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The Aquo Ammono Phosphoric Acids. II. Preparation of N-Substituted Derivatives of the Phenyl Esters of Amido- and Diamidophosphoric Acids

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A previous investigation[1] in this Laboratory had shown that phosphoryl chloride and phenol react in the presence of pyridine in chloroform solution to form a mixture of the pyridine complexes of the phenyl dichloro- and diphenyl chlorophosphates which upon ammonolysis produces the phenyl esters of amido- and diamidophosphoric acids, $(C_6H_5O)_2PONH_2$ and $C_6H_5OPO(NH_2)_2$, respectively. Although a mixture is always obtained it was found possible to prepare either of these as the predominating product by varying both the $POCl_3$:C_6H_5OH ratio andt he experimental conditions. This method has now been extended to aminolytic reactions for the preparation of the N-substituted derivatives by the action of typical amines upon the $POCl_3$–C_6H_5OH–C_5H_5N reaction product. For purposes of identification, the N-substituted derivatives were also prepared by the direct action of various amines, specifically, methylamine, cyclohexylamine, aniline, and morpholine, upon the phenyl dichloro- and diphenyl chlorophosphates.

The preparation of the N-substituted derivatives by the aminolysis of the $POCl_3$–C_6H_5OH–C_5H_5N mixture was only partially successful due to the fact that mixtures are always obtained. Phenyl di-(methylamido)-phosphate was obtained in good yield because of the fact that it is less soluble in cold carbon tetrachloride than the by-product diphenyl methylamidophosphate. In case of the phenyl di-(cyclohexylamido)- and di-(anilido)-phosphates, suitable solvents for the separation of these compounds from the by-product N-substituted diphenyl amidophosphates were not found. The phenyl di-(morpholido)-phosphate is soluble in water, permitting its separation from the water insoluble by-product.

In preparing the N-substituted diphenyl amidophosphates a $POCl_3$:C_6H_5OH ratio of 1:2 was used. While previous study had shown that diphenyl amidophosphate could be separated easily from by-product triphenyl phosphate by difference in solubility in various cold organic solvents, substitution of amine for the ammonia gave compounds resembling more and more closely triphenyl phosphate in solubility, thus making it more difficult, if not impossible, to separate them.

Experimental

A. Aminolysis of Phenyl Dichloro- (I) and Diphenyl Chlorophosphates (II).—

$$(1)\quad C_6H_5OPOCl_2 + 4RNH_2 \longrightarrow C_6H_5OPO(NHR)_2 + 2RNH_2{\cdot}HCl$$

$$(2)\quad (C_6H_5O)_2POCl + 2RNH_2 \longrightarrow (C_6H_5O)_2PONHR + RNH_2{\cdot}HCl$$

(1) **Phenyl Di-(methylamido)-phosphate.**—An excess of an aqueous methylamine solution was placed in a 500-cc 3-neck flask equipped with a thermometer, a stirrer, and a dropping funnel. Forty-two grams (0.2 mole) of (I) was added slowly with stirring, the temperature being maintained at 0 ± 2°. When the addition was completed, the reaction mixture was allowed to come to room temperature and the precipitate removed by filtration and washed free of chloride with ice-water. The filtrate was then evaporated to dryness and the residue was extracted with absolute ether. An additional quantity of the product was thus obtained upon evaporation of the ether extract, giving a total yield of 33.6 g. (84%). The compound was found to be insoluble in cold carbon tetrachloride, hot or cold high-boiling petroleum ether and slightly soluble in cold water, ethyl acetate, benzene, and hot carbon tetrachloride. It is very soluble in absolute alcohol, chloroform, acetone, ether, and hot benzene. Upon recrystallization from carbon tetrachloride, the melting point was found to be 103–105°.

Anal. Calcd. for $C_6H_5OPO(NHCH_3)_2$: N, 14.0; H, 6.55; C, 48.0. Found: N, 13.7; H, 6.34; C, 48.5.

(2) **Phenyl Di-(cyclohexylamido)-phosphate.**—Twenty-one grams (0.1 mole) of (I) dissolved in 50 cc. of chloroform was allowed to react with 43.5 g. (0.44 mole) of cyclohexylamine dissolved in 150 cc. of chloroform. The amine hydrochloride was removed by filtration and the residue washed with 100 cc. of chloroform. The chloroform solution upon distillation over a steam-bath yielded an oily substance which solidified upon cooling. It was washed free of amine hydrochloride by means of water. A yield of 31 g. (92.2%) was obtained. It was recrystallized from hot 60% ethyl alcohol; m. p. 124–125°. The product was insoluble in water but very soluble in ether, chloroform, and hot absolute alcohol.

Anal. Calcd. for $C_6H_5OPO(NHC_6H_{11})_2$: N, 8.33; H, 8.68; C, 64.3. Found: N, 8.31; H, 8.54; C, 64.6.

(3) **Phenyl Di-(anilido)-phosphate.**—Twenty-one grams (0.1 mole) of (I) dissolved in 50 cc. of chloroform was allowed to react with 37.2 g. (0.4 mole) of aniline dissolved in 150 cc. of chloroform. A yield of 31.5 g. (97.2%) of the product was obtained. It was recrystallized once

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(1) Audrieth and Toy, THIS JOURNAL, **63**, 2117 (1941)

from 80% hot ethyl alcohol; m. p. 179–180°, corresponding to the compound prepared previously.[2]

(4) **Phenyl Di-(morpholido)-phosphate.**—One hundred and seventy-four grams (2 moles) of morpholine dissolved in 330 cc. of chloroform was permitted to react with 105.5 g. (0.5 mole) of (I) dissolved in 100 cc. of chloroform. The precipitated morpholine hydrochloride was removed by filtration and washed with 100 cc. of chloroform. Upon the removal of the solvent from the combined filtrates, a residue was obtained which solidified into a brown mass upon standing. The solid was ground up and extracted several times with carbon tetrachloride to separate the desired product from the insoluble morpholine hydrochloride. The carbon tetrachloride was then removed by distillation and the residue recrystallized by solution in hot high-boiling petroleum ether and subsequent cooling. The purified product is a white crystalline compound; m. p. 85–86°. The yield of the purified material was 108 g. (69.3%). The compound possesses extraordinary solubility in a wide variety of solvents. It is very soluble in water, methyl and ethyl alcohol, benzene, ether, acetone, carbon tetrachloride, and chloroform. When heated to 200° for five minutes it is not decomposed. At 260°, it turns slightly brown, but its melting point is not altered by this treatment.

Anal. Calcd. for $C_6H_5OPO(NC_4H_8O)_2$: N, 8.97; H, 6.76; C, 53.8. Found: N, 8.83; H, 6.86; C, 54.0.

(5) **Diphenyl Methylamidophosphate.**—An excess of aqueous methylamine solution was allowed to react with 42.2 g. (0.157 mole) of (II) at 0°. The product, m. p. 95°, was found to be insoluble in water and cold high-boiling petroleum ether, but very soluble in absolute alcohol, chloroform, carbon tetrachloride, acetone, ether, ethyl acetate, benzene, and hot high-boiling petroleum ether. The yield was 31 g. (75%).

Anal. Calcd. for $(C_6H_5O)_2PONHCH_3$: N, 5.33; H, 5.37; C, 59.3. Found: N, 5.22; H, 6.02; C, 59.3.

(6) **Diphenyl Morpholidophosphate.**—Seventeen and four-tenths g. (0.2 mole) of morpholine dissolved in 150 cc. of carbon tetrachloride was allowed to react with 26.8 g. (0.1 mole) of (II) dissolved in 50 cc. of carbon tetrachloride. The precipitated morpholine hydrochloride was removed by filtration, washed with 200 cc. of dry carbon tetrachloride. Removal of solvent from combined filtrates yielded a yellowish oily liquid which solidified upon cooling. The solid mass after washing with water to remove traces of morpholine hydrochloride was recrystallized from high-boiling petroleum ether to give a product of m. p. 72.5–73.5°. A yield of 30 g. (94%) was obtained. Diphenyl morpholidophosphate was found to be only very slightly soluble in water but very soluble in alcohol and a large number of organic solvents.

Anal. Calcd. for $(C_6H_5O)_2PO(NC_4H_8O)$: N, 4.39; H, 5.69; C, 60.2. Found: N, 4.29; H, 5.98; C, 58.9.

(7) **Diphenyl Cyclohexylamidophosphate.**—Twenty-seven grams (0.1 mole) of (II) dissolved in 50 cc. of carbon tetrachloride was allowed to react with 22 g. (0.22 mole) of cyclohexylamine in 150 cc. carbon tetrachloride at 0°. A chloride-free product weighing 32.5 g. (98.5%) was obtained from the carbon tetrachloride solution. It was recrystallized from hot 80% alcohol to give a white needle-like substance; m. p. 104–105°. It was found to be very soluble in chloroform and carbon tetrachloride.

Anal. Calcd. for $(C_6H_5O)_2PONHC_6H_{11}$: N, 4.23; H, 6.69; C, 65.3. Found: N, 4.06; H, 6.76; C, 64.7.

(8) **Diphenyl Anilidophosphate.**—Twenty-seven grams (0.1 mole) of (II) dissolved in 50 cc. of carbon tetrachloride was allowed to react with 20.5 g. (0.22 mole) of aniline dissolved in 150 cc. of carbon tetrachloride. A yield of 32 g. (98.5%) was obtained. The product was recrystallized from absolute alcohol and found to melt at 129–130° corresponding with the compound prepared previously by the action of phenol and aniline on phosphorus pentachloride.[3]

B. Preparation of the N-Substituted Derivatives by the Action of Amines on the C_6H_5OH–$POCl_3$–C_5H_5N Reaction Product

(1) **The N-Substituted Derivatives of Phenyl Diamidophosphoric Acid.**—The $POCl_3$–C_6H_5OH–C_5H_5N mixture was prepared using a molar ratio of 1:0.77:3. Forty-six grams (0.3 mole) of phosphoryl chloride was dissolved in 225 cc. of chloroform and the mixture cooled in an ice–salt-bath. A solution containing 21.7 g. (0.231 mole) of phenol dissolved in 71 g. (0.9 mole) of pyridine was then added dropwise to the chloroform solution. The temperature of the reaction was maintained at $-2 \pm 2°$. The reaction product thus obtained was used for the following aminolytic reactions.

a. **Phenyl Di-(methylamido)-phosphate.**—The $POCl_3$–C_6H_5OH–C_5H_5N mixture was added slowly with stirring to an aqueous solution containing an excess of methylamine. The temperature was maintained at $3 \pm 2°$. Upon completion of the reaction, the product separated into an aqueous and a chloroform layer. Both solutions were evaporated to dryness under slightly reduced pressure. The residue from the evaporation of the aqueous layer was extracted with absolute ether from which a small quantity of the pure di-(methylamido) derivative was obtained upon evaporation. The residue from the chloroform layer was found to consist mainly of phenyl di-(methylamido)-phosphate slightly contaminated with the diphenyl derivative. The pure di-(methylamido) compound was obtained by fractional recrystallization from a carbon tetrachloride solution in which diphenyl methylamidophosphate is more soluble. The total yield of phenyl di-(methylamido)-phosphate was 31.6 g. (68.4% based on the quantity of phenol used).

b. **Phenyl Di-(cyclohexylamido)-phosphate.**—The $POCl_3$–C_6H_5OH–C_5H_5N product was allowed to react with 193 g. (1.95 mole) of cyclohexylamine dissolved in 150 cc. of chloroform. The precipitate of cyclohexylamine hydrochloride was separated by filtration and the residue washed with 200 cc. of chloroform. The combined filtrates were evaporated under vacuum to remove the solvent. The amber oily residue was insoluble in water, but was dissolved in 70% boiling alcohol. A white crystalline mass formed upon cooling and long standing. The filtrate was evaporated further and crystalline fractions obtained on successive evaporations. A yield of crude material amounting to 66.6 g. (88.5% based upon the

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(2) Michaelis and Nathanson, *Ann.*, **326**, 248 (1903).

(3) Wallach and Heymer, *Ber.*, **8**, 1235 (1875).

phenol used) was obtained consisting largely of the desired product, contaminated with some diphenyl cyclohexylamidophosphate.

c. **Phenyl Di-(anilido)-phosphate.**—The $POCl_3$–C_6H_5OH–C_5H_5N product was allowed to react with 139.5 g. (1.81 mole) of aniline in 150 cc. of chloroform cooled in an ice-bath. The oily residue obtained after removal of the solvent was dissolved in hot 80% alcohol. A crystalline product separated upon cooling. A yield of 69.5 g. (96% based on the phenol used) was obtained. A portion of the crude product upon recrystallization several times from 80% alcohol gave a product melting at 178–179°, corresponding to phenyl di-(anilido)-phosphate.

d. **Phenyl Di-(morpholido)-phosphate.**—The $POCl_3$–C_6H_5OH–C_5H_5N mixture was allowed to react with 169 g. (1.95 mole) of morpholine dissolved in 150 cc. carbon tetrachloride. The precipitate was removed by filtration and washed with 200 cc. of carbon tetrachloride. The combined filtrates were evaporated under reduced pressure. The residue turned into a dark red solid mass. The solid was extracted with 200 cc. of absolute ether and then twice with 400 cc. of boiling carbon tetrachloride. The procedure left the morpholine hydrochloride in the residue. The combined extracts were evaporated to dryness, giving a crude solid weighing 59 g. The latter upon several recrystallizations from high-boiling petroleum ether, yielded 50.5 g. of phenyl di-(morpholido)-phosphate, corresponding to 70% of the phenol used. A small quantity of diphenyl morpholidophosphate was isolated from the mother liquors obtained from the various recrystallizations. Purification of the phenyl di-(morpholido)-phosphate was also effected by vacuum distillation, the portion coming over between 220–230° (2 mm.) being collected. The diphenyl compound is insoluble in water while the monophenyl compound is very soluble in water, consequently the two products may be separated easily in this manner.

(2) **The N-Substituted Derivatives of Diphenyl Amidophosphoric Acid.**—On the basis of a study of the ammonolysis of $POCl_3$–C_6H_5OH–C_5H_5N reaction mixture a reaction product consisting of these components in the molar ratio of 1:2:3 was employed with the expectation that aminolysis of this product would give mixtures containing appreciable quantities of the N-substituted derivatives of diphenyl amidophosphoric acid. In actual experiments, 46 g. (0.3 mole) of phosphoryl chloride, 56.4 g. (0.6 mole) of phenol and 71 g. (0.9 mole) of pyridine in 225 cc. of chloroform were used. This mixture was refluxed for fifteen minutes before aminolysis.

a. **Diphenyl Methylamidophosphate.**—The mixture was added slowly through a dropping funnel to an excess of aqueous methylamine cooled in an ice–salt-bath. After the completion of the addition, the product separated into an aqueous and a chloroform layer. After 80% of the solvent had been removed from the chloroform layer, crystals were obtained, which were filtered off. These were recrystallized from high-boiling petroleum ether and found to be diphenyl methylamidophosphate. Triphenyl phosphate contaminated with some of the product was found in the filtrate. Triphenyl phosphate and the desired product were found to have practically identical solubilities in a whole series of organic solvents except in hot 30% alcohol in which the latter is slightly soluble whereas the former is quite insoluble. Consequently, the chloroform mother liquor was evaporated to dryness and the residue extracted with 30% alcohol. Total yield of the diphenyl methylamidophosphate was 29.5 g. (37.5% based on the quantity of phenol used).

b. **Diphenyl Anilidophosphate.**—In order to decrease the yield of triphenyl phosphate as the by-product, the $POCl_3$:C_6H_5OH:C_5H_5N ratio was changed to 1:1.54:3. This corresponds to a 30% excess of phosphoryl chloride assuming the theoretical ratio of $POCl_3$:C_6H_5OH to be 1:2. In the actual experiment 46 g. (0.3 mole) of phosphoryl chloride, 43.5 g. (0.462 mole) of phenol and 71 g. (0.9 mole) of pyridine were used. The reaction product was aminolyzed with 125 g. (1.34 mole) of aniline in 150 cc. of chloroform. The product was dissolved in absolute alcohol from which water precipitated a product consisting largely of diphenyl anilidophosphate contaminated with some phenyl di-(anilido)-phosphate. Since the solubilities of both are rather similar, the separation of the product into its constituents was not undertaken.

c. **Diphenyl Morpholidophosphate.**—The $POCl_3$–C_6H_5OH–C_5H_5N product similar to that used in the preceding experiment was aminolyzed with 115.4 g. (1.33 mole) of morpholine dissolved in 150 cc. of carbon tetrachloride. The product was purified by vacuum distillation, the portion distilling at 240–250° (5 mm.) being collected. The distillate crystallized upon cooling. The product was washed with water yielding the diphenyl ester contaminated with some triphenyl phosphate. Recrystallization from high-boiling petroleum ether yielded 14 g. (19% based on the phenol used) of the pure diphenyl morpholidophosphate.

Summary

The N-substituted derivatives of the phenyl esters of amido- and diamidophosphoric acids may be prepared either by the aminolysis of the corresponding chlorophosphates or by the aminolysis of the $POCl_3$–C_6H_5OH–C_5H_5N reaction mixture. The latter procedure was found to be satisfactory for preparing the N-substituted derivatives of phenyl diamidophosphoric acid, but is not recommended for the preparation of the corresponding compounds from diphenyl amidophosphoric acid. The properties of the N-substituted compounds derived from methylamine, cyclohexylamine, aniline, and morpholine are described.

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