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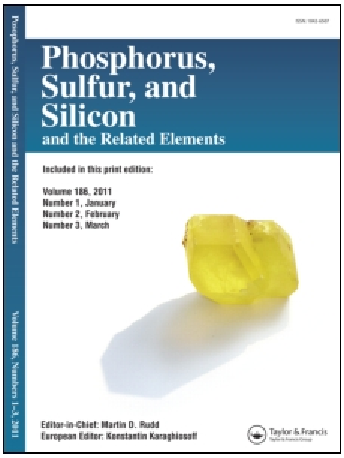

Phosphorus, Sulfur, and Silicon and the Related Elements

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AN APPROACH TO THE DEVELOPMENT OF ORGANOPHOSPHORUS FUNGICIDES

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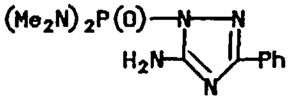
Abstract Phosphoramidates, phosphorodiamidates, phosphoric triamides, aminophosphonic acids, guanidinophosphonic acids, and phosphonopeptides are discussed as fungicides with potential for application in agriculture.

Following the discovery of systemic fungicidal activity in triamiphos (1) and the development of this compound under the name Wepsyn by Philips-Duphar,[1] a large number of organophosphorus compounds, mainly ester and amide derivatives of phosphoric or thiophosphoric acid (2), were investigated as potential fungicides.[2] Of these, four compounds (iprobenfos, edifenphos, pyrazophos, and fosetyl) are currently available for commercial use.[3] There is still much active research in this area, with numerous papers each year reporting new fungicidal organophosphorus compounds.



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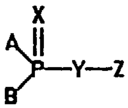
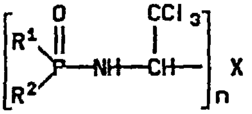


(2)

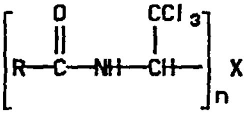
A, B = RO or R_2N
X, Y = O or S
Z = heterocyclic, benzyl, etc.

We have followed two lines of investigation, the first dealing with novel phosphoramidates, phosphorodiamidates, and phosphoric triamides, and the second with aminophosphonic acids, guanidinophosphonic acids, and phosphonopeptides.

Our approach in the first series of investigations was to prepare phosphorus-containing analogues (3) of known fungicidal carboxamide derivatives (4), in which an *N*-(1-substituted-2,2,2-trichloroethyl) group is present.[4] A well known example is triforine (4, R = H, X = piperazine-1,4-diyl, n = 2).[3] The phosphoramidates (3, $R^1 = R^2 =$ EtO) were obtained[5] by condensation of diethyl phosphoramidate with chloral, replacement of hydroxy in the so-formed adduct with chlorine



(3)



$$\left[R-\overset{\overset{O}{\|}}{C}-NH-\overset{\overset{CCl_3}{|}}{CH}- \right]_n X$$

(4)

n = 1 or 2

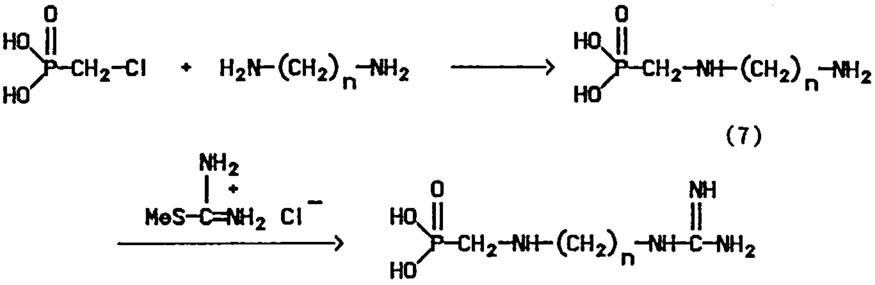
to give the tetrachloro compound $(EtO)_2P(O)NHCH(CCl_3)Cl$ (5), elimination of hydrogen chloride to give the imine $(EtO)_2P(O)N{=}CHCCl_3$ (6), and addition to the latter of a nucleophilic species e.g. imidazole, triazole, morpholine, piperazine, *N*-formylpiperazine, thioethanol, or various carboxamides or phosphoramides. Derivatives containing dithiocarbamate substituents (3, $R^1 = R^2 = EtO$, $X = Me_2NCS_2$, Et_2NCS_2, n = 1) or the ethyl xanthate group (3, $R^1 = R^2 = EtO$, $X = EtOCS_2$, n = 1) were obtained by direct reaction of the corresponding sodium dithiocarbamate or potassium ethyl xanthate with the tetrachloride (5).

Phosphoramides (3, $R^1 = R^2 = Me_2N$, X = NHCOR, n = 1) were obtained by a sequence of reactions involving the initial preparation of an *imine derived from a carboxamide,* i.e. *$RCON{=}CHCCl_3$*,[6] *followed by the* addition of *N,N,N',N'*-tetramethylphosphoric triamide. The product derived from chloroacetamide, $X = NHCOCH_2Cl$, was a useful intermediate in which the chlorine atom could be replaced by nucleophilic reagents, e.g triazole, dithiocarbamate, xanthate, and other thio derivatives.

Among the diethyl phosphoramidates (3, $R^1 = R^2 = EtO$), the most active were the dithiocarbamate and ethyl xanthate derivatives which, at 500 ppm, gave 99 - 100% control *in vitro* of *Fusarium, Helminthosporium*, and *Ophiobolus* species. Under similar conditions, the triazole, hydroxyethylthio, imidazole, and *N*-formylpiperazinyl derivatives, gave *ca.* 90, 90, 50 and 50% control, respectively. Other compounds of this class were less active. An imidazole derivative in which both an ethoxy and a dimethylamino group were attached to phosphorus (3, $R^1 = EtO$, $R^2 = Me_2N$, X = imidazolyl, n = 1), showed higher activity than the corresponding diethyl analogue *in vitro*.

Tested as seed dressings at 400 ppm against *Drechslera teres* the most active compounds (3, $R^1 = R^2 = EtO$, $X = Me_2NCS_2$, Et_2NCS_2, $EtOCS_2$, imidazolyl, NHCOMe, $NHCOCCl_3$, 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxamido, n = 1; 3, $R^1 = R^2 = Me_2N$, X = NHCHO, NHCOMe, $NHCOCH_2Cl$, n = 1), gave 50 - 75% of the control shown by guazatine.

Our second series of investigations was based on the known activity of guanidines as fungicides[3] and the biological importance of phosphonic acids.[7] A series of compounds was therefore prepared (Scheme 1) by condensation of chloromethylphosphonic acid with α,ω-diamines, and conversion of the terminal amino group to guanidino.



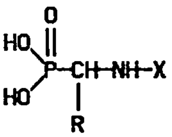
(7)

(8)

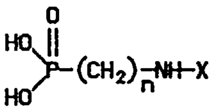
SCHEME 1

Fungicidal activity of the guanidines varied with chain length, and reached a maximum for the decamethylene derivative (8, n = 10), which at 500 ppm gave 100% control *in vitro* of *Piricularia oryzae*, *Botrytis cinerea*, *Septoria nodorum*, and *Drechslera sativa*, and > 50% control of *Rhizoctonia solani* and *Fusarium avenaceum*.[8] Activity against *D. sativa* and *S. nodorum* was also demonstrated for the ω-amino compounds (7), albeit at a lower level.

The above results led us to investigate the fungicidal potential of simple α- and ω-aminoalkanephosphonic acids (9, 10) and the corresponding guanidino compounds (11, 12), all of which were prepared by known methods.[7] Biological testing was directed mainly towards possible use of these compounds as seed-dressings for the replacement of organomercurials in the control of *Drechslera* spp. and other pathogens of cereal crops[9] and it was noted that the amino



[9, X = H; 11, X = C(:NH)NH_2]



[10, X = H; 12, X = C(:NH)NH_2]

compounds were generally more active than the guanidino analogues. The α-amino series (9, R = Me, Et, Pr^n, Bu^n, n-C_7H_{15}) all gave 75 - 100% control of *D. sativa* or *D. teres* when tested *in vitro* at 500 ppm. In field trials, the use of α-aminopropanephosphonic acid (9, R = Et) as a seed dressing agent at 400 ppm gave 95 - 100% control of *D. teres*, *D. avenae*, *D. graminea*, and *Ustilago avenae*, and 70 - 80% control of *Septoria nodorum*, *Ustilago hordei*, and *Tilletia caries*. Laboratory tests, using seeds infected with *D. teres*, showed the α-amino compounds (9) to be more active then those of the the ω-amino series (10) and that optimum activity in both types of compound occurred for the C_3 structure. Activity was less in the branched-chain derivatives.

A number of peptide derivatives of α-aminopropanephosphonic acid were also prepared by a standard synthetic procedure[10] and it was shown that the *N*-(*L*-ala)- and *N*-(*L*-ala-*L*-ala)-peptides had similar activity to that of the parent aminophosphonic acid. Peptides containing a glycyl residue were slightly less active. Those in which a *D*-alanyl residue was attached directly to the nitrogen atom of the aminophosphonic acid residue showed little or no activity.

Further studies are necessary in order to determine mechanisms of action for the above types of compound and to provide more detailed information on structure-activity relationships which may lead to compounds of improved performance. The low mammalian toxicity and environmental acceptability of α-aminopropanephosphonic acid (ampropylfos)[11] indicate that compounds of this type provide a promising area for further investigations.

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