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Organophosphorus Fungicides

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The review examines the applications of organic derivatives of phosphorus as agricultural fungicides. Trends in the development of research in this field have been noted and data are presented on the mechanism of the action of certain preparations. The bibliography includes 263 references.

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I. INTRODUCTION

The use of organic derivatives of phosphorus as fungicides and herbicides constitutes a new and promising field of their application in the national economy [1-8]. The first studies in which the microbiological action of organic derivatives of phosphorus was noted were made at the beginning of the 1940's, but systematic investigations of their fungicidal and bactericidal properties were begun much later [9-11]. By 1972, 450 publications had been devoted to organophosphorus fungicides, some preparations found practical application, and others are being tested as experimental fungicides.

At the present time the main advances in the field of phosphorus-containing fungicides have been made in combating diseases of rice caused by the fungi *Piricularia* and *Pellicularia sasaki*. The reduction of the rice crop due to infection by *Piricularia* in the countries of South East Asia reaches 10%. As a result of vigorous measures taken to protect rice from disease, the losses in Japan have been reduced to 3%. Nevertheless they have been estimated at 250 000–350 000 tons of rice per year in an overall crop of 12–14 million tons [12,13].

The main preparations for the treatment of the infection of rice by Piricularia in Japan are phosphorus-containing fungicides (kitazin, kitazin P, inezin, hinosan, and cerezin) and antibiotics (kasugamycin and blasticidin). The industrial manufacture of these preparations was begun in 1966 [14] and in 1970 the manufacture of kitazin and kitazin P reached a total output of 1600 tons and that of hinosan 700 tons.

Phosphorus compounds with microbiological activities have a wide variety of chemical properties. Among these one encounters potential alkylating, acylating, and phosphorylating agents, oxidants, reductants, and complex-forming agents. These findings show that their action on the fungal cell is not unambiguous.

The advances in the chemistry of organic phosphorus-containing insecticides are in many ways related to the creation of a reliable model of the mechanism of the insecticidal action. For the mechanism of the fungicidal action, such a model has not been established so far. In view of the different types of action of organophosphorus preparations on the fungal cell, it is probably necessary to develop not one but several models. Unfortunately there have been virtually no biochemical studies on the action of phosphorus-containing preparations on processes in the fungal cell.

The bulk of the information on the fungicidal action of organic derivatives of phosphorus is concentrated in patent publications. The present review covers only the literature for the period 1967–1971 inclusive, since earlier studies on this question have been examined in a previous review [4].

II. DERIVATIVES OF PHOSPHOROUS AND PHOSPHINOUS ACIDS

The fungicidal and bactericidal activities of phosphorus(III) derivatives are probably associated with their reducing properties [4]. Dialkyl-, dicyclohexyl-, diphenyl-, and di(phenylethyl)-phosphinites exhibit bactericidal and bacteriostatic activities [15,16]. Cyclohexylammonium, piperidinium, and furfurylammonium salts of *O*-methyl- and *O*-phenyl-phosphorous acids also show germicidal properties [17]. It has likewise been noted that triaryl, tri(naphthylmethyl), and tri-(α-cyanopentachlorobenzyl) phosphites [19,20,21], dinitrophenyl phenylene phosphites [22], and a mixture of β-aminoethyl phosphite and *N*-β-hydroxyethyl phosphoramidite, obtained from *OO*-dimethylphosphorous acid and monoethanolamine [18], exhibit a high fungicidal activity against phytopathogenic fungi and also as antiseptics for the protection of wood.

The anhydrides of phenylphosphonous and arenesulphonic acids and dialkyl trimethylstannyl phosphites have been patented as agents effective against *Pellicularia sasaki* on rice [23,24].

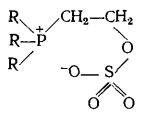
III. PHOSPHINES AND PHOSPHONIUM SALTS

Substituted phosphines show a low fungicidal activity. Chlorotri(diphenylphosphino)methane at a concentration of 30–100 mg litre^{-1} destroys the spores of *Venturia inaequalis* on apple seedlings [25]. Trialkylstannylhydroxyethyldialkylphosphines have been patented as germicidal preparations [26].

Trialkylbenzylphosphonium, triarylbenzylphosphonium, tetra-(α-hydroxybenzyl)phosphonium, and tetra(arylamino)phosphonium salts suppress the growth of pathogenic micro-organisms much more effectively than

phosphines and aminophosphines [27-31]. Thus trialkylbenzylphosphonium salts suppress the growth of the spores of *Alternaria solani*, *Monilinia fructicola*, and *Stemphylium sarcinaeforme* and are effective against anthracnose and tomato blights [29]. The structure of both the cationic and anionic components of the molecule has a marked influence on its activity and the selectivity of its action. For example, alkyltriphenylphosphonium phosphorothioates and phosphorodithioates are several times as effective as the corresponding salts with inorganic anions in their action on the fungi *Alternaria* and *Botrytis* [30]. The considerable phytocidal activity of the preparations, which limits the scope of their application in plant cultivation, must be regarded as a disadvantage of this group of compounds [4].

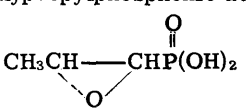
Phosphonium zwitterions, obtained by the reaction of trialkylphosphines with cyclic sulphates, suppress the growth of *Bacillis subtilus* and *Pullularia pullulans* [32].



IV. ACIDS OF TETRACOORDINATE PHOSPHORUS AND THEIR SALTS

O-Alkyl-, *O*-aryl-, and *OO*-diaryl-phosphorous acids and their salts show a moderate fungicidal activity against the fungi *Fusarium*, *Phytophthora*, *Pythium*, and *Aspergillus* [33-36]. For example, *O*-(1-diethylamino-2-propyl)*O*-dodecylphosphorous acid protects cucumber plants from mildew under greenhouse conditions at a dose of 2 kg per hectare [32]. The salts of alkylaminomethylphosphonic, *N*-substituted *O*-(α-aminobenzyl)phosphoric, phosphanilic, and difluorophosphanilic acids as well as laurylammonium *N*-laurylchloromethylphosphonamidate have been patented as germicides [37-39].

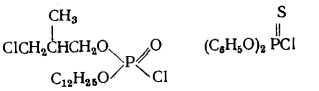
Studies on the microbiological activities of 1,2-epoxypropylphosphonic acid and its salts have been made in the laboratories of the Merck Company. The acid itself at a concentration of 0.01% completely suppresses the growth of the spores of *Macrosporium sarcinaeforme* and *Sclerotinia fructicola* [40-45]. The geometrical and optical isomers of 1,2-epoxypropylphosphonic acid



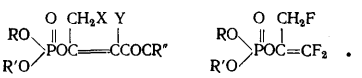
and its salts may be synthesised by the reaction of formylphosphonates and substituted ethylides [46], the thermolysis of sodium dioxolan-4-ylphosphonate [47], the reaction of α-hydroxypropionaldehyde with phosphorus tribromide followed by a rearrangement [48], by the oxidation of vinylphosphonates [49], and by other methods [44,50-53].

V. ESTERS OF TETRACOORDINATE PHOSPHORUS ACIDS

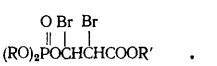
The halides of *O*-alkyl- or *O*-arylphosphoric and phosphorothioic acids are rarely used as organophosphorus pesticides in view of their low stability. However, some of them have been patented as the active principles of fungicidal preparations against *Alternaria* and *Tilletia* [35,54]:



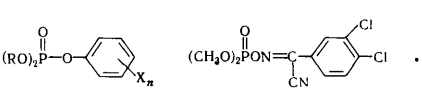
Phosphoric acid esters as a rule exhibit a moderate toxicity with respect to fungi. Among these, mention should be made of halogenovinyl phosphates obtained by the Perkow reaction from trialkyl phosphites and α-halogenocarbonyl compounds [55-57]:



Dialkyl 2-alkoxycarbonyl-1,2-dibromoalkyl phosphates can be used as soil fungicides and in the treatment of seeds to prevent root rot. They are synthesised by the addition of bromine to the double bond of the corresponding vinyl phosphates [58]:



Nitrobenzyl, pentachlorophenyl, cyanophenyl, and cyanohalogenophenyl esters of phosphoric acid (with two other alkyl groups) [59-61] and the dimethylphosphate derivative of the oxime of 3,4-dichlorophenylglyoxylonitrile [62] also exhibit a fungicidal activity:



The last preparation effectively destroys the soil fungi *Fusarium oxysporum*, *Pythium debarianum*, *Rhizoctonia solani*, and *Sclerotium rolfsii*.

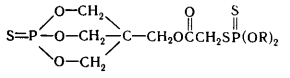
Among the esters of phosphonic and phosphinic acids, tested as fungicides, mention may be made of dialkyl 1,2-epoxyalkylphosphonates [63-65], alkyl halogenophenyl phenylphosphonates [67,69], dialkyl halogenobenzylphosphonates [68], and substituted amidines of dialkoxyphosphinyldichloroacetic acid [69]. These preparations are effective against various Gram-negative and Gram-positive microorganisms, the infection of rice by *Piricularia*, and tomato blight (due to *Phytophtora*); the majority of the preparations show little toxicity for warm-blooded animals and fish. Dialkyl sulphonylcarbamoylphosphonates are most toxic towards fungi; for example at a concentration of 0.01% diethyl toluene-*p*-sulphonylcarbamoylphosphonate suppresses the growth of more than 20 species of various phytopathogenic fungi [70,71]. Preparations of this group have been obtained by the addition of dialkyl phosphites to sulphonyl isocyanates:

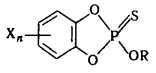


There are only isolated data about the fungicidal properties of the aryl esters of phosphorothionic and phosphonothionic acids containing various substituents in the aryl group—halogeno-, alkylthio-, alkylsulphonyl, alkylsulphonyl, trichloromethylthio-, ββ-dicyanovinyl, and certain others [72-80].

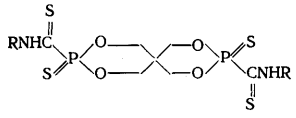
Cyclic phosphorothionates exhibit a moderate fungicidal activity in the treatment of diseases of fruit caused by

Phytophthora and *Fusarium* and of wheat smut in the *Graminae* [81-84].

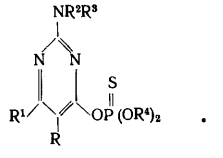




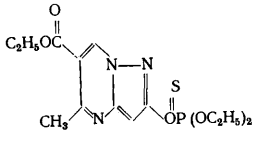
Bisthiocarbamoyl spirophosphonothioates can be used as soil fungicides and fungicides for the treatment of green plants [85]:



Phosphorothioic acid esters containing pyrimidine residues exhibit a high funcigidal activity against *Erysiphe cichoracearum* on cucumbers, *Phytophtora infestans* on tomatoes, *Puccinia recondita* and *Erysiphe graminis* on wheat, *Uncinula necator* and *Plasmopara viticola* on the vine, and *Podosphaera leucotricha* on the apple tree [86,87]:



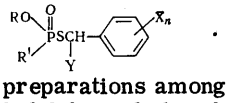
The Hechst Company has proposed a new fungicide for the treatment of the mildew of wheat and other agricultural plants—diethyl 6-ethoxycarbonyl-5-methylpyrazolopyrimidine-2-phosphorothionate (Hoe 2873) [88].



Its toxicity is 140 mg kg^{-1} for rats, 435 mg kg^{-1} for rabbits, and 184 mg kg^{-1} for guineapigs. The preparation exhibits systemic activity.

Almost all the industrial phosphorus-containing fungicides which are being manufactured in Japan belong to the group of phosphorothiolic and phosphorodithiolic acids.

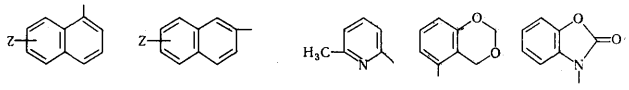
The fungicidal activity of *S*-benzyl derivatives of phosphorus acids has been investigated in detail mainly as an agent against the infection of rice by *Piricularia* [89-114]:



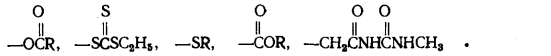
The most effective preparations among compounds of this class are *OO*-diethyl *S*-benzyl phosphorothiolate (kitazin), *OO*-di-isopropyl *S*-benzyl phosphorothioate (kitazin P), and *O*-ethyl *S*-benzyl phenylphosphonothioate (inezin).

The phosphoric, phosphorothioic, and phosphotodithioic analogues of kitazin are much less effective. The methyl and higher homologues also exhibit a lower fungicidal activity. The introduction of various substituents (alkyl, halogeno-, nitro-, methylthio-, dialkylamino-, and alkanesulphonyl) into the phenyl ring or the introduction of the COOR and CN groups in the α-position of the benzyl residue decrease the fungicidal activity of these compounds.

Kitazin analogues containing the groups indicated below in place of the phenyl ring were investigated [111-114]:



as well as analogues with various electronegative groups [115,116]:



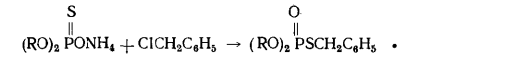
The effect of a change in the distance between the phosphorothiolic group and the phenyl ring was also studied [99]. All the preparations investigated exhibited a very moderate antipiriculariasis activity.

Kitazin, kitazin P, and inezin possess systemic fungicidal activity and are used against the diseases of rice caused by the fungi *Piricularia orizae* and *Pellicularia sasaki* at a dose of 1 kg per hectare. The toxicity of kitazin for rats is LD_{50} = 320 mg kg^{-1}, that of kitazin P is LD_{50} = 640 mg kg^{-1}, and that of inesine is LD_{50} = 750 mg kg^{-1}.

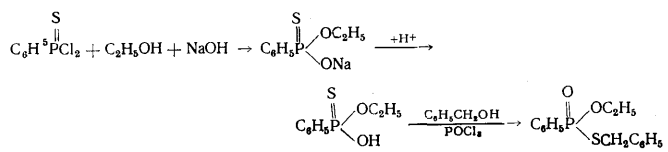
Studies on the mechanism of the action of kitazin showed that it acts on the permeability of the cell membrane of *Piricularia* fungi preventing the passage of carbohydrates and aminosugars, in particular glucose and glucosamine, into the fungal cell and promotes the loss of intracellular substances. Probably kitazin interferes with the biosynthesis of phytin in the fungal cell. It has almost no influence on the synthesis of proteins, phosphorylation processes, and endogenic and exogenic respiration [117-119].

It is noteworthy that *OO*-diethyl *S*-benzyl phosphorothioate was obtained for the first time by Kabachnik, Mastryukova, and Kurochkin in 1956 by the Michaelis–Bekker reaction [120,121]. At that time no one could even suggest that the compound might have fungicidal properties.

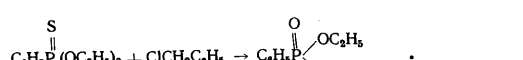
The industrial synthesis of kitazin and kitazin P consist in the benzylation of the ammonium salts of dialkyl phosphorothioates by benzyl chloride [122]:



In the manufacture of inezin, the dichloride of phenylphosphonothioic acid is treated with 3.4–3.6 moles of NaOH in 80% alcohol. The alcohol is distilled off, the residue dissolved in water, and the small amount of the *OO*-diethyl phenylphosphonothioate formed is extracted with ether. The aqueous layer is acidified and the hydrogen *O*-ethyl phenylphosphonothioate formed is esterified by benzyl alcohol in the presence of phosphoryl chloride [108,122,123]:

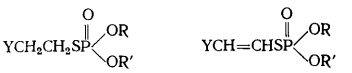


An interesting method for the preparation of inezin consists in the high-temperature *S*-benzylation of *OO*-diethyl phenylphosphonothioate by Pishchimuka's method [124]:

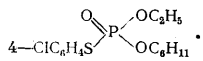


To extend the spectrum of fungicidal activity, it is suggested that mixtures of *OO*-dialkyl *S*-benzyl phosphorothioates with pentachlorobenzyl alcohol[125] or *O*-naphthyl-(*O*-aryl) *N*-methylcarbamates and also mixtures[126] of inezin with the antibiotic kasugamycin[127] be employed.

A number of studies have been made on the biological properties of β- and αβ-substituted *S*-ethyl phosphorothiolates and also *S*-vinyl phosphorothiolates:

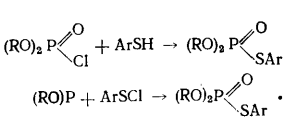


where Y = halogeno-, aryl-, alkoxy-, arylthio-, and arenesulphinyl groups and the *O*-ethyl phenylphosphorothiolate residue. All the compounds tested showed a moderate fungicidal activity in relation to *Piricularia oryzae*[128-132]. Apart from *S*-benzyl derivatives *S*-aryl esters of phosphorus acid are also effective against fungal diseases of plants[133-140]. The most active preparation in this series is *O*-cyclohexyl *O*-ethyl *S*-(4-chlorophenyl) phosphorothiolate—the active principle of cerezin. It destroys fungi of the *Corticium*, *Cochliobolus*, *Piricularia*, *Cercospora*, *Alternaria*, *Botrytis*, *Fusarium*, and *Verticillium* species:

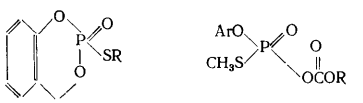


The toxicity of cerezin *per os* is 160 mg kg^{-1} for rats. *O*-Cyclohexyl *O*-ethyl *S*-(4-chlorophenyl) phosphorothiolate synergises the fungicidal activity of another preparation—hinosan. Their use in a mixture ranging from 1 : 3 to 3 : 1 makes it possible to lower the active concentrations and to improve the effectiveness of the treatment[141].

Double decomposition reactions of dialkyl phosphorochloridates (phosphonochloridates) with thiophenols or the interaction of trialkyl phosphates with arenesulphinyl chlorides have been suggested for the synthesis of *S*-aryl phosphorothiolates and phosphonothiolates[134,136-138]:



2-Alkylthio-2-hydroxy- or 2-arylthio-2-hydroxy-4-*H*-1,3,2-benzodioxaphosphorine[142-144] and the mixed anhydride of dihydrogen *S*-methyl phosphorothiolate and carbonic acid[145] have also been patented as funcigides:



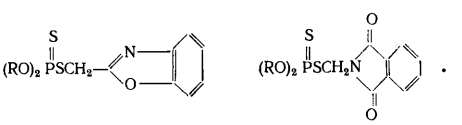
The simplest phosphorodithioates and phosphonodithioates do not exhibit a significant funcigidal activity[4]. The introduction of various electronegative substituents (halogeno-, nitro-, alkylthio-, arylthio-, alkylseleno-, trichloromethyl, alkynesulphonyl, acyl, alkoxycarbonyl, carbamoyl, and trialkylstannyloxycarbonyl groups) into the α-position of the *S*-alkyl group improves the fungidical properties of the preparations[116,146-152]. For example, *OO*-diethyl *S*-trichloromethyl phosphorodithioate at a concentration of 110 mg kg^{-1}, frees soil from infestation by *Fusarium solani*[147].

In the series of carbamoyl methyl phosphorodithioates, fungicidal activity increases on passing from *OO*-dialkyl to *O*-alkyl *O*-phenyl and further to *O*-alkyl *O*-(4-chlorophenyl) derivatives[151]:



OO-Dimethyl *S*-carbamoylmethyl phosphorodithioate forms with phenols molecular compounds the bactericidal activity of which towards *Staphylococcus aureus* and *Escherichia coli* exceeds that of the initial phenols by a factor of 10-30.[153]

Methyl phosphorodithioates containing heterocyclic residues have fairly pronounced fungicidal properties[154,155]

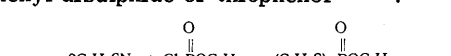


One should also note the fungicidal properties of *OO*-dialky *S*-(ω-dihalogenovinylalkyl) phosphorodithioates[156], αα-bis(dialkoxyphosphinodithioyl methyl)naphthalenes[157], 1-alkoxy-2,4-bis(dialkoxyphosphinothioylmethyl)benzenes[158], *OO*-dialkyl *S*-dialkylarsinophosphorodithioates[159], *OO*-dialkyl *S*-*O*-allylphenoxyphosphorodithioates[160], and bis(dimethoxyphosphinothioyl) sulphides and disulphides[161].

The study of the fungicidal properties of phosphorodithiolic acid derivatives led to the synthesis of the preparation quinosan—*O*-ethyl *SS*-diphenyl phosphorodithiolate[162-169]. Alkylphosphonodithiolate, phenylphosphonodithiolate, and benzylphosphonodithiolate esters have much weaker fungicidal properties[170-175]. The toxicity of hinosan for rats *per os* is LD_{50} = 150-340 mg kg^{-1}, for mice LD_{50} = 218 mg kg^{-1}, and for guineapigs and rabbits LD_{50} = 350-400 mg kg^{-1}.[176]

Hinosan is used to combat the diseases of rice caused by *Piricularia orizae*, *Pellicularia sasaki*, *Cochliobolus myiabeamus*, *Helminthosporium*, and *Hormodendrum* in doses of 0.7-1 kg of the emulsified concentrate, the treatment being repeated 2-4 times. At high concentrations the preparation is phytotoxic for the cabbage, tomatoes, and radishes[166,167]. Quinosan may be combined with cerezin (as stated above) and ethylenethiuram monosulphide as synergistic agents[176].

In the industrial synthesis of hinosan, ethyl phosphorodichloridate is treated with sodium thiophenoxide obtained from diphenyl disulphide or thiophenol[162,177]:



OS-Dialkyl *S*-phenyl phosphorodithioates are effective fungicides against the diseases of rice caused by *Piricularia*, *Helminthosporium*, and *Rhizoctonium*[178,179]. *O*-Alkyl *S*-alkyl *S*-benzyl phosphorodithiolates and *O*-alkyl *SS*-dibenzyl phosphorodithiolates have a relatively weak fungicidal activity[171,180,181].

Only a few studies have been made in recent years on the fungicidal properties of phosphorotrithioate and phosphorotetrathioate esters. *SSS*-Trialkyl, *SSS*-triaryl, and *SSS*-tribenzyl phosphorotrithioates, *SS*-diaryl chloromethyl phosphonotrithioates, and *SS*-di(alkylcarbamoylmethyl) phosphorotrithioates exhibit a moderate fungicidal activity[182-186].

The most effective preparation of this group is *O*-(2,4,5-trichlorophenyl) *SS*-di(methylcarbamoylmethyl) phosphorotrithioate, which, at a concentration of 0.003%, causes 100% suppression of the growth of the mycelia of the *Botrytis*, *Aspergillus*, *Fusarium*, and *Venturia* fungi

but it is completely non-toxic for the spores of the same fungi. It can be used against brown spot of leguminous plants and wheat grain mildew [187-190].

Products prepared by the addition of 1–8 atoms of sulphur to phosphorotetrathioates [191] and bis(dialkoxyphosphinothioyl) tri- and tetra-sulphides [192] have also been patented as fungicides.

VI. PHOSPHORUS ACID AMIDES

In the series of monoamides of phosphoric and phosphonic acids, *O*-aryl alkylphosphonamidates, phosphorylureas, and phosphorylthioureas, *OO*-dialkyl *N*-(β-aminoethyl)phosphoramidothioates, and 2-amino-2-oxo-1,3,2-benzodioxaphosphorines exhibit appreciable fungicidal activity [193-208].

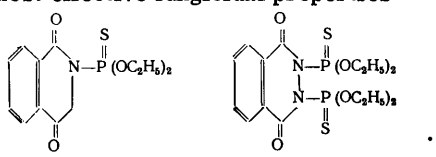
O-Pentachlorophenyl and *O*-(2,4,5-trichlorophenyl) *NN*-diethylmethylphosphonamidates suppress the growth of *Botrytis cinerea*, *Fusicladium dendriticum*, and *Fusarium oxysporum* [193]. 2,4-Dichlorophenyl derivatives exhibit a lower activity [205,206]. *OO*-Diarylphosphorylthioureas are active against *Piricularia* on rice [197-199]. *N*-Phosphorylated derivatives of 6-aminopenicillanic acid exhibit antistaphylococcal properties [201].

Phosphoramidates and phosphonamidates with alkenyl, benzyl, phosphorylalkyl and triazolyl groups attached to the oxygen or sulphur atoms as well as *N*-phosphorylated iminoesters of dihalogenocarboxylic acids proved to be weak fungicidal agents [204-208].

Among the group of amides of phosphorothiolic and phosphonothiolic acids, kitazin and inezin analogues have been patented as fungicides, but they have no advantages over their ester analogues [209-211].

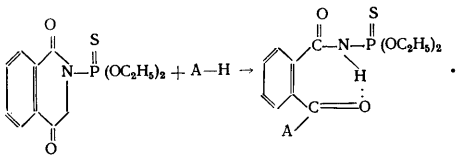
The fungicidal activity of the amides of *S*-benzyl benzylphosphonothiolic acid and ethoxycarbonyldichlorophosphoramidylmethyl disulphide and *S*-alkyl *NN*-dialkylphenylphosphonamidothiolates [212-216], which are effective against *Piricularia orizae*, *Pythium*, *Fusarium*, and *Verticillium*, is also noteworthy.

Among the large number of compounds which Tolkmith synthesised and tested in the study of *N*-acylated and *NN*-diacylated phosphoramidothioates, *OO*-diethyl phthalimidophosphonothioate (Dowco 199 preparation) and *NN'*-bis(diethoxyphosphinothioyl)benzopyridazinedione exhibit the most effective fungicidal properties [217-226]:



The Dowco 199 preparation is used against apple scab, powdery mildew of cucumbers, *Sphaerothaeca* on rose bushes, and certain other diseases at a concentration of 0.015–0.06%. The preparation is highly toxic for warm-blooded animals (5000–5500 mg kg^{-1}).

In order to explain the mechanism of the fungicidal activity of *OO*-diethyl phthalimidophosphonothioate, Tolkmith suggests that it acylates amidases interfering thereby with vital metabolic processes in the fungal cell:

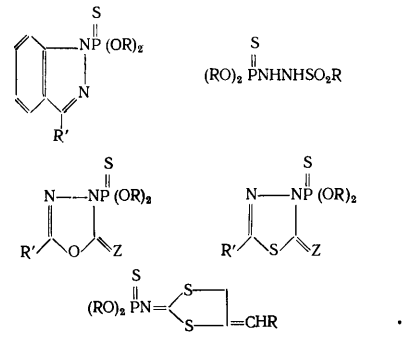


The high activating capacity of the Dowco 199 preparation accounts for its low anticholinesterase activity.

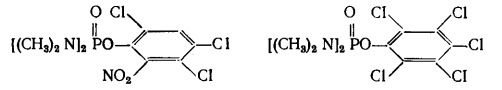
Several methods have been described for the synthesis of *OO*-diethyl phthalimidophosphonothioate: by the interaction of phthaloyl chloride with *OO*-diethyl phosphoramidothioate and triethylamine, by treating potassium phthalimide with *OO*-diethyl phosphorochloridothioate, and by the reaction of phthalic anhydride with the *OO*-diethyl phosphoramidothioate anion obtained from the corresponding amide and sodium hydride in dimethylformamide [219,221,225].

In the study of the effect of the chemical structure of chemical analogues of the Dowco 199 preparation on their biological activity, it was shown that the introduction of substituents into the phenyl ring and its hydrogenation decrease the fungicidal activity by a factor of 10–20.

In the series of phosphonamidothionates and phosphonothionates, *OO*-diethyl indazolylphosphonothioates [227,228], *N*-(*OO*-diethylphosphorothioyl)-*N'*-sulphonylhydrazines [229], *N*-(*OO*-dialkylphosphorothioyl)oxadiazines and *N*-(*OO*-dialkylphosphorothioyl)thiadiazines [230], and 4-alkylene-2-(*OO*-dialkylphosphorothioylimino)-1,3-dithiolanes [231] also possess fungicidal properties:

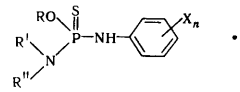


Among phosphoric acid diamides, *O*-aryl *NNNN'*-tetramethylphosphorodiamidates containing electronegative atoms and groups in the aryl substituent exhibit a high fungicidal activity [232-237]:



The above two preparations are now being tested as experimental fungicides. The first was developed in the Czechoslovak Socialist Republic. Its toxicity for warm-blooded animals is 10 mg kg^{-1} when introduced to rats via the stomach. The second preparation was patented as early as 1962 (Schoot et al. [236]), but its field tests were reported only at the Fifth British Conference on Insecticides and Fungicides [237]. The preparations are effective against the fungi (*Erysiphe graminis* and *Erysiphe cichoracearum*) responsible for the powdery mildew on barley and cucumbers.

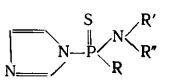
Mel'nikov and Vladimirova made a systematic study of the fungicidal activity of *N*-arylphosphorodiamidothioate esters [238,239]:



The introduction of the methyl group and of chlorine atoms in the aryl substituent increases the fungicidal activity of the preparation; alkyl esters are more active than aryl esters and *N*-alkylamido-derivatives are more effective than the dialkylamido-derivatives. *O*-Ethyl *N*-(4-chlorophenyl-*N*-methylphosphoramidothioate yielded satisfactory

results against the *Peronospora* infection of tobacco and the wilting of fodder beans caused by *Fusarium*[238].

Imidazolylphosphoramidothioates and imidazolylphosphonamidothioates possess a high fungicidal activity[220,230-246]:



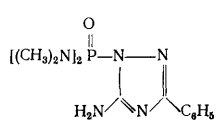
In a study of the biological activity of this group of preparations against the powder mildew of cucumbers and the potato disease caused by *Phytophtora*, it was shown that in such cases the fungicidal activity of the compounds is maximal when R is a planar substituent, for example phenyl. Derivatives of dihydrogen *O*-ethyl and dihydrogen *O*-aryl phosphorothioates and also of cyclohexylphosphonothioic acid are less effective[220,246]. The influence of the polarity and steric properties of the substituent at the phosphorus atom on the fungicidal activity of imidazolylphosphoramidothioates is more complicated than for cholinergic preparations.

It is interesting to note that the toxicity of the optical isomers of *NN*-diethylaminophenyl imidazolylphosphonothioate for *Phytophtora infestans* is independent of the sign of the optical rotation of the isomer, while the toxicity of the (−)-isomer for white mice is twice as high as that of the (+)-isomer (147 and 316 mg kg^{-1} respectively)[241]. Probably the mechanism of the fungicidal activity is related to the dissociation of the P–N bond, the elimination of the imidazole residue, and its inclusion in the metabolic processes of the fungus[244].

2-Aryloxy-2-thionobenzo-1,2,3-diazaphospholens, *O*-aryl *N*-acylphosphorodiamidothioates[247], *S*-benzyl phosphorodiamidothioates[248], 3-[*O*-alkyl-*N*-alkylphosphoramidothioyl]-5-alkoxy-1,3,4-thiadiazol-5-ones[249], and 1-(*O*-alkyl-*NN*-dialkylphosphoramidothioyl)imidazolidine-2-thiones[250] have also been proposed as fungicides.

There are only isolated data about the fungicidal activity of phosphorodiamidodithioic acid. *NNNN'*-Tetraalkyl-*S*-thiocarbamoylphosphorodiamidodithioates[251] and 2-anilino-2-thiono-3-phenyl-4,5-benzo-1,3,2-thia-aza-phosphorin-6-one possess fungicidal properties[252].

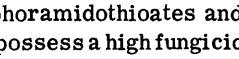
The study of the fungicidal activity of phosphorus acid triamides is associated mainly with the work of van den Bos on the *N*-phosphorylation of nitrogen-containing heterocycles by phosphorodiamidochloridates and phosphorothioates. Among this group of compounds, the preparation "Wepsyn", 2-amino-4-phenyl-1,3,5-triazolylphosphonic acid *NNNN'*-tetramethyldiamide, is used on a small scale against the fungi responsible for the powder mildew on decorative and fruit-bearing cultivated plants. The preparation is active both on spraying the leaves and when administered through the roots. It exhibits a systemic activity. Wepsyn makes the plants resistant or, in other words, it stimulates the synthesis of phytoalexins[253,254]:



Some of the Wepsyn analogues are effective against *Erysiphe cichoracearum* on cucumbers and *Erysiphe graminis* on barley and oats[255].

In order to enhance their fungicidal activity and decrease their phytotoxicity, imidazolylphosphonodiamidothioates can be used as complexes with calcium, cobalt, copper, iron, manganese, nickel, and zinc salts[256].

The fungicidal properties of phosphorodiamidoyl- and phosphorothioyl-sulphonylhydrazides are also noteworthy[257]:



Among other classes of organic phosphorus compounds, tetra-arylalkylenebisphosphine oxides[258], triphenylphosphinomethylenes[259], di-iodotriphenylphosphorane[260], arenesulphonylphosphazo-compounds[262], derivatives of cyclotriphosphazine[262], and 5-alkyl-1,1,3,3-tetraphenyl-1,3-diphospha-5-bora-2,4,6-triazines[263] have been patented as fungicides.

The review has shown that intensive studies on the fungicidal properties of organophosphorus compounds are being made in different countries. One of the useful properties of phosphorus compounds is their relatively low stability and rapid metabolic breakdown in plants, in animal organisms, in soil, and other components of the environment with formation of products which are safe for man and domestic animals. Another important feature of these compounds is the high selectivity of their action.

Phosphorus-containing fungicides act on metabolic processes within the fungal cell, on the permeability of the cell membrane, as well as on the inter-relation between the host plant and the parasitic fungus.

For a specific synthesis of new fungicidal preparations, it is necessary to extend biochemical research on the mechanism of the action of phosphorus-containing fungicides on the fungal cell.

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