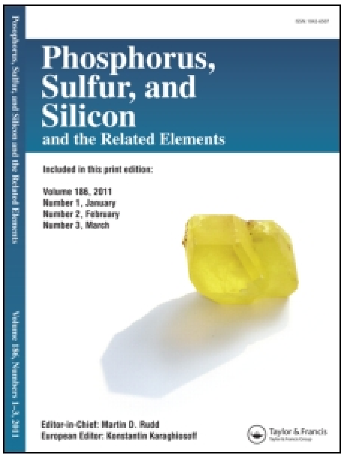

Phosphorus, Sulfur, and Silicon and the Related Elements

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Phosphorus-Containing Fungicides: a Review of Current Research and Prospects

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Two main types of phosphorus-containing compound are currently under investigation as potential fungicides: (a) esters of phosphoric, phosphorothioic, phosphorodithoic, or alkylphosphonic acids, including examples containing terpenoid or heterocyclic structures, and (b) aminophosphonic or aminophosphinic acids and their derivatives. The latter types are especially attractive environmentally but none has yet been commercialised.

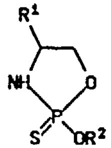
All phosphorus-containing fungicides that are currently available for use in agriculture[1] were introduced some twenty to thirty years ago and are mainly of a similar chemical type, being mixed esters of phosphoric, thiophosphoric, or dithiophosphoric acid. Several have specific areas of application, thus iprobenfos (1; R^1 = R^2 = i-PrO;

$R^1R^2P(X)R^3$ (1) $[EtOP(O)(H)O]_3Al$ (2)

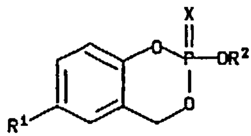
R^3 = benzylthio, X = O) and edifenphos (1; R^1 = EtO, R^2 = R^3 = phenylthio, X = O) are used in the control of rice blast and related diseases, as was phosdiphen (1; R^1 = EtO, R^2 = R^3 = 2,4-dichlorophenoxy, X = O), although the latter is now superseded. Pyrazophos (1; R^1 = R^2 = EtO; R^3 = 6-ethoxycarbonyl-5-methylpyrazolo-[1,5a]pyrimidin-2-yloxy, X = S), is used on a number of fruit and vegetables, and tolcophos-methyl (1; R^1 = R^2 = MeO; R^3 = 2,6-dichloro-4-methylphenoxy, X = S), for the control of seed-borne diseases. One different type, fosetyl, is a phosphonic acid ester formulated as the aluminium salt (2); it is active against Phycomycetes. Beyond these, no new commercial products have emerged.

Recent work on substituted aryl esters has included quantitative structure-activity relationship studies of methyl 2-chloroethyl aryl phosphates (1; R^1 = MeO, R^2 = $ClCH_2CH_2O$, R^3 = aryloxy)[2] and of several groups of bisaryl alkylphosphonates (1; R^1 = Me, i-Pr, $MeCCl_2$, s-Bu; R^2 = R^3 = aryloxy).[3] In general it has been found that fungitoxicity can be correlated with hydrophobic and steric factors. Several of the new compounds were found to have high fungicidal activity, thus the *pentachlorophenyl phosphate* (1; R^1 = MeO, R^2 = $ClCH_2CH_2O$, R^3 = C_6Cl_5O) and the bis(2,4,5-trichlorophenyl) alkylphosphonates (1; R^1 = Me or i-Pr; R^2 = R^3 = 2,4,5-$C_6H_2Cl_3O$) were more active than the reference fungicide (edifenphos). Nevertheless, they have not been commercialised, pending more extensive toxicity studies.[3]

New 1,3,2-oxazaphospholidine-2-sulfides (3)[4] have been prepared



(3)



(4)

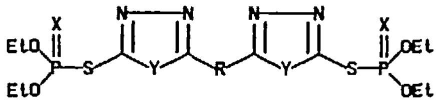
from (S)-2-aminoalcohols (R^1 = alkyl), thiophosphoryl chloride, and alcohols derived from essential oils (R^2OH = geraniol, isothymol, thymol, citronellol, or eugenol). The same group has also reported[5] a series of 4H-benzodioxaphosphorin-2-sulfides (4; R^1 = alkyl; X = S), incorporating a wide range of alkoxy groups R^2O (several derived from terpenoid alcohols), or a phenoxy group, at the 2-position, and a range of acyclic derivatives (5 and 6),[6] obtained by the interaction of terpenoid alcohols (R^3OH) (or 2-phenylethanol) with thiophosphoryl

$R^1R^2P(S)OR^3$ (5)

$R^1P(S)(OR^3)_2$ (6)

mono- or di-chlorides (R^1 and R^2 = MeO, EtO, or Ph). All products (3 - 6) showed activity against *Pythium* and *Corticum* spp.[4-6]

Phosphorothioates and phosphorodithioates (7), aimed at fungal pathogens causing diseases of sugar cane, were obtained[7] by the interaction of diethyl phosphorochloridate (X = O) or diethyl phosphorochloridothionate (X = S) with bis(mercaptotriazoles) (Y = NH), bis(mercaptooxadiazoles) (Y = O), or bis(meracptothiadiazoles) (Y = S). In each case the two heterocyclic rings are joined at the 2-position, either directly, or by $(CH_2)_2$, $(CH_2)_4$, $(CHOH)_2$, or C_6H_4.



(7)

A review by Sasaki[8] of his own work has drawn attention, *inter alia*, to α-hydroxyethylphosphinic acid, ethyl α-hydroxy-(p-fluorophenyl)-3-pyridylmethylphosphinate, and a new class of triazoles, the 1H-1,2,4-triazol-1-ylmethyldiphenylphosphine sulfides, as compounds with potentially useful activity.

Also reported recently is a new 1-N-hydroxyhydantoin 5-phosphate, with weak but reproducible activity against *Erisyphe graminis.*[9]

Aminophosphonic or aminophosphinic acids and their derivatives are particularly attractive for use in agriculture, because of their low mammalian toxicity and their envirmonmental compatibility. Derivatives of interest include the analogues of phenylalanine (i.e. 1-amino-2-arylethylphosphonic acids) (8; R = $ArCH_2$), the 4-fluorophenyl compound being an effective seed dressing against *Fusarium nivale.*[10] Whereas the phosphonous and phosphinic analogues (9; R = $ArCH_2$) were less active, several 2-amino-2-arylethylphosphonic acids showed similar activity to the 1-amino compounds.[11]

$RCH(NH_2)PO_3H_2$ (8) $RCH(NH_2)P(R^1)(O)OH$ (9)

Our own studies of aminophosphonic and guanidinophosphonic acids,[12] showed that α-aminopropanephosphonic acid (ampropylfos) (8; R = Et) had potential for use as a seed-dressing agent in cereal crops, e.g. to control *Drechslera* spp., and that it was virtually non-toxic to mammals (LD_{50} > 5000 mg Kg^{-1}).[13] Of the guanidino compounds, the most promising were those derived from α,ω-diamines (10), with optimum activity when n = 10. In extension of these studies[14] we have examined some related phosphonous and phosphinic acids [9, R^1 = H, Me, or Ph;

$H_2NC(:NH)NH(CH_2)_nNHCH_2PO_3H_2$ (10) $X\text{-}NH(CH_2)_nNHCH_2P(R^1)(O)OH$ (11)

11, X = H, R^1 = H, Me, or Ph; 11, X = $H_2N(C:NH)$, R^1 = Ph] but, in all cases, fungicidal activity was less than for the phosphonic analogues. In addition we have prepared some phenylglycine analogues (8 and 9; R = Ar).[15] Certain phosphonic derivatives gave 90% control of *Puccinia* *recondita* at 1000 ppm (8; R = Ph, 4-MeC_6H_4, 4-EtC_6H_4, 4-FC_6H_4, 4-$O_2NC_6H_4$) or at 300 ppm (8; R = 4-MeOC_6H_4, 2-FC_6H_4, 4-$CF_3C_6H_4$), when applied as foliar sprays, but phosphonous analogues (8; R = 2-HOC_6H_4, 4-MeC_6H_4, 4-FC_6H_4) were inactive.

Two examples of phosphorylated guanidines (12; R = Me or Et), prepared by a modified Atherton-Todd Reaction, were as active against *Piricularia oryzae*, *Rhizoctonia solani*, *Botrytis cinerea*, and *Septoria nodorum* as the parent dodecylguanidine (dodine).[14]

$$C_{12}H_{25}NH(C{:}NH)NH{-}P(O)(OR)_2$$

(12)

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