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The Preparation of Amides of Arylphosphonic Acids. II. Phosphanilamide and Diamides of Primary Aliphatic Amines[1]

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p-Nitrophenylphosphonic dichloride condenses readily with alkyl amines to yield *p*-nitrophenylphosphonic diamides. A similar condensation was carried out with ammonia, but a different technique was necessary for separating the resulting amide from ammonium chloride. All of these nitro-substituted amides were readily reduced to the corresponding amino compounds.

We have recently described a series of phosphonic diamides prepared by the condensation of *p*-nitrophenylphosphonic dichloride with a number of aromatic and heterocyclic primary amines. The nitrosubstituted amides were readily reduced to the corresponding amino compounds which are of interest as possible therapeutic agents because of their structural similarity to the sulfa drugs.[2] We are reporting here a similar series of phosphonic diamides prepared from aliphatic amines and from ammonia.

No difficulty was experienced in condensing *p*-nitrophenylphosphonic dichloride with alkyl amines. In general the reaction was carried out by adding a carbon tetrachloride solution of the acid chloride to four molecular equivalents of the amine dissolved in carbon tetrachloride. With ethanolamine[3] and 3-methoxypropylamine we obtained neutral, water-soluble sirups which we were unable to crystallize. With 3-methoxypropylamine the yield of amine hydrochloride obtained indicated that the reaction had gone essentially to completion.

We experienced considerable difficulty in preparing phosphanilamide, *i.e.*, *p*-aminophenylphosphonic diamide. Our first attempts to prepare *p*-nitrophenylphosphonic diamide yielded crystalline solids which gave analytical values for nitrogen slightly lower than the theoretical. These solids were generally insoluble in organic solvents other than alcohols. Recrystallization of the crude amide did not raise, and in several instances, actually lowered the nitrogen values. Just when it seemed that we would not succeed in obtaining the desired amide in a pure state, a paper appeared describing the preparation of phosphoric triamide.[4] Using the technique described by these authors we readily prepared *p*-nitrophenylphosphonic diamide. It was then reduced to phosphanilamide.[5]

Experimental

The preparation of *p*-nitrophenylphosphonic dichloride has been previously described.[2] 3-Methoxypropylamine was kindly furnished by the American Cyanamid Company, and *t*-butylamine was kindly furnished by the Rohm and Haas Company. The other amines used were either Eastman Kodak Co. White Label or Matheson research grade. All these amines were dried over Drierite and, except for ethylamine, fractionated before use. The solvents used were also dried over Drierite.

p-Nitrophenylphosphonic Diamide.—One hundred and fifty ml. of dry chloroform, in a 3-necked flask, was saturated with dry ammonia at −10°. A solution of 9.95 g. of *p*-nitrophenylphosphonic dichloride was added dropwise over a one-hour period. The stream of ammonia gas was continued during this period, and the temperature was kept below −10°. The reaction mixture was stirred an additional 1.5 hours, then filtered, and the precipitate dried. This solid was then suspended in a mixture of 40 ml. of chloroform and 35 ml. of diethylamine and refluxed for 2 hours. The undissolved material was removed by filtration, washed with chloroform and finally recrystallized from methanol.

A number of other attempts had been made to prepare this compound before the above synthesis succeeded. The condensation was carried out in dioxane at room temperature, in aqueous ammonia at −20°, and in liquid ammonia in a sealed tube. The ammonium chloride which formed was removed by washing with cold water. It is probable that some hydrolysis occurred at this step since the nitrogen values on the resulting compounds were always slightly lower than theoretical. Recrystallization from methanol did not improve the nitrogen values. In one attempt to recrystallize the crude compound from boiling ethanol the nitrogen value fell to 12.5%. This result suggests alcoholysis of the amide linkage.

N,N′-Diethyl-P-(p-nitrophenyl)-phosphonic Diamide.—A solution of 7.3 g. of *p*-nitrophenylphosphonic dichloride in 140 ml. of carbon tetrachloride was added dropwise to a solution of 7 g.[6] of anhydrous ethylamine in 100 ml. of carbon tetrachloride. The reaction was performed in a 3-necked flask equipped with a dropping funnel, sealed stirrer and a condenser to which a drying tube was attached. When all the acid chloride solution had been added, the mixture was refluxed for one hour and then allowed to stand overnight. The white solid was removed by filtration, and washed with carbon tetrachloride. Any adhering solvent was removed *in vacuo*, and the dry solid was dissolved in a minimum of hot water. The solution was treated with Darco and filtered. When the filtrate was cooled, colorless crystals of the desired diamide crystallized from solution.

The reaction was also run without heating; the resulting yield was only slightly lower. With aliphatic amines other than ethylamine, heating was found to be necessary in order to obtain satisfactory yields.

N,N′-Dipropyl-P-(p-nitrophenyl)-phosphonic Diamide.—The reaction conditions were similar to those used for the preceding compound. However, since the amide was insoluble in water, the ammonium chloride was extracted from the reaction mixture with water, and the residue was recrystallized from aqueous alcohol. The following *p*-nitrophenylphosphonic diamides were prepared under similar

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(1) Presented, in part, before the Division of Organic Chemistry at the 126th Meeting of the American Chemical Society, New York, N. Y., September, 1954.

(2) G. O. Doak and L. D. Freedman, This Journal, **76**, 1621 (1954).

(3) J. B. Dickey, U. S. Patent 2,596,660, has described the preparation of N,N′-bis-(β-hydroxyethyl)-P-(3-nitro-4-chlorophenyl)-phosphonic diamide from 3-nitro-4-chlorophenylphosphonic dichloride. No mention was made of any reaction between the acid chloride and the hydroxyl group.

(4) R. Klement and O. Koch, *Chem. Ber.*, **87**, 333 (1954).

(5) Phosphanilamide has been reported by N. S. Limaye and B. V. Bhide, *J. Ind. Chem. Soc.*, **25**, 251 (1948). These authors, however, were not able to obtain satisfactory analyses on their compound. Furthermore, there is considerable disparity between the physical properties of the phosphanilamide described in the present paper and the compound reported by Limaye and Bhide. We do not believe that these authors had the desired compound.

(6) An excess of amine was used in this case because of the low b.p. of ethylamine.

TABLE I

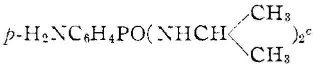
p-NITROPHENYLPHOSPHONIC DIAMIDES

Compound	Yield, %	M.p.,[a] °C.	Phosphorus, %[b] Calcd.	Phosphorus, %[b] Found	Nitrogen, % Calcd.	Nitrogen, % Found
p-$O_2NC_6H_4PO(NH_2)_2$	65	>137[c]	15.40	15.17	20.89	20.84
p-$O_2NC_6H_4PO(NHC_2H_5)_2$	67.5	139–140	12.04	12.01	16.33	16.34
p-$O_2NC_6H_4PO(NHCH_2CH_2CH_3)_2$	58	139–140	10.86	10.84	14.73	14.56
p-$O_2NC_6H_4PO[NHCH(CH_3)_2]_2$	56.5	169–171	10.86	10.66	14.73	14.83
p-$O_2NC_6H_4PO(NHCH_2CH_2CH_2CH_3)_2$	58.5	78–78.5	9.88	9.88	13.41	13.35
p-$O_2NC_6H_4PO[NHCH_2CH(CH_3)_2]_2$	80.5	130–131	9.88	9.83	13.41	13.45
p-$O_2NC_6H_4PO[NHCH(CH_3)C_2H_5]_2$	74	128–129	9.88	9.80	13.41	13.35
p-$O_2NC_6H_4PO[NHC(CH_3)_3]_2$	69	221–224	9.88	9.86	13.41	13.31
p-$O_2NC_6H_4PO(NHCH_2C_6H_5)_2$	52.5	110–112	8.12	8.20	11.02	10.95

[a] Melting points were taken as previously described; *cf.* G. O. Doak and L. D. Freedman, THIS JOURNAL, **73**, 5658 (1951). [b] Phosphorus was determined by a recently described procedure; B. C. Stanley, S. H. Vannier, L. D. Freedman and G. O. Doak, *Anal. Chem.*, **27**, 474 (1955). [c] This compound does not give a sharp melting point.

TABLE II

p-AMINOPHENYLPHOSPHONIC DIAMIDES

Compound	Yield, %	M.p., °C.	Phosphorus, % Calcd.	Phosphorus, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
p-$H_2NC_6H_4PO(NH_2)_2$	64	>122[a]	18.10	18.00	24.55	24.25
p-$H_2NC_6H_4PO(NHC_2H_5)_2$[b]	79	111–112	13.63	13.56	18.49	18.53
p-$H_2NC_6H_4PO(NHCH_2CH_2CH_3)_2$[c]	75	162–163	12.13	12.05	16.46	16.36
 $p\text{-}H_2NC_6H_4PO(NHCH\genfrac{}{}{0pt}{}{\diagup CH_3}{\diagdown CH_3})_2$[c]	74	131–133	12.13	12.03	16.46	16.62
p-$H_2NC_6H_4PO(NHCH_2CH_2CH_2CH_3)_2$[d]	62	118–119	10.93	10.92	14.83	14.74
p-$H_2NC_6H_4PO[NHCH_2CH(CH_3)_2]_2$[d]	64	105–106	10.93	10.83	14.83	14.84
p-$NH_2C_6H_4PO[NHCH(CH_3)C_2H_5]_2$	94	~36[a]	10.93	10.64	14.83	14.86
p-$NH_2C_6H_4PO[NHC(CH_3)_3]_2$[d]	70	217–218	10.93	10.86	14.83	14.79
p-$H_2NC_6H_4PO(NHCH_2C_6H_5)_2$	61	90–94	8.82	8.87	11.96	11.78

[a] This compound does not give a sharp melting point. [b] The recrystallizing solvent was benzene. [c] The recrystallizing solvent was water. [d] The recrystallizing solvent was aqueous alcohol.

reaction conditions: **N,N′-diisopropyl-, N,N′-diisobutyl-, N,N′-di-*sec*-butyl-, N,N′-di-*t*-butyl-** and **N,N′-dibenzyl-P-(*p*-nitrophenyl)-phosphonic diamide**. All of these compounds were recrystallized from aqueous alcohol.

N,N′-Dibutyl-P-(*p*-nitrophenyl)-phosphonic Diamide.—The reaction was run in a similar manner to the preceding reaction, but it was found necessary to reflux for 15 hours. The sticky precipitate was removed by filtration and washed with acetone. The acetone washings were then combined with the carbon tetrachloride filtrate, and the solvents were stripped off *in vacuo*. An oily residue was obtained which solidified after being treated with cold water and allowed to stand. It was then recrystallized from ether.

***p*-Aminophenylphosphonic Diamide (Phosphanilamide).**—A solution of 2.01 g. of *p*-nitrophenylphosphonic diamide in 75 ml. of methanol was shaken with Raney nickel catalyst under an initial hydrogen pressure of 60 lb. After the uptake of hydrogen ceased, the catalyst was removed, the solution was evaporated to incipient crystallization and then cooled in the deep-freeze at −25°. The crystals obtained were dried *in vacuo*.

N,N′-Diethyl-P-(*p*-aminophenyl)-phosphonic Diamide.—The corresponding nitro compound in alcohol solution was reduced with Raney nickel. The reduction was rapid and complete. The catalyst was removed, the solvent was evaporated to incipient crystallization, and the product was recrystallized. The other nitro compounds were reduced in a similar manner. **N,N′-Dibenzyl-P-(*p*-aminophenyl)-phosphonic diamide** was obtained as a sirup which solidified when triturated repeatedly with ether.

The nitro compounds obtained are given in Table I, the amino compounds in Table II.

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