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Phosphorus Acid Hydrazides

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The review is devoted to the methods of synthesis, chemical reactions, and physicochemical properties of phosphorus acid hydrazides, among which biologically active substances have been discovered.
The bibliography includes 106 references.

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I. INTRODUCTION

The studies in the field of phosphorus acid hydrazides, which began to attract the attention of investigators as early as the end of the past century, have developed particularly vigorously during the last two decades. The presence of two nucleophilic nitrogen atoms together with the nucleophilic phosphorus atom in phosphorus acid hydrazides have led to extensive synthetic possibilities of these compounds. Substances with properties useful in practice have been discovered among phosphorus acid hydrazides. The hydrazides of phosphorothioic acid esters exhibit a pesticidal activity.[1-3] The dihydrazides of halogenophenol esters of phosphorothioic acid and the sulphonyl hydrazides of phosphorothioic acid have been used as bactericides and fungicides.[4,5] Certain hydrazides of phosphoramidothioic acid have been shown to exhibit a weak acaricidal and fungicidal activity.[6] Among phosphorus acid hydrazides, substances with insecticidal activity have been found.[7] The hydrazides of diarylphosphinic acids and esters of methylphosphonic and methylphosphonothioic acid have been synthesised as potential biologically active substances with cytostatic, insecticidal, and pesticidal properties.[8-10]

It has been shown that the hydrochlorides of *O*-aryl-*NN*-di(2-chloroethyl)phosphoramidohydrazidates have a pronounced antitumour activity[11,12] and act selectively in the absence of inhibition of blood generation. Some of the compounds mentioned have shown a high antitumour activity not inferior to that of chlorobutyne.[13,14] Thus the need to search for substances with antitumour activity among phosphorus acid hydrazides by the structural modelling of "carriers" of cytotoxic groups in order to increase the selectivity of the antitumour activity of the compounds has been demonstrated.

Hitherto there have been no reviews of phosphorus acid hydrazides. Bearing in mind that phosphorus acid hydrazides are of both theoretical and practical interest for research, we thought it useful to write the present review of literature data concerning the methods of synthesis and chemical and physicochemical properties of the given class of organophosphorus compounds. The review covers the literature up to the beginning of 1983.

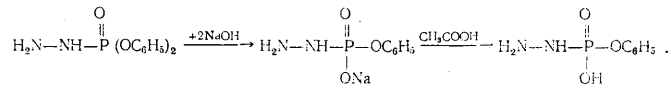
II. METHODS OF SYNTHESIS

1. Hydrazides of Phosphoric Acid

Among all the known phosphorus hydrazides, the largest group comprises the hydrazides of phosphoric acid. These include the hydrazides of phosphoric acid monoesters and diesters, phosphoramidate esters, phosphorodiamidic acids, the dihydrazides of phosphoric esters and phosphoramidic acids, and phosphoric trihydrazides.

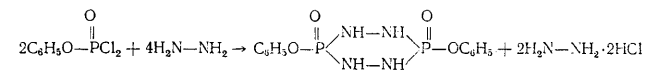
(a) The Hydrazides and Dihydrazides of Phosphoric Acid Monoesters

One of the methods of synthesis of the hydrazides of monoaryl and monoalkyl phosphate esters involves the partial hydrolysis of the hydrazide of the corresponding phosphoric acid diesters on heating with concentrated solutions of sodium hydroxide or ammonia,[15,16] for example:

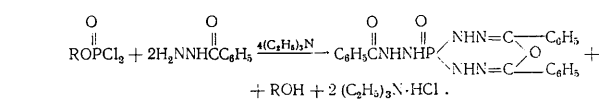


The catalytic hydrogenation of diphenyl phosphorohydrazidate in the presence of platinum dioxide also results in the formation of monophenyl phosphorohydrazidate.[17]

Phenyl phosphorodihydrazidate has been obtained by treating phosphoryl chloride with a calculated amount of phenol and then with hydrazine hydrate in alcoholic solution.[16] *o*-Biphenylyl and *p*-cumenylphenyl phosphorodihydrazidates have been synthesised similarly.[18] The reaction of phenyl phosphorodichloridate with anhydrous hydrazine in ethereal solution also affords only the dihydrazide when hydrazine is used in excess.[16] On reaction with two moles of hydrazine in an aqueous medium, the above acid dichloride gives rise to 3,6-dioxo-3,6-diphenoxy-1,2,4,5,3,6-tetra-azadiphosphane:[19,20]

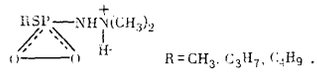


A study of the reaction of alkyl (and aryl) phosphorodichloridates with benzoylhydrazine in the presence of triethylamine showed that its product is 3-benzoylhydrazido--3-oxo-6,8-diphenyl-3-phospha-7-oxa-1,2,4,5-tetra-aza-cyclo-octa-5,8-diene:[21]



Interesting data have been obtained in a study of the reaction between *S*-alkyl phosphorodichloridothioates and 1,1-dimethylhydrazine.[22] *S*-Alkyl-2,2-dimethylphosphorohydrazidates were isolated in 26–40% yield and were found to exhibit unusual acid–base properties. Their basic

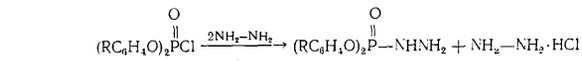
properties proved to be very weak ($pK_a < 2$) and so were their acid properties. The pK_a in water were 5.22 ± 0.05 for R = CH_3 and C_3H_7. On the basis of these properties and IR and ^1H NMR spectroscopic data, it has been suggested that the above compounds exist in the form of the dipolar ions:



R = CH_3, C_3H_7, C_5H_9 .

(b) Hydrazides and Substituted Hydrazides of Phosphoric Acid Diesters

The most widely used method of synthesis of the hydrazides of phosphoric acid diesters involves the reaction of the corresponding chlorides of phosphoric acid diesters with hydrazine, hydrazine hydrate, or substituted hydrazines. The reaction can also be carried out in the presence of water, using sodium carbonate to bind the hydrogen chloride evolved. Diaryl phosphorohydrazidates have been obtained in this way: [16,23,24]



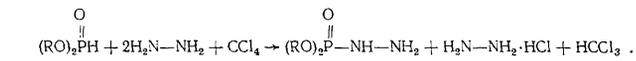
The phosphorylation of hydrazine, *NN*-dimethylhydrazine, phenylhydrazine, and acetylhydrazine by alkyl 2-chlorophenyl phosphorochloridates has been studied and it has been established that, when the reaction is carried out in benzene solution and the reactants are in molar proportions of 1 : 2, then the monohydrazides of the mixed phosphoric acid diesters are produced. [25]

It is of interest that the nature of the hydrazine hardly influences the rate of reaction, since the basicity of substituted hydrazines changes insignificantly, in contrast to the amines.

The reaction of hydrazine with 2-chlorophenyl ethyl phosphorochloridate yielded, together with the monohydrazide, also the *NN*-bishydrazide as a side product. The amount of the bishydrazide increases when anhydrous hydrazine is used.

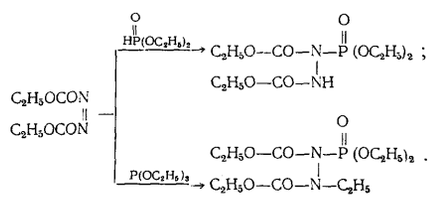
1-Alkyl-substituted hydrazides of phosphorus acids have been described for the first time by Shanduk et al., [23] in particular diaryl phosphoro(1-ethylhydrazidates) $(C_6H_5O)_2$.
O
‖
.$PN(C_2H_5)NH_2$. The 1-substitution of the resulting hydrazide has been confirmed by its ability to form the corresponding hydrazones with *p*-nitrobenzaldehyde.

Dialkyl phosphorohydrazidates can be obtained by the Todd–Atherton reaction by treating dialkyl phosphites with two moles of hydrazine and carbon tetrachloride: [16,26]



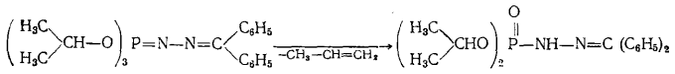
A modification of the Todd–Atherton method, based on the use of anhydrous potassium carbonate as the base in the presence of the phase transfer catalyst $(C_2H_5)_3\overset{+}{N}CH_2C_6H_5Cl^-$ in the reactions of dialkyl phosphites with hydrazine hydrate and carbon tetrachloride. [27]

Dialkyl or trialkyl phosphites react with azo-compounds to form the corresponding dialkyl phosphorohydrazidates: [28]

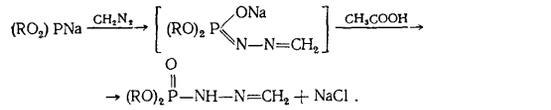


Dialkyl phosphorohydrazidates can be obtained also by reducing dialkyl azophosphoric acids with various reductants. [29]

The thermal decomposition of trialkoxyphosphazines at 170–180 °C is accompanied by the elimination of propene and the formation of di-isopropyl phosphoro(2-diphenylmethylenehydrazidate): [30]



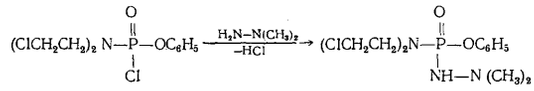
The salts of dialkyl phosphorous acids react with diazomethane to form dialkyl phosphoro(2-methylenehydrazidates): [31]



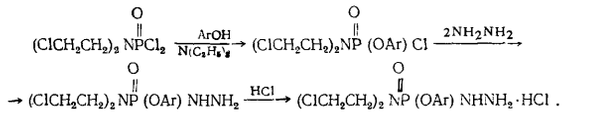
A communication about the synthesis of diethyl phosphoro(diphenylhydrazidates), which have been little investigated, has been published recently. [32]

(c) Hydrazides of Phosphoramidate Esters

There are comparatively few literature data on the hydrazides of phosphoramidate esters. Phenyl phosphoro[di(2-chloroethyl)amido](2,2-dimethylhydrazidate), formed when phenyl phosphoro[di(2-chloroethyl)amido]chloridate reacts with dimethylhydrazine, has been described: [33]

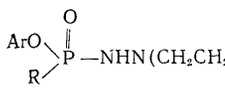


A method of synthesis of the hydrochlorides of aryl phosphoro[*NN*-di(2-chloroethyl)amido]hydrazidates, consisting in the reaction of aryl phosphoro[*NN*-di(2-chloroethyl)amido]chloridates with hydrazine in a mixture of anhydrous benzene and methanol and subsequent bubbling of a benzene solution with hydrogen chloride, has been developed: [34]



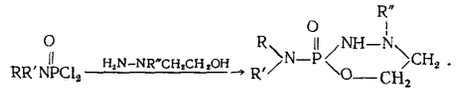
It has been established that the reaction between aryl phosphoro[*NN*-di(2-chloroethyl)amido]chloridates and phenylhydrazine proceeds in benzene in the presence of triethylamine with formation of the corresponding phenylhydrazides. [34]

The reaction between substituted phosphoromonochloridates and di(2-chloroethyl)hydrazine has been investigated and phosphorylated hydrazines having the formula



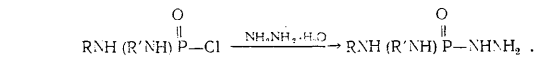
where R is a tetra-acetylglucose residue, were synthesised for the first time. [35]

Cyclic hydrazides of phosphoramidate esters, formed from phosphoramidic dichlorides and the corresponding substituted hydrazines, are known: [36]



(d) Hydrazides and Dihydrazides of Phosphoramidic Acids

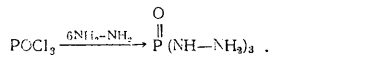
A preparative method for the synthesis of phosphorodiamidic hydrazides involves the interaction of the corresponding phosphorodiamidic chlorides with hydrazine hydrate in solution in benzene, dioxan, or tetrahydrofuran at 60 °C:[24,37]



There are comparatively few literature data on phosphoramidic dihydrazides. The synthesis of phosphoramidic dihydrazides from the corresponding phosphoramidic dichlorides and phenylhydrazine has been described.[38]

(e) Phosphoric Trihydrazides

Phosphoryl trihydrazides can be obtained by treating phosphoryl chloride with six moles of hydrazine:[16]



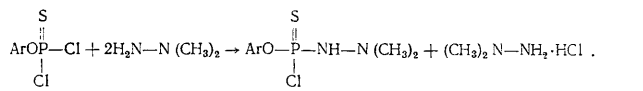
Phosphoryl chloride reacts analogously with six moles of arylhydrazines (phenyl- or 4-methylphenyl-hydrazine) in solution in ether or chloroform. The corresponding phosphoric tris(*N*-arylhydrazides) were isolated in these reactions.[39,40]

2. Hydrazides of Phosphorothioic Acid

Among the hydrazides of phosphorothioic acid, the dihydrazides of phosphorothioic esters and hydrazides of phosphorothioic diesters have been most thoroughly investigated.

(a) The Hydrazides and Dihydrazides of Phosphorothioic Esters

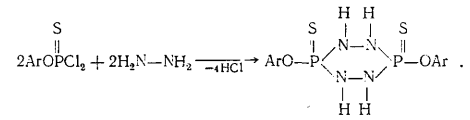
The reaction of *N*-mono- or *NN*-di-substituted hydrazines (*N*-phenyl or *NN*-dimethylhydrazines) with aryl phosphorodichloridothioates, involving the selective substitution of only one chlorine atom and the formation of the corresponding aryl phosphorochloridohydrazidothioates, has been described:[41]



When unsubstituted hydrazine was used under the conditions of this reaction (room temperature or a temperature below 0 °C, two moles of the corresponding hydrazine), the required monohydrazide could not be obtained.

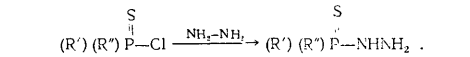
Analysis of the literature data concerning the effect of hydrazines on aryl (and alkyl) phosphorodichloridothioates shows that the nature of the products formed under these conditions depends on the electronic and steric effects, the basicity of the nucleophiles, the reaction temperature, the reactant ratio, and the order in which the reactants are added.

Thus data have been published[41,42] on the synthesis of aryl phosphorodihydrazidothioates by treating one mole of the corresponding phosphorodichloridothioate ester with four moles of hydrazine hydrate, phenylhydrazine, or 1,1-dimethylhydrazine. Phenyl phosphorodihydrazidothioate has been obtained similarly.[16] On the other hand, the formation of a cyclic product, namely 3,6-diphenoxy-3,6-dithiono-1,2,4,5,3,6-tetra-azadiphosphene by the reaction of phenyl phosphorodichloridothioate with two or three moles of hydrazine has been demonstrated:[43]

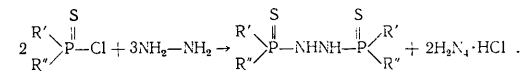


(b) Hydrazides and Substituted Hydrazides of Phosphorothioic Diesters

Diaryl (or dialkyl) phosphorochloridothioates, hydrazine, or a substituted hydrazine are used to synthesise the hydrazides of phosphorothioic diesters:



In certain cases the above reaction leads to the formation of secondary hydrazides:



The reaction may be controlled by the polar effects of the groups R′ and R″. Thus the reaction of diaryl phosphorochloridothioates with hydrazine hydrate always affords a high yield of primary hydrazides for an equimolar reactant ratio.[42,44]

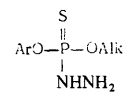
The formation of primary hydrazides from diaryl phosphorochloridothioates and hydrazine hydrate has been established also when the latter was used in excess.[23]

Dialkyl phosphorochloridothioates give rise to not only primary but also secondary hydrazides. The maximum yield of the latter of the type $[(R'O)(R''O)P(S)NH]_2$ is attained when anhydrous hydrazine is added to the corresponding acid monochloride in molar proportions of 3 : 2.

The most convenient method of synthesis of dialkyl phosphorohydrazidothioates is based on the reaction of dialkyl phosphorochloridothioates with two moles of hydrazine hydrate or a substituted hydrazine.[45–47]

The reaction leading to the synthesis of secondary hydrazides becomes more effective with increase of the electron-donating capacity of the substituents R′ and R″. It has been established that, when the sum of the constants ($\Sigma\sigma^*$) of the polar substituents R′ and R″ is greater than +4 (in the presence of aryl substituents), the above reaction does not occur. When $\Sigma\sigma^* = +1$, which happens for the secondary hydrazine $[(CH_3O)_2P(S)NH]_2$, the formation reaction leading to secondary hydrazides proceeds more rapidly and incorporates two bimolecular S_N reactions. In the first of these the corresponding dialkyl phosphorochloridothioates and hydrazine react to form a primary hydrazide. In the second reaction the above intermediate primary hydrazide is phosphorylated with formation of a secondary hydrazide.[47]

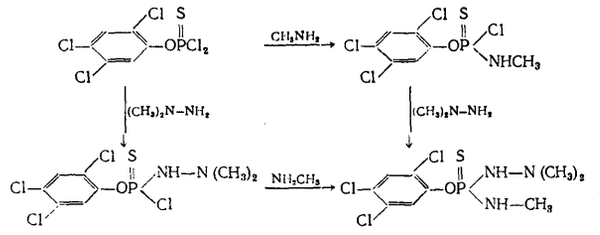
Mixed diesters of phosphorohydrazidothioic acid, formed from the corresponding phosphorochloridothioates and hydrazine hydrate and having the structure



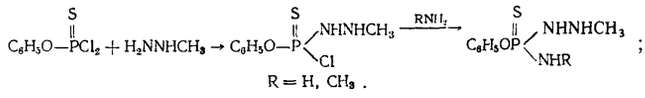
are known.[1,25]

(c) Hydrazides of Phosphoramidothioic Acid Esters

Phenyl phosphoramidohydrazidothioates can be obtained by the reaction of 2,4,5-trichlorophenyl phosphorochloridohydrazidothioate or phosphorochlorido(1,1-dimethylhydrazido)thioate with the corresponding amine or by the reaction of, for example, 2,4,5-trichlorophenyl phosphoro(*N*-methylamido)chloridothioate with the corresponding hydrazine.[41,47]



The first method of synthesis of phosphoramidohydrazidothioates has also been described[48] in connection with the synthesis of the following phenyl phosphoramidohydrazidothioates:

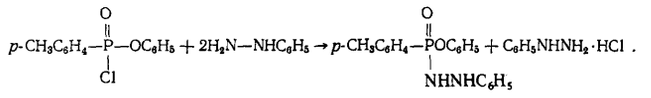


A series of phosphoramidohydrazidothioates have been synthesised by treating alkyl phosphoramidochloridothioates with dimethylhydrazine in boiling benzene in the presence of triethylamine.[6]

3. Hydrazides of Phosphonic and Phosphonothioic Acids

(a) Hydrazides of Phosphonic and Phosphonothioic Acid Esters

The hydrazides of phosphonic and phosphonothioic acid esters are usually formed when the chlorides of the corresponding acid esters react with hydrazine or a substituted hydrazine. Thus phenyl *p*-tolylphosphonochloridate reacts with phenylhydrazine to form the corresponding phenylhydrazide:[49]

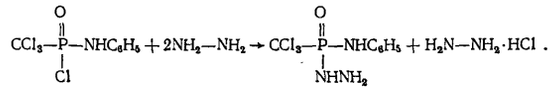


When methyl phosphonochloridate and methylphosphonochloridothioate are added to an excess of hydrazine or hydrazine hydrate, the hydrazides of the above acid esters are formed. When the order in which the reactants are mixed was altered, bisphosphorylated hydrazines were isolated.[9]

The phosphorylation of hydrazine by 2-chlorophenyl methylphosphonochloridate or methylphosphonochloridothioate in proportions of 2 : 1 led to the formation of the corresponding monohydrazide.[25] Aryl methylphosphonochloridates and methylphosphonochloridothioates also react with hydrazine hydrate to form monohydrazides, but, in order to facilitate their isolation, it is necessary to treat the reaction mixture with potassium carbonate.[10]

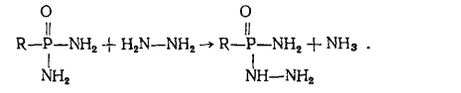
(b) The Hydrazides of Phosphonamidic Acids

The usual method of synthesis of phosphonamidic acid hydrazides involves the interaction of phosphonamidochloridates with hydrazine or its derivatives, for example:[50]



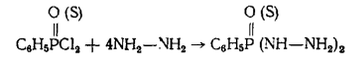
Solutions of strong inorganic bases can also be used to remove the hydrogen chloride formed.

It is of interest that treatment of phosphonic diamides with hydrazine also leads to the formation of phosphonamidic hydrazides:[51]

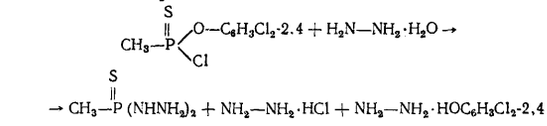


(c) Dihydrazides of Phosphonic and Phosphonothioic Acids

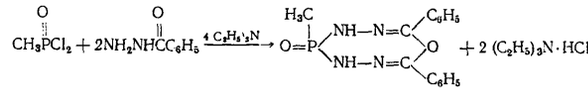
One of the methods of synthesis of the dihydrazides of phosphonic or phosphonothioic acids involves the treatment of the dichlorides of the corresponding acids with hydrazine, for example:[51]



A novel method of synthesis of methylphosphonothioic dihydrazides has also been described.[52] It was found that the interaction of hydrazine hydrate with 2,4-dichlorophenyl methylphosphonochloridate entails the hydrazinolysis of not only the acid chloride but also of the labile ester linkage with formation of a dihydrazide:



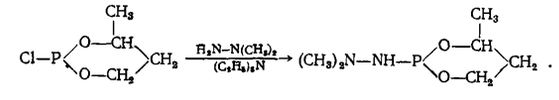
The reaction of methylphosphonic dichloride with two moles of benzoyl hydrazide and four moles of triethylamine in solution in toluene takes place in an unusual manner. The formation of 3-methyl-3-oxo-6,8-diphenyl-3-phospha-7-oxa-1,2,4,5-tetra-azacyclo-octa-5,8-diene was demonstrated in this instance:[53]



The reaction proved to be general for the synthesis of 3-alkyl(aryl)-3-oxo-6,8-diphenyl-3-phospha-7-oxa-1,2,4,5-tetra-aza-cyclo-octa-5,8-dienes.

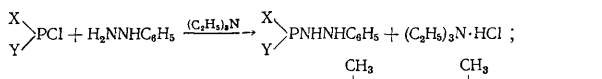
4. The Hydrazides of Phosphorous Acid

The first representative of the hydrazides of phosphorous acid was described by Nifant'ev in 1964.[54] It was obtained by the reaction of 1,3-butylene phosphorochloridite with 1,1-dimethylhydrazine in the presence of triethylamine:



The methods of synthesis of the hydrazides of phosphorous acid were investigated in detail in later studies.[55,56] It was

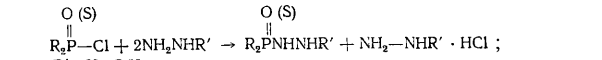
found that the hydrazides can be obtained from the corresponding acid chlorides and phenylhydrazine in the presence of triethylamine as the hydrogen chloride acceptor:



X = Y = OC_2H_5; OC_3H_7; OC_4H_9; —O $(CH_2)_2$O—; —OCHCH$_2$O—; —OCH $(CH_2)_2$O— .

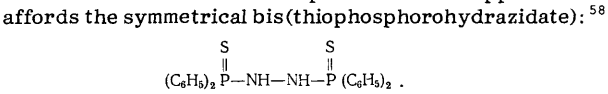
5. The Hydrazides of Phosphinic, Phosphinothioic, Phosphinous, and Phosphinothious Acids

The hydrazides of phosphinic and phosphinothioic acids have been synthesised by the reaction of the corresponding acid chlorides with two moles of hydrazine or a substituted hydrazine in an inert solvent: [57]

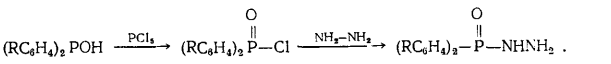


R′=H; C_6H_5 .

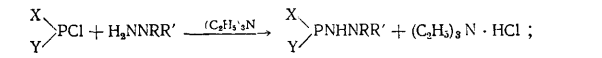
Diphenylphosphinothioic acid hydrazide has been synthesised by adding the chloride of the above acid to hydrazine hydrate. The addition of the components in the opposite order affords the symmetrical bis(thiophosphorohydrazidate): [58]



The hydrazides of diarylphosphinic acids containing both identical and different aromatic substituents at the phosphorus atom have been described. [23] They have been synthesised in accordance with the following schemes:

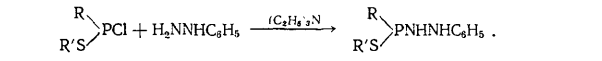


The hydrazides of phosphinous acids, obtained from the corresponding acid chlorides and phenylhydrazine or 1,1-dimethylhydrazine in the presence of triethylamine, are known: [56]



X=CH_3, C_2H_5; Y=SC_2H_5; SC_3H_7; SC_4H_9; *изо*-$C_6H_{11}S$; SC_6H_5; R=H; R′=C_6H_5; R=R′=CH_2.

2-Phenylhydrazides of alkylphosphinothious acids are formed analogous to the phenylhydrazides of dialkyl phosphorous acids: [59]



The properties characteristic of compounds with a tervalent phosphorus atom are also typical for the hydrazides of phosphinous and phosphinothious acids: they readily combine with elemental sulphur and with copper monohalide salts.

III. CHEMICAL AND PHYSICOCHEMICAL PROPERTIES

Extensive data characterising the chemical properties of phosphorus acid hydrazides have now accumulated. The presence of nitrogen atoms together with the nucleophilic phosphorus atom leads to the manifestation of amphoteric properties by the above compounds.

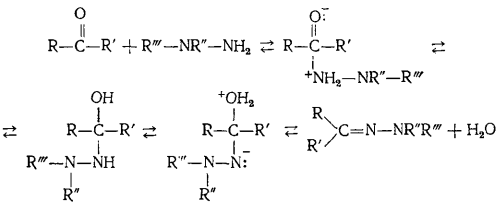
N-Unsubstituted hydrazides of phosphorus acids exhibit properties characteristic of other hydrazine derivatives by virtue of the presence of the free amino-group. Firstly, they undergo numerous reactions with electrophiles (aldehydes and ketones, diketones, β-ketoesters, monosaccharides, Schiff bases, carboxylic acids, carboxylic acid chlorides, alkyl chlorocarbonates, chlorides of alkane(arene)-sulphonic acids, phosphorus acid chlorides, picryl chloride, isocyanates, and isothiocyanates). Secondly, they react with nucleophiles (ethanol, phosphoric acids, water, caustic alkalies, and inorganic acids). In addition oxidation reactions are characteristic of phosphorus acid hydrazides.

1. Reactions with Electrophiles

(a) Interaction with Aldehydes and Ketones

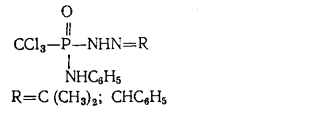
Analysis of the literature data on the interaction of phosphorus acid hydrazides with aldehydes and ketones shows that they can involve both NNH_2 and NNH groups.

If the nucleophilic centre of the attacking nucleophile is a nitrogen atom linked to two hydrogen atoms, the reactions with aldehydes and ketones proceed in accordance with the following scheme:



Ultimately the carbonyl group is substituted by the C=NNR″R‴ group, while the intermediate stages involve the highly mobile tautomeric equilibria shown in the scheme above. Acid catalysts accelerate the first stage as a result of the formation of conjugate acids, which polarises the carbonyl group still further. [60,61]

The aldehyde and ketone hydrazones derived from trichloromethylphosphono(*N*-phenylamidic) hydrazides have been described. [50]



The hydrazones derived from phosphoramidates, synthesised from both aliphatic and aromatic aldehydes and ketones, have been described. [24,62]

The following compounds have been used [24] to synthesise the hydrazones: formaldehyde, acetone, ethyl methyl ketone, methyl propyl ketone, acetaldehyde, propioaldehyde, acetophenone, 3,4-dichlorobenzaldehyde, 2-nitrobenzaldehyde, 4-dimethylaminobenzaldehyde, 4-chlorobenzaldehyde, etc.

The reactions of the hydrochlorides of aryl phosphoro[*NN*-di(2-chloroethyl)amido]hydrazidates with formaldehyde, benzaldehyde, and acetophenone have been investigated. [62,63] The reactions were carried out with heating in an alcoholic medium, without isolating the phosphoramidohydrazidate base, with formation of aryl phosphoro[*NN*-di(2-chloroethyl)-amido][2-alkylidene(arylalkylidene)hydrazidates].

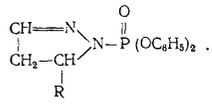
Kitaev and co-workers [64,65] established that the arylhydrazones can exist in aqueous-methanolic solutions in three tautomeric forms.

Ovrutskii et al. [66] used polarography at a dropping mercury electrode for the first time to investigate the tautomeric transformations of aryl phosphoro[*NN*-di(2-chloroethyl)-amido](2-methylene, benzylidene-, and methylbenzylidene-hydrazidates). The investigation showed that the half-wave potentials of the hydrazo-group in these phosphoroalkylidene-(arylalkylidene)hydrazidates differ little and remain constant

when the solutions of the test compounds are kept for a long time. This factor as well as the finding that half-wave potentials ranging from −0.6 to −0.96 V correspond to the azo-forms of the aldehyde and ketone arylhydrazones, while half-wave potentials ranging from −1.34 to −1.56 V have been obtained for the hydrazones derived from the above phosphorohydrazidates at pH 5.8 and 9.2, suggest that these hydrazones do not undergo reversible transformations under the polarographic conditions and do not have the structure of the azo-form but are in fact true hydrazones.

The influence of various substituents in the aromatic ring on the polarographic reduction has been estimated quantitatively. The quantities ρ^* at pH 5.8 and 9.2 are 0.25 and 0.20 respectively ($r = 0.99$; $S = \pm 0.2$). The constant ρ^* for the reduction of the C=N group at pH 5.8 and 9.2 is virtually invariant, which indicates the absence of changes in the mechanism of reduction at a dropping mercury electrode.

It is of interest that, when unsaturated aldehydes and ketones (acrolein and crotonaldehyde) are used in the reaction with diphenyl phosphorohydrazidate, five-membered heterocycles, namely pyrazolines, are formed:[56,67]

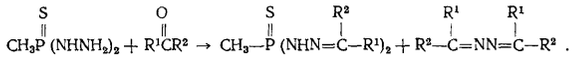


Diphenyl phosphoro(2-dimethylmethylenehydrazido)thioate has been obtained by the reaction of diphenyl phosphorohydrazidothioate with acetone.[25]

The reaction of dialkyl phosphorohydrazidothioates with aldehydes and ketones lead to the formation of the corresponding hydrazones derived from the phosphorothioic acids,[47,68] while the reactions with benzoquinone afford the compound



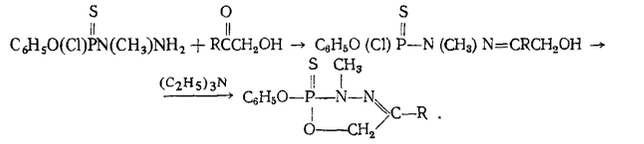
Grapov and co-workers[69] were the first to investigate the reactions of the dihydrazides of phosphorothioic acids with aldehydes and ketones and established that methylphosphonothioic dihydrazide reacts with benzaldehyde, *p*-chlorobenzaldehyde, *o*-, *m*-, and *p*-nitrobenzaldehydes, and *p*-dimethylaminobenzaldehydes to form the corresponding dihydrazones derived from methylphosphonothioic acids. Aldazans were isolated as side products. The reactions with acetone and acetophenone yielded the dihydrazones:



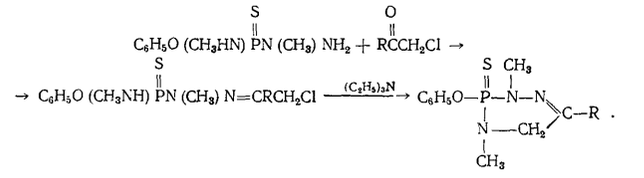
At the same time the reaction of methylphosphonothioic dihydrazide with benzophenone led to the isolation of only tetraphenylketazine.

The bisbenzylidenehydrazones derived from methylphosphonothioic acid have also been synthesised by the reaction of benzaldehyde and its substituted derivatives with methylphosphonothioic dihydrazide in the presence of acetic acid in an alcoholic medium as the catalyst.[52]

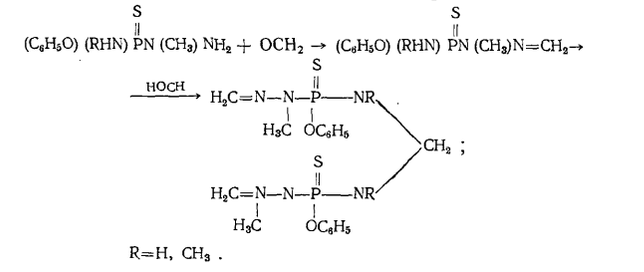
Interesting data have been obtained in the study of the reactions of asymmetric *N*-methylhydrazides of phosphorus acid with aldehydes and ketones.[48] Thus phenyl phosphorochlorido(1-methylhydrazido)thioate reacts with aldehydes and ketones to form hydrazones, which are converted in the presence of triethylamine into the corresponding 3-methyl-2-phenoxy-2-thiono-1,3,4,2-oxadiazaphosphorines:



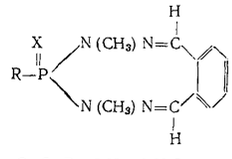
1,3-Dimethyl-2-phenoxy-2-thiono-1,3,4,2-triazaphosphorines have been obtained by treating phenyl phosphoro(*N*-methylamido)(1-methylhydrazido)thioate with various ketones in the presence of triethylamine:



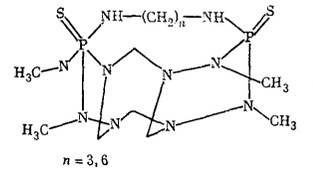
Treatment of phenyl phosphoro(*N*-alkylamido)(1-methylhydrazido)thioates with an excess of formaldehyde results in a reaction in accordance with the following mechanism:



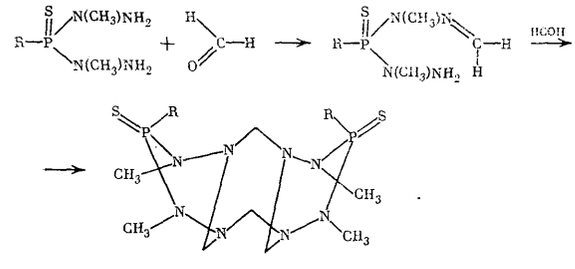
Di(1-methylhydrazides) of phosphoric, phosphonic, phosphorothioic, and phosphonothioic acids react with phthalic dialdehyde to form the dihydrazones:



The tetra(1-methylhydrazides $(H_2NCH_3N)_2PNH(CH_2)_nNHP.(NCH_3NH_2)_2$ react with formaldehyde to form the compounds

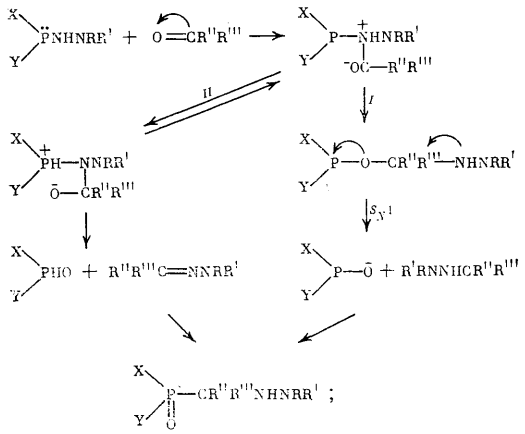


Treatment of the asymmetric phosphorodi(1-methylhydrazido)-thioate with one mole of formaldehyde leads to the corresponding perhydro-1,2,4,5-tetra-azaphosphorines, which react with formaldehyde to form tetracyclic compounds:



The structure of these compounds has been demonstrated by ^{1}H and ^{31}P NMR, IR and UV spectroscopy, and mass spectrometry.

The interaction of phosphorus acid hydrazides containing the NNH group with aldehydes and ketones has been investigated.[56,70] The reaction of dialkyl phosphoro(2-phenylhydrazidites) and *S*-alkyl alkylphosphono(2-phenylhydrazido)thioites with aldehydes and ketones yielded α-hydrazinophosphinates [and phosphonates?]. A reaction mechanism involving the formation of a four-membered ring as a result of the attack by the nucleophilic nitrogen atom on the electrophilic carbon atom of the carbonyl group, similar to that of the Staudinger–Wittig reaction, has been proposed:

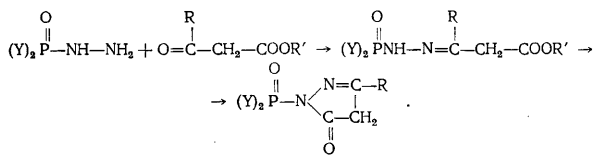


I: X=Y=OC_2H_5; OC_3H_7; OC_4H_9; $-O(CH_2)_2O-$;
$-OCH(CH_3)(CH_2)_2O-$; $-OCH(CH_3)(CH_2)_2O-$; R=H; R′=C_6H_5;
II: X=CH_3; C_2H_5; Y=SC_2H_5; SC_4H_9; SC_3H_7;
neo-$C_5H_{11}S$; R=H; R′=C_6H_5; R=R′=CH_3; R″=C_3H_7; R‴=H; R″=C_4H_9; R‴=C_2H_5.

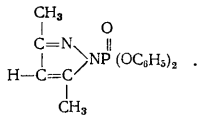
It is suggested that the initial intermediate can rearrange, as in case I, to produce an α-hydrazinophosphinite, which then rapidly decomposes via an S_N1 mechanism to form the final product. There is also a possibility of a proton shift (case II) with formation of a phosphonobetaine and the subsequent final stage of the Staudinger–Wittig reaction.

(b) Interaction with β-Ketoesters and α- and β-Diketones

Ketoesters react with diphenylphosphinic hydrazide and diphenyl phosphorohydrazidate to form the corresponding hydrazones, which split off the alcohol on heating in solution to form phosphorylated pyrazolones:[56,67,71]

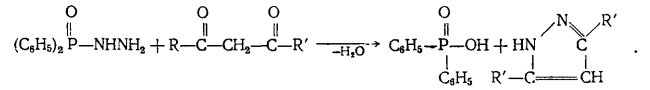


The use of acetylacetone instead of acetoacetic ester in the above reaction leads to the formation of 1-diphenoxyphosphoryl-3,5-dimethylpyrazole.[67]

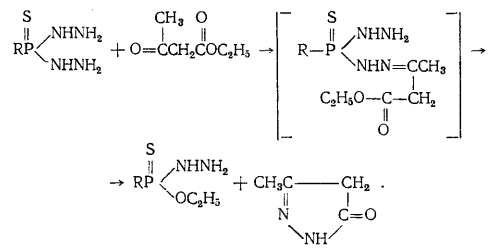


According to the data of Jahns et al.,[72] the reaction of diphenylphosphinic hydrazide with acetylacetone in equimolar proportions yielded 3,5-dimethyloxopyrazolyl diphenylphosphinate. Its structure was demonstrated by a specific synthesis from 3,5-dimethylpyrazole and diphenylphosphinic acid. After the reactions with benzoylacetone and dibenzoylmethane, only the corresponding hydrazones were isolated.

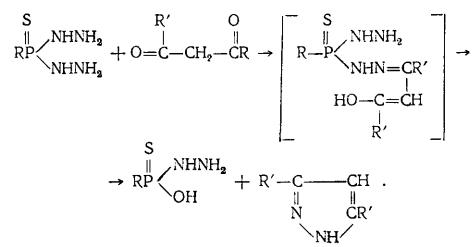
The reaction of diphenylphosphinic hydrazide with acetylacetone in proportions of 2 : 1 gave a 50% yield of an adduct from which diphenylphosphinic acid and 3,5-dimethylpyrazole were isolated after hydrolysis:



The reactions of the dihydrazides of various phosphorothioic acids with β-ketoesters and α-diketones have been studied in fair detail.[69] The reactions of phosphorodihydrazidothioic acids and phosphonothioic dihydrazides with acetoacetic ester proceed on heating in alcohol with dissociation of the P–N bond and the formation of 3-methylpyrazolone and ethyl phosphorohydrazidate and phosphonohydrazidothioate respectively:

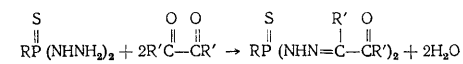


Methyl(phenyl)phosphonothioic dihydrazides and phosphorodihydrazidothioic acids react with acetylacetone and dibenzoylmethane to form respectively 3,5-dimethylpyrazole and 3,5-diphenylpyrazole. In addition, a hydrazidoacid is apparently formed, but its stability is low and the authors were unable to isolate it in a pure form:



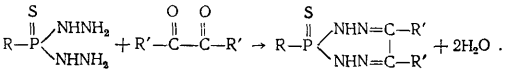
The interaction of dihydrazides of methylphosphonothioic and a number of other phosphorus thioacids with α-diketones (diacetyl and dibenzoyl) proceeds in different ways depending on the reactant ratio.

The reaction of one mole of methylphosphonothioic dihydrazide or phosphorodihydrazidothioic acid with two moles of α-diketone in alcohol at 50–60 °C affords a high yield of phosphonothioic di(2-acetylalkylidenehydrazide) or (2-benzoylbenzylidenehydrazide) (or the corresponding phosphorothioate):



The dihydrazides of methyl- and phenyl-phosphonothioic acids and ethyl and phenyl phosphorodihydrazidothioates react with α-diketones or glyoxal in proportions of 1 : 1 to give 3-thiono-3,1,2,4,5-phosphatetra-azacyclohepta-5,7-

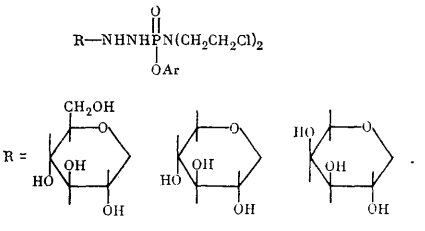
dienes:



Thus the structure of the products of the reactions of phosphorus acid hydrazides with β-ketoesters and diketones depends on the nature of the substituents in the carbonyl and hydrazone residues and on the nature of the initial reactants. The hydrazone cyclisation reactions with formation of a pyrazoline ring take place at the instant of the formation of the hydrazones or on heating the latter in solution and take place either with the dissociation of the P–N bond or with its retention.

(c) Interaction with Monosaccharides

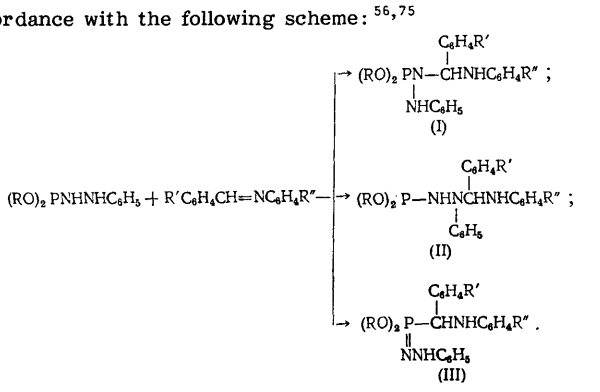
The interaction of phosphorus acid hydrazides with monosaccharides has been investigated in recent years.[73] The corresponding [*O*-aryl-*NN*-di(2-chloroethyl)amidophosphoryl]-hydrazo-derivatives of D-glucose, D-xylose, and L-arabinose having the following formulae were obtained:



The IR spectra of these derivatives were investigated and it was established that the shift of the band characteristic of the OH group can be accounted for by the formation of an intramolecular hydrogen bond characteristic of the ring (ν = 3420–3380 cm^{-1}). The hypothesis of a cyclic structure of monosaccharides is also confirmed by the data characteristic of the antisymmetric vibrations of the pyranose ring (ν = 930–920 cm^{-1}). It has been shown that the products of the interaction of phosphorus acid hydrazides with D-glucose and D-xylose show deformation vibrations due to the equatorial position of the C–H bond relative to the pyranose ring (ν = 840–835 cm^{-1}), while in the case of the products of the interaction of phosphorus acids with L-arabinose, deformation vibrations of the C–H bond corresponding to the axial position of the hydrogen atom (ν = 900 cm^{-1}) were found. The bands in the range 1680–1600 cm^{-1}, characteristic of the hydrazone C=N group, are missing from the spectra of all the compounds.[74] The data obtained permit the conclusion that in the free crystalline states the compound synthesised do not exist as the true hydrazones (derivatives of the acyclic forms) but are in fact derivatives of the cyclic pyranose forms.

(d) Interaction with Schiff Bases

The reactions of the 2-phenylhydrazides of phosphonous acids with Schiff bases have been investigated. The reaction can involve both the NH groups of the phenylhydrazide and the phosphorus atom, i.e. can proceed with or without the transfer of the reaction centre and can give adducts in accordance with the following scheme:[56,75]



The properties of the products isolated from the reaction mixture (they do not combine with elemental sulphur and their hydrolysis gives rise to a phenylhydrazine salt) correspond to the structure of the product of the addition of the Schiff base to the phosphorus atom (structure III).

Ethylene phosphoro(1-phenylhydrazidites) react with Schiff bases to form the corresponding ethylene (α-anilino)-benzyl-*N*-anilinophosphazines.

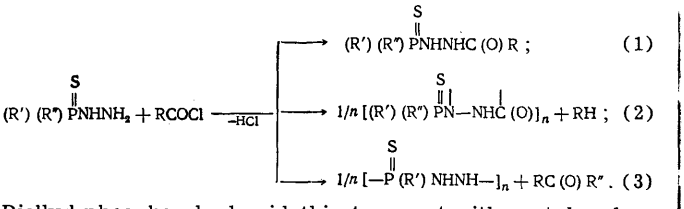
(e) Interaction with Carboxylic Acids

The interaction of diethyl, dibutyl, ethylene, and propylene phosphoro(2-phenylhydrazidites) with carboxylic acids (acetic, propionic, and butyric) is of the type of a double decomposition reaction with formation of carboxylic acid hydrazides and the corresponding phosphorus acids.[76]

The reactions of dialkyl and alkylene phosphoro(2-phenylhydrazidites) with acrylic or methacrylic acid proceeds with formation of phosphorous acid and probably with the initial formation of the hydrazide of an unsaturated acid, which cyclises to the corresponding pyrazolidinone or pyrazolone. 1-Phenyl-5-pyrazolidinone, 1-phenyl-5-pyrazolone, 4-methyl-1-phenyl-5-pyrazolidinone, and 4-methyl-1-phenyl-5-pyrazolone were obtained.

(f) Interaction with Carboxylic Acid Chlorides, Alkyl Chlorocarbonates, Alkane(arene)sulphonic Acid Chlorides, and Phosphorus Acid Chlorides

The monohydrazides of phosphorus acids readily react with carboxylic acid chlorides to form acyl derivatives. The pathway followed in the reactions of phosphoric (phosphorothioic) hydrazide derivatives with acyl chlorides, benzoyl chloride, and ethyl chlorocarbonate depends on the structure of the derivatives of the phosphorus acid hydrazides and also on the electrophile:[47]

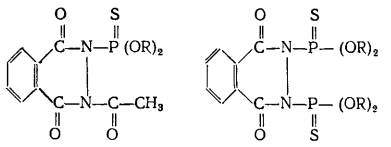


Dialkyl phosphorohydrazidothioates react with acetyl and benzoyl chlorides to form *N*-thiophosphoryl-*N'*-acylhydrazides [via reaction (1)].

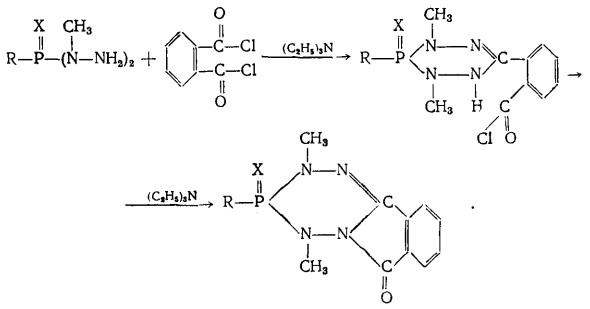
The reaction of phosphorodi(*N*-methylamidic) hydrazide with acetyl chloride leads to the formation of *NN*-dimethylacetamide and a condensed phosphorohydrazidate system [via reaction (3)].

NNN'-Triacyl-*N*-thiophosphoryl hydrazides and *NNN'*-triacetyl-*N*-dialkoxythiophosphoryl hydrazides have also been described.[47]

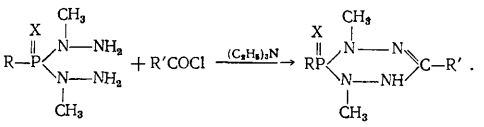
When phthaloyl chloride was allowed to react with *N*-acetyl-*N*-dialkoxythiophosphoryl hydrazides and *NN'*-bis(dialkoxythiophosphoryl) hydrazides, 3-acetyl-2-dialkoxythiophosphoryl-1,4-phthalazinediones and 2,3-bis(dialkoxythiophosphoryl)-1,4-phthalazinediones were obtained.[47]



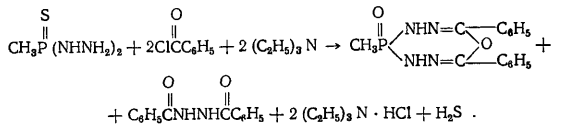
The di(1-methyl)hydrazides of phosphorus acids react with phthaloyl chlorides in the presence of triethylamine via the mechanism[48]



The interaction of di(1-methyl)hydrazides of phosphorus acids with formyl, acetyl, and benzoyl chlorides has been investigated. The reaction proceeds via the mechanism[48]

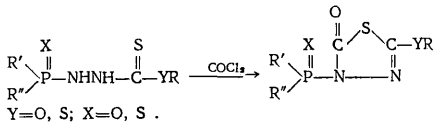


The acylation of methylphosphonothioic dihydrazide[69] with 2 moles of benzoyl chloride leads to the formation of 3-phospha-7-oxa-1,2,4,5-tetra-azacyclo-octa-5,8-diene:

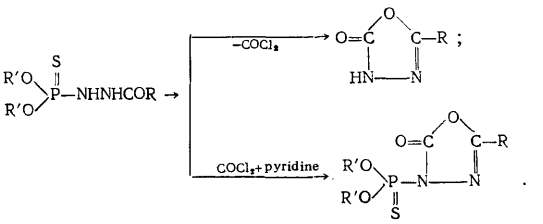


Sulphur is evolved in this reaction in the form of hydrogen sulphide.

The reactions of *N*-alkoxy(alkylthio)thiocarbonyl hydrazides of dialkyl phosphoric (phosphorothioic, phosphonothioic) acids with phosgene yielded the corresponding phosphorylated thiadiazoles:[77]

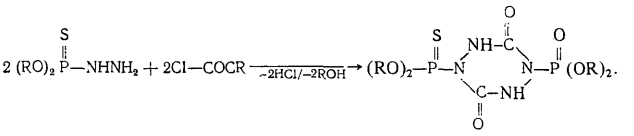


When dialkyl phosphorohydrazidothioates are treated with phosgene, the P–N bond is retained or broken depending on the reaction conditions. When the reaction is carried out in pyridine, phosphorylated oxadiazoles are formed. If the reaction proceeds in the presence of phosgene alone, the P–N bond is broken with formation of the phosphorothioic acid residue and oxadiazoles:

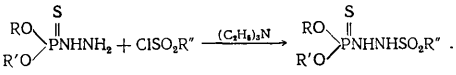


The reactions of phosphorus acid hydrazides with alkyl chlorocarbonates yielded aryl phosphoro[*NN*-di(2-chloroethyl)amido[(2-ethoxycarbonylhydrazidates),[62] diphenyl phosphoro(2-ethoxycarbonylhydrazidates),[78] and phosphorodi(*NN*-alkylphenylamidic) 2-methoxy(ethoxy)carbonylhydrazides.[79]

When dialkyl phosphorohydrazidothioates are treated with ethyl chlorocarbonate in the presence of alkaline reagents and in an inert organic solvent, 1,4-di(alkoxythiophosphoryl)-3,6-dioxo-1,2,4,5-tetrazines are formed in accordance with the mechanism[47,68]



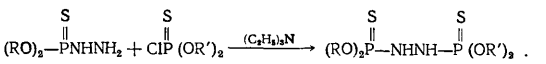
The reactions of phosphorohydrazidothioate esters with alkane (arene)sulphonyl chlorides take place in organic solvents in the presence of triethylamine with formation of 2-sulphonylhydrazides:[80,81]



The syntheses of phosphoramido(2-sulphonylhydrazido)-thioic acid and phosphorodi(*NN*-dialkylamido)thioic 2-sulphonylhydrazides,[5,82] aryl phosphoro[*NN*-di(2-chloroethyl)amido[(2-methanesulphonylhydrazidates),[62] aryl phosphoro[*NN*-di(2-chloroethylamido](2-*p*-toluenesulphonylhydrazidates),[63] phosphorodi(*NN*-alkylphenylamidic)-2-toluene-*p*-sulphonylhydrazides,[71] and phosphorodi[β-alkane-(arene)sulphonylhydrazido]thioic acids[83] have also been achieved.

The reaction of diphenyl phosphorohydrazidate with diphenyl phosphorochloridate leads to the formation of *NN'*-bis(diphenoxyphosphoryl)hydrazide.[16]

Bis(1,2-thiophosphoryl)hydrazides with various substituents at both phosphorus atoms have been obtained in the presence of triethylamine:[47,84,85]

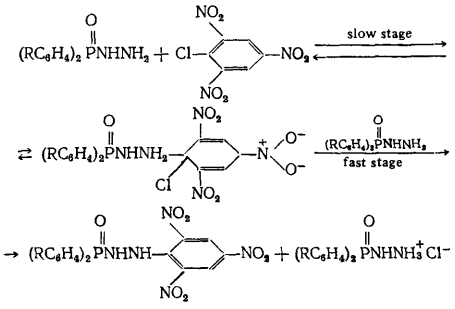


The formation of bis(1,2-dialkoxythiophosphoryl)hydrazide by the reaction of dialkyl phosphorohydrazidothioate with dialkyl phosphorochloridothioate has been described.[8,16,50]

(g) Interaction with Picryl Chloride

Diarylphosphinic hydrazides have been synthesised, the kinetics of their reactions with picryl chloride have been investigated, and a mechanism has been proposed for this

reaction:[8]

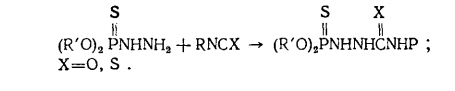


The reaction kinetics are described by a second-order equation, which is demonstrated by the linear time variation of the reciprocal of the current concentration. The reaction investigated obeys the Arrhenius equation. The activation energy E_a, the frequency factor $\lg A$, and the activation entropy have been calculated. It has been shown that the reactivity of diphenylphosphonic acid in the reaction with picryl chloride increases after the introduction of electron-donating substituents and diminishes in the presence of electron-accepting substituents.

(h) Interaction with Isocyanates and Isothiocyanates

Numerous studies have been made on the mechanism and kinetics of the reactions of phosphorus acid hydrazides with isocyanates and isothiocyanates.[47,86–94]

The interaction of dialkyl phosphorohydrazidothioates with isocyanates and isothiocyanates was first described by Tolkmith[47,86] and takes place in accordance with the mechanism presented below with formation of the corresponding semicarbazides and thiosemicarbazides:



Diphenylphosphinylthiosemicarbazides[87] and 4-acetyl-1-diphenylphosphinylthiosemicarbazides[88] are known.

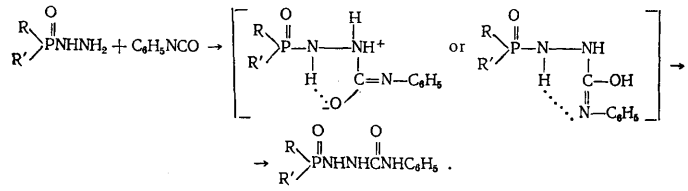
β-Phosphorylated semicarbazides and thiosemicarbazides are formed on interaction of aryl methylphosphonohydrazidates and methylphosphonohydrazidothioates and ethylphosphono(*NN*-diethylamido)thioic hydrazide with alkyl and aryl isocyanates and alkyl and aryl isothiocyanates.[89]

Phosphonohydrazidic acids react more readily with isocyanates than phosphonohydrazidothioic acids. In the former case the reactions proceed in the absence of a catalyst, while in the latter catalytic amounts of triethylamine are required. In the series of isothiocyanates only aryl isothiocyanates combine with phosphonohydrazidic and phosphonohydrazidothioic acid; methyl isothiocyanate does not react with these hydrazides.

Chlorophenyl isocyanate and phenyl isothiocyanate add to methyl phosphorodihydrazidothioate with formation of bis-(semicarbazido)- and bis(thiosemicarbazido)-methylphosphonothioates.[69] The β-structure of the compounds obtained has been demonstrated by IR and ^{1}H NMR spectroscopy.[69,89]

Analysis of a series of studies on the mechanisms and kinetics of the reactions of phosphorus acid hydrazides with isocyanates and isothiocyanates[90–94] permits the following conclusions.

Since the reactions of diarylphosphinic hydrazides and diaryl phosphorohydrazidates with phenyl isocyanate[90] are nucleophilic addition reactions, it follows that, by analogy with the reactions of carboxylic acid hydrazides with isocyanates,[95,96] one can postulate that they proceed via a multistage addition mechanism with formation of a tetrahedral intermediate:



The decomposition of the intermediate is facilitated by the formation of a hydrogen bond between the hydrogen atom of the imino-group of the hydrazide and the electronegative oxygen or nitrogen atom of the isocyanate. The substitution of the hydrogen atom of the imino-group by the ethyl group rules out the formation of an intramolecular hydrogen bond, which decreases the rate constants for the reactions of diarylphosphinic 1-ethylhydrazides and phosphoro(1-ethylhydrazidates) with isocyanates.

The kinetics of the reactions of diarylphosphinic hydrazides and diaryl phosphorohydrazidates,[90] diaryl phosphorohydrazidothioates,[91] and diaryl phosphoro(1-ethylhydrazido)-thioates[92] with phenyl isocyanate in benzene have been investigated at different temperatures. The rate constants calculated from a second-order equation remain satisfactorily invariant during the process at different concentrations of the initial reactants in the presence of the reaction products.

The reactions of phosphorus acid hydrazide with phenyl isocyanate proceed with low activation energies and high negative activation entropies. The high negative activation entropies ($\Delta S^{\neq} = -49.5$–57.4) in the above reactions show that the approach of the electrophile to the molecule of a hydrazide having a tetrahedral configuration is sterically more hindered than the approach to the planar molecule of a carbonyl-containing hydrazide ($\Delta S^{\neq}$ for the reaction of benzoyl hydrazide with phenyl isocyanate is −41.8 cal mol^{-1} K^{-1}).[95] The reactivities of the phosphorus acid hydrazides investigated vary in parallel with the basicity constants of the hydrazides.

The kinetics of the reactions of phosphorus acid hydrazides and 1-ethyl hydrazides with phenyl isothiocyanate in benzene have also been investigated. The reaction takes place quantitatively with formation of phosphorus acid thiosemicarbazides. The kinetics of these reactions are described by a second-order equation and the rate constants calculated from these equations remain satisfactorily invariant throughout the process.[93]

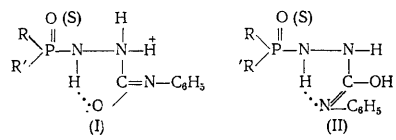
In the study of the kinetics of the reactions of phosphorus acid hydrazides with phenyl isocyanate,[97] questions concerning the influence of solvents on the rate and mechanism of this reaction were considered. The catalytic activity of dimethylformamide, dioxan, and pyridine in the reactions of diphenylphosphinic acid [hydrazide?] with phenyl isocyanate and picryl chloride shows that the solvation of the initial or transition state, involving the more acidic hydrogen atom of the imino-group in the initial hydrazide, is of decisive importance.

(i) The α-Effect in Reactions with Electrophiles

The α-effect is manifested as a positive deviation of the point corresponding to α-nucleophiles from the Brønsted straight line for compounds with the usual reactivity. Quantitatively the α-effect is defined as the ratio of the rate constants in the reactions of the α-nucleophile and a primary aromatic amine of equal basicity.

Hydrazine and its derivatives exhibit an enhanced reactivity in reactions with carbonyl- and sulphonyl-containing compounds.[94,98] Under the influence of the substituents in the aromatic rings of phosphorus acid hydrazides, the α-effect in the reaction changes.[8,90–94] However, the sequence in which the α-effect varies under the influence of such substituents is different in different series. In the reactions of diarylphosphinic hydrazides with phenyl isocyanate and picryl chloride,[8,90] electron-donating substituents reduce the α-effect, while electron-donating accepting substituents increase it. On the other hand, in the reactions of diaryl phosphorohydrazidates, diaryl phosphorohydrazidothioates,[90,92] and diaryl phosphoro(1-ethylhydrazido)thioates[94] with phenyl isocyanate, the substituents in the aromatic ring exert the opposite influence. The α-effect is linearly related to the basicity constants of the hydrazides.

Several possible causes of the manifestation of the α-effect have now been established but none, considered separately, can fully account for the nature of the phenomenon under consideration. On the assumption that the α-effect is to a large extent determined by the structure of the transition state, the enhanced reactivity of phosphorus acid hydrazides can be explained by their ability to form the cyclic complex (I) and (II) via a hydrogen bond between the oxygen or nitrogen atom of phenyl isocyanate and the hydrogen atom of the imino-group and also via a new bond between the carbon atom and the amino-group of the nucleophile.



(I) (II)

The transition states are distinguished by high stability as a consequence of the aromatic character and the presence of $4n + 2$ electrons. In addition a cyclic transition state promotes a more complete shift of the electron pair from the nucleophilic centre, facilitating thereby the formation of a new C–N bond.

In the reactions of phosphorus acid hydrazides with phenyl isothiocyanate, an appreciable decrease of the α-effect is observed compared with phenyl isocyanate, which can be explained by the lower capacity of the sulphur atom for the formation of a hydrogen bond in the transition state, which reduces the possibility of the formation of the cyclic complexes (I) and (II).[99]

Thus the extent to which the α-effect is manifested depends on the nature of both the nucleophile and the substrate and depends on the reaction mechanism. The reactions of phosphorus acid hydrazides involving the formation of cyclic atomatic complexes are energetically more favourable and are characterised by a higher α-effect.

2. Reactions with Nucleophiles

(a) Interaction with Ethanol and Diaryl Phosphoric acids

In order to discover the possible phosphorylating properties of phosphorodi(*NN*-alkylarylamidic) hydrazides, a study was made of their interaction with various nucleophiles in the presence of iodine:[79] ethanol, diphenyl phosphoric acid, and phosphorodi(*N*-phenylamidic) acid. The synthesis was carried out in accordance with the following scheme:

$$(C_6H_5NR)_2\overset{O}{\overset{\|}{P}}NHNH_2 + HX \xrightarrow{I_2} (C_6H_5NR)_2\overset{O}{\overset{\|}{P}}X +$$

$$+ (C_6H_5NR)_2\overset{O}{\overset{\|}{P}}OP(O)(NHC_6H_5)(RNC_6H_5) + (C_6H_5NR)_2\overset{O}{\overset{\|}{P}}OP(O)(RNC_6H_5)_2 ;$$

R=CH$_3$, X=OC$_2$H$_5$; R=CH$_3$, X=OP(O)(OC$_6$H$_5$)$_2$;

R=CH$_3$, X=OP(O)(NHC$_6$H$_5$)$_2$.

Phosphorodi(*NN*-cyclohexylphenylamidic)hydrazides are phosphorylating agents and give rise to the corresponding pyrophosphates on reaction with phosphorodi(*N*-arylamidic) acids:[79]

$$(RNH_2)_2\overset{O}{\overset{\|}{P}}NHNH_2 + (R'NH)_2\overset{O}{\overset{\|}{P}}OH \xrightarrow{I_2} (RNH)_2\overset{O}{\overset{\|}{P}}OP(O)(NHR')_2 .$$

(b) Interaction with Water, Caustic Alkalies, Hydrogen Chloride, and Nitric Acid

It is known that in the presence of moisture one ester linkage in diaryl phosphorohydrazides is hydrolysed:[16]

$$(C_6H_5O)_2\overset{O}{\overset{\|}{P}}NHNH_2 + H_2O \rightarrow H[PO_2(OC_6H_5)(NHNH_2)] + C_6H_5OH .$$

Diaryl phosphorohydrazidates are stable only in the absolutely dry state.

In the reactions of diaryl phosphorohydrazidates and *OO'*-diaryl phosphorohydrazidothioates with caustic alkalies, the hydrolysis of one or two ester linkages, depending on reaction conditions, is observed, with formation of the mono- and di-sodium (potassium) salts of phosphorus acid hydrazides. The ester linkage is also hydrolysed in the hydrolysis of phenyl phosphorodihydrazidate and *O*-phenyl phosphorodihydrazidothioate[16,42] with formation of a salt. When sodium (potassium) salts of phosphorus acid hydrazides are treated with hydrochloric and acetic acids, the corresponding acids are produced.[16]

N-Substituted phosphorus acid hydrazides react with hydrochloric acid to form several products:[100]

$$(CH_3)_3C\overset{O}{\overset{\|}{P}}(OCH_3)NC(CH_3)_3NHC(CH_3)_3 \xrightarrow[15\ min]{6M\,HCl} (CH_3)_3C\overset{O}{\overset{\|}{P}}(OCH_3)NHNHC(CH_3)_3 \xrightarrow{\Delta}$$

$$\rightarrow (CH_3)_3C\overset{O}{\overset{\|}{P}}(OH)_2 + (CH_3)_3CNHNHC(CH_3)_3 \cdot HCl + (CH_3)_3CNHNH_2 \cdot HCl .$$

t-Butylhydrazine hydrochloride is formed from 1,2-di-t-butylhydrazine as a result of the dissociation of the C–N bond. On further hydrolysis, trimethylmethanol, chloromethane, and methanol were isolated.

On interaction with dry hydrogen chloride, phosphorus acid hydrazides form hydrochloride salts of the following type:[25,34,101]

$$(C_2H_5O)(o\text{-}ClC_6H_4O)\overset{X}{\overset{\|}{P}}NHNH_2 \cdot HCl ;$$

$$(ClCH_2CH_2)_2\overset{O}{\overset{\|}{N}}P(OAr)NHNH_2 \cdot HCl ;$$

X=O; S .

On treatment with sodium nitrite in solution in hydrochloric acid, phosphorodi[*N*-cyclohexyl(benzyl)amidic] hydrazides are converted into phosphorodi(*N*-cyclohexylamidic) and phosphorodi(*N*-benzylamidic) azides.[24] The structure of the azides has been demonstrated by IR spectroscopy: ν_{max}(NH) = 3368, 3260, and 3220 cm^{-1}; $\nu(N_3)$ = 2150–2140 cm^{-1}; ν(P=O) = 1210–1205 cm^{-1}.

3. Oxidation Reactions

The oxidation of phosphorodi(*NN*-alkylarylamidic) 2-methoxy(ethoxy)carbonylhydrazides with lead tetra-acetate leads to the formation of the corresponding azo-derivatives:[79]

$$(C_6H_5NR)_2\overset{\overset{O}{\|}}{P}NHNHR' + Pb(OAc)_4 \rightarrow (C_6H_5NR)_2\overset{\overset{O}{\|}}{P}N{=}NR + Pb(OAc)_2 + AcOH\ ;$$
$$R{=}CH_3,\ C_2H_5;\ R'{=}COOC_2H_5,\ C_6H_5\ .$$

The relation is carried out in a 20 : 1 mixture of absolute chloroform and glacial acetic acid at 0 °C. Phosphorodi(*NN*-methylphenylamidic) 2-toluene-*p*-sulphonylhydrazide decomposes vigorously under the conditions of this reaction.

Bromosuccinimide, mercury(II) oxide, and nitrogen dioxide are weak oxidants. The oxidation with bromosuccinimide is carried out in absolute chloroform at −5 °C in accordance with the following scheme:

$$(C_6H_5O)_2\overset{\overset{O}{\|}}{P}NHNHCOOC_2H_5 + \begin{matrix}CH_2{-}CO\\ \\ CH_2{-}CO\end{matrix}\!\!>\!NBr \rightarrow (C_6H_5O)_2\overset{\overset{O}{\|}}{P}N{=}NCOOC_2H_5\ .$$

N-Unsubstituted hydrazides of phosphorus diesters are oxidised by iodine in aqueous solutions in the presence of tertiary amines with liberation of nitrogen and the formation of phosphoric acid diesters.[102]

4. Acid–Base Properties

The presence of nitrogen atoms together with the nucleophilic phosphorus atom results in the manifestation of amphoteric properties by phosphorus acid hydrazides. In connection with the investigation of the acid–base properties of phosphorus acid hydrazides, studies were made of the basic (pK_{a_1}) and acid (pK_{a_2}) ionisation constants of diarylphosphinic hydrazides and diarylphosphorohydrazidates[90,93] and the basic ionisation constants (pK_{a_1}) of *OO'*-diaryl phosphorothioates and *OO'*-diaryl phosphoro(1-ethylhydrazido)thioates have been determined.[91,92] Analysis of the data obtained showed that the ionisation constants of phosphorus acid hydrazides are satisfactorily correlated with $\Sigma\sigma^{ph}$;

$$pK_{a_1} = 2.57-0.37\sum\sigma^{ph}\ (r = 0.992;\ S = 0.0222)\ \ [90]$$
$$pK_{a_2} = 12.78-0.54\sum\sigma^{ph}\ (r = 0.99,\ S = 0.006)\ .$$

Comparison of the constants ρ in the equation shows that the secondary amino-group is more sensitive to structural changes in the diphenylphosphinic hydrazide molecule than the primary amino-group, which is more remote from the substituents. The same behaviour has been observed for the hydrazides of aromatic carboxylic acids.[103,104]

The acid–base properties of the hydrochlorides of aryl phosphoro[*NN*-di(2-chloroethyl)amido]hydrazidates, whose ionisation constants are satisfactorily linearly related to the Hammett σ^0 constants and Taft σ^* constants, have been investigated:[105]

$$pK_a = 3.20-1.04\sigma^0\ \rho = -1.04\ (r = 0.99;\ S = 0.028)\ .$$

The constant $\rho = -1.04$ for aryl phosphoro[*NN*-di(2-chloroethyl)amido]hydrazidates compared with $\rho = -0.37$ for diarylphosphinic hydrazides indicates a greater sensitivity of phosphorohydrazidates to structural changes than that of the phosphinic acid derivatives.

5. Polarography of Phosphorus Acid Hydrazides

The polarographic behaviour of aryl phosphoro[*NN*-di(2-chloroethyl)amido]hydrazidates has been investigated.[105] The study of the half-wave potentials of phosphorus acid hydrazides containing the di(2-chloroethyl)amino-group showed that these quantities are in the range from −1.30 to −1.45 V. Satisfactory results have been obtained in alkaline media at pH 9.2, in agreement with literature data for the polarographic activity of the chloroethylamino-group.[106] The influence of various substituents in the *para*-position in the aromatic ring on the polarographic reduction has been estimated. The constant $\rho^* = 0.23$ ($r = 0.99$; $S = \pm 0.025$). The positive value of ρ^* shows that the primary reaction at the electrode involves nucleophilic attack on the electron of the bond being reduced and the comparatively low value of ρ^* indicates a weak influence of the substituents on the electrochemical reaction.

The replacement of the hydrogen atom in the hydrazide group by the toluene-*p*-sulphonyl group changes the direction of the oxidation-reduction process, the sign of the constant ρ^* for which alternates.[63]

6. Spectroscopic Properties

The most varied physicochemical methods have been used to study the structure of phosphorus acid hydrazides: IR, UV, and ^1H NMR spectroscopy;[24,34,48,56,69,70,73,75,89] the present Section deals with problems in the IR spectroscopic study of the influence of electron-donating and electron-accepting substituents in the aromatic ring on the shift of the bands due to the NH and P=O groups.[90–92]

The complex behaviour of the spectroscopic characteristics of the stretching vibrations of the NH groups in phosphorus acid hydrazides is due to the presence of the imino- and amino-groups at different distances from the P=O group in the aromatic ring and interacting with one another. The influence of substituents on the stretching vibrations of the imino-group (NH) is dominant and is transmitted more effectively by virtue of the considerable amount of double bond character of the P–N bond. The influence of the substituent on the amino-group is transmitted via more extensive molecular systems, incorporating the N–N unit, where the transmission of the electronic influence takes place solely via the *I* effect.

Studies of the IR spectra of diaryl phosphorohydrazidates and *OO'*-diaryl phosphorohydrazidothioates and of the influence of electron-donating and electron-accepting substituents in the aromatic ring on the NH and P=O band shift have been reported.[90–92]

The IR absorption spectra of diaryl phosphorohydrazidates show the following frequencues: ν(P=O) = 1191–1213 cm^{-1}, ν(NH) = 3368–3321 and 3227–3204 cm^{-1}; the frequencies in the spectra of *OO'*-diaryl phosphorohydrazidothioates are as follows: ν(P=S) = 660–652 cm^{-1} and ν(NH) = 3350–3330 and 3195–3138 cm^{-1}.

The NH and P=O stretching vibration frequencies of diaryl phosphorohydrazidates are satisfactorily correlated with the constants σ^{ph} and can be expressed by the following equations:

$$\nu(NH) = 3222+45\sum\sigma^{ph}\ (r = 0.868;\ S \pm 4.889)\ ;$$
$$\nu(NH') = 3327-63\sum\sigma^{ph}\ (r = 0.945;\ S \pm 3.958)\ ;$$
$$\nu(P{=}O) = 1206+51\sum\sigma^{ph}\ (r = 0.987;\ S \pm 1.526)\ .$$

The stretching vibration frequencies in *OO'*-diaryl phosphorohydrazidothioates change slightly under the influence

of substituents of different electronic nature. A tendency is observed towards a linear relation between the logarithms of the reaction rate constants and the NH and P=S stretching vibration frequencies.

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