b]	M.p. (°C)	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
N,N'-Dimethyl-*o*-phenylenediamine	81[c]	0.12	132.5–133.5[q]	65.11	5.85	10.85	64.75	5.83	10.76
N-(*n*-Butyl)-*o*-phenylenediamine.2HCl	88[g]	0.06	178–179[d]	67.12	6.68	9.79	67.10	6.94	9.71
N-Cyclohexyl-*o*-phenylenediamine	99[e]	0.08	260.5–262[d]	69.21	6.78	8.97	68.96	6.90	8.91
With ethylphosphonic dichloride									
o-Phenylenediamine	9.5[c]	0.16	193–194	52.76	6.09	15.38	52.02	6.18	15.49
N-Methyl-*o*-phenylenediamine.2HCl	20[g]	0.4	107.5–108[r]	55.08	6.68	14.28	54.88	6.97	14.50

[a]Crude product suitable for most purposes.
[b]Approximate, for the reagents were mixed at room temperature, then heated to reflux. The figures are not all comparable, for the boiling points of the solvents used determined the reaction temperatures.
[c]In refluxing bromobenzene.
[d]From $CHCl_3$–CCl_4.
[e]In refluxing chlorobenzene, pentane added to precipitate the product.
[f]From a $CHCl_3$ solution passed through alumina.
[g]In refluxing bromobenzene, pentane added to precipitate the product.
[h]The crude product contained solvent which could not be removed by heating in vacuum. The pure product crystallized after several days from a dilute bromobenzene–pentane solution.
[i]From $CHCl_3$–CH_3OH (9:1).
[j]From tetrahydrofuran.
[k]In refluxing *o*-dichlorobenzene.
[l]From bromobenzene.
[m]From $CHCl_3$.
[n]From CCl_4.
[p]A $CHCl_3$ solution was chromatographed on alumina and eluted with $CHCl_3$, and the eluent was evaporated and cooled.
[q]From CH_3OH.
[r]A CCl_4 solution was passed through alumina, then pentane was added.

RESULTS AND DISCUSSION

Cyclization Reactions

A series of 1,3,2-benzodiazaphosphole 2-sulfides (Table II) as well as some 2-oxides (Table III) have been prepared, most commonly by the condensation of a diamine with a phosphonothioic or phosphonic dichloride in a refluxing inert solvent. When these reagents are mixed at room temperature a precipitate usually forms immediately. In a previous paper (1), it was suggested that with phenylphosphonic dichloride the initial precipitate consisted of the non-cyclic intermediate I.



I

II

A halogen analysis of the precipitate corresponded very roughly to I and treatment with water produced a white solid thought to be II. In the present work, from the initial precipitate it has been possible to isolate only diazaphosphole 2-oxide and *o*-phenylenediamine hydrochloride. The hydrolysis product, originally thought to be II, now has been proved to be not the amide but instead the salt of *o*-phenylenediamine and phenylphosphonic acid. The inability to isolate a non-cyclic intermediate or its hydrolysis product indicates that the cyclization step proceeds with comparable rapidity, if not with greater rapidity, than the half-amide I formation.

To accomplish the cyclizations the hydrogen chloride formed was either removed physically by its insolubility in a refluxing solvent or removed chemically by combination with a tertiary amine. When a phosphonothioic dichloride reacts with an *o*-diamine in a refluxing solvent some hydrogen sulfide is evolved. Since it is evolved in less than 2% yield, the quantity of diazaphosphole 2-sulfide obtained is not appreciably affected. In the initial phases of the present work the hydrogen sulfide formation was thought to be more significant and, to avoid it, some of the desired heterocycles were obtained at room temperature by adding tertiary amines. However, the reactions in refluxing bromobenzene usually give better yields with greater convenience because the products are much more easily isolated.

In the thermal condensations, as the diazaphosphole is initially formed the hydrogen chloride liberated reacts with unchanged diamine to form a salt. This salt must be decomposed to the free base to permit its utilization in additional diazaphosphole formation. This salt dissociation is not merely the shift of a simple equilibrium process controlled by diffusion of the hydrogen chloride to the surface of the solution, for condensations of both phosphonic and phosphonothioic dichlorides with *o*-phenylenediamine in refluxing bromobenzene were found to proceed more rapidly than the decomposition of *o*-phenylenediamine hydrochloride alone under the same conditions.

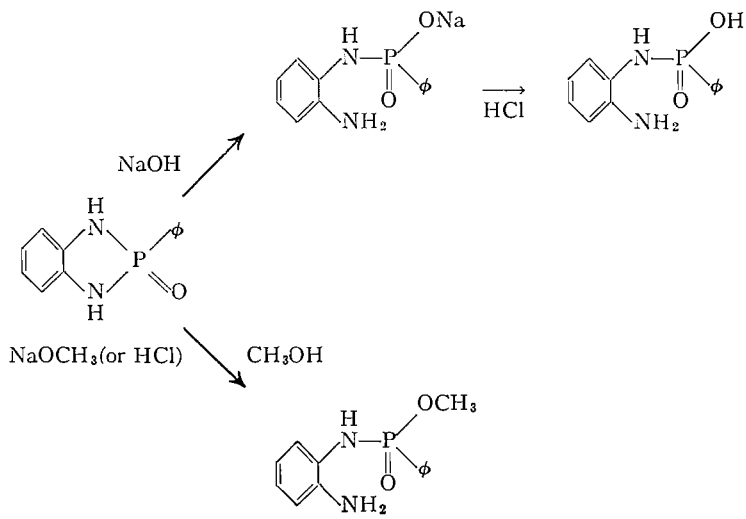
Invariably the condensations of a diamine with a phosphonothioic dichloride required a much longer time than with a phosphonic dichloride. This lower reactivity of the phosphonothioic dichlorides is not unexpected for it has been firmly established in other investigations (18). The course of each reaction was followed by titrating the evolved hydrogen chloride. Despite the lack of temperature control other than that of a refluxing solvent medium, frequently (but not regularly) good first-order rate constants were obtained from these titrations. Thus with *N,N'*-dimethyl-*o*-phenylenediamine in refluxing bromobenzene both phenylphosphonic dichloride ($k = 95 \times 10^{-5}$ s^{-1}) and phenylphosphonothioic dichloride ($k = 2.9 \times 10^{-5}$ s^{-1}) gave first-order constants.

With phosphonothioic dichlorides the condensations with diamines containing electron-withdrawing substituents in the ring were invariably slower than with *o*-phenylenediamine itself. Much faster reactions occurred with amines containing electron-donating substituents. The presence of alkyl groups on the amino-nitrogen facilitated condensation while *N*-phenyl-*o*-phenylenediamine reacted sluggishly. All these data, as well as the lower reactivity of the phosphonothioic dichloride as compared to the phosphonic dichloride, are consistent with the rate-determining step being the nucleophilic displacement on phosphorus.

Using phosphonic dichlorides the condensations do not follow as clear a kinetic pattern. The reactions are so much faster that not only are the observed differences in time less significant but in addition the amine salt decomposition may be a factor in determing the overall rate.

Chemical Properties

The hydrolysis and alcoholysis of the benzodiazaphosphole 2-oxides have been briefly studied. Cleavage of only one amide linkage is possible under mild conditions.



Under more drastic conditions (e.g. refluxing sodium hydroxide) complete hydrolysis to the diamine is obtained. The 2-sulfide analogue was somewhat more resistant to hydrolysis than the 2-oxide compound. The *N,N'*-dimethyl derivatives of the 2-phenyldiazaphosphole 2-oxide and 2-sulfide were much more resistant to hydrolysis than their unsubstituted counterparts. This hydrolytic stability is essential to any potential pharmaceutical use of the heterocycles.

Methylation of the diazaphosphole 2-sulfides was achieved with dimethyl sulfate and sodium hydroxide. These successful methylations offer encouragement for a future attachment of a sugar moiety to the diazaphosphole 2-sulfide to prepare a nucleoside analogue. The diazaphosphole 2-oxides hydrolyzed when subjected to the alkylation procedure and methylated products could not be isolated.

ACKNOWLEDGMENTS

Grateful acknowledgement is made to the U.S. Public Health Service for financial support by Grant No. CY-04104 and to Leonard T. Capell and Kurt L. Loening of Chemical Abstracts Service for aid in the nomenclature.

REFERENCES

1. R. L. DANNLEY and P. L. WAGNER. J. Org. Chem. **26**, 3995 (1961).
2. W. AUTENRIETH and O. HILDEBRAND. Ber. **31**, 1111 (1898).
3. W. AUTENRIETH and W. MEYER. Ber. **58**, 848 (1925).
4. P. L. WAGNER. Ph.D. Thesis, Western Reserve University. 1961.
5. M. S. KHARASCH, E. V. JENSEN, and S. J. WEINHOUSE. J. Org. Chem. **14**, 429 (1949).
6. F. GUTCHARD. Ber. **32**, 1572 (1899).
7. H. JEAN. Bull. Soc. Chim. France, 569 (1956).
8. A. M. KINNEAR and E. A. PERREN. J. Chem. Soc. 3437 (1952).
9. L. GATTERMAN. Ber. **18**, 1487 (1885).
10. B. W. ASHTON and H. SUSCHITZKY. J. Chem. Soc. 4559 (1957).
11. J. H. BERGEIM, K. LOSEE, and W. A. LOTT. J. Am. Chem. Soc. **69**, 586 (1947).
12. W. B. WHALLEY. J. Chem. Soc. 2792 (1950).
13. E. NOELTING and S. FOREL. Ber. **18**, 2683 (1885).
14. O. FISCHER. Ber. **25**, 2842 (1892).
15. A. M. SIMONOV and P. A. UGLOV. J. Gen. Chem. USSR **21**, 884 (1951). Chem. Abstr. **46**, 498^e (1952).
16. G. W. H. CHEESEMAN. J. Chem. Soc. 3308 (1955).
17. H. STETTER. Ber. **86**, 161 (1953).
18. D. J. HEATH. J. Chem. Soc. 3796 (1956).