Phosphorus-Nitrogen Compounds III. Phenyl Esters of *N*-Tolyl- and *N*-Pyridylthiocarbamylphosphoramidic Acids

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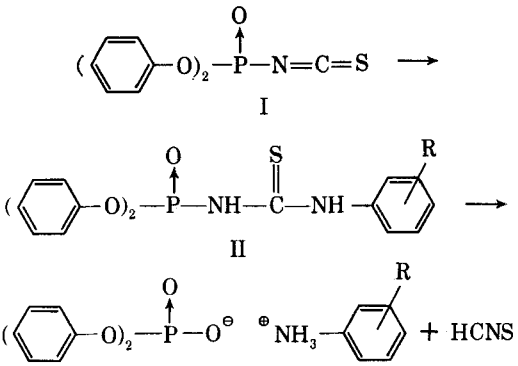
The preparation of phosphoramidates containing moieties with potential antimetabolic activity is reported. Hydrolytic decomposition products obtained in the attempted isolation and purification of some of these compounds are also described.

THE AMMONOLYSIS of isothiocyanates has been employed widely in the preparation of thioureas. This process, however, has found application in the field of organophosphorus compounds only within the past decade.

Elmore and Ogle (1) found that diphenyl phosphoroisothiocyanatidate (I) condensed with aromatic amines in inert solvents to yield the corresponding thioureas (II). These investigators were surprised



that certain of these diphenyl *N*-arylthiocarbamylphosphoramidates readily underwent hydrolysis to yield anilinium diphenylphosphates (III) and thiocyanic acid. They attributed the instability of these compounds principally to the influence of electron-attracting substituents since, while they could not recrystallize the *p*-aminobenzoic acid derivative due to ready decomposition, the electron-donating butyl and cyclohexyl groups gave stable thioureas.

Apparently the ester portion of the molecule also can play a role in the stability of compounds of this nature. The stabilizing tendency of an electron-donating radical, such as an alkyl, is shown by the work of Levchenko and Sheinkman (2), who reported the preparation of the sodium salt of diethyl 3 - hydroxy - 4 - carboxyphenylthiocarbamylphosphoramidate and other esters that were treated with alkali and/or acid during their isolation and purification.

The cytotoxic activity of substituted thioureas has been investigated extensively, particularly in regard to growth inhibition of *M. tuberculosis*. Since thiocarbamylphosphoramidates contain the thiourea moiety, it is not unexpected that such derivatives have been reported to have tuberculostatic properties (2).

The compounds reported in this paper were synthesized for testing as antineoplastic agents. The rationale for the incorporation of substituted toluidines into these derivatives is given in an earlier report in this series (3). Inclusion of substituted 2-aminopyridine moieties in this series of compounds is based upon the observed antileukemic effect of related derivatives, as reported by Humphreys and co-workers (4). These investigators observed antimetabolic activity in certain pyridines and attributed their effect to an *in vivo* exchange with nicotinamide in DPN with the formation of fraudulent DPN. The pyridines chosen for this synthetic work are related to 6-aminonicotinamide, an active metabolite-antagonist, in which the carbamyl portion is replaced by a chlorine, a bromine, or a methyl group. The synthesis of other phosphoramidates employing substituted pyridines is the subject of a paper to be published at a later date.

Samples of the compounds reported in this paper have been submitted to the Cancer Chemotherapy National Service Center for preliminary evaluation.

EXPERIMENTAL

Syntheses.—The thiocarbamylphosphoramidates (Table I) were formed by addition of equimolar amounts of amine in the indicated solvent to diphenyl phosphoroisothiocyanatidate, followed by standing overnight at room temperature according to previously prescribed methods (1, 2).

In certain cases, only diphenylphosphates (Table II) were isolated. These products are believed to have resulted either from hydrolytic decomposition of the formed esters upon attempted purification (*i.e.*, compound *12*) or from the use of impure starting materials. Unstable derivatives (*i.e.*, compound *8*) were anticipated in certain cases, owing to the nature of substituents on the amines.

All of the compounds reported were white or pale yellow crystalline products.

Isolation and Purification.—Compounds *1* and *2* were precipitated from their solvent by addition of petroleum ether. Compounds *3* and *4* were purified by removal of solvent *in vacuo* and recrystallized from ethyl acetate–petroleum ether. Compounds *5* and *6* precipitated from the reaction mixtures during the condensation and were recrystallized from dioxane–petroleum ether. Compound *7* was isolated from the precipitate formed in the reaction mixture by collecting on a filter and washing with acetonitrile and ether. Compounds *8* through *12* were isolated from the precipitates formed in the reaction mixtures by washing with acetonitrile and ether and recrystallized from dioxane. In the case of compounds *8*, *9*, and *10*, the washed materials had a melting point the same as the recrystallized products.

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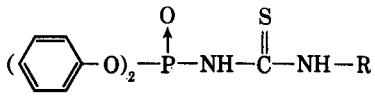
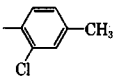
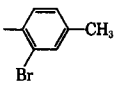
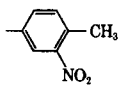
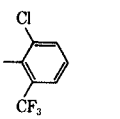
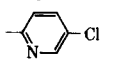
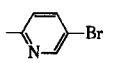
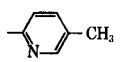
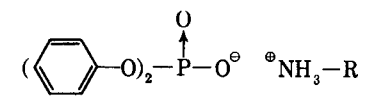
TABLE I.—DIPHENYL THIOCARBAMYLPHOSPHORAMIDATES

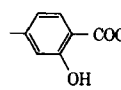
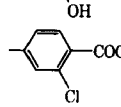
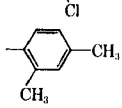
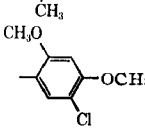
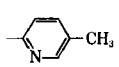


No.	R	M.p., °C.[a]	Formula	Solvent	Anal., %[b] P Calcd.	P Found	N Calcd.	N Found
1		114–115	$C_{20}H_{18}ClN_2O_3PS$	Benzene	7.2	7.2	6.5	6.7
2		127–128	$C_{20}H_{18}BrN_2O_3PS$	Benzene	6.5	6.6	5.9	5.7
3		139–140	$C_{20}H_{18}N_3O_5PS$	Ether	7.0	6.9	9.5	9.6
4		118	$C_{20}H_{15}ClF_3N_2O_3PS$	Ether	6.4	6.4	5.8	5.9
5		145	$C_{18}H_{15}ClN_3O_3PS$	Acetonitrile	7.4	7.3	10.0	10.3
6		149–150	$C_{18}H_{15}BrN_3O_3PS$	Acetonitrile	6.7	6.7	9.1	9.2
7		137–138	$C_{19}H_{18}N_3O_3PS$	Acetonitrile	7.8	7.5	10.5	9.7

[a] All melting points are uncorrected. [b] Analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

TABLE II.—DIPHENYLPHOSPHATES



No.	R	M.p., °C.[a]	Formula	Anal., %[b] P Calcd.	P Found	N Calcd.	N Found
8		155	$C_{19}H_{18}NO_7P$	7.7	7.5	3.5	3.7
9		164	$C_{19}H_{18}ClNO_6P$	7.3	7.0	3.3	3.4
10		138	$C_{20}H_{22}NO_4P$	8.3	8.3	3.8	3.9
11		151–153	$C_{20}H_{21}ClNO_6P$	7.1	6.8	3.2	3.3
12		125	$C_{18}H_{18}N_2O_4P$	8.6	8.5	7.8	7.8

[a] All melting points are uncorrected. [b] Analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

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(3) Cates, L. A., and Ferguson, N. M., THIS JOURNAL, **53**, 973(1964).
(4) Humphreys, S. R., *et al.*, *Cancer Res., suppl.* **22**, *part* 2, **1962**, 483.