SYNTHESIS, CHARACTERIZATION AND FUNGICIDAL ACTIVITY OF SOME DIALKYL ALKYLPHOSPHONATES AND DIALKYL PHENYLPHOSPHONATES

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ABSTRACT

Some dialkyl alkylphosphonates and dialkyl phenylphosphonates were synthesized by the reactions between trialkyl phosphite and alkyl/aryl halide in the presence of benzene. The synthesized compounds were characterized by elemental analysis, thin layer chromatography (TLC), fourier –transform infrared, (^{1}H, ^{13}C) nuclear magnetic resonance (NMR) spectroscopic techniques. *In vitro* fungicidal activity of the synthesized compounds against *Aspergillus flavus, Aspergillus niger, Fusarium oxysporium, Rhizopus stolonifer, Leveillula taurica* and *Peronospora tabacina* showed that they were fungicidal. The 'Minimum Inhibitory Concentration' (MIC) of the synthesized compounds ranged between 1000ppm and 5ppm. While their 'Inhibitory Concentration at 50% inhibition' (IC_{50}) ranged between 500ppm and 2ppm. These results showed that the fungicidal activity of the synthesized phosphonates varied from one compound to another.

Based on the results obtained from the *in-vitro* screening, the four most active synthesized compounds (diethyl ethylphosphonate, diisopropyl ethylphosphonate, diethyl *p*-hydroxyphenylphosphonate and diethyl *p*-methoxyphenylphosphonate) were subjected to *in-vivo* screening. The results of the *in-vivo* screening showed that diethyl p-methoxyphenyl phosphonate gave the highest fungicidal activity against powedery mildew. All the compounds subjected to *in-vivo* screening were phytotoxic at a concentration greater than 50ppm.

Keywords: *Dialkyl alkylphosphonates/dialkyl phenylphosphonates, synthesis, characterization, fungicidal activity.*

1. INTRODUCTION

Organophosphorus compounds have found a wide range of application in the areas of industrial, agricultural and medicinal chemistry owing to their biological and physical properties, as well as their utility as synthetic intermediates. Organophosphorus compounds are gradually replacing organochlorine compounds as pesticides because of the problem of residual contamination of the environment associated with organochlorine pesticides.[1] The toxic effect of organophosphorus insecticides is based on phosphorylation of the hydroxy group in serine at the esteratic site of the active centre of the enzyme, thereby leading to inhibition of the action of acetycholinesterase enzyme.[2] Unlike organophosphorus insecticides, the activity of organophosphorus fungicides is not due to the inhibition of acetycholinesterase enzyme but to the acylation of enzymes containing mercapto groups.[3]

The synthesis of phosphate esters is an important chemical reaction in organic synthesis since they have found use in the preparation of biologically active molecules.[4] and also versatile intermediate in the synthesis of amides and esters.[5] Among the phosphate esters, phosphonate derivatives are of interest as effective fungicides.[6] The Michaelis – Arbuzov reaction is a very versatile way of forming a Phosphorus – Carbon bond from the reaction between trialkyl phosphite and alkyl/aryl halide.[7] Michaelis – Arbuzov reaction could be carried out with highly activated benzene as solvent, by heating under reflux a mixture of trialkyl phosphite and alkyl/aryl halide.[8] An unstable trialkoxyphosphonium intermediate formed is subsequently attacked by an halide anion to give a phosphonate.

Phosphonates are also synthesized by Modified Mannich's procedure. This involves reaction between a phosphorus acid, amine and formaldehyde.[9] This reaction proceeds efficiently only under acidic condition. A further limitation of this reaction is that only formaldehyde could be used as the carbonyl source at low pH.

Another way of synthesizing phosphonates is through Michaelis-Becker reaction. This involves the reaction between alkyl halide and potassium or sodium dialkyl phosphonates.[10]

A number of other methods.[11] are available for the synthesis of alkyl/aryl phosphonates, but none of these procedures possess the generality of the Michaelis-Arbuzov reaction.[12]

Phosphonates are of interest as protective and curative fungicides for the control of mildews and soil-borne fungi. An example of a fungicidal phosphonate is Aliette [Aluminum tris (0-ethyl phosphonate)] marketed in combination with a protective fungicide as Mikal (50% Aliette and 25% folpet). Mikal is active against downy mildews in tropical crops and temperate crops.[3]

Great progress had been made in recent years in the development of different types of systemic fungicides. Their usefulness in crop protection is undeniable. However the development of resistance often experienced is of great concern.[13]

In our laboratory, series of alkyl/arylphosphonates were synthesized by Michaelis-Arbuzov reaction and their fungicidal activity were subsequently determined.

2. MATERIALS AND METHODS

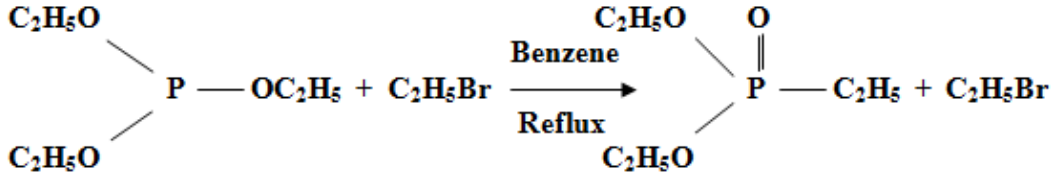
General Procedure

All reagents were of commercial grade. Benzene solvent was dried over sodium wire and then re-distilled. Trialkyl phosphites were distilled prior to use. IR spectra were recorded on a Fourier- transform infrared (FTIR) spectrometer using KBr discs and Nujor mulls. The ^{1}H and ^{13}C NMR analyses were carried out on Varian Mercury FT –NMP spectrometer operating at 200 MHz for ^{1}H and 100 MHz for ^{13}C. All the compounds were dissolved in $CDCl_3$. TMS was used as internal reference for ^{1}H and ^{13}C.

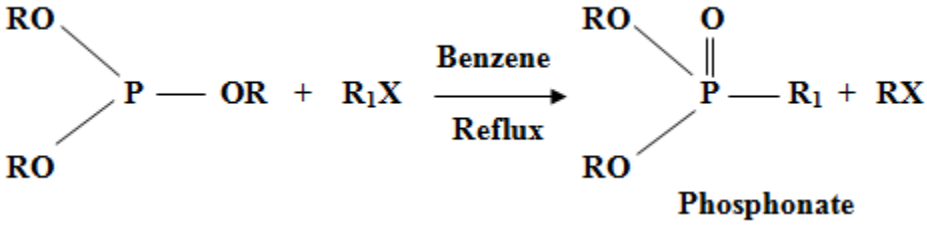
Synthesis

The synthesis of dialkyl alkylphosphonates and dialkyl phenylphosphonates were carried out according to Michaelis-Arbuzov reaction.[8] Equimolar quantities of the starting materials were heated under reflux with dry benzene as the reaction medium. Dialkyl alkylphosphonates were synthesized by the reaction between trialkyl phosphite and alkyl halide while dialkyl phenylphosphonates were synthesized by the reaction between trialkyl phosphite and aryl halide. The following procedure for the synthesis of diethyl ethylphosphonate is typical: Triethyl phosphite (17.4cm^3, 0.1 mol.) was mixed with ethyl bromide (7.5cm^3, 0.1 mol.) (in 25cm^3 of dry benzene) inside a 250cm^3 two-necked quick-fit round bottom flask, equipped with a thermometer and reflux condenser fitted with a $CaCl_2$ guard tube. The whole reaction mixture was heated under reflux by placing the flask in an oil bath. The reaction mixture was stirred by means of a magnetic stirrer at reflux temperature for 2h. The reaction mixture was finally left to stir overnight at room temperature. Both the solvent and ethyl bromide were removed on a rotary evaporator. The desired product, diethyl ethylphosphonate (1) was isolated by fractional distillation at reduced pressure as a colourless liquid (10.6g, 63%); bp 56^{0}C (scheme 1).

The general scheme for the synthesis of phosphoantes is as shown in scheme 2 below:



Scheme 1: Synthesis of diethyl ethylphosphonate



Scheme 2: Synthesis of phosphonates

Biological Screening

The synthesized compounds were diluted with dimethyl sulphoxide (DMSO) prior to bioassay. Phenylmercury acetate, a known fungicide was used as standard, while mixture of DMSO and water (8:2) was used as control. The compounds were assayed for fungicidal activity against six fungi isolates obtained from Microbiology Laboratory of Department of Pure and Applied Biology, Ladoke Akintola University of Technology, Ogbomoso, Nigeria. The fungi included *Aspergillus flavus, Aspergillus niger, Fusarium oxysporium, Rhizopus stolonifer, Leveillula taurica*

and Peronospora tabacina. The *in-vitro* testing of the synthesized compounds for their fungicidal activity was carried out in Microbiology laboratory. The inhibition of germinated spores was assessed by measuring the diameter of growth of treated plates and comparing it with that of control.

The Potato Dextrose Agar (PDA) plates were flooded with spore suspension of each fungus. About 6 mm diameter filter paper discs were sterilized in petri-dishes at 160^0C for 2 hours. Filter paper discs were soaked in various concentrations of the synthesized compound and then allowed to dry. With the aid of sterilized pair of forceps, filter paper disc that had been previously soaked in one of the concentrations of the synthesized compound was put on the surface of the inoculated PDA plate. Filter paper disc of each of the other concentrations of the synthesized compound were also introduced onto each PDA plate. Filter paper discs were also soaked in the standard and the control, and each was then placed on the surface of the inoculated PDA plates. All the PDA plates were incubated overnight at 37^0C for 24 hrs. The growth diameter of the fungal spores was measured in mm. at every 6 hours until when there was a complete growth of fungus on the control plate. Each value was the mean of three measurements of the colony diameter and the percentage of growth inhibition was calculated from the mean value according to the equation below:

$$\% \text{ Inhibition} = \frac{d_c - d}{d_c} \times 100$$

Where, d_c is the diameter of fungus growth in control and d is the diameter of fungus growth in synthesized compound. The procedure was repeated for other synthesized compounds. The bioassay of control and standard were carried out without the test compound.

The minimum concentration of each synthesized compound that gave 100% inhibition of fungus growth (i.e. the concentration at which there was no visually detectable fungus growth) was taken as the 'Minimal Inhibitory Concentration' (MIC) of the compound.[8] While the 'Inhibitory Concentration of the synthesized compound at 50% inhibition of the fungus population' (IC_{50}) was extrapolated from the graph of percentage inhibition of fungus (expressed in probit units) against concentration of the synthesized compound.[14]

Four of the compounds that gave the highest fungicidal activity against the fungi species were subjected to *in-vivo* screening in a glasshouse. The screening was carried out at the Department of Agronomy, Ladoke Akintola University of Technology, Ogbomoso, Nigeria.

Pepper seedlings were inoculated with powdery mildew (*Leveillula taurica).* The inoculated seedlings were sprayed with the sample solutions of various concentrations of the synthesized compounds. The various concentrations (4ppm to 60 ppm) of the samples were prepared in a mixture of water and dimethyl sulphoxide (5:1). The percentage powdery mildew left after 6, 9 and 12 days post – inoculation was determined.[15] The result of the *in-vivo* screening of the four compounds at a concentration of 4 ppm against powdery mildew is shown in Table 5. The procedure was repeated for downy mildew (*Peronospora tabacina)* and the result is shown in Table 6.

3. RESULTS AND DISCUSSION

The chemical structures of the synthesized compounds were confirmed by physical, elemental and spectroscopic analyses as shown in Tables 1 and 2.

There was no visible fungus growth in the control. Generally the fungus growth was found to be lowest in the standard. The percentage of growth inhibition of all the fungi species increased with increase in concentration of both the synthesized compounds and the standard. Similar results had been reported earlier by other authors.[16] The percentage growth inhibition of the six fungi species towards diethyl ethylphosphonate (one of the synthesized compounds) showing the determination of MIC is as shown in Table 3. From the results, it was observed that the response of the fungi species towards diethyl .ethylphosphonate varied. *Leveillula tauricla* and *Peronospora tabacina* had the least MIC (40 ppm.) while *Rhizopus stolonifer* had the highest MIC (1000ppm). The implication of this result was that diethyl ethylphosphonate would be more active towards the two former fungi species than the latter, since a lower concentration of the fungicide would be needed to completely inhibit these two fungi species.

The IC_{50} of each synthesized compound was extrapolated from the graph of inhibition of fungus (in probit unit; where l probit unit represents 10%) against concentration of compound. Figure 1 is the graph of inhibition of *Fusarium oxysporium* against logarithm of concentration of diethyl ethylphosphonate, showing the extrapolation of IC_{50}. The values of MIC and IC_{50} of the synthesized compounds are as presented in Table 4. The results showed that the synthesized compounds were all fungicidal and their fungicidal activity varied from one compound to another. Just like many active organophosphorus fungicides, the synthesized phosphonates probably owed their fungicidal activity to their interference with chitin synthesis at the cell membrane of the fungus.[17] The interference was made possible by the polar nature of the P=0 group of the phosphonates, leading to passage of the phosphonates

through the fungus cell membrane. The fungicidal activity of the phosphonates (being phosphoryl derivatives) could also be due to direct attack on the enzyme system of the fungus.[13]

Diethyl *p*-hydroxyphenylphosphonate and diethyl *p*-methoxyphenylphosphonate showed the highest fungicidal activity at lower concentration against all the fungi species as indicated by their MIC and IC_{50} in Table 4. The presence of a phenyl group in the two compounds might have been responsible for their high fungicidal activity, since compounds devoid of phenyl group did not exhibit such high activity (Table 4). The polarity of the P=0 group of the phosphonate have been found to be enhanced by the presence of large lipophilic groups, such as phenyl, cyclohexyl or butyl.[18,19] Diethyl methylphosphonate and diisopropyl methylphosphonate showed the lowest fungicidal activity even at the highest concentration.

Diethyl *p*-methoxyphenylphosphonate showed the greatest disease control against powdery mildew (*Leveillula taurica*) as indicated by the results of the *in-vitro* and *in– vivo* screenings of the synthesized compounds (Tables 4, 5 and 6). Going by these results, the devastating effect of powdery mildew on plants would be put under control.

All the compounds were tested at concentrations of 50 ppm and below for the *in-vivo* screening. At higher concentrations, the synthesized compounds were found to be phytotoxic, causing damage to the pepper plants.

It is worthy to note that *fusarium* oxysporium responded better to the four most active synthesized organophosphonate than our earlier synthesized organosulphur compounds.[19] This is an indication of the selectivity that exists amongst pesticides towards their target organisms.

4. CONCLUSION

Two of the synthesized phosphonates have shown promising activities against the economic agricultural fungi. It is therefore very encouraging to observe the selectivity exhibited by diethyl p-methoxyphenylphosphonate towards powdery mildew. This is a fungus that has a devastating effect on many plants. Through the application of the synthesized phosphonates, there would be growth of healthy plants, thereby leading to increased food production.

The continual treatment of crops with organophosphorus fungicides would prevent formation of stable residues as experienced with inorganic fungicides like mercury, copper and sulphur and their compounds. These stable residues containing high concentrations of mercury copper and sulphur remain in the soil for long periods, causing damage to soil fauna and worms, leading to the pollution of the entire ecosystem.

Table 1: Physical properties and elemental analysis of the synthesized phosphonates

							Elemental Analysis (%) Calculated		Found	
S/N	R	R_1	X	Bp, ^{0}C	% Yield	M. Formula	C	P	C	P
1.	C_2H_5	C_2H_5	Br	56	63	$C_6H_{15}O_3P$	43.36	18.64	43.40	18.60
2.	C_2H_5	CH_3	I	51	71	$C_5H_{13}O_3P$	39.47	20.36	39.22	20.25
3.	i-C_3H_7	CH_3	I	46	85	$C_7H_{17}0_3P$	46.65	17.19	46.94	16.98
4.	i-C_3H_7	C_2H_5	Br	61	75	$C_8H_{19}0_3P$	49.46	15.94	49.38	15.75
5.	C_2H_5	C_6H_5-*p*-OH	Br	71	72	$C_{10}H_{15}0_4P$	52.17	13.45	52.20	13.34
6.	C_2H_5	C_6H_5-*p*-0CH_3	Br	105	78	$C_{11}H_{17}0_4P$	54.09	12.68	53.85	12.49

Table 2: Spectroscopic data for the synthesized phosphonates

S/N	Synthesized compounds	IR (cm^{-1})	(^1H, and ^{13}C NMR spectral data (δ, $CDCl_3$)	
		P=0	^1H-NMR	^{13}C- NMR
1.	Diethyl ethylphosphonate	1265	1.3 (CH_3-C, t, 3H) 1.5 (CH_3-C-O,t, 6H), 3.9 (C-CH_2, q, 2H), 4.1 (C-CH_2-O ,q, 4H),	15 (P-$\underline{C}H_3CH_2$) 20(OCH_3), 41 (P-$CH_3\underline{C}H_2$), 50 (OCH_2)
2.	Diethyl methylphosphonate	1233	1.4 (CH_3-C-O, t, 6H), 1.7 (CH_3-P, s, 3H), 4.0 (C-CH_2-O, q, 4H).	12 (P-CH_3), 25 (OCH_3), 52 (OCH_2)
3.	Diisopropyl methylphosphonate	1240	1.3 (CH_3-C,d,6H), 1.5 (CH_3-C-O,t, 6H), 1.7 (CH_3-P, s, 3H), 4.7 (C-CH-O, q,2H).	11 (P-CH_3), 24 (CH_3), 30 (OCH_3), 70 (0CH).
4.	Diisopropyl ethylphosphonate	1271	1.2 (CH_3-C,d 6H) 1.3 (CH_3-C,t, 3H), 1.7 (CH_3-C-O, t, 6H), 3.8 (C-CH_2, q, 2H), 4.6 (C-CH-O, q, 2H).	13 (P-$\underline{C}H_3$ CH_2), 25 (CH_3), 32 (OCH_3), 60 (P- $CH_3\underline{C}H_2$), 65 (OCH)
5.	Diethyl *p*-hydroxyphenylphosphnate	1210	1.4 (CH_3-C-O,t,6H) 4.2 (C-CH_2-O,q, 4H) 6.5 (Ar –OH,s, H) 7.4 (Ar-H, d, 2H) 7.8 (Ar-H, d, 2H)	16 (OCH_3), 61 (OCH_2), 110 (ArC-1), 117 (ArC-2,6), 132 (ArC-3,5), 160 (ArC-4),
6.	Diethyl *p*-methoxyphenyl phosphonate	1230	1.4(CH_3-C-O,t,6H) 3.8 (OCH_3,s, 3H), 4.2 (C-CH_2-O,q,4H), 7.4 (Ar-H,d,2H) 7.7 (Ar-H,d,2H)	15(OCH_3) 58 (Ar.OCH_3) 65 (OCH_2) 115 (ArC-1) 120 (ArC-2,6) 130 (ArC-3,5) 155 (ArC-4)

Table 3: Determination of percentage growth inhibition (%I) of fungi species by diethyl ethylphosphonate

Fungi species	Percentage growth inhibition (%I)											
	1000 ppm	500 ppm	250 ppm	100 ppm	50 ppm	40 ppm	30 ppm	20 ppm	10 ppm	5 ppm	2 ppm	0 ppm
Aspergillus flavus	100	100	100	100	52	40	29	19	11	6	2	0
Aspergillus niger	100	100	100	100	48	38	30	20	9	5	1	0
Fusarium oxysporium	100	100	100	100	100	75	55	40	15	10	3	0
Rhizopus stolonifer	100	55	25	10	5	3	2	0	0	0	0	0
Leveillula taurica	100	100	100	100	100	100	70	45	20	10	5	0
Peronospora tabacina	100	100	100	100	100	100	67	47	25	15	4	0

Table 4: Inhibitory effect of the synthesized phosphonates on fungi species expressed through MIC and IC_{50} in parts per million (ppm)

		Aspergillus flavus		*Aspergillus niger*		*Fusarium oxysporium*		*Rhizopus stolonifer*		*Leveillula taurica*		*Peronospora tabacina*	
S/N	Synthesized compounds	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}
1.	Diethyl ethylphosphonate	100	48	100	47	50	25	1000	510	40	18	40	21
2.	Diethyl methylphosphonate	500	270	500	260	500	230	1000	480	500	255	500	280
3.	Diisopropyl methylphosphonate	500	260	500	230	250	120	1000	490	250	123	500	245
4.	Diisopropyl ethylphosphonate	100	45	100	51	50	23	1000	490	40	20	40	19
5.	Diethyl *p*-hydroxyphenylphosphonate	100	46	100	45	50	24	1000	500	30	16	20	14
6.	Diethyl *p*-methoxyphenylphosphonate	100	40	100	50	50	20	1000	505	5	2	20	16
7.	Phenylmercury acetate [standard]	5	2	5	1	5	2	5	3	5	1	5	
8.	DMSO/H2O (8:2) [Control]	0	0	0	0	0	0	0	0	0	0	0	0

Table 5: Post –inoculation treatment of pepper seedlings against powdery mildew (*Leveillula taurica)*

		Percentage leaf area infected after treatment		
S/N	Compounds (At 4ppm.each)	Six days after Treatment	Nine days after treatment	Twelve days after treatment
1.	Diethyl ethylphosphonate	80	80	85
4.	Diisopropyl ethylphosphonate	80	80	80
5.	Diethyl *p*-hydroxyphenylphosphonate	15	15	20
6.	Diethyl *p*-methoxyphenylphosphonate	10	12	15
7.	Phenylmercury acetate (Standard)	10	10	10
8.	DMSO/H2O (8:2)[control]	100	100	100

Table 6: Post –inoculation treatment of pepper seedlings against downy mildew (*Peronospora tabacina)*

		Percentage leaf area infected after treatment		
S/N	Compounds (At 4 ppm each)	Six days after Treatment	Nine days after treatment	Twelve days after treatment
1.	Diethyl ethylphosphonate	85	85	95
4.	Diisopropyl ethylphosphonate	90	90	95
5.	Diethyl *p*-hydroxyphenylphosphonate	15	18	25
6.	Diethyl *p*-methoxyphenylphosphonate	15	20	25
7.	Phenylmercury acetate (Standard)	10	10	10
8.	DMSO/H_2O (8:2)[control]	100	100	100

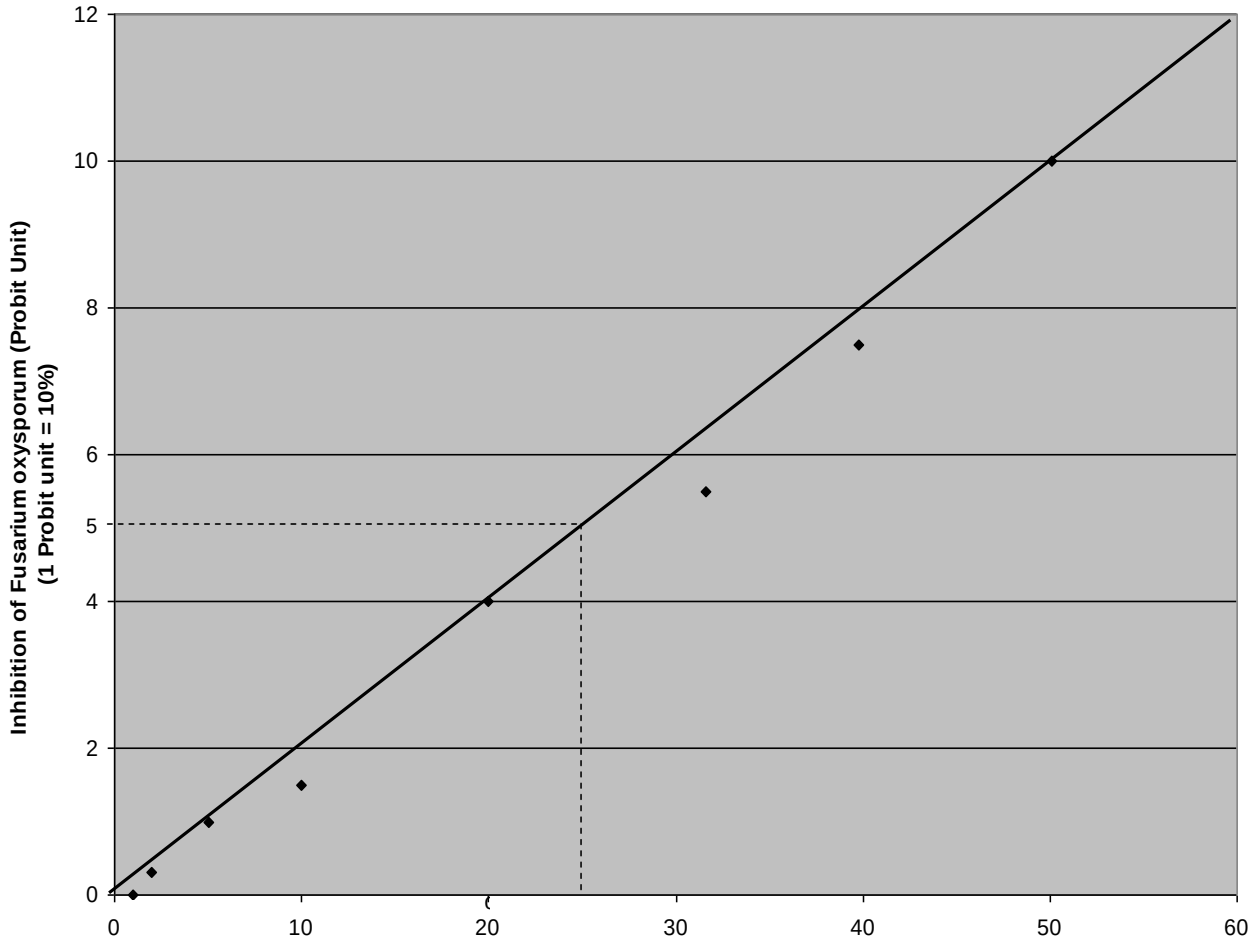


Fig. 1: **Determination of 50% inhibitory concentration (IC_{50}) of diethyl ethylphosphonate**

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