Phosphorus-Nitrogen Compounds I. Carboxy and Carbethoxy-Substituted Aryl Derivatives

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Since certain aromatic compounds in which carboxy and carbethoxy groups are situated *para* to an amino group possess medicinal value, a number of similar organophosphorus derivatives were prepared. The compounds that were synthesized include three phosphorodiamidic acids, two phosphoramidates, a phosphorodiamidic chloride, and a phosphenimidic amide.

PHOSPHORODIAMIDIC ACIDS are generally prepared by the hydrolysis of the corresponding phosphorodiamidic chlorides which can be derived from the reaction of either 2 or 4 moles of a primary or secondary amine with 1 mole of phosphorus oxychloride in an inert solvent[1] (1, 2). A modification of this procedure involves the interaction of a phosphorus oxychloride-pyridine complex with the amine in chloroform solution. This method was employed by Audrieth and Toy (3) for the preparation of *N*-substituted derivatives of phosphoryl triamides using a ratio of $POCl_3$:amine:C_6H_5N = 1:6:3. This scheme can also be used to prepare phosphorodiamidic chlorides in good yield. However, the poor solubility of some amines in chloroform, and of the $POCl_3$–C_6H_5N complex in solvents other than chloroform (*i.e.*, dioxane), restricts the applications of this method. Primary amines (2 moles) react smoothly with phosphoryl halides (1 mole) in inert solvents[1] to form the corresponding phosphoramidates in a manner analogous to the preparation of phosphorodiamidic acids (4).

Michaelis (2) prepared an ethyl phosphoramidate by reacting the chloro derivative with sodium ethoxide. The action of a nonaqueous alkaline reagent on a phosphorodiamidic chloride, however, results in dehydrohalogenation of the compound with the formation of a phosphenimidic amide (2, 5). Such a product results from the reaction of *N,N'* - di(*p* - carbethoxyphenyl)phosphorodiamidic acid with sodium ethoxide. Treatment of a carbethoxy-substituted phosphorodiamidic acid with an aqueous alkaline reagent under controlled conditions yields a hemiester.

It has been shown that some compounds containing a phosphorus-nitrogen bond have high solubilities in various solvents (3). This property is attributed to the pronounced hydrogen bonding tendencies displayed by the phosphoryl group. Since the solubilities of such compounds are remarkable even in substances of large molecular weight, some difficulty is encountered in their isolation and purification.

Several organophosphorus compounds containing carboxyl groups are reported as having high melting points, and in some cases no definite melting points are indicated (6, 7). These latter compounds apparently decompose over a range without having true melting points.

p-Aminobenzoic acid (PABA) and its esters have been extensively investigated for various therapeutic applications. The acid is considered to be an essential nutrilite for a number of microorganisms whose biological activity is dependent upon incorporation into the pteroylglutamic acid molecule. PABA has also been shown to be valuable in treating rheumatic fever and human rickettsial infections (8). It is also interesting that large amounts of PABA are reported to cause a striking lowering of the leucocyte counts in some cases of myelogenous leukemia (9). Alkyl esters of *p*-aminobenzoic acid are well known for their local anesthetic properties. Substitution of the amine nitrogen of *p*-aminobenzoates in certain cases (*i.e.*, tetracaine) has resulted in increased anesthetic potency; whereas similar alterations of simple esters often produce a loss of activity.

To ascertain the effect of phosphorus substitution on the physiological activity of PABA and its ethyl ester, certain organophosphorus compounds have been synthesized. Compounds containing the N—P link are quite stable at biological pH (10); however, a potentially free amino group is present in these substances since hydrolysis of this bond may be accomplished through the enzymatic influence of phosphamidases. This enzymatic hydrolysis constitutes the rationale for the selective cytotoxic activity of some alkylating antineoplastic agents (11).

EXPERIMENTAL[2]

N,N' - di(*p* - Carboxyphenyl)phosphorodiamidic Acid (I).—A mixture of 60 mmoles of *p*-aminobenzoic acid in 200 ml. of reagent dioxane and 15 mmoles of phosphorus oxychloride were stirred under reflux for 1 hour. The formed precipitate was separated from the cooled reaction mixture and stirred with dilute hydrochloric acid. The suspension was filtered, the residue washed with water, and recrystallized from boiling water to yield the white crystalline product.

N,N' - di(*p* - Carbethoxyphenyl)phosphorodiamidic Acid (II).—A solution of 50 mmoles of ethyl *p*-aminobenzoate in 150 moles of dry benzene was slowly added to 100 ml. of dry benzene containing 25 mmoles of phosphorus oxychloride. No reaction was apparent at 5°, but a precipitate began to form upon heating. The reaction mixture was refluxed for 4 hours and allowed to stand overnight. The reaction mixture was then taken to dryness with an air stream and steam bath. Recrystallization of the residue from hot, dilute ethanol yielded the white crystalline product.

N,N' - di(*p* - Carbethoxyphenyl)phosphorodiamidic Chloride (III).—A mixture of 100 mmoles of

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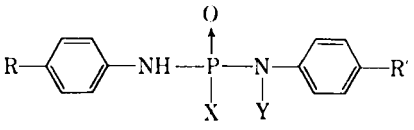
[1] We found reagent dioxane to be a good solvent when *p*-aminobenzoic acid constitutes the amine in this reaction.

[2] See Tables I and II.

TABLE I.—PHOSPHORODIAMIDIC ACIDS, CHLORIDE, AND PHOSPHENIMIDIC AMIDE



No.	R	R′	X	Y	M.p., ° C.[a]	Analysis % C Calcd.	C Found	H Calcd.	H Found
I	COOH	COOH	OH	H	200 dec.	50.0	49.4	3.9	4.2
II	COOEt	COOEt	OH	H	200–202 dec.	55.1	55.0	5.4	5.2
III	COOEt	COOEt	Cl	H	172–173	56.5	57.0	5.3	5.8
IV	COOH	COOEt	OH	H	154–157	52.8	52.5	4.7	4.8
V	COOEt	COOEt	..	..	188–189	57.7	57.7	5.1	6.0

[a] All melting points are uncorrected.

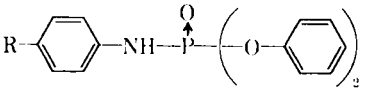
ethyl *p*-aminobenzoate, 17 mmoles of phosphorus oxychloride, and 50 mmoles of pyridine were reacted in reagent chloroform according to the method of Audrieth and Toy (3). The pink, waxy residue was washed with dilute hydrochloric acid and water until the washings gave a negative chloride test with silver nitrate T.S. Recrystallization of the residue from ethanol following Norit A treatment yielded the white crystalline product.

N - (*p* - Carboxyphenyl) - N′ - (*p* - carbethoxyphenyl)phosphorodiamidic Acid (IV).—A suspension of 1.3 mmoles of III in 50 ml. of 10% sodium hydroxide was stirred and heated at 70° for 15 minutes. The reaction mixture was filtered and the colorless filtrate acidified with concentrated hydrochloric acid to form, upon cooling, the white crystalline product.

N,N′ - di(*p* - Carbethoxyphenyl)phosphenimidic Amide (V).—A mixture of 2.7 mmoles of III in 25 moles of absolute ethanol and 20 mmoles of sodium metal previously reacted with 20 ml. of absolute ethanol was heated and stirred for 45 minutes. The formed suspension was added to 300 ml. of cold water, and the resulting solution was rendered neutral with concentrated hydrochloric acid. Cooling of this solution produced a white precipitate that was collected and suspended in 10% sodium carbonate solution. The suspension was heated and stirred for 15 minutes, filtered, and the residue washed with water until the washings were neutral. Recrystallization of the residue from dilute ethanol yielded the white crystalline product.

Diphenyl *p*-Carbethoxyphenylphosphoramidate (VI).—When 100 mmoles of ethyl *p*-aminobenzoate and 50 mmoles of diphenylphosphoryl chloride in 250 ml. of dry benzene were heated, a precipitate formed which disappeared at reflux temperature. The reaction mixture was allowed to reflux for 1 hour, and the clear solution evaporated to near dryness with a warm air stream. The residue was stirred with an excess of dilute hydrochloric acid to yield a pink waxy solid which was recrystallized from ethanol-dilute hydrochloric acid to yield the white product in the form of needles.

TABLE II.—PHOSPHORAMIDATES



No.	R	M.p., ° C.[a]	Analysis % P Calcd.	P Found
VI	COOEt	151–152	7.8	7.9
VII	COOH	194–195	8.4	8.2

[a] All melting points are uncorrected.

Diphenyl *p*-Carboxyphenylphosphoramidate (VII).—A mixture of 100 mmoles of *p*-aminobenzoic acid and 50 mmoles of diphenylphosphoryl chloride in 250 ml. of reagent dioxane was refluxed for 1 hour. The reaction mixture was cooled and the formed brown precipitate was collected. This material was boiled with water and filtered. The pink crystals that developed in the cooled filtrate were stirred with excess glacial acetic acid. The residue was washed with water and recrystallized from boiling water to yield the product in the form of white needles.

REFERENCES

(1) Caven, R. M., *J. Chem. Soc.*, **81**, 1362(1902).
(2) Michaelis, A., *Ann.*, **326**, 129(1903).
(3) Audrieth, L. F., and Toy, A. D. F., *J. Am. Chem. Soc.*, **64**, 1337(1942).
(4) Autenrieth, W., *Ber.*, **30**, 2369(1897).
(5) Michaelis, A., *Ann.*, **407**, 290(1915).
(6) *Ibid.*, **293**, 193(1896).
(7) Arnold, G. B., and Hamilton, C. C., *J. Am. Chem. Soc.*, **63**, 2637(1941).
(8) Goodman, L., and Gilman, A., "The Pharmacological Basis of Therapeutics," 2nd ed., The Macmillan Co., New York, N. Y., 1960, p. 1716.
(9) Zarafonetic, S. J. D., *et al.*, *Blood*, **3**, 780(1948).
(10) Saunders, B. C., and Todd, A., "Some Aspects of the Chemistry and Toxic Action of Organic Compounds Containing Phosphorus and Fluorine," Cambridge University Press, London, 1957, p. 173.
(11) Freidman, O. M., and Seligman, A. M., *J. Am. Chem. Soc.*, **76**, 655(1954).