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Phosphorylated and Thiophosphorylated Aminoheterocycles

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The review is devoted to the methods of synthesis, chemical reactions, reactivities, and transformations of phosphoryl- and thiophosphoryl-aminoheterocycles in living organisms and in the surrounding medium. Many of these substances are biologically active and are used in the national economy.
The bibliography includes 170 references.

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I. INTRODUCTION

Many derivatives of aminoheterocycles are used in various branches of the national ecomony; particular mention should be made of the use of sulphamidoheterocycles as medicinal drugs.. Phosphorylated and thiophosphorylated aminoheterocycles of similar structure also exhibit a varied biological activity. The nature of the activity is influenced significantly both by the nature of the heterocycle and by the structure of the phosphorus-containing residue. Phosphorylated and thiophosphorylated aminothiadiazoles[1], aminotriazoles[2-8], and aminothiazoles[1] have been patented as fungicides. Diethyleneaminophosphoryl-derivatives of 2- and 4-aminopyrimidines[9-12], aminopurine[13-15], 3-aminopyridazine[16], and 2-amino-1,3,4-thiadiazole[17-19] exhibit a carcinolytic activity against various strains of leukaemia and sarcoma. Data exist on the herbicidal and growth regulating activity of phosphorylaminothiazoles[20], phosphorylaminotriazoles[21], and phosphorylaminotriazines[22-27]; derivatives of 4-phosphazopyridazine also possess a herbicidal activity[28]. The weaker bactericidal activity of derivatives of phosphorylaminopyridine has been noted[29].

However, most phosphorylaminoheterocycles exhibit insecticidal and acaricidal activities. Derivatives of aminopyran[30], aminothietan[31-34], aminodithiolan[35-37], amino-oxazole and amino-oxazoline[38-41], aminothiazole and aminothiazoline[38,41-48], amino-oxazine[41], aminotriazole[2,4,5,8,21], amino-1,3,4-thiadiazole and amino-1,2,4-thiadiazole[49,50], aminotriazine[51], and aminophenothiazine[52] have been described as insecticides and acaricides.

Some of the phosphoryl- and thiophosphoryl-aminoheterocycles have found practical applications as chemical plant protecting agents and medicinal drugs. 2-Diethoxythiophosphorylamino-1,3-dithiolan and 2-diethoxythiophosphorylamino-4-methyl-1,3-dithiolan under the commercial names "Cyolan" (dithiolene) and "Dithiolan" [53] are used as broad-spectrum insecticides against a group of pests on the cotton plant. 5-Amino-3-phenyl-1H-1,2-triazol-1-yl, *N*,*N*-dimethylphosphoramidate (triamiphos, vepsin) has been employed on a small scale as a systemic fungicide against powder mildew[53-57]. 4-Bromo-2-phenyl-5-(trimethoxyphosphazo)pyridazin-2-one (SGA 18796 preparation) has been tested as an experimental herbicide against weeds in sugar beet plantations[53]. Diaziridinyl 2-pyrimidinyl phosphoramidate (phosphamide) has been used in medical practice for the treatment of hypodermiasis[11]. The antitumour preparation 6-diaziridinylphosphorylamino-2-dimethylamino-7-methylpurine (fopurine) is effective against various forms of leukaemia in laboratory animals[58,59].

Bearing in mind the increasing importance of phosphorylated and thiophosphorylated aminoheterocycles for practical applications in the national economy, we thought it timely to compile this review of the literature data concerning the methods of synthesis and the chemical and physical properties of compounds of this class. The review covers the literature up to the middle of 1980.

II. METHODS OF SYNTHESIS OF PHOSPHORYLATED AMINOHETEROCYCLES

The commonest method of synthesising phosphoryl- and thiophosphoryl-aminoheterocycles is the reaction involving the phosphorylation of aminoheterocycles. Phosphoryl chloride, the chlorides and isothiocyanides of phosphorus acids, diphosphadithietans, acid phosphites, phosphorus pentachloride, etc. can be used as phosphorylating agents.

1. Phosphorylation with Chlorides of Tetracoordinate Phosphorus Acids

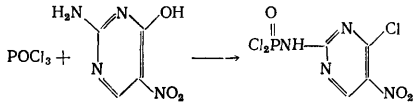
When phosphoryl chloride interacts with aminoheterocycles, the corresponding dichlorides of phosphoramidic acids are formed (Het is the residue of the heterocycle):

$$POCl_3 + H_2N\text{—}Het \xrightarrow[-HCl]{} Cl_2\overset{\overset{O}{\|}}{P}NH\text{—}Het \quad .$$

2-, 3-, and 4-Aminopyridines[10,60], 2- and 4-aminopyrimidines[10,12,61-65], 2-aminothiadiazoles[17,19,60,66], 2-aminobenzothiazole[67], 3-aminoindole[68], aminopurines[14,69], 3-aminopyridazine[70], creatinine[71], and sydnone imine[72] have been used as the initial aminoheterocycles. These reactions are usually carried out with refluxing in an excess of phosphoryl chloride for several hours and sometimes with heating in an organic solvent, for example, in benzene[64] or dichloromethane[72,73].

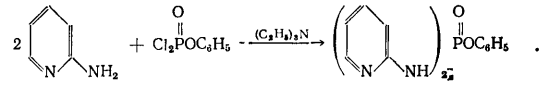
The reactions with secondary heterocyclic amines such as 2-alkylamino-1,3,4-thiadiazoles[18,19], 2-alkylamino-*sym*-triazines[24,73], and 2- and 4-alkylaminopyridines[74-76] proceed analogously. We may note that, when 6-chloro-2,4-bis-ethylamino-*sym*-triazine is refluxed with phosphoryl chloride for several hours, the products of the phosphorylation of only one amino-group are formed[23,25].

In the reaction with 2-amino-4-hydroxy-5-nitropyrimidine, phosphoryl chloride behaves not only as a phosphorylating agent but also as a chlorinating agent[77,78]:

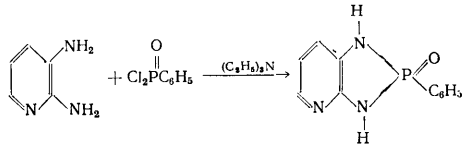


This method has been used to synthesise labelled compounds[15].

When phosphorus acids dichlorides were allowed to react with aminoheterocycles in the presence of tertiary amines, the corresponding phosphorus acid diamides were isolated[29,79,80]. *N*,*N*-di-(2-pyridyl)- and *N*,*N*-di-(2-pyrimidinyl)-*p*-nitrophenylphosphonodiamidates have been obtained in yields of 43 and 7% respectively by refluxing in dioxan 1 mole of *p*-nitrophenylphosphonic acid dichloride with 4 moles of the aminoheterocycle. Aryl *N*,*N*-di-(2-pyridyl)phosphorodiamidates have been obtained under similar conditions[29]:

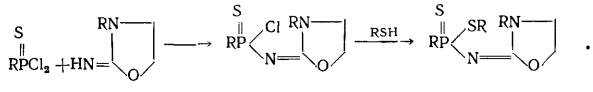


It is of interest to note that 2,4-diaminopyridine and the dichloride of phenylphosphonic acid react on heating in bromobenzene at 90–100 °C in the presence of an excess of a tertiary amine[81] to form a bicyclic condensation product:



4,5-Diaminopyrimidine does not enter into a similar reaction[81].

In many instances it is possible to achieve a controlled substitution of only one chlorine atom in the dichlorides of phosphonothionic acids by an aminoheterocycle residue and in such reactions the acid monochlorides are as a rule treated with nucleophiles without isolation in a pure form and the corresponding amidoesters of phosphonothionic acids are obtained. For example, the dithiophosphoryl derivatives of imino-oxazolidine are obtained by the reaction of the dichlorides of phosphonothionic acids with imino-oxazolidine and subsequent treatment with a thiol in the presence of sodium hydroxide[38,82]:



The reaction of the dichloride of chlorobutylphosphonic acid with 2-aminopyridine and subsequent hydrolysis with water in the presence of triethylamine yielded the acid ester of the corresponding pyridylphosphonamidic acid[83].

The reactions with the monochloride, ester, amide, and ester-amide derivatives of phosphorus acids with 2-, 3-, and 4-aminopyridines[29,84–88], 2- and 4-aminopyrimidines[85,89,90], 2-aminodithiolan and its salt[36], 2-iminodithiole and its salt[91], derivatives of 4-aminopyrazole[92], 2-aminoimidazoline[79], 2-aminothiazole[79,85,93,94], 3-alkyl-2-iminothiazolines[43,44,95], 2-aminothiazoline[79], 3-alkyl-2-iminothiazolidines[38,41,82,96–97], 2-imino-oxazolidines[38,41,82,96–98], 2-imino-1,3,4-thiadiazole[49], 3-alkyl-2-iminoperhydro-oxazines[38,41,97], 2-aminoquinoline[86], 2-aminobenzimidazole[99], 2-imino-1,3-dimethylbenzimidazoline[99], 2-aminobenzothiazole[85,99], 3-alkyl-2-iminobenzothiazoline[85,99], 2-aminobenzoxazole[99], 3-alkyl-2-iminobenzoxazoline[99], and 2-aminophenothiazine[52] have been investigated.

The reaction is carried out by heating a mixture of the phosphorus acid chloride with the aminoheterocycle or its salt in an organic solvent in the presence of a tertiary base and a double excess of the aminoheterocycle or an inorganic base, and also in a water–organic solvent two-phase system in the presence of alkali. The reaction and the yield of final products are influenced significantly by the structure of the phosphorus acid chloride, the basicity of the initial aminoheterocycle, and the nature of the solvent.

As a rule, the chlorides of oxygen-containing phosphorus acids react smoothly with aminoheterocycles in the presence of tertiary bases in non-polar and polar solvents and give rise to the corresponding amides in high yields. However, dialkyl phosphorochloridates do not react with 2-aminoquinoline in benzene; phosphorylation products have been obtained in 35% yield when the process was carried out in dioxan at 100 °C.[86] On reaction with dialkylphosphorochloridates, 2-aminopyridine *N*-oxide is converted into the corresponding hydrochloride[87].

It is noteworthy that dialkyl phosphorochloridates sometimes act as alkylating and not phosphorylating agents. Dimethyl phosphorochloridate reacts vigorously with 2-aminopyridine, the process being accompanied by a spontaneous temperature rise to 230 °C. *N*-Methylpyridone imine was isolated from the reaction products[100].

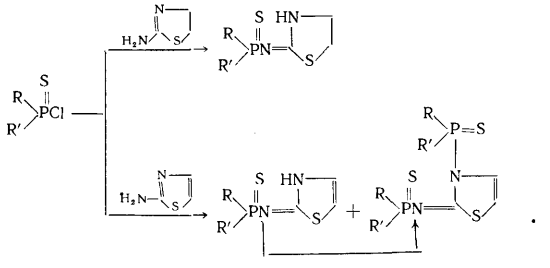
When 2-aminoquinoline *N*-oxide reacts with dialkyl phosphorochloridates, the products of its alkylation at the exocyclic nitrogen atom are formed[86].

The decrease of reactivity on passing from diaryl phosphorochloridates and diaryl phosphorochloridothioates to the chloride of dimethylphosphinothionic acid, caused by the decrease of electron density at the phosphorus atom, can be followed in relation to the reaction of 2-aminopyridine with phosphorus acid chlorides. For example, 2-aminopyridine reacts smoothly with diaryl phosphorochloridates and phosphorochloridothioates in benzene or toluene in the presence of tertiary bases[29]; the yields reach 60%. Aryl *N*-(2-pyridyl)methylphosphonoamidates and *N*-(2-pyridyl)-methylphosphonoamidothioates have been obtained in 40–70% yield on refluxing of the components in benzene for several hours[84]. Under these conditions, ethyl methylphosphonothioate was isolated in a yield less than 20%,[84] and, when the reaction of the chloride of dimethylphosphinothionic acid with 2-aminopyrimidine was carried out in moist benzene, only tetramethyl pyrophosphinodithioate was isolated[85]. However, when anhydrous pyridine is used as the solvent, thiophosphorylation of 2-aminopyridine (and also 2-aminopyrimidine, 2-aminothiazole, and 2-aminobenzothiazole) leads to dimethylthiophosphorylaminoheterocycles in yields of 60–70%.[85]

In the general case highly basic aromatic aminoheterocycles and heterocyclic imino-compounds substitute chlorine relatively readily in the chlorides of phosphoric, phosphonic, and phosphinic acids and also their thio-analogues when the reactions are carried out in both non-polar and polar solvents. Heteroaromatic compounds of the type of 2-aminopyridine and 2-aminopyrimidine react poorly or not at all in the required manner. The transition from non-polar to polar solvents sometimes leads to an increase of the reactivity of the initial components and the formation of phosphoryl- or thiophosphoryl-aminoheterocycles[85,86].

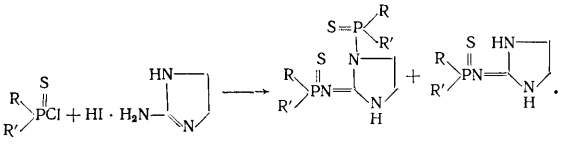
In the study of the reactions of aminoheterocycles containing the amidine system with the chlorides of oxygen- and sulphur-containing phosphorus acids it was noted that, depending on the phosphorylating agent, mono- or diphosphorylated products are formed[79]. The reactions with the chlorides of phosphonic acids result in the formation of

only 2 phosphorylamino-derivatives in all cases. The reactions with the chlorides of the sulphur-containing phosphorus acids proceed specifically as a function of the nature of the amine. 2-Aminothiazoline reacts with the chlorides of phosphonothioic acids to form the products of thiophosphorylation at the exocyclic nitrogen atom, while the reaction with 2-aminothiazole yields a mixture of products of thiophosphorylation at the exocyclic nitrogen atom alone and at both nitrogen atoms:



The diphosphorylation product is apparently obtained as a result of the stepwise substitution of the hydrogen atoms of the amino-groups by the phosphonothioic acid residue.

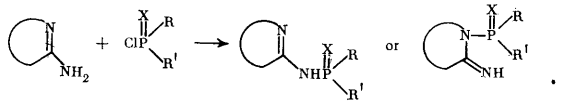
The reaction of equimolar amounts of 2-aminoimidazoline hydriodide with the chlorides of phosphonothioic acids in the presence of 2 moles of triethylamine led to the isolation of the products of diphosphorylation of 2-aminoimidazoline in 20% yield. The reaction of 3 moles of phenyl methylphosphonochloridothioate with 1 mole of 2-aminoimidazoline hydriodide leads to a mixture of di- and mono-phosphorylation products[79]:



The difference between the thiophosphorylation reactions is a consequence of the decrease of the nucleophilicity of the ring nitrogen atom in the series of thiophosphorylated 2-aminoimidazoline, 2-aminothiazole, and 2-aminothiazoline[79]. The absence of diphosphorylation products in the series of phosphonic acids can be explained not only by the decrease of the electron density at the endocyclic nitrogen atom in phosphorylaminoheterocycles compared with their thiophosphoryl analogues, as a consequence of the greater electron-accepting influence of the phosphoryl group, but also by the presence of a strong intramolecular bond between the phosphoryl oxygen and the hydrogen atom at the ring nitrogen atom.

The reaction of 3,5-diamino-1,2,4-thiadiazole or its salt with the chlorides of phosphorus acids leads to the formation of the products of the phosphorylation of only one amino-group[49].

Aminoheterocycles containing the amidine fragment N = C–N, in which one of the nitrogen atoms is exocyclic, can be phosphorylated at both endocyclic and exocyclic nitrogen atoms:



Furthermore, 2-phosphoryl(thiophosphoryl)amino-1-azaheterocycles can exist in the amino- or imino-forms:

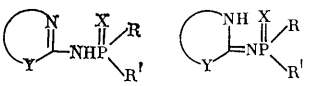


amino imino

In the determination of the structures of phosphoryl-(thiophosphoryl)aminoheterocycles, various spectroscopic methods were used for each group of compounds: ultraviolet and infrared spectroscopy and ^1H and ^{13}C NMR.[79,84,89,99,105]. Compounds with a fixed structure were used as standards. ^{31}P NMR could not be used for these purposes because of the complex dependence of the chemical shifts of the signals and their form on the immediate environment of the phosphorus atom[101]. It follows from the results that in all the cases investigated the phosphorylation (thiophosphorylation) of 2-amino-1-azaheterocycles involves the exocyclic nitrogen atom[79,84,89,99], except for derivatives of 3-amino-1,2,4-triazole[102–104].

The existence of a phosphorylated (thiophosphorylated) heterocyclic amine in the amino- or imino-form depends significantly on both the nature of the heterocycle and on the electron-accepting properties of the phosphorus-containing residue. Phosphorylated and thiophosphorylated aromatic aminoheterocycles, namely pyridine[84] and pyrimidine[89], exist exclusively in the amino-form regardless of the nature of the solvent and the phosphorus-containing residue. For derivatives of 2-aminobenzimidazoles and 2-aminobenzothiazole[99], whose aromaticity is lower, the influence of the phosphorus-containing residue is decisive. Phosphoryl derivatives exist in the imino-form, while thiophosphoryl derivatives exist in the amino-form. 2-Aminobenzoxazole[99], 2-amino-1-methylbenzimidazole[99], and 2-aminothiazole[79] are still less aromatic and their derivatives have the imino-structure. Phosphorylated 2-aminoazaheterocycles, whose rings are not stabilised to some extent as a result of aromaticity, exist only in the imino-form[79] (see Table).

The structure of phosphorylated and thiophosphorylated 2-amino-1-azaheterocycles.

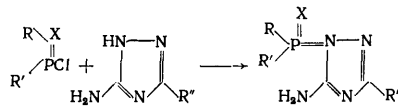


amino (A), imino (I)

Initial aminoheterocycle	X		Method of investigation	References
	O	S		
2-Aminopyridine	(A)	(A)	u.v.	84, 105
4-Aminopyridine	(A)	(A)	u.v.	84, 105
2-Aminopyrimidine	(A)	(A)	u.v.	105, 89
2-Aminothiazole	(I)	(I)	^1H NMR	105, 79
2-Aminobenzimidazole	(I)	(A)	u.v., i.r.	99
2-Aminobenzothiazole	(I)	(A)	u.v., i.r.	99
2-Aminobenzoxazole	(I)	(I)	u.v., i.r.	99
2-Amino-1-methylbenzothiazole	(I)	(I)	u.v., i.r.	99
2-Aminoimidazoline	(I)	(I)	^1H NMR	79
2-Aminothiazoline	(I)	(I)	^1H NMR	79

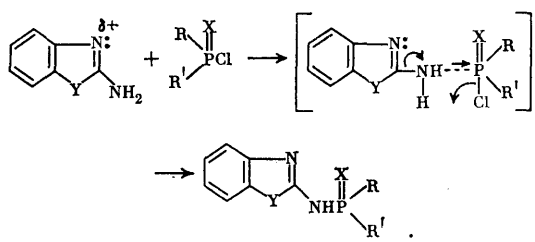
Prototropic tautomerism in these compounds has not so far been observed. We may also mention an NMR study of the diastereoisomers of phosphorylimino-oxazolidines[106].

The phosphorylation of 5-substituted 3-amino-1,2,4-triazole with phosphorus acid chlorides of different structure (including phosphoryl chloride) involves the nitrogen atom of the heterocycle in the 2-position[2-4,7,8,21,102-104,107-111]:



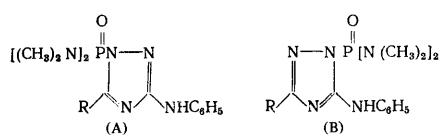
The structure of 1-phosphorylamino-derivatives, attributed by some workers to the phosphorylation products of 2-aminobenzimidazole[109], 5-aminotetrazole[110], and 4-amino-3,5-dimethylpyrazole, is either correct (cf. Grapov et al.[99]) or is insufficiently well founded.

According to quantum-mechanical calculations, the electron density maximum in heterocyclic amines containing the N = C–NH_2 group is located at the endocyclic nitrogen atom[112,113]. To account for the phosphorylation of the majority of such amines at the exocyclic nitrogen atom, one can postulate, in conformity with Katritzky's ideas[113], that heterocyclic amines react with acid halides in the tautomeric imino-form at the "hard" exocyclic nitrogen atom. The hypothesis that the polarisability of the aminoheterocycle molecule has an influence appears more probable. Under the influence of the phosphinyl (phosphinothionyl) group, the aminoheterocycle molecule is polarised and the electron could undergo a redistribution, which leads to an increase of electron density at the exocyclic nitrogen atom, which is then attacked by the phosphorus atom[99]:

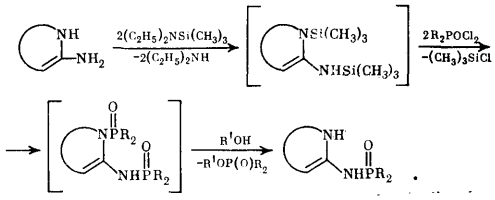


However, one cannot rule out the possibility of the initial attack by the phosphorus atom on the endocyclic nitrogen atom and subsequent migration of the phosphoryl group to the exocyclic nitrogen atom (cf. Simonov and Anisimova[114]).

Only isolated data are available for the reactions of 2-alkylamino- and 2-arylamino-heterocycles with phosphorus acid chlorides. When 2-methylaminobenzothiazole was allowed to react with phenyl methylphosphonochloridothioate, the product of thiophosphorylation at the exocyclic nitrogen atom was obtained[99]. 5-Alkyl-3-anilino-1,2,4-triazoles react with *N,N*-dimethylphosphoramidochloridate to form products of phosphorylation at the nitrogen atoms in both 2- and 1-positions, the product ratio being A : B = 2 : 13.[111]



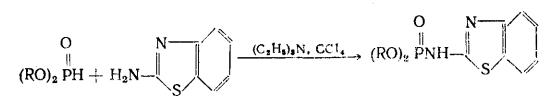
The method of phosphorylating 2-aminobenzimidazole, 3-amino-1,2,4-triazole, 2-aminobenzothiazole, and 2-aminopyrimidine with phosphorus acid chlorides using the trimethylsilyl protecting group is of interest[115]. When aminoheterocycles are treated with two equivalents of trimethylsilyldiethylamine, 1-trimethylsilyl-2-trimethylsilylaminoheterocycles are formed (except for 2-aminobenzothiazole, which reacts with only one equivalent of silylamine). When the reaction mass is treated with 2 moles of the acid chloride, the subsequent decomposition of the resulting 1-phosphoryl-2-phosphorylaminoheterocycles with alcohol results in the formation of 2-phosphorylaminoheterocycles:



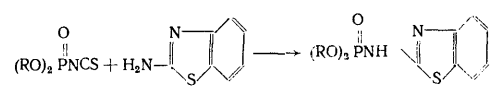
Although this method does provide for the consumption of twice the amount of the acid chloride, it makes it possible to obtain products which are known to be phosphorylated at the exocyclic nitrogen atom, including 3-phosphorylamino-1,2,4-triazoles, which cannot be obtained by the direct phosphorylation of 3-amino-1,2,4-triazole with phosphorus acid chlorides; however, we believe that this requires additional evidence.

2. Phosphorylation by Various Tetracoordinate Phosphorus Derivatives

A convenient method of synthesising phosphorylated aminoheterocycles is provided by the Todd–Atherton reaction. When acid phosphites or phosphonites were allowed to react with 2-aminobenzothiazole[116], 2-aminothiazole, and 2-aminothiazoline[79], the corresponding phosphorylated derivatives were obtained:

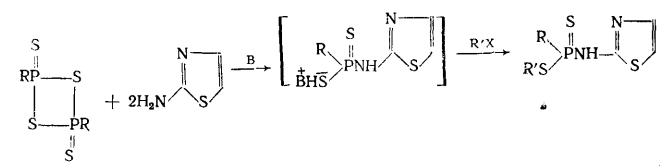


The isothiocyanates of phosphorus acids can also be used as phosphorylating agents. Levchenko and Sheinkman[117] showed for the first time that the reaction of diethyl and diphenyl phosphoroisothiocyanatidates with 2-aminobenzothiazole results in the formation of the corresponding 2-phosphorylaminobenzothiazoles:



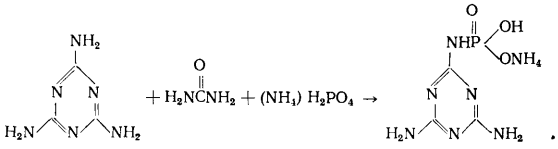
Methylphosphonoisothiocyanatidothioates react analogously with 2-aminothiazole and 2-aminothiazoline[79]. The isothiocyanate group then reacts as a pseudohalogen.

Dithiophosphorylaminothiazoles and aminopyridines have been obtained by the phosphorylation of the corresponding aminoheterocycles with dithioanhydrides of phosphonic acid, or more precisely with diphosphadithietans, and subsequent alkylation[42,45,118]:



Phosphate salts can also be used as phosphorylating agents. The monoammonium salt of 4,6-diamino-2-dihydroxyphosphorylamino-*sym*-triazine has been obtained by heating a mixture of ammonium dihydrogen phosphate, urea, and

melamine at 170–200 °C:[51]



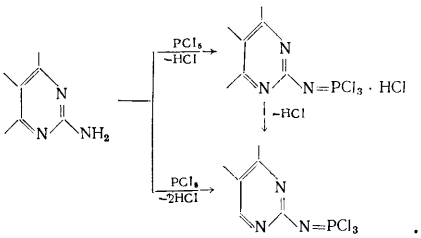
3. Phosphorylation with Phosphorus Pentachloride

One of the general methods of synthesising phosphorylated aminoheterocycles is the Kirsanov or phosphazo-reaction, an interaction of primary amines, in the given instance aminoheterocycles, with phosphorus pentachloride of halogenophosphoranes. 2-Aminopyridines[119], 4-aminopyridines[120], 2-aminopyrimidines[9,11,61,74,76,121], 4-aminopyrimidines[75,122], aminopurines[13], 3-aminobenzoisothiazole 1,1-dioxide[123], and aminotriazines[124,125] have been made to undergo this reaction.

The reactions of aminoheterocycles with phosphorus pentachloride are usually carried out in a boiling solvent (benzene, dichloroethane, and chlorobenzene).

It has been shown for 2- and 4-aminopyrimidines that, when the basicity of the initial aminopyrimidine is relatively low ($pK_a \leq 3.62$ for substituted 2-aminopyrimidines[76] and $pK_a \leq 3.7$ for 4-aminopyrimidines[75]), then two equivalents of hydrogen chloride are evolved in the reaction[75] and monomeric phosphazo-compounds are formed.

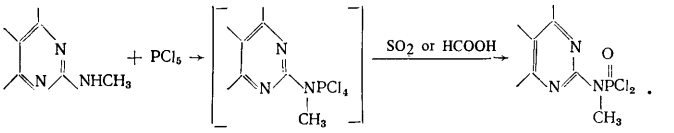
If the pK_a of the initial aminopyrimidines are greater than 3.62 for the 2-amino-derivatives and greater than 5.19 for the 4-amino-derivatives, then only one equivalent of hydrogen chloride is evolved and the hydrochlorides of phosphazopyrimidines are formed (the structure of pyrimidylaminophosphorus tetrachlorides was attributed to them previously[121]); on refluxing in chlorobenzene, one equivalent of hydrogen chloride is split off and the hydrochlorides are converted into monomeric phosphazo-compounds[75]. In contrast to heteroarylaminophosphorus tetrachloride derivatives, the hydrochlorides of phosphazoheterocycles do not react with anhydrous sulphur dioxide[75,76].



[^{32}P]Phosphazopyrimidines can be obtained by the same method[11].

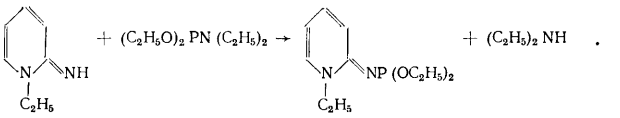
With increase of the number of amino-groups in amino-*sym*-triazines, the rate of the phosphazo-reaction diminishes[124]. The reaction of 2-amino-4,6-dichlorotriazine with 1 mole of PCl_5 terminates after 30 min and that of 2,4-diamino-6-chlorotriazine with 2 moles of PCl_5 terminates after 2–3 h, while the reaction of melamine with 3 moles of PCl_5 terminates after 5 h in dichloroethane and after 3–4 h in phosphoryl chloride.

On treatment with phosphorus pentachloride, 2- and 4-methylaminopyrimidines are converted into *N*-methyl-*N*-pyrimidinylaminophosphorus tetrachlorides, whose structure has been established by conversion into the corresponding acid dichlorides on treatment with sulphur dioxide or formic acid[74–76]:

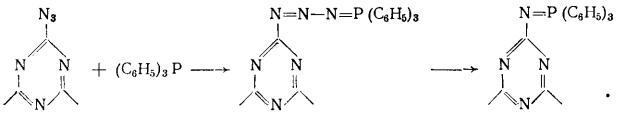


4. Phosphorylation with Tervalent Phosphorus Derivatives

When aminoheterocycles are phosphorylated with tervalent phosphorus derivatives, the reaction can proceed both without a change in valence and with formation of derivatives of tetracoordinate phosphorus. The transamidation of diethyl *N*,*N*-diethylphosphoramidite with 1-ethyl-2-pyridone imine yielded the corresponding phosphoramidite[126]:

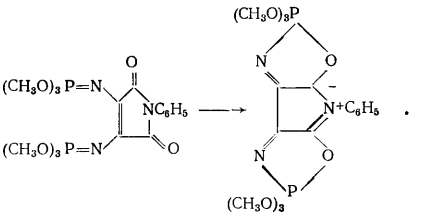


When heterocyclic azides are treated with tertiary phosphines or fully esterified phosphites, phosphazo-compounds are formed in high yields; in many instances it is possible to isolate the intermediate phosphazines. 4-Azido-5-chloro-1-phenyl-1*H*-pyridazin-6-one[127], 4-azidopyrrolin-2-ones[128], azido-*sym*-triazines[129,130], 9-azido-1,2,3,4-tetrafluoroacridine[131], 4-azido-5*H*-furan-2-ones[128], diazidopyrroline-2,5-dione[132], 2-azido-3-ethylbenzothiazolinium fluoroborate[126], and 3-azido-1-ethylpyridinium fluoroborate[126] have been made to undergo this reaction. The reaction is carried out by allowing the azides of the heterocycles to interact with triphenylphosphine in an organic solvent (methylene chloride, ether):



In the reaction of azidotriazines with trialkylphosphites at 5–10 °C it was possible to isolate the intermediate phosphazidotriazines, which split off a nitrogen molecule on heating and are converted into phosphazotriazines[129].

3,4-Diazidopyrroline-2,5-dione reacts with 2 moles of trimethyl phosphite to form the stable 3,4-bisphosphazopyrroline-2,5-dione. The authors explain its stability[132] by the fact that it exists in the form of a dipolar ion:

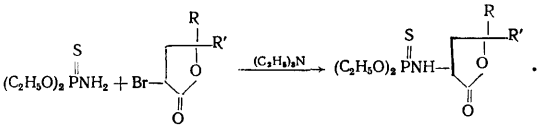


5. Phosphorylamidation Reactions

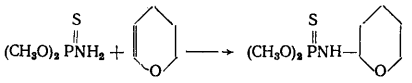
Whereas the methods for the phosphorylation of aminoheterocycles are general for the synthesis of various derivatives of this class, the phosphorylamidation and cyclisation methods are to a large extent specific and can

be used only for the synthesis of a small group of compounds of similar structure.

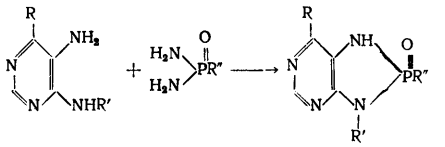
A small group of methods for the synthesis of phosphorylaminoheterocycles is based on the reaction of phosphorus acid amides with different derivatives of the heterocycles. When 3-halogenolactones are heated with diethyl phosphoramidothioate in the presence of triethylamine, the corresponding derivative of 3-aminohydrofuran-2-one is formed[133]:



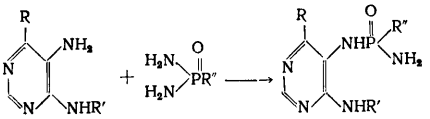
O,O-Dimethyl and *O,S*-dimethyl phosphoramidothioates add to dihydropyran in the presence of catalytic amounts of toluene-*p*-sulphonic acid[30]:



The condensation of phosphonodiamidates with 4,5-diaminopyrimidines usually results in the formation of 1,3-diaza-1,3-dihydro-2-phospholo[4,5-*d*]pyrimidines[134,135]:

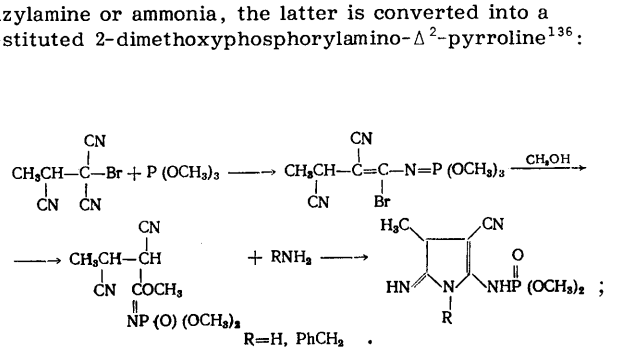


In certain cases only one amino-group, in the 5-position, is involved in the reaction and 4-amino-5-phosphorylaminopyrimidines are formed[135]:

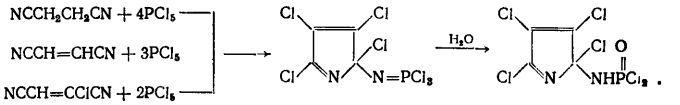


6. Cyclisation Reactions

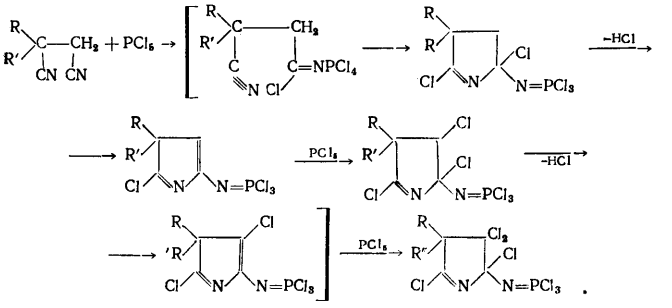
(*a*) *Derivatives of five-membered aminoheterocycles with one heteroatom.* The phosphorylated derivatives of aminopyrroline are obtained from di- and tri-nitriles. When α-bromo-α,α,β-tricyanopropane is treated with trimethyl phosphite, the corresponding iminotrimethoxyphosphorane is obtained and on treatment with methanol is converted into an *N*-methylenephosphonamidate. On treatment with benzylamine or ammonia, the latter is converted into a substituted 2-dimethoxyphosphorylamino-Δ^2-pyrroline[136]:



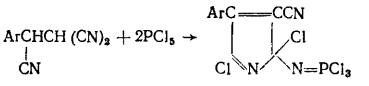
The dinitriles of unsubstituted, monosubstituted, and disubstituted succinic acid as well as the dinitriles of maleic, fumaric, and chloromaleic acids react with phosphorus pentachloride to form 2-trichlorophosphazopolyhalogenopyrrolenines. On controlled hydrolysis, the latter are readily converted into dichlorophosphorylaminopolyhalogenopyrrolenines[137–140]:



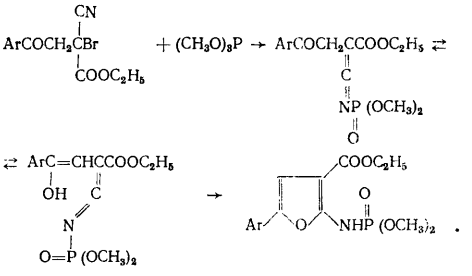
The presence of substituents in the α-position in the dinitriles of succinic acid does not prevent their cyclisation. Since nitriles not containing a hydrogen atom in the α-position do not react with phosphorus pentachloride, the following mechanism of the cyclisation reaction has been proposed[139]:



The reaction begins with the addition of phosphorus pentachloride to the cyano-group at the primary carbon atom. 2-Aryl-1,1,2-tricyanoethanes react via a similar mechanism[141]:

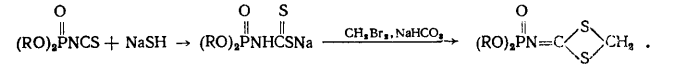


Substituted aminofurans are formed when ethyl α-bromo-α-cyano-β-benzoylpropionate is treated with trimethyl phosphite[142]:

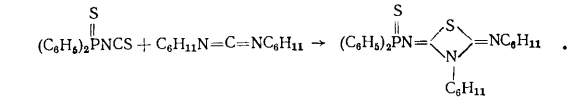


The authors[142] postulated the formation of a keten imine as an intermediate.

(*b*) *Derivatives of four- and five-membered aminoheterocycles with two heteroatoms.* *N*-Phosphorylated 2-amino-1,3-dithietans are obtained by the cyclisation of the sodium salts of *N*-phosphoryldithiocarbamic acids, which are formed when sodium hydrogen sulphide reacts with phosphoroisothiocyanatidates; the cyclisation takes place on treatment with methylene bromide in the presence of sodium dicarbonate[31–34]:

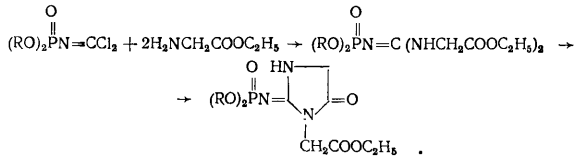


When diphenylphosphinothionyl isothiocyanate is heated with dicyclohexylcarbodi-imide, a 1,2-cycloaddition reaction takes place and a 1,3-thia-azetidine derivative is formed[143]:

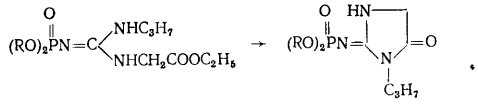


Thus it has been shown that the cycloaddition of isothiocyanates with electron-accepting groups to carbodi-imides takes place at the C–S- and not the C = N bond.

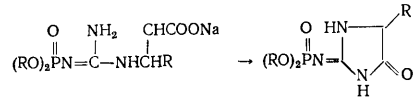
The method of synthesis of phosphorylated imino-imidazolidinones from dichloro-methyleneamides of phosphorus acids is of interest[144]. The reaction of *N*-dichloromethylene-phosphoramidate with ethyl glycinate results in the formation of the corresponding substituted guanidine, which splits off an alcohol molecule on distillation and is converted into a derivative of phosphoryliminoimidazolidinone:



Phosphorylated 1-alkyl-2-iminoimidazolidinones are synthesised via an analogous mechanism involving the thermal decomposition (*in vacuo* at 80–120 °C) of *N*-ethoxycarbonyl-methyl-*N'*-propyl-*N''*-diethoxyphosphinylguanidine[145,146]:

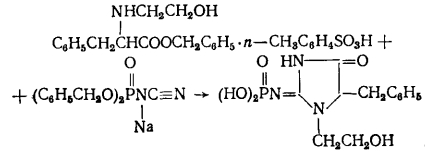


Yet another method of synthesis of phosphorylated imidazolidines consists in the cyclisation of derivatives of *N*-α-carboxyalkyl-*N'*-phosphorylguanidine. The latter are obtained by heating phosphoryl-*N*-methylisothiourea with mercury(II) oxide and subsequent treatment with aminoacids or their derivatives[147,148]:

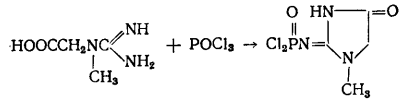


When the disodium salt of *N*-(1,2-dicarboxyethyl)-*N'*-phosphorylguanidine is reduced with hydrogen (on the Pd/C catalyst), 5-ethyl-2-phosphoryliminoimidazolidin-4-one is obtained[147].

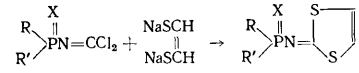
The condensation of the tosylates of the esters of *N*-β-hydroxyalkylaminoacids with salts of phosphorylated cyanamides followed by hydrolysis results in the formation of 1-(β-hydroxyethyl)-2-phosphoryliminoimidazolidin-4-ones[149]:



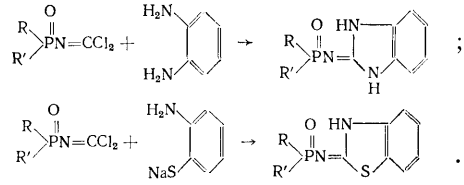
When creatine is refluxed with an excess of phosphoryl chloride, dichlorophosphorylcreatinine is formed[150]:



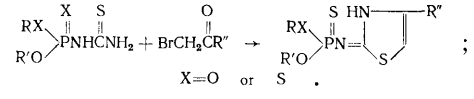
Derivatives of iminodithiole are obtained by the reaction of dialkyl *N*-dihalogenomethylenephosphoramidates with the disodium salt of *cis*-1,2-dimercaptoethylene[91]:



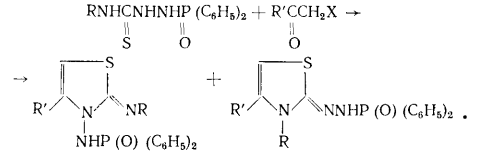
Derivatives of phosphorylaminobenzimidazole and phosphoryl-aminobenzothiazole have been obtained analogously from *N*-dichloromethylenephosphoramidates or *N*-dichloromethylene-phosphonamidates and a diamine of the sodium salt of *o*-aminothiophenol[99]:



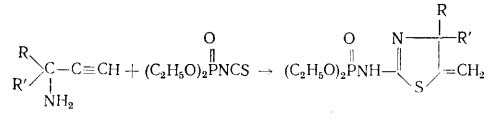
A method of synthesis of aminothiazoline derivatives, consisting in the reaction of thio- or dithio-phosphoryl-thioureas with α-halogenoketones, has been developed[48]:



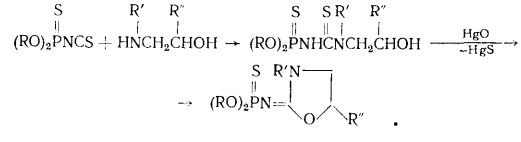
When α-halogenoketones were allowed to react with diphenylphosphorylthiosemicarbazide, mixtures containing 2-alkylimino-3-phosphorylamino-1,3-thiazolines and phosphorylated 2-hydrazino-1,3-thiazolines were obtained[151]:



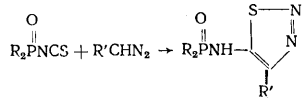
The reaction of diethyl phosphoroisothiocyanatidates with α-aminoacetylenic derivatives takes place vigorously and results in the formation of diethoxyphosphorylamino-thiazoline having a methylene substituent in the 5-position[152]:



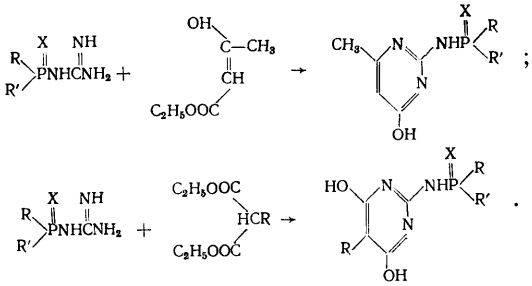
Phosphorylated 2-imino-oxazolidines are obtained by the reaction of the isothiocyanates of phosphorus thioacids with *N*-alkylethanolamines followed by the elimination of hydrogen sulphide from the resulting phosphorylated urea under the influence of mercury(II) oxide[38,40,41,82,96,153]:



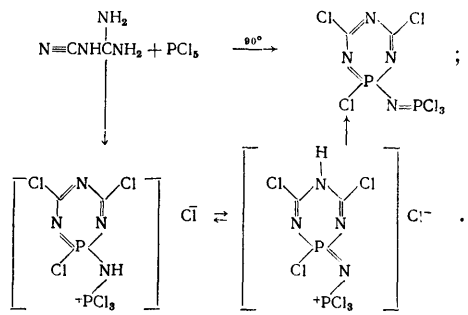
Phosphinyl isothiocyanates react with aliphatic diazo-compounds via the 1,3-dipolar cycloaddition mechanism and form 5-phosphorylamino-1,2,3-thiadiazoles[154]:



(*c*) *Derivatives of six-membered aminoheterocycles.* One of the possible ways of synthesising phosphorylated 2-aminopyrimidin-4-ones and 2-aminopyrimidine-2,6-diones may be the condensation of guanidinophosphoric acid with β-carbonyl compounds, for example with acetoacetic or malonic esters[89,155]:



The reaction of dicyanodiamide with phosphorus pentachloride leads to two compounds depending on the conditions[156]. When a 1:2 mixture of the components is heated at 90 °C for 4–5 h, 1,3,5-trichloro-1-trichlorophosphazo-1-phospha-2,4,6-triazine is formed. On the other hand, if the reaction is carried out in dichloroethane at 35 °C, it is possible to detect the formation of an intermediate salt-like product which splits off hydrogen chloride on being refluxed in dichloroethane and is converted into a phosphazo-compound:



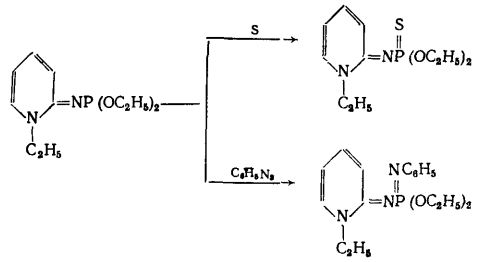
III. REACTIONS OF PHOSPHORYLATED AND THIOPHOSPHORYLATED AMINOHETEROCYCLES

Phosphorus-containing aminoheterocycles, obtained by the methods described in the previous sections, can undergo in many instances addition, substitution, oxidation, reduction, etc. reactions, forming new derivatives of phosphorylaminoheterocycles with a different environment at the phosphorus atom or with new substituents in the heterocyclic ring.

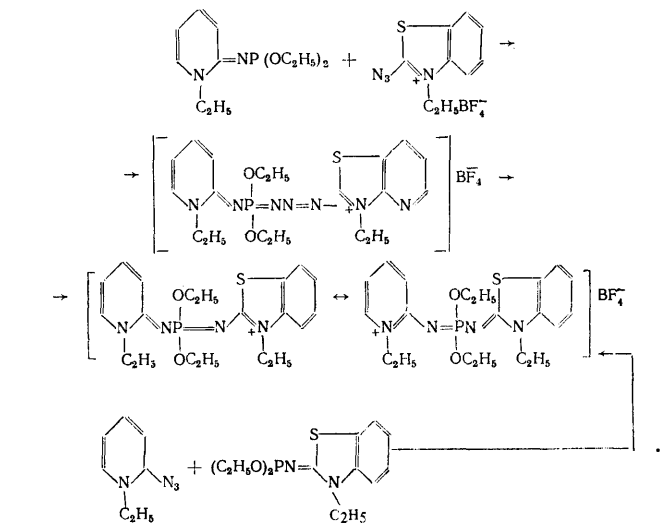
1. Reactions of Tervalent Phosphorus Derivatives

Phosphorylated aminoheterocycles, containing a tervalent phosphorus atom, enter into reactions characteristic also of other tervalent phosphorus derivatives.

Diethyl *N*-(1-ethyl-1,2-dihydropyridylidene)phosphoramidite readily combines with sulphur or phenyl azide and forms the corresponding phosphoramidothionate or iminophosphorane[126]:



The phosphorus analogues of carbocyanines have been obtained by the same procedure[126]. When diethyl imidophosphite *N*-(1-ethyl-1,2-dihydro-2-pyridylidene)-phosphonamidite reacts with 2-azido-1-ethylbenzothiazolium fluoroborate in chloroform at 20 °C, the product is a phosphatriazene, which decomposes on heating in chlorobenzene to form a phosphacyanine. The same phosphacyanine has been obtained by the reaction of 2-azido-1-ethylpyridinium fluoroborate with the corresponding phosphoramidite:

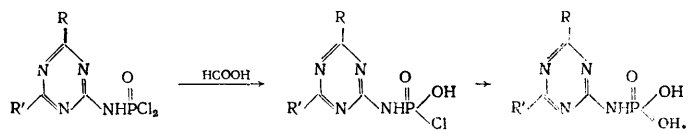


The results show that the positive charge is delocalised over the terminal nitrogen atoms in the phosphacyanine formed.

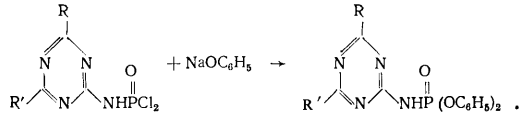
2. Reactions of Tetracoordinate Phosphorus Derivatives

Phosphorylaminoheterocycles can undergo reactions accompanied by a change in the environment at the phosphorus atom or in the heterocyclic ring and also with the dissociation of the nitrogen–phosphorus bond.

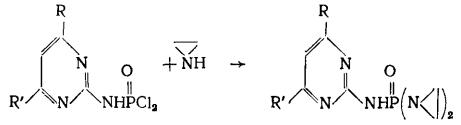
(*a*) *Nucleophilic substitution reactions of dichlorophosphorylaminoheterocycles.* Dichlorophosphorylaminoheterocycles readily react with various nucleophiles: water, acids, alcohols, phenols, and amines. Controlled hydrolysis of dichlorophosphorylaminotriazines has been achieved[124] by treatment with anhydrous formic acid:



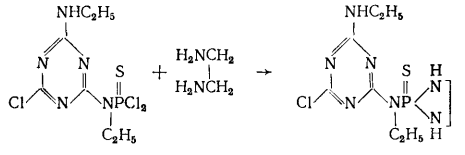
Dichlorophosphorylaminoheterocycles readily react with alcohols[157] and phenoxides[120,123,157], forming the corresponding ester-amides:



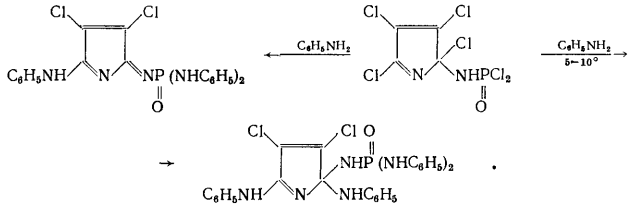
They also readily react with ammonia[23,25,73,78], primary[123] and secondary[103] aliphatic amines, anilines[123,157], piperidine[76], and morpholine[61,76]. This method has acquired particular importance for the synthesis of aziridinyl phosphates with carcinolytic activity[9,11–19,60–66,68,69,158,159]:



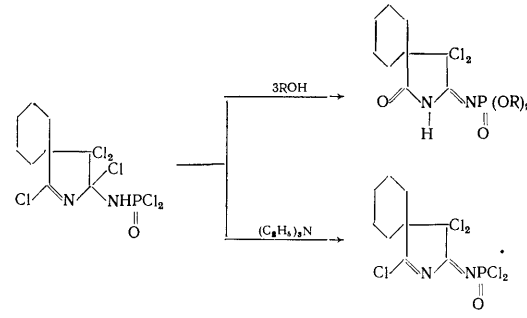
The hydrochloride of dichlorophosphorylaminopyrimidine can also be introduced into the reaction[75]. When 6-chloro-2-(*N*-dichlorothiophosphoryl-*N*-ethylamino)-4-ethylamino-*sym*-triazine reacted with ethylenediamine, the corresponding triazinylaminodiazaphospholane was obtained[26]:



The aminolysis and alcoholysis of dichlorophosphorylaminoperchloropyrrolenines and pyrrolines do not proceed via the standard mechanism. When the dichloride of *N*-perchloropyrroleninylphosphoramidic acid is treated with aniline in boiling benzene, hydrogen chloride is split off and at the same time both the chlorine atoms of the acid chloride groups and that in the 2-position are substituted; the reaction with aniline at 5–10 °C results in the substitution of four chlorine atoms[139]:

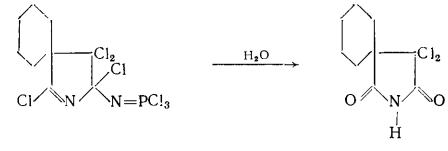


When the dichloride of 2,4,4,5-tetrachloro-3,3-pentamethylene-5-pyrrolinylphosphoramidic acid interacts with three equivalents of alcohol the chlorine atoms in the 2- and 5-positions in the pyrroline ring react, apart from the chlorine atoms attached to the phosphorus atoms[138,139,160]. When the same dichloride was treated with triethylamine, the 2,4,4-trichloro-derivative was obtained[139]:

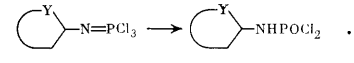


(*b*) *Nucleophilic substitution reactions of trichlorophosphazoheterocycles.* Trichlorophosphazoheterocycles also readily react with various nucleophiles. They rapidly hydrolyse under the influence of atmospheric moisture and cold water with cleavage of the nitrogen–phosphorus bond and the formation of hydrogen chloride, phosphoric acid, and the initial aminoheterocycles[123,139–141].

2,4,4,5-Tetrachloro-5-trichlorophosphazo-3,3-pentamethylenepyrroline is hydrolysed by water to the corresponding succinic acid amide[139]:

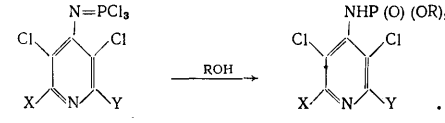


The acidolysis of trichlorophosphazoheterocycles by formic[74,75,120–122,124,141,146] or acetic[11,75,122,123,139,140] acids results in the formation of dichlorophosphorylaminoheterocycles:



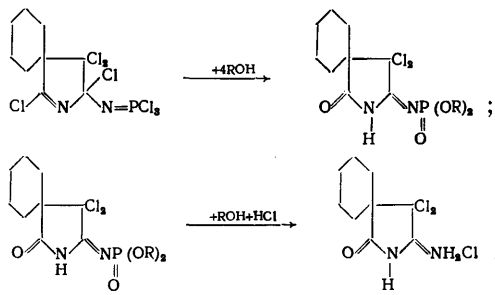
4-Trichlorophosphazopyrimidine reacts with glacial acetic acid to form dichlorophosphorylaminopyrimidine, while the reaction with anhydrous formic acid results in the corresponding hydrochloride[75].

On treatment with alcohols, not only are chlorine atoms substituted but also a rearrangement of the type of the second stage of the Arbuzov reactions takes place and the diesters of *N*-heterylphosphoramidic acid are formed[120,140,157]:

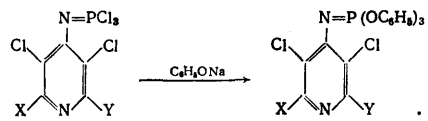


The interaction of 2,4,4,5-tetrachloro-2-trichlorophosphazopyrroline with four moles of alcohol in benzene at 80 °C or in carbon tetrachloride for 20–30 min involves not only the chlorine atoms of the phosphazo-group but also the chlorine atoms in the 2- and 5-positions of the pyrroline ring with formation of the esters of 3,3-dichloro-5-oxo-2-pyrrolidinylidenephosphonamidic acid[138,139,160]. If this reaction is carried out in a large excess of boiling alcohol without a solvent but in the presence of hydrochloric acid,

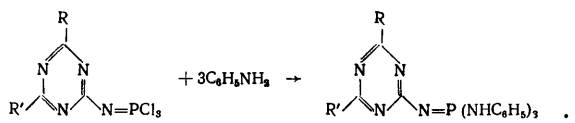
the P–N bond is ruptured[138,139,160]:



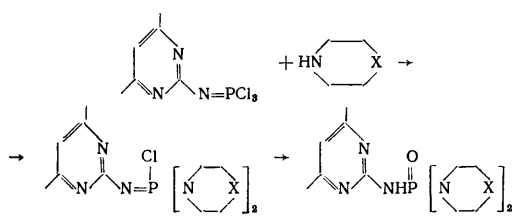
Trichlorophosphazo-derivatives also readily react with alkali metal phenoxides to form the corresponding triphenoxyiminophosphoranes[120,125,127]:



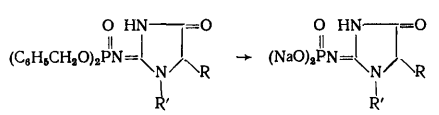
When phosphazoheterocycles are treated with amines, three chlorine atoms are as a rule substituted with formation of triaminoiminophosphoranes[125,140]:



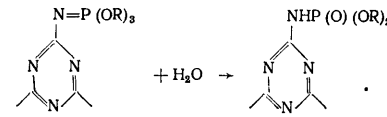
However, the reaction of 2- and 4-trichlorophosphazopyrimidines with morpholine and piperidine proceeds with substitution of only two chlorine atoms and the formation of diaminochloroiminophosphoranes[75,76,119,146], which are converted into phosphorotriamides on heating with 96% alcohol. The hydrochlorides of 2- and 4-trichlorophosphazopyrimidines react analogously[75,76].



(c) *Nucleophilic substitution reactions of other phosphorylaminoheterocycles.* The acid hydrolysis of phosphorylaminoheterocycles results in the rupture of the nitrogen-phosphorus bond and the liberation of the initial heterocycles[159]. The alkaline hydrolysis of dibenzyl *N*-heterylidenephosphoramidates involves the dissociation of the P–O bonds and the formation of alkali metal salts of *N*-heterylidenephosphoramidic acids[147,149,161]:

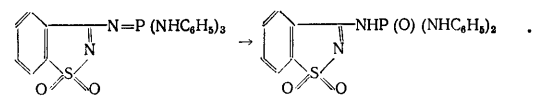


The kinetics of the hydrolysis of the dialkyl esters of phosphoryliminohydantoins have been studied[162]. The hydrolysis of triphenoxy- and trialkoxy-*N*-heterylidenephosphoranes results in the formation of the corresponding esters of phosphoramidic acid[29,120,125,129,157]:

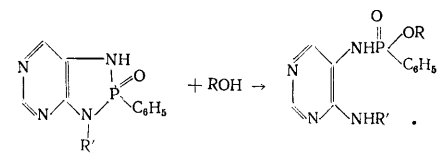


Under these conditions, triphenoxy-*N*-triazinyliminophosphoranes are stable—they do not hydrolyse on being refluxed with 1 *N* hydrochloric acid[130].

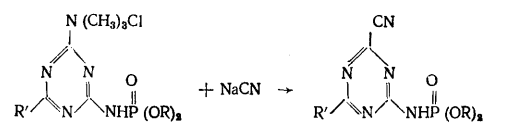
The trianilino-derivatives hydrolyse even on being refluxed in 96% alcohol and give rise to dianilinophosphorylaminoheterocycles[123]:



The diazaphosphole ring in 1,3-diaza-1,3-dihydro-2-phospholo[4,5-*d*]pyrimidine 2-oxide is readily cleaved at the P–N bond on treatment with water or alcohol; derivatives of 4-amino-5-phosphorylaminopyrimidine are formed[135]:



N-Phosphorylated derivatives of aminotriazines[22,27,163,164], aminopyrimidines[159], and aminoacridines[165], containing labile atoms or groups in the heterocyclic ring, readily exchange them under the influence of various nucleophiles. For example, (2-phosphorylamino-4-*sym*-triazinyl)trimethylammonium chloride is converted into the corresponding 4-cyano- or 4-azido-derivative under the influence of sodium cyanide[22]:

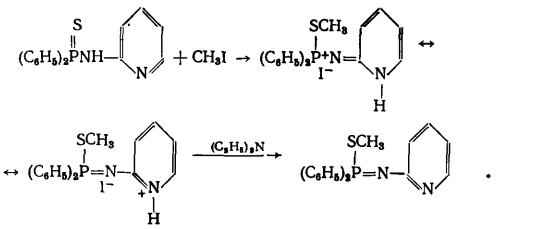


Polyfluoro-9-acridinyliminotriphenylphosphoranes react with alkoxides, phenoxides, and primary and secondary amines with substitution of only one fluorine atom[165].

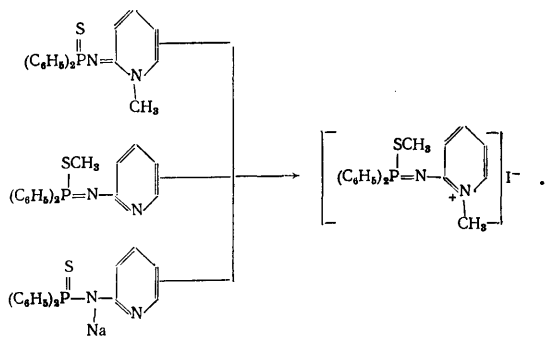
(d) *Electrophilic substitution reactions.* Interesting data have been obtained in the study of electrophilic substitution reactions involving phosphorylated and thiophosphorylated aminoheterocycles containing the amidine system.

Phosphorylaminoheterocycles do not undergo the electrophilic substitution reaction[166]. 2-Dimethylthiophosphorylamino-derivatives of pyridine, pyrimidine, and triazole are readily methylated by methyl iodide at the sulphur atom with dissociation of the P–S bond and are converted into phosphonium salts stabilised by resonance with the iminophosphorane structure[167]. 2-Diphenylaminothiophosphorylaminopyrimidine reacts with methyl iodide to form an adduct of a phosphonium salt with methyl iodide, from which a stable adduct of the phosphonium salt and benzene was obtained on treatment with an excess of benzene. The latter adduct is converted into the corresponding imino-

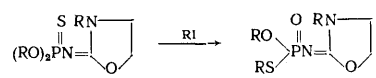
phosphorane on treatment with ammonia or triethylamine:



On being refluxed in benzene, the iminophosphorane isomerises to methyl *N*-(1,2-dihydro-2-pyridylidene)diphenylphosphinamidothiolate[167]. Its methylation as well as the methylation of methylthiodiphenyl-*N*-(2-pyridyl)iminophosphorane and the sodium salt of *N*-(2-pyridyl)diphenylphosphinamidothioate with methyl iodide in nitromethane leads to the same product:

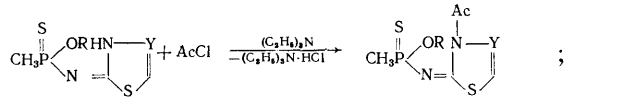


The attempts to methylate dialkoxyphosphoryl- and aryloxymethylthiophosphorylamino-derivatives of thiazoles, thiazolines, and thiadiazoles were unsuccessful[166]. On treatment with alkyl iodides, dialkoxythiophosphorylaminothiazolidines and the corresponding oxazolidines isomerise via the Pishchimuka reaction and give rise to the corresponding phosphoramidothiolates[38,153]:



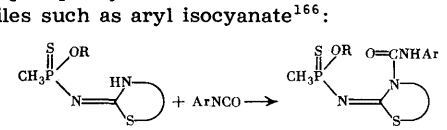
As a rule, 2-phosphorylaminoazaheterocycles are not protonated and do not form salts with acids. The picrates and nitroindandionates of phosphorylated 2-aminopyrimidines have been described[86].

Thiophosphorylated derivatives of 2-aminothiazole and 2-amino-1,3,4-thiadiazole react with the chlorides of phosphorus thioacids and benzenesulphonyl chloride to form products of substitution at the endocyclic nitrogen atom[166]:



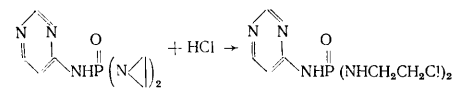
Y=N or CH; Ac=CH_3 (RO) P (S), or $C_6H_5SO_2$.

Under analogous conditions, thiophosphorylaminothiazolidines do not react. However, not only thiophosphorylated 2-aminothiazoles and 2-aminothiadiazoles, but also 2-thiophosphorylaminothiazolines react with hard electrophiles such as aryl isocyanate[166]:



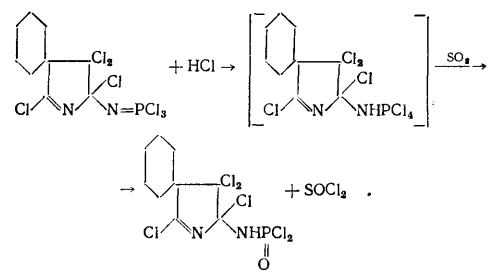
The greater ease of electrophilic substitution reactions for thiophosphorylated derivatives of aminothiazole and aminothiadiazole compared with the derivatives of aminothiazoline can be explained by the more pronounced nucleophilic properties of the endocyclic nitrogen atom in the thiophosphoryliminoheterocycles as a consequence of the electron-donating influence of the neighbouring π-bond.

(*e*) *Other reactions.* In many instances diaziridinoheteryl-aminophosphine oxides are converted by anhydrous hydrogen chloride into the corresponding bis(β-chloroethylamino)-derivatives in high yields[10,62]:

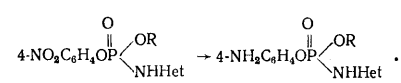


It has been noted[159] that, when diaziridino(4-chloropyrimidinyl-2-morpholinylamino)phosphine oxide is refluxed in dilute hydrochloric acid, a mixture of the hydrochloride of the initial pyrimidine and *N*,*N*'-bis(2-chloroethylamino)-pyrimidinylphosphonamidate is formed.

Trichlorophosphazoheterocycles readily combine with anhydrous hydrogen chloride at the P=N double bond and give rise to phosphorus tetrachloride derivatives. The latter are unstable and are converted under the influence of sulphur dioxide into the corresponding dichlorophosphorylated derivatives[139-141]:



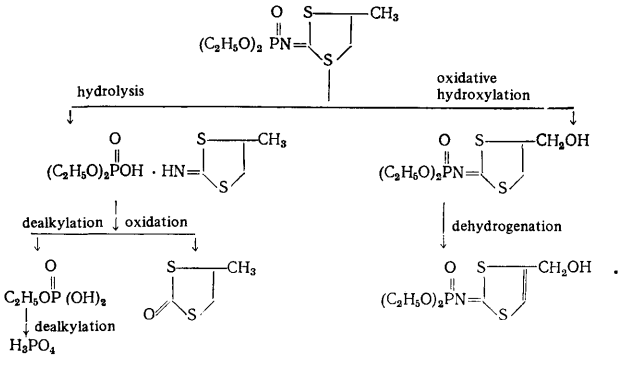
The amides of *p*-nitrophenylphosphonic acid, containing the heterocyclic residue at the nitrogen atom, are reduced with hydrogen in the presence of Raney nickel to the corresponding derivatives of *p*-aminophenylphosphonic acid[80,168]:



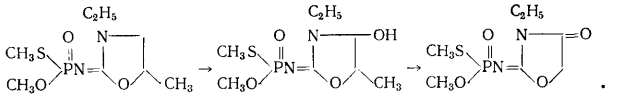
(*f*) *Reactions of phosphorylaminoheterocycles in the environment and in living organisms.* In connection with the high biological activity of certain phosphorylaminoheterocycles and their use as plant protecting agents, their photolysis and behaviour in living organisms have been investigated.

After the exposure of aqueous solutions of 2-diethoxyphosphorylimino-4-methyl-1,3-dithiolan to sunlight, its hydrolysis products were isolated: diethylphosphoric acid, monoethylphosphoric acid (in small amounts), and 2-imino-4-methyldithiolan[169]. The preparation decomposes via the same mechanism in paddy rice plants[170]. When a 2% aqueous solution of acetone was used as the solvent in the study of the photolysis of 2-diethoxyphosphorylimino-4-methyl-1,3-dithiolan, the main decomposition product was *S*,*S*-1,2-propylene dithiocarbonate[169].

The main process determining the metabolism of 2-diethoxyphosphorylimino-4-methyl-1,3-dithiolan in the cotton plant is oxidative hydroxylation of the methyl group in the 4-position with partial dehydrogenation of the molecule:



3-Ethyl-2-methoxymethylthiophosphorylimino-5-methyl-1,3-oxazolidine also undergoes oxidative phosphorylation in the cotton plant, in the organisms of house flies, and in enzymatic and model oxidation systems; the 4-hydroxy derivative is readily converted into the 4-oxo-derivatives[39]:



* * *

In conclusion one may note that, as shown by the data presented above, this interesting branch of chemistry, related, on the one hand, to the chemistry of organoelemental compounds and, on the other hand, to the chemistry of heterocycles, has been developing vigorously in recent years. The results permit one to hope that new physiologically active compounds of this class will be found in the immediate future and experimental data of theoretical value will be obtained.

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