using unsubstituted α-alkyloximinocarboxamides as well as ascertain the feasibility of preparing the corresponding nitriles which would be interesting intermediates for further investigations.

Powdered α-alkyloximinocarboxamides were mixed thoroughly with a slight excess of phosphorus pentoxide and then heated with a Bunsen flame under reduced pressure. In all cases a vigorous reaction ensued during which oils were collected in reasonable yields and characterized as α-alkyloximinonitriles by infrared analysis. The characteristic nitrile peak showed up as a medium sharp band at 2235 cm.$^{-1}$ for α-benzyloximinobutyronitrile, and a medium sharp band at 2236 cm.$^{-1}$ for α-benzyloximinopropionitrile. The values are well within the reported range (2). Alkaline hydrolysis of the nitriles produced the corresponding α-alkyloximino acids.

The success of the dehydration reaction would then indicate that the failure of the Bischler-Napieralski reaction in the instance cited must be attributed to factors other than the stability of the alkyloximino group.

EXPERIMENTAL

Amides prepared according to the procedure of Woolley and co-workers (3) have been reported (4).

α-Benzyloximinobutyronitrile.—A 30.9-Gm. quantity (0.15 mole) of α-benzyloximinobutyramide was ground in a mortar and transferred to a round-bottom flask. Then 28.4 Gm. (0.2 mole) of phosphorus pentoxide was added, the flask was stoppered and manually shaken until the mixture was homogeneous. The flask was connected to a vacuum system set for downward distillation. The system was evacuated to 0.35 mm. and heating was started. Frothing and discoloration ensued as a brown oil distilled. Heating was discontinued when the temperature of the vapors fell from 129° to 50°. The reaction mixture was cooled and exhaustively extracted with benzene. The benzene extract was combined with the distillate, the benzene removed, and the residue distilled under reduced pressure. Five grams (17.3%) of an oil was collected at 102–105°/0.5 mm. The procedure followed was that outlined in the literature (5). A small amount of the oil was heated with 10% NaOH, cooled, and acidified. The solid obtained was filtered off, crystallized from alcohol-water. The melting point was 88–90°, as compared to the reported value of 86° (6). A mixed melting point showed no depression.

α-Benzyloximinopropionitrile.—In like manner, α-benzyloximinopropionamide was converted to the nitrile. In this case, in an effort to reduce mechanical losses, smaller vessels were used to run smaller amounts. Only the reaction vessel was changed for each run and in this way the yield was increased to 32%. The observed boiling point of α-benzyloximinopropionitrile was 74–76°/0.2 mm. Basic hydrolysis of the oil produced a solid melting at 85°. The melting point was consistent with that obtained when the acid was prepared in this laboratory by standard procedures (6). The melting point was not in agreement with the reported value of 73–75° (6), but nitrogen analysis of the amide did check (4). A mixed melting point showed no depression.

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Phosphorus-Nitrogen Compounds II. Some *p*-Toluidine Derivatives

By LINDLEY A. CATES and NOEL M. FERGUSON

Certain organophosphorus compounds containing substituted *p*-toluidine moieties were prepared for evaluation as cancer chemotherapeutic agents. The compounds that were synthesized include phosphoramidochloridic acids, phosphoramidates, phosphoramidothionates, a phosphorodiamidate, and a phosphorodiamidic chloride. The *S*-*p*-chlorobenzylthiuronium salt of a phosphoramidochloridic acid is also reported.

THE FIRST paper in this series (1) reported the synthesis of some carboxy- and carbethoxy-substituted aryl derivatives containing phosphorus-nitrogen bonds. This series has been extended to include some related *P–N* compounds involving substituted *p*-toluidine moieties.

Phosphoramidochloridic acids (I) constitute a relatively new class of organophosphorus compounds, of which there are few examples in the literature. Most of these compounds are arylsulfonamide derivatives (2–6), one of which was included in a group of derivatives said to possess tumor-inhibiting activities (6). All reported phosphoramidochloridic acids were prepared by treating phosphorimidic trichlorides or phosphoramidic dichlorides with formic acid (2–8). The use of an acidic reagent is not necessary in this type of synthesis, however, since the *p*-toluidine derivatives were prepared by aqueous hydrolysis of the corresponding phosphoramidic dichlorides. In either case, the acid chloride character of phosphor-

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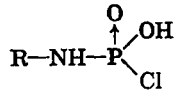

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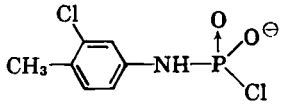

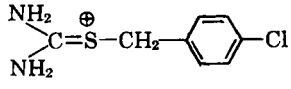

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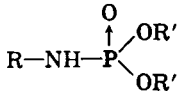

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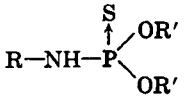

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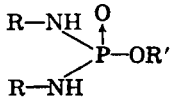

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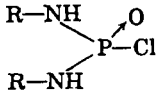


VI

amidic dichlorides is sufficiently suppressed by the amido group so that the second chlorine atom is stable in neutral, or near neutral, media. Thus, the salt of a phosphoramidochloridic acid can be formed by the careful addition of dilute sodium hydroxide solution.

Investigators in the field of organophosphorus chemistry have encountered problems in the isolation and purification of some acids and esters. Phosphoramidochloridic acids possess a fair degree of water solubility and, therefore, pose similar difficulties. They can be crystallized from a dry, inert solvent to yield the anhydrous product or from an ethanol-water media to give the lower melting, hydrated form. A recent report (9) has shown that certain phosphorus-containing acids and esters can be converted to insoluble, sharp melting *S-p*-chlorobenzylthiuronium salts. Our investigations indicate that the sodium salt of (*N*-3-chloro-4-methylphenyl)phosphoramidochloridic acid is also precipitated by *S-p*-chlorobenzylthiuronium chloride to yield the pure insoluble salt II. This is the first instance of a benzylthiuronium salt of a compound containing a phosphorus-nitrogen bond and indicates another application of a new procedure for the isolation of certain organophosphorus products.

The synthetic scheme for the phosphoramidates III, phosphoramidothionates IV, and phosphorodiamidate V follows the classical preparatory methods whereby a ratio of 2 or 4 moles of amine are reacted with 1 mole of phosphorochloridate or phosphorochloridothionate in an inert solvent. The phosphorodiamidic chloride VI resulted from the refluxing of the appropriate amine with phosphorus oxychloride (2:1) in benzene over a long period of time.

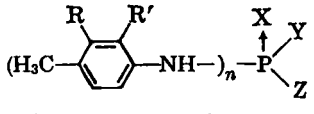
Monosubstituted *p*-aminobenzoic acids have been investigated for antibacterial properties and the chlorinated and fluorinated derivatives are among those shown to inhibit bacterial cell growth. 2-Chloro-4-aminobenzoic acid has been found to have relatively high bacteriostatic activity (10) and some antileukemic effect (11). For these reasons more attention was directed to the preparation of organophosphorus derivatives of the methyl analog of this acid. One can hypothesize that *in vivo* oxidation of the methyl group may yield the corresponding substituted *p*-aminobenzoic acid. Such a conversion may precede or follow the hydrolysis of the phosphorus-nitrogen bond by phosphamidase enzymes. Since phosphamidases are reported to occur in higher concentration in neoplastic cells than in normal cells (12), this enzymatic action is the basis for postulating a specific antimetabolic activity by the parent moiety. Also, in view of the fact that *p*-toluidine has antibacterial (13) and carcinogenic (14) properties, these derivatives may have application as antineoplastic agents.

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

EXPERIMENTAL

Preparation of Phosphoramidochloridic Acids.—Compounds I, II, and III were prepared by adding the appropriately substituted *p*-toluidine (0.4 mole)

TABLE I.—*p*-TOLUIDINE DERIVATIVES



No.	*n*	R	R′	X	Y	Z	M.p., °C.[a]	Formula	Analyses, % P Calcd.	P Found	Cl Calcd.	Cl Found
I	1	Cl	H	O	Cl	OH	218–220	$C_7H_8Cl_2NO_2P$	12.90	12.98	29.54	29.81
II	1	H	Cl	O	Cl	OH	88–90 dec.	$C_7H_8Cl_2NO_2P\cdot 3H_2O$	10.53	10.50		
III	1	H	CH_3	O	Cl	OH	178–179 dec.	$C_8H_{11}ClNO_2P\cdot 3H_2O$	11.32	11.33		
IV	1	Cl	H	O	OEt	OEt	85–86	$C_{11}H_{17}ClNO_2P$	11.15	11.02		
V	1	Cl	H	O	OPh	OPh	139–140	$C_{19}H_{17}ClNO_2P$	8.29	8.27		
VI	1	F	H	O	OEt	OEt	91–92	$C_{11}H_{17}FNO_2P$	11.86	12.00		
VII	1	F	H	O	OPh	OPh	115–116	$C_{19}H_{17}FNO_2P$	8.67	8.71		
VIII	1	Cl	H	S	OEt	OEt	52–54	$C_{11}H_{17}ClNO_2PS$	10.54	10.74		
IX	1	H	CH_3	S	OEt	OEt	Oil	$C_{12}H_{20}NO_2PS$	11.33	11.58		
X	2	Cl	H	O	Cl	...	154–156	$C_{14}H_{16}Cl_3N_2OP$	8.52	8.32		
XI	2	Cl	H	O	OPh	...	149	$C_{26}H_{18}Cl_3N_2O_2P$	7.35	7.36		
XII	1	Cl	H	O	Cl	$O^{\ominus}$	87–89	$C_{15}H_{17}Cl_3N_3O_2PS$	7.03	6.99		

$ClC_6H_4CH_2\overset{\oplus}{S}{=}C(NH_2)_2$

[a] All melting points are uncorrected.

dropwise with stirring to phosphorus oxychloride (0.2 mole) in 250 ml. of anhydrous ether and allowing the mixture to stand for 3 days. The suspensions were evaporated to near dryness and stirred with water for 1 hour. The residues were recrystallized following decolorization with charcoal to yield the white powdery products. Compound I was recrystallized from reagent dioxane; compounds II and III from ethanol-water.

Preparation of Phosphoramidates.—Compounds IV through VII were prepared by adding 0.1 mole of the appropriately substituted *p*-toluidine to 0.05 mole of diethyl or diphenyl phosphorochloridate in 300 ml. of reagent benzene and refluxing for 2 hours. The suspensions were evaporated to a moist mass with an air stream and gentle heat. The residues were stirred with dilute hydrochloric acid and washed with water by decantation. Recrystallization from ethanol-water following charcoal decolorization yielded the products in the form of white needles.

Preparation of Phosphoramidothionates.—Compounds VIII and IX were prepared by adding 0.2 mole of diethyl phosphorochloridothionate to 0.4 mole of 3-chloro-4-methylaniline or 2,4-dimethylaniline in 300 ml. of reagent benzene and refluxing for 2 hours. The suspensions were evaporated to a moist mass with an air stream and gentle heat. The residues were stirred with dilute hydrochloric acid and washed with water by decantation to yield red liquids. Compound VIII upon drying in a vacuum desiccator gave a red solid which was recrystallized from ethanol-water following charcoal decolorization to yield the white crystalline product having a pungent odor. Compound IX was stirred with 10% potassium hydroxide solution and dilute hydrochloric acid; each procedure was followed by water washings. The red, oily residue was dissolved in ether, decolorized with charcoal, and filtered to give a nearly colorless, clear filtrate. The filtrate was treated with anhydrous calcium sulfate, filtered and the ether removed under reduced pressure to yield the pale yellow, undistillable oil having a pungent odor.

Preparation of (N,N'-3-Chloro-4-methylphenyl)-phosphorodiamidic Chloride X.—A mixture of 3-chloro-4-methylaniline (0.1 mole) and phosphorus oxychloride (0.05 mole) in 300 ml. of reagent benzene was refluxed until negligible hydrogen chloride evolution was detected (65 hours). The reaction mixture was evaporated to dryness with an air stream and gentle heat. Recrystallization from ethanol-water following charcoal decolorization yielded the white, powdery product.

Preparation of Phenyl (N,N'-3-Chloro-4-methylphenyl)phosphorodiamidate XI.—A mixture of 3-chloro-4-methylaniline (0.2 mole) and phenyl phosphorodichloridate (0.05 mole) in 300 ml. of reagent benzene was refluxed for 2 hours. The reaction mixture upon drying in a vacuum desiccator gave a moist mass which changed to a liquid upon washing with water. Treatment with dilute hydrochloric acid yielded a yellow, waxy solid which was washed with water. Recrystallization from ethanol-water following charcoal decolorization gave the white, crystalline product.

Preparation of S-p-Chlorobenzylthiuronium Salt of (N,N' - 3 - Chloro - 4 - methylphenyl)phosphoramidochloridic Acid XII.—Five grams of compound I were suspended in water, one drop of phenolphthalein T.S. added, and 1 *N* sodium hydroxide introduced dropwise with stirring to attainment of a pale pink color and partial dissolution of the suspended material. The suspension was filtered and brought to near boiling. Ten milliliters of saturated ethanolic solution of *S-p*-chlorobenzylthiuronium chloride (9) was added to give a white viscous mass which was washed with water and dried to yield the white glassy product.

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