[CONTRIBUTION FROM THE MORLEY CHEMICAL LABORATORY, WESTERN RESERVE UNIVERSITY]

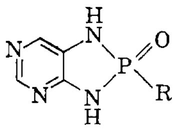
The Condensation of Phosphonic Dichlorides with *o*-Diamines

RALPH L. DANNLEY AND PHILIP L. WAGNER[1]

Received February 15, 1961

The reaction of phosphonic dichlorides with equimolar quantities of *o*-diamines in refluxing bromobenzene has been found to give nearly quantitative yields of dihydro-1,3,2-benzodiazaphosphole 2-oxides. These compounds are crystalline solids which hydrolyze rapidly in dilute acidic and basic solutions.

Current interest has been developed in analogs of naturally occurring purines because of their potential use as antimetabolites, particularly in cancer chemotherapy. The present work is concerned with the synthesis of dihydro-1,3,2-diazaphospholes by the reactions of phosphonic dichlorides with *o*-diamines. The dihydrodiazaphosphole ring may be considered an imidazoline system, spatially similar to the imidazoles, in which phosphorus has been substituted for carbon in the 2-position. As the imidazole structure is present as a part of the purine molecule, the condensation of phosphonic dichlorides might ultimately be accomplished with *o*-diaminopyrimidines to give structures of type I.



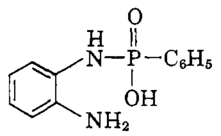
I

Before attempting the preparation of such purine-like heterocycles, it was necessary first to study the syntheses and properties of the diazaphosphole ring in simpler systems. This was accomplished by the condensations of phosphonic dichlorides with *o*-phenylenediamine and its derivatives (see Table I).

Condensations involving phosphoric dichlorides and phosphoric thiodichlorides with *o*-diamines have been reported.[2-4] These reactions were accomplished by heating the reagents together at 150–170° or by fusing the mixture. The compounds prepared were reportedly stable to dilute acids[2] but unstable to alkali. No condensations of a phosphonic dichloride with *o*-diamines have been reported.

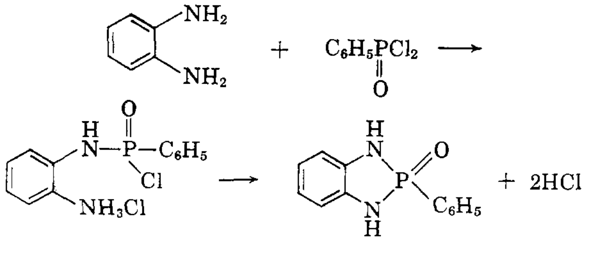
In the present work, addition of a phosphonic dichloride to an *o*-diamine in bromobenzene solution generally led to an immediate formation of a precipitate. Upon heating to 130–135°, a quantitative yield of hydrogen chloride was evolved in about twenty minutes, and the precipitate reacted to give a clear solution. Cooling the hot bromobenzene mixture usually gave the relatively pure dihydro-1,3,2-diazaphosphole in excellent yield. The structures of the products were confirmed by infrared spectra and elemental analyses.

Attempts were made to identify the precipitate which immediately formed on mixing the reagents, using the product of phenylphosphonic dichloride and *o*-phenylenediamine as a model substance. The product was too unstable, both hydrolytically and thermally, to yield a sample of analytical purity. A halogen analysis corresponded roughly to a simple addition product of the reagents. Recrystallization from alcohol or water gave phenylphosphonyl-2-aminoanilide (II).



II

As the corresponding diazaphosphole did not hydrolyze under these conditions, the original precipitate could not be cyclic in nature. These facts support the following reaction sequence:



Bromobenzene was found to be the most uniformly acceptable reaction solvent for the following reasons. First, its reflux temperature was high enough to dissociate aromatic amine hydrochlorides to liberate the amino groups for condensation but low enough so that the diazaphospholes were not decomposed. Second, most of the diazaphospholes were soluble in hot bromobenzene but insoluble cold, and so an initial recrystallization was obtained from the reaction mixture. Third, as hydrogen chlo-

---

[1] National Science Foundation Cooperative Fellow, 1960–1961. From a thesis submitted to the Graduate School of Western Reserve University in partial fulfillment of the requirements for the doctor's degree. Presented at the New York Meeting of the American Chemical Society, September, 1960. This work received support from Public Health Service Grant CY-4104 and from an Institutional Grant to Western Reserve University from the American Cancer Society.

[2] W. Autenrieth and E. Bolli, *Ber.*, **58**, 2144 (1925).

[3] W. Autenrieth and O. Hildebrand, *Ber.*, **31**, 1111 (1898).

[4] W. Autenrieth and W. Meyer, *Ber.*, **58**, 848 (1925).

TABLE I

DESCRIPTIONS OF PRODUCTS FROM CONDENSATIONS OF PHOSPHONIC DICHLORIDES WITH *o*-DIAMINES

Diamine	Phosphonic Dichloride	% Yield[a]	M.P.[b]	Calcd. C	H	N	P	Found C	H	N	P
o-Phenylenediamine	Phenyl	100	277–278	62.69	4.78	12.17	13.48	62.60	5.03	12.32	13.29
o-Phenylenediamine	*n*-Butyl	95	177[c]	57.14	7.14	13.33		57.45	7.37	13.33	
o-Phenylenediamine	Cyclohexyl	97	233–235[d]	61.01	7.21	11.86		60.85	7.28	11.86	
o-Phenylenediamine	*p*-Nitrophenyl	93	258[e]	52.36	3.63	15.27		51.94	3.68	15.37	
4-Chloro-*o*-phenylenediamine	Phenyl	100	233–235[f]	54.44	3.78	10.59		54.45	4.08	10.60	
4-Methyl-*o*-phenylenediamine	Phenyl	78	237–239	63.93	5.33	11.48		63.79	5.46	11.43	
4-Carboxy-*o*-phenylenediamine	Phenyl	0	—	—	—	—		—	—	—	
4-Carbomethoxy-*o*-phenylenediamine	Phenyl	96	241–242	58.33	4.51	9.72		58.46	4.55	9.63	
4-Nitro-*o*-phenylenediamine	Phenyl	100	261–263[g]	52.36	3.63	15.27		52.22	3.67	15.27	
1,2-Diaminonaphthalene	Phenyl	98	278[h]	68.57	4.65	10.00		68.12	4.72	9.80	
2,3-Diaminonaphthalene	Phenyl	86	319–322	68.57	4.65	10.00		68.12	4.70	9.98	
2,3-Diaminopyridine	Phenyl	33	299–301	57.14	4.33	18.18		57.31	4.66	18.18	
N-Phenyl-*o*-phenylenediamine	Phenyl	79	214–216[i]	70.59	4.90	9.15		71.23	4.87	9.20	

[a] Crude product. [b] All melting points are uncorrected. All compounds melt with decomposition. Compounds are recrystallized from chloroform unless specified otherwise. [c] Fractionally crystallized from 95% ethanol. [d] Recrystallized from benzene or a 1:4 methanol-ether solution. [e] Purified by dissolving in hot methanol, cooling and adding water to precipitate bright yellow plates. [f] Purified by boiling in a Norit-ether mixture, filtering and evaporation to one-half volume to obtain crystals. [g] Crude product was not soluble in hot bromobenzene and was obtained in impure form. It was insoluble in all organic solvents except alcohol and acetone, but hydrolyzed rapidly in both. A very poor yield of pure product was obtained by dissolving the crude material in 95% ethanol and rapidly adding water to precipitate the solid, collecting it by suction filtration, washing with water, and vacuum drying. [h] Also prepared by condensation of equimolar quantities of phenylphosphonic dichloride and 1,2-diaminonaphthalene dihydrochloride in bromobenzene. [i] Recrystallized from benzene.

ride is so insoluble in this refluxing solvent, the course of the reaction could be followed by titration of the evolved gases.

In lower boiling solvents such as heptane, cyclization often did not occur unless a tertiary amine was added to scavenge the hydrogen chloride, and even then the yields were somewhat low and reaction times were longer. The necessity of addition of a tertiary amine led to new problems of purification requiring separation of the product from the amine hydrochloride.

Variation of the organic residue attached to phosphorus theoretically might have an effect upon the reactivity of the phosphonic dichloride in condensation with *o*-phenylenediamine and the stability of the resulting 1,3-dihydro-2-substituted-2*H*-1,3,2-benzodiazaphosphole 2-oxide. Condensations of *o*-phenylenediamine with phenyl, *n*-butyl, cyclohexyl, and *p*-nitrophenylphosphonic dichlorides were found to occur in similar reaction times to give nearly quantitative yields of the corresponding diazaphospholes. These products were all of comparable hydrolytic stability. It is not too surprising that variation of the organic substituent on phosphorus has such little effect, for the other groups attached to phosphorus have powerful electronegative influences that are difficult to overcome.

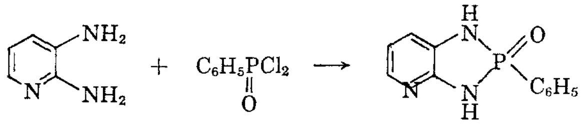
In contrast, the presence of a substituent in the diamine nucleus had a very profound effect upon the condensation with phenylphosphonic dichloride. Although substitution of a methyl, chloro, or carbomethoxy group for hydrogen in the 4-position had little influence on rate of reaction, yield, or stability of the product, the presence of a nitro group required a longer reaction time and the 5-nitro-1,3-dihydro-2-phenyl-2*H*-1,3,2-benzodiazaphosphole 2-oxide was hydrolytically unstable. Resonance in the free diamine involving the nitro group would reduce the electron density on the *p*-amino nitrogen necessary for the displacement reaction leading to ring closure. Similarly, in the diazaphosphole, the nitro group would reduce the electron density in the heterocyclic ring and thus promote cleavage by nucleophilic reagents.

The carboxy substituent would be expected to have an effect similar to that of the nitro group. Actually, no condensation could be obtained with 3,4-diaminobenzoic acid, but this might be due to its existence as a zwitterion and consequent insolubility.

Normal condensations in good yields were obtained with 1,2- and 2,3-diaminonaphthalenes, which may be considered disubstituted phenylenediamines, to give 1,3-dihydro-2-phenyl-2*H*-naphtho(1,2-*d*)-1,3,2-diazaphosphole 2-oxide and 1,3-dihydro-2-phenyl-2*H*-naphtho(2,3-d)-1,3,2-diazaphosphole 2-oxide, respectively. *N*-Phenyl-*o*-phenylenediamine reacted in the usual fashion to give

1-hydro-2,3-diphenyl-2*H*-1,3,2-benzodiazaphosphole 2-oxide. The product had an exceptionally low melting point, which could be attributed to reduction of the hydrogen bonding between amidic hydrogens and phosphoryl oxygen atoms. A similar trend in melting points was found in linear substituted phosphoramides by Audrieth and Toy.[5]

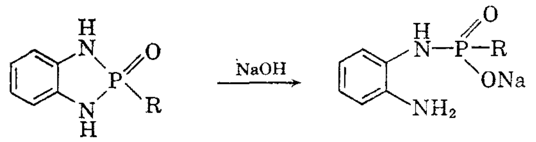
Attempted condensations of phenylphosphonic dichloride with 2,3-diaminopyridine were unsuccessful until a slightly greater than 2:1 ratio of tertiary amine to acid chloride was used in bromobenzene solution. A 33% yield of 2-(phenyl)-1,3-dihydro-2*H*-1,3,2-diazaphospholo(4,5-b)pyridine 2-oxide (III) was thus produced:



III

Of all the structures obtained, this most closely approached that of a phosphorus analog of a purine for all attempts to effect condensation with diaminopyrimidines were unsuccessful.

All the diazaphospholes synthesized in the present work were crystalline solids with limited solubilities in organic solvents. They were generally soluble, but slowly hydrolyzed, in hot water, alcohol and acetone. They were completely hydrolyzed by 1.0 and 0.1*N* sodium hydroxide at 25° within fifteen minutes according to the following equation.



Although insoluble in dilute aqueous acids, the compounds were completely hydrolyzed by a 50% dioxane–aqueous hydrochloric acid solution (0.1*N*) at 25° within fifteen minutes. These results are contrary to the stabilities to acid hydrolysis of similar compounds reported by Autenrieth and Bolli.[2] The stabilities they reported may have been due to insolubility of their products in dilute aqueous acids.

EXPERIMENTAL

Phenylphosphonic dichloride was obtained from Victor Chemical works as the practical grade and was not further purified before use. *n*-Butylphosphonic dichloride was prepared according to the procedure of Clay,[6] b.p. 75–76.8°, 10 mm. (lit. b.p.$_{3.5}$ 68–70° [7]). Cyclohexylphosphonic dichloride, m.p. 37° (lit. m.p. 37–37.5° [8]) and *p*-nitrophenylphosphonic dichloride, m.p. 94–96° (lit. m.p. 97–98° [9]) were prepared by the procedures described in the literature references. The diamines were all commercially available and were recrystallized when necessary.

1,3-Dihydro-2-phenyl-2H-1,3,2-benzodiazaphosphole 2-oxide. A solution of 9.75 g. of phenylphosphonic dichloride (0.05 mole) in 10 ml. of bromobenzene was added dropwise, with vigorous stirring at room temperature, to a solution of 5.4 g. of *o*-phenylenediamine (0.05 mole) in 200 ml. of bromobenzene. Immediate formation of a white solid was observed during the 15-min. addition period. The mixture was then heated. Above 130° hydrogen chloride was evolved quantitatively (0.10 mole) within 20 min. It was passed through water and titrated with 1.00*N* sodium hydroxide. During the hydrogen chloride evolution, the solid formed during the original addition reacted to yield a product which dissolved in the refluxing bromobenzene to give a clear yellow solution. Reflux was continued for an additional 10 min. and the solution cooled to yield 11.5 g. (100% yield) of relatively pure 1,3-dihydro-2-phenyl-2*H*-1,3,2-benzodiazaphosphole 2-oxide, m.p. 275–277°. It was collected by suction filtration, washed with bromobenzene, then with pentane and dried. Recrystallization from chloroform gave an analytical sample, m.p. 277–278° with decomposition.

Anal. Calcd. for $C_{12}H_{11}N_2OP$: C, 62.69; H, 4.78; N, 12.17; P, 13.48. Found: C, 62.60; H, 5.03; N, 12.32; P, 13.29.

Phenylphosphonyl-2-aminoanilide. The dropwise addition of phenylphosphonic dichloride to a stirred solution of an equimolar quantity of *o*-phenylenediamine in bromobenzene, heptane, or ether at room temperature caused the immediate formation of a precipitate. This product was collected by suction filtration, washed with the solvent used, and vacuum dried. Recrystallization of this product from alcohol or alcohol-water solutions gave phenylphosphoryl-2-aminoanilide, m.p. 228° dec. as a white crystalline solid. The product is insoluble in organic solvents.

Anal. Calcd. for $C_{12}H_{13}N_2O_2P$: N, 11.29. Found: N, 11.02.

An attempt was made to prepare an analytical sample of the original precipitate before hydrolysis. The thermal and hydrolytic instability prevented satisfactory purification, but a chloride analysis (21.9%) corresponded roughly to the theoretical percentage (23.8%) of a simple adduct of the reagents.

2-(Phenyl)-1,3-dihydro-2H-1,3,2-diazaphospholo(4,5-b)-pyridine 2-oxide. A solution of 9.75 g. of phenylphosphonic dichloride (0.05 mole) in 10 ml. of bromobenzene was added dropwise over a 15-min. period to a stirred solution of 5.5 g. of 2,3-diaminopyridine (0.05 mole) and 17.2 g. of tri-*n*-propylamine (0.12 mole) in 250 ml. of bromobenzene at 90–100°. An oil was formed immediately. Upon continued heating, the solution became clear and after 5 min. of reflux, a grainy white solid formed. Reflux was continued for 16 hr., the mixture was filtered while hot, and the solid was washed with bromobenzene, then with heptane and dried. A yield of 3.81 g. (33% yield) was obtained, m.p. 220–235°.

Dissolving the majority of the crude product in 30 ml. of pyridine at room temperature followed by filtration and addition of hexane to the filtrate precipitated a crude product which decomposed above 260°. Upon allowing the filtrate to stand, 0.2 g. of pure 2-(phenyl)-1,3-dihydro-2*H*-1,3,2-diazaphospholo(4,5-b)pyridine 2-oxide slowly crystallized. The product melted at 299–301° dec. (sealed tube).

Anal. Calcd. for $C_{11}H_{10}N_3OP$: C, 57.14; H, 4.33; N, 18.18. Found: C, 57.31; H, 4.66; N, 18.18.

This product has appreciable solubility only in pyridine.

Acknoweldgment. The authors would like to express their appreciation to Leonard T. Capell of the Chemical Abstracts Service for his advice in naming the heterocyclic compounds in this article.

CLEVELAND, OHIO

---

(5) L. F. Audrieth and A. D. F. Toy, *J. Am. Chem. Soc.*, **64**, 1553 (1942).

(6) J. P. Clay, *J. Org. Chem.*, **16**, 892 (1951).

(7) R. Graf, *Chem. Ber.*, **85**, 19 (1952).

(8) J. O. Clayton and W. L. Jensen, *J. Am. Chem. Soc.*, **70**, 3880 (1948).

(9) G. O. Doak and L. D. Freedman, *J. Am. Chem. Soc.*, **73**, 5658 (1951).