Some Properties of Compound VII.—A 13.1-g. sample of the diol was heated for 16 hours with 200 ml. of boiling benzene containing 0.5 g. of iodine and the water formed, 0.11 ml. (calcd. 1.00 ml.), was measured in a Stark–Dean water trap. Refluxing a 5.25-g. sample with 250 ml. of xylene containing 0.5 g. of iodine and 0.5 g. of β-naphthalenesulfonic acid gave 0.38 ml. of water (calcd. 0.40 ml.) after 16 hours.

In contrast to the more ordinary di-*n*-alkylsilanediols, *e.g.*, diethylsilanediol, whose heat sensitivity required a special procedure for melting point determinations involving preheating of the melting point bath to 75° and then raising the temperature at the rate of 5° per minute,[6] compound VII gave reproducible melting points by using an ordinary procedure employing a conventional melting point block and raising the temperature at the rate of 2° per minute. Thus, compound VII is somewhat more heat stable than diethylsilanediol but far less stable than di-*t*-butylsilanediol which distils without decomposition at 210°. Compound VII gave extensive condensation when held at 150° for several hours in a melting point capillary.

Reaction of Compound II with Liquid Ammonia.—Liquid ammonia, 150 g., was placed in a flask cooled in a Dry Ice–methanol-bath, and a solution of 57 g., 0.24 mole, of compound II in 200 ml. of dry pentane was added slowly over a two-hour period. After 12 hours of stirring and slow evaporation of the excess ammonia, the ammonium chloride, 23 g. (calcd. 23 g.), was separated by successive decantations and washings. Fractionation under vacuum gave no monomeric diaminosilane; the product boiled over a wide range, 92° at 10 mm., to 208° at 1 mm., and no constant-boiling material was obtained.

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[CONTRIBUTION FROM THE VENEREAL DISEASE EXPERIMENTAL LABORATORY, U. S. PUBLIC HEALTH SERVICE, SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF NORTH CAROLINA]

The Preparation of Amides of Arylphosphonic Acids. I. Diamides of Primary Aromatic and Heterocyclic Amines[1]

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p-Nitrophenylphosphonic dichloride was readily prepared by the action of phosphorus pentachloride on the appropriate acid. Condensation of this acid chloride with primary aromatic or heterocyclic amines gave a series of *p*-nitrophenylphosphonic diamides. Two different condensation procedures are described. The nitro-substituted amides were reduced with Raney nickel to the corresponding amino compounds.

There is considerable evidence that *p*-aminophenylphosphonic acid (phosphanilic acid) possesses chemotherapeutic properties similar to the sulfa drugs and acts on bacteria by antagonizing *p*-aminobenzoic acid.[2] Since conversion of sulfanilic acid to an amide greatly enhances the activity of the parent compound, particularly when the amide group is suitably substituted, it seemed a matter of considerable interest to find out whether amides of phosphanilic acid comprise a class of potentially useful antibacterial agents.

Only one amide of phosphanilic acid has been reported in the literature. Limaye and Bhide prepared *p*-aminophenylphosphonic diamide (phosphanilamide)[3] in small yield by heating *p*-bromophenylphosphonic diamide with aqueous ammonia in the presence of cuprous oxide. They were unable, however, to extend this synthesis to the preparation of the phosphorus analog of sulfathiazole.

Since a satisfactory method for the preparation of *p*-nitrophenylphosphonic acid has recently been described,[4] we decided to use this compound as an intermediate in the preparation of a series of amides of phosphanilic acid. The following reaction sequence was employed

$$p\text{-}O_2NC_6H_4PO_3H_2 + 2PCl_5 \longrightarrow p\text{-}O_2NC_6H_4POCl_2 + 2POCl_3 + 2HCl \quad (1)$$

$$p\text{-}O_2NC_6H_4POCl_2 + 4RNH_2 \longrightarrow p\text{-}O_2NC_6H_4PO(NHR)_2 + 2RNH_3Cl \quad (2)$$

$$p\text{-}O_2NC_6H_4PO(NHR)_2 + 3H_2 \xrightarrow{Ni} p\text{-}NH_2C_6H_4PO(NHR)_2 + 2H_2O \quad (3)$$

p-Nitrophenylphosphonic dichloride was prepared without difficulty according to equation 1. Two general procedures were then investigated for the preparation of the nitro-substituted amides from this acid chloride. Procedure 1, which was similar to a method used by Buchner and Lockhart,[5] consisted of refluxing one mole of *p*-nitrophenylphosphonic dichloride with four moles of amine in an organic solvent and isolating the crude amide from the reaction mixture. The majority of the amides were insoluble in the reaction solvent and precipitated from solution together with the amine hydrochloride. In those cases in which the amide was soluble in the reaction solvent, the amine salt was removed by filtration and the crude amide obtained by evaporating the filtrate. Procedure 1 is probably more generally applicable than procedure 2 and gives higher yields and more easily purified materials; furthermore, if the required amine is scarce or expensive, the condensation can be performed with one mole of the acid chloride, only two moles of amine and two (or more) moles of pyridine.

Procedure 2 (based on a method described by Michaelis[6]) consisted of melting together a mixture

(1) The organophosphorus nomenclature in this paper is that proposed by the Organic Division's Advisory Committee on the Nomenclature of Organic Phosphorus Compounds; *cf. Chem. Eng. News*, **30**, 4515 (1952).

(2) R. Kuhn, E. F. Möller, G. Wendt and H. Beinert, *Ber.*, **75**, 711 (1942); J. D. Thayer, H. J. Magnuson and M. S. Gravett, *Antibiotics and Chemotherapy*, **3**, 256 (1953).

(3) N. S. Limaye and B. V. Bhide, *J. Indian Chem. Soc.*, **25**, 251 (1948). The purity of their preparation is open to question, since they were unable to obtain satisfactory analyses on this compound.

(4) (a) G. O. Doak and L. D. Freedman, THIS JOURNAL, **73**, 5658 (1951); (b) see also L. D. Freedman and G. O. Doak, *ibid.*, **75**, 4905 (1953).

(5) B. Buchner and L. B. Lockhart, Jr., *ibid.*, **73**, 755 (1951). Somewhat similar reaction conditions were used earlier by A. Michaelis, *cf.* ref. 6.

(6) A. Michaelis, *Ann.*, **293**, 193 (1896).

TABLE I

p-NITROPHENYLPHOSPHONIC DIAMIDES

p-$O_2NC_6H_4PO(NHR)_2$ R =	Yield, %	M.p.,[a] °C.	Formula	Phosphorus,[b] % Calcd.	Phosphorus,[b] % Found	Nitrogen,[c] % Calcd.	Nitrogen,[c] % Found
C_6H_5[d]	73[e]	195–197.5	$C_{18}H_{16}N_3O_4P$	8.77	8.64	11.89	11.82
o-ClC_6H_4[f]	77[e]	187–190	$C_{18}H_{14}Cl_2N_3O_3P$	7.34	7.24	9.95	9.87
m-ClC_6H_4[d]	70[e], 74[g]	187–188	$C_{18}H_{14}Cl_2N_3O_3P$	7.34	7.27	9.95	9.83
p-ClC_6H_4[d]	72[g]	187–190	$C_{18}H_{14}Cl_2N_3O_3P$	7.34	7.30	9.95	9.94
m-BrC_6H_4[d]	60[e]	190.5–193.5	$C_{18}H_{14}Br_2N_3O_3P$	6.06	6.00	8.22	8.17
p-$CH_3C_6H_4$[d]	84[g]	185–187	$C_{20}H_{20}N_3O_3P$	8.12	8.07	11.02	10.95
p-$C_2H_5SO_2C_6H_4$[f]	77[g,h]	213–215	$C_{22}H_{24}N_3O_7PS_2$	5.76	5.79	7.82	7.81
m-$CF_3C_6H_4$[d]	43[g]	178–180	$C_{20}H_{14}F_6N_3O_3P$	6.33	6.29	8.59	8.58
m-$C_2H_5OC_6H_4$[d]	60[g]	131.5–132	$C_{22}H_{24}N_3O_5P$	7.02	6.97	9.52	9.55
p-$C_2H_5OOCC_6H_4$[f]	88[i], 84[h]	198–200	$C_{24}H_{24}N_3O_7P$	6.23	6.12	8.45	8.35
p-NCC_6H_4[j]	61[e]	153–156	$C_{20}H_{14}N_5O_3P$	7.68	7.63	17.36	17.20
2-$C_{10}H_7$ (2-naphthyl)[k]	61[g]	215–217	$C_{26}H_{20}N_3O_3P$	6.83	6.84	9.27	9.11
2-C_5H_4N (2-pyridyl)[l]	43[m]	200–202	$C_{16}H_{14}N_5O_3P$	8.72	8.67	19.71	19.35
2-$C_4H_3N_2$ (2-pyrimidyl)[l]	7[m]	182–184	$C_{14}H_{12}N_7O_3P$	8.67	8.61	27.45	[n]

[a] Melting points were taken as previously described; *cf.* ref. 4a. [b] Phosphorus was determined by a modification of the method of M. D. Bachofer and E. C. Wagner, *Ind. Eng. Chem., Anal. Ed.*, 15, 601 (1943). [c] Nitrogen was determined by a micro-Kjeldahl procedure. [d] Recrystallized from aqueous ethanol. [e] This yield was obtained when procedure 2 was used. [f] Recrystallized from absolute ethanol. [g] This yield was obtained when procedure 1 was used; the acid chloride was dissolved in carbon tetrachloride and the amine in benzene. [h] Pyridine was used as the condensing agent; see text and the Experimental section. [i] This yield was obtained when procedure 1 was used; both the acid chloride and the amine were dissolved in carbon tetrachloride. [j] The amide was best purified by solution of the crude amide in warm ethanol, treatment of this solution with charcoal, and precipitation by slowly pouring the clarified solution into water. [k] Recrystallized from a mixture of acetone and absolute ethanol. [l] Recrystallized from absolute methanol. [m] This yield was obtained when procedure 1 was used; both the acid chloride and the amine were dissolved in dioxane. [n] Nitrogen analysis on this compound by the micro-Kjeldahl procedure was unsatisfactory.

TABLE II

p-AMINOPHENYLPHOSPHONIC DIAMIDES (PHOSPHANILAMIDE DERIVATIVES)

p-$NH_2C_6H_4PO(NHR)_2$[a] R =	Yield, %	M.p., °C.	Formula	Phosphorus, % Calcd.	Phosphorus, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
C_6H_5[b]	78	210–213	$C_{18}H_{18}N_3OP$	9.58	9.44	13.00	12.89
o-$ClC_6H_4 \cdot HCl$[b,c]	57	145–150	$C_{18}H_{17}Cl_3N_3OP$	7.23	7.19	9.80	9.84
m-ClC_6H_4[b]	89	148–151	$C_{18}H_{16}Cl_2N_3OP$	7.90	7.75	10.71	10.57
p-ClC_6H_4[b]	91	202–205	$C_{18}H_{16}Cl_2N_3OP$	7.90	7.78	10.71	10.71
m-BrC_6H_4[b,d]	76	154–157	$C_{18}H_{16}Br_2N_3OP$	6.44	6.31	8.73	8.81
p-$CH_3C_6H_4$[b]	90	238.5–241.5	$C_{20}H_{22}N_3OP$	8.82	8.75	11.96	11.85
p-$C_2H_5SO_2C_6H_4$[b,e]	84	247–248	$C_{22}H_{26}N_3O_5PS_2$	6.10	5.98	8.28	8.15
m-$CF_3C_6H_4$[f]	76	157–158	$C_{20}H_{16}F_6N_3OP$	6.74	6.73	9.15	9.10
m-$C_2H_5OC_6H_4$[f]	77	146–146.5	$C_{22}H_{26}N_3O_3P$	7.53	7.44	10.21	10.06
p-$C_2H_5OOCC_6H_4$[g]	94	124–127	$C_{24}H_{26}N_3O_5P$	6.63	6.51	8.99	8.94
p-$HOOCC_6H_4$[h,i]	64	182–185	$C_{20}H_{18}N_3O_5P$	7.53	7.40	10.22	9.94
2-$C_{10}H_7$ (2-naphthyl)[b]	68	210–213	$C_{26}H_{22}N_3OP$	7.32	7.19	9.92	9.89
2-C_5H_4N (2-pyridyl)[j]	62	209–210	$C_{16}H_{16}N_5OP$	9.52	9.51	21.53	[k]

[a] These compounds separated from solution with solvent of crystallization; therefore, they were dried *in vacuo* at 100°. [b] The solvent used for the reduction was a mixture of acetone and absolute ethanol. [c] This amide was isolated as the hydrochloride because the free base separated from solution as an oil. [d] Recrystallized from aqueous ethanol. [e] Recrystallized from a mixture of acetone and absolute ethanol. [f] The solvent used for the reduction was absolute ethanol. [g] The solvent used for the reduction was 95% ethanol. [h] This compound was prepared by the saponification of the corresponding ester. Details are given in the Experimental section. [i] Calcd.: neut. equiv., 205.7. Found: neut. equiv., 209.1. [j] The solvent used for the reduction was absolute methanol. [k] Nitrogen analysis on this compound by the micro-Kjeldahl procedure was unsatisfactory.

of the acid chloride and the amine, adding the melt to a very dilute hydrochloric acid solution and removing the crude amide by filtration. This process has the advantage of being rapid and requiring only the simplest equipment. In one case, we were able to obtain the desired amide [N,N′-bis-(*p*-cyanophenyl)-P-(*p*-nitrophenyl)-phosphonic diamide] by procedure 2 but not by procedure 1.

In one case neither procedure was successful. Thus, several attempts were made, under varying reaction conditions, to prepare the N,N′-bis-(*p*-carboxyphenyl)-P-(*p*-nitrophenyl)-phosphonic diamide by condensing *p*-aminobenzoic acid and *p*-nitrophenylphosphonic dichloride. The desired amide was readily obtained by alkaline hydrolysis of N,N′-bis-(*p*-carboethoxyphenyl)-P-(*p*-aminophenyl)-phosphonic diamide.

The *p*-nitrophenylphosphonic diamides, prepared by either procedure 1 or 2, were reduced to the corresponding amino derivatives with Raney nickel and hydrogen at 40 lb. pressure. The solvents used were absolute methanol, absolute ethanol or a mixture of acetone and absolute ethanol. After the catalyst was removed by filtration, the amino-substituted compound was obtained by concentration of the colorless filtrate and, in most cases, the addition of water. In one case the reduction product was isolated as the hydrochloride by evaporat-

ing the filtrate from the nickel to a small volume and adding an equal volume of concentrated hydrochloric acid.

The amides prepared, together with their analyses, yields and m.p.'s are listed in Tables I and II. None of these compounds have previously been described. Preliminary investigation by J. D. Thayer of this Laboratory indicates that several of the phosphanilamide derivatives are markedly superior to phosphanilic acid in antibacterial properties *in vitro*. The chemotherapeutic results will be reported in detail elsewhere.

Experimental

Materials.—With the exception of *p*-aminophenyl ethyl sulfone, the amines used in the condensations with *p*-nitrophenylphosphonic dichloride, were obtained from commercial sources and were redistilled or recrystallized before use. The solvents used for the condensations were stored over anhydrous calcium sulfate.

***p*-Nitrophenylphosphonic Dichloride.**—This compound was readily prepared by the interaction of 10 g. of *p*-nitrophenylphosphonic acid and 21.6 g. of phosphorus pentachloride. The two powders were intimately mixed in a two-necked 500-ml. flask which was then quickly equipped for vacuum distillation. Both the air leak for the prevention of bumping and the vacuum line were protected from atmospheric moisture by drying tubes. The evolution of hydrogen chloride commenced almost immediately after mixing and proceeded quite vigorously until most of the material in the flask had become liquid. Toward the end of the reaction, it was usually found necessary to apply heat until no solid particles remained. Vacuum from a water pump was then carefully applied. The phosphorus oxychloride distilled into the receiver, and the contents of the reaction flask solidified. The apparatus was then reassembled for high-vacuum distillation and the *p*-nitrophenylphosphonic dichloride was distilled[7] without a condenser; b.p. 121–134° at *ca.* 0.1 mm. The yield was 87–95%; m.p. 98–99°.

Anal. Calcd. for $C_6H_4Cl_2NO_3P$: N, 5.84. Found: N, 5.73.

The Condensation of *p*-Nitrophenylphosphonic Dichloride with Aromatic and Heterocyclic Amines.—The conditions used for the preparation of the amides listed in Table I were similar to those given in the following examples.

N,N'-Bis-(*m*-chlorophenyl)-P-(*p*-nitrophenyl)-phosphonic Diamide. (Procedure 1).—This reaction and all other procedure 1 reactions were performed in an all-glass apparatus consisting of a three-necked flask equipped with a sealed stirrer, a dropping funnel, and a condenser to which a calcium chloride tube was attached. To a stirred solution of 19.2 ml. of freshly distilled *m*-chloroaniline in 25 ml. of benzene was added 10.1 g. of *p*-nitrophenylphosphonic dichloride dissolved in 250 ml. of carbon tetrachloride. The mixture was refluxed gently for 6 hours and then allowed to stand overnight at room temperature. The resulting crystals were removed by filtration and washed first with 25 ml. of benzene, then with water until the washings were free of chloride ion. The crude amide was then purified by recrystallization.

N,N'-Bis-(*p*-ethylsulfonylphenyl)-P-(*p*-nitrophenyl)-phosphonic Diamide. (Procedure 1).—*p*-Nitrophenyl ethyl sulfide, prepared by the method of Waldron and Reid,[8] was oxidized to *p*-nitrophenyl ethyl sulfone[9] with a slight excess of 30% hydrogen peroxide.[10] The yield was 90%; m.p. 137.5–139°. The sulfone (10.8 g.) was dissolved in a mixture of 100 ml. of ethanol and 75 ml. of acetone, and was shaken for about one hour with Raney nickel and hydrogen at 40 lb. pressure. After the catalyst was removed by filtration, the amine was obtained by evaporating the filtrate to 90 ml. and cooling in the deep-freeze at −25°. The yield of *p*-aminophenyl ethyl sulfone[11] was 88%; m.p. 88–88.5°.

To a stirred solution of 12.6 g. of the above amine and 8.2 ml. of pyridine in 300 ml. of benzene was added 8.2 g. of *p*-nitrophenylphosphonic dichloride dissolved in 200 ml. of carbon tetrachloride. The mixture was refluxed gently for 2.5 hours, and the amide was then isolated and purified as in the preceding example.

N,N'-Di-2-pyridyl-P-(*p*-nitrophenyl)-phosphonic Diamide. (Procedure 1).—This compound was prepared from four moles of 2-aminopyridine and one mole of *p*-nitrophenylphosphonic dichloride in dioxane solution. The crude compound was recrystallized by dissolving it in warm methanol and cooling the solution rapidly. Even with rapid cooling some splitting of the amide linkage occurred in methanol solution. No other suitable recrystallizing solvent was found.

The reaction was also run with two moles of pyridine and two moles of 2-aminopyridine. While the yield was essentially the same as that obtained with four moles of 2-aminopyridine, the compound was colored yellow, and the color was not removed with Darco.[12] Carbon tetrachloride was unsatisfactory as a solvent for this reaction.

N,N'-Bis-(*o*-chlorophenyl)-P-(*p*-nitrophenyl)-phosphonic Diamide. (Procedure 2).—*p*-Nitrophenylphosphonic dichloride (5.5 g.) was added to 10.7 ml. of freshly distilled *o*-chloroaniline. The mixture was heated until a homogeneous melt was obtained and then poured into 100 ml. of 0.6 *N* hydrochloric acid. The solid obtained was removed by filtration and washed first with 0.6 *N* hydrochloric acid and then with water until the washings were free of chloride ion. The crude amide was then purified by recrystallization.

Preparation of the Phosphanilamide Derivatives.—The conditions used for the reduction of the nitro-substituted amides are illustrated by the following example.

N,N'-Bis-(*m*-chlorophenyl)-P-(*p*-aminophenyl)-phosphonic Diamide.—A solution of 13.1 g. of bis-(*m*-chlorophenyl)-P-(*p*-nitrophenyl)-phosphonic diamide in a mixture of 25 ml. of acetone and 75 ml. of absolute alcohol was shaken with Raney nickel catalyst under an initial hydrogen pressure of 40 lb. After the uptake of hydrogen almost ceased, the solution was evaporated to 75 ml. and added to 75 ml. of water. The resulting solution was cooled in the deep-freeze at −25°. The crystals obtained were dried *in vacuo* at 100°.

N,N'-Bis-(*p*-carboxyphenyl)-P-(*p*-aminophenyl)-phosphonic Diamide.—N,N'-Bis-(*p*-carboethoxyphenyl)-P-(*p*-aminophenyl)-phosphonic diamide (4.67 g., 0.01 mole) was dissolved in about 25 ml. of acetone and 210 ml. of 0.1 *N* sodium hydroxide solution were added.

After the mixture was refluxed gently for six hours, titration of an aliquot indicated that the saponification was virtually complete. The solution was filtered and the acetone removed on the steam-bath. When the solution was then acidified to *p*H 3.4, the desired compound precipitated. It was purified by reprecipitation from alkaline solution and was finally dried *in vacuo* at 100°. This compound could not be recrystallized from any of the solvents that were successfully used for the other amides described in this paper.

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CHAPEL HILL, N. C

(7) In one experiment in which the compound was distilling at 200° at 16 mm., an explosion occurred. No difficulty has ever been experienced when the temperature of the Glas-Col mantle, used for heating the distilling flask, was kept below 200°.

(8) W. R. Waldron and E. F. Reid, THIS JOURNAL, **45**, 2399 (1923).

(9) Previously prepared by W. R. Waldron and E. E. Reid, ref. 8; m.p. 138.5°.

(10) *Cf.* D. A. Shirley, "Preparation of Organic Intermediates," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 102.

(11) Previously prepared by W. R. Waldron and E. E. Reid, ref. 8; m.p. 89.3°.

(12) A similar phenomenon was noted in the preparation of sulfapyridine by M. L. Crossley, E. H. Northey and M. E. Hultquist, THIS JOURNAL **62** 372 (1940).