O, O-Dialkyl O-aryl phosphorothioatesおよび関連化合物の合成と抗菌活性

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Original Article

Synthesis and Antifungal Activity of *O,O*-Dialkyl *O*-Aryl Phosphorothioates and Related Compounds*

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In order to examine the structural requirement for the antifungal activity against *Rhizoctonia solani* a number of *O,O*-dialkyl *O*-aryl phosphorothioates and related compounds were prepared and their ED_{50} values based on the molar concentration for a 50% reduction of the mycelial growth of the fungi were determined by using the agar dilution method. It was found that the methoxyphosphinothioyl moiety and the substituents at 2-, 4-, and 6-positions on benzene ring in the phosphorothioates were essential for enhancing the antifungal activity. In a series of *O,O*-dimethyl *O*-(4-substituted-2,6-dichlorophenyl) phosphorothioates the change in the activity was paraborically related to the variation in both the length and the hydrophobicity of substituents by means of the multiple regression analysis using physicochemical substituent parameters. Moreover, the degree of the activity for a series of *O*-alkyl *O*-methyl *O*-(2,4,6-trichlorophenyl) phosphorothioates decreased with an increase of the hydrophobicity of the alkyl group. These results were quite different from those seen in this type of organophosphorus insecticides whose activity is greatly influenced by the electronic factor of benzene ring substituents. On the basis of both the efficacy of antifungal activity and the ease of preparing in a high yield, *O,O*-dimethyl *O*-(2,6-dichloro-4-methylphenyl) phosphorothioate (tolclofos-methyl) was best selected as a practical fungicide for controlling soil borne diseases caused by *R. solani*.

INTRODUCTION

A large number of *O,O*-dialkyl *O*-aryl phosphorothioates have been almost exclusively developed as insecticides since the discovery of parathion (**1**).[2] For instance, fenitrothion (**2**) has been widely used as a broad spectrum insecticide with low toxicity to mammals.[3]

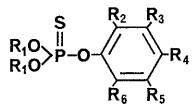
In our continuing studies on a series of the phosphorothioates we have found that the 2,4,6-trichlorophenyl derivative (**3**) possesses a potent antifungal activity against *Rhizoctonia solani* though does not show any insecticidal activity. The compound (**3**) had been patented without the knowledge of its antifungal property.[4] In addition, an insecticide chlorthion (**4**) has already been reported to have an antibacterial activity against certain plant pathogenic bacteria.[5] These facts prompted us to examine the structural requirement for antifungal activity in a series of *O,O*-dialkyl *O*-aryl phosphorothioates.

This paper deals with their synthesis and relationships between chemical structure and antifungal activity against *R. solani*.

MATERIALS AND METHODS

All melting points are uncorrected. The structure of new compounds was confirmed by IR and ^{1}H-NMR spectra using JASCO IRA-1 and Hitachi R-24B spectrometers, respectively. The organophosphorus compounds synthesized were also submitted to phosphorus anal-

* Studies on Organophosphorus Fungicides (Part 2). For Part 1, see Ref. 1).



	R_1	R_2	R_3	R_4	R_5	R_6
1	C_2H_5	H	H	NO_2	H	H
2	CH_3	H	CH_3	NO_2	H	H
3	CH_3	Cl	H	Cl	H	Cl
4	CH_3	H	Cl	NO_2	H	H

ysis and the deviation from the theoretical phosphorus content of each compound was within the range of $\pm 0.6\%$.

1. Synthesis of Phenols

2,6-Dichloro-4-alkoxyphenols were obtained by selective demethylation of 2,6-dichloro-4-alkoxy-1-methoxybenzene with a mixture of 48% hydrobromic acid and acetic acid, as shown in the following example.

A mixture of 2,6-dichloro-1,4-dimethoxybenzene (10 g), 48% hydrobromic acid (20 ml) and acetic acid (50 ml) was heated at 100–105°C for 5 hr. After cooling, the mixture was poured onto ice (100 g). The oil separated was extracted with ether. The ethereal solution was washed with water and extracted with 5% sodium hydroxide solution. The extract was acidified with 20% hydrochloric acid and the oil separated was again extracted with ether. The ethereal solution was concentrated *in vacuo* and the residue was chromatographed over silica gel. Elution with hexane–acetone (3 : 1, v/v) gave 5.5 g (59%) of 2,6-dichloro-4-methoxyphenol, mp 76–77°C (Ref. 6), 76°C). 2,6-Dichloro-4-methylthiophenol was prepared by methylation of 2,6-dichloro-4-mercaptophenol (purchased from Philips-Duphur Co.) with equimolar amounts of methyl iodide and sodium methoxide in methanol.[7] Phenols except for those described above were prepared by the known method[8] or were commercially available.

2. Synthesis of Organophosphorus Compounds

O,O-Dimethyl O-aryl phosphorothioates (general procedure)

To a suspension of phenols (0.05 mol), finely powdered potassium carbonate (0.06 mol) and copper (I) chloride (0.5 g) in toluene (30 ml) *O,O*-dimethyl phosphorochloridothioate (0.05 mol) was added dropwise at 80–85°C for 3 hr. After cooling, the reaction mixture was filtered through Celite. The filtrate was concentrated *in vacuo* and the residue was purified by recrystallization or by column chromatography on silica gel. The yield and the physical property of each synthesized compound are summarized in Tables 1 and 2. Other *O,O*-dialkyl *O*-aryl phosphorothioates were prepared by the method described above except that the reaction temperature was kept at 100–105°C (Table 3).

O-Alkyl O-methyl O-(2,4,6-trichlorophenyl) phosphorothioates (general procedure)

To a solution of 2,4,6-trichlorophenol (0.05 mol) in toluene (50 ml), triethylamine (0.05 mol) was added dropwise at 0–5°C while stirring. The resultant mixture was kept at 20–25°C for 2 hr. After cooling to 0°C, sodium methoxide (0.06 mol) was added to the mixture, and then toluene (50 ml) and 5% hydrochloric acid solution (50 ml) was added. The toluene solution separated was successively washed with water, 5% sodium carbonate solution and water, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with hexane–acetone (14 : 1, v/v) gave the desired product. The results are listed in Table 4.

O-Methyl N-alkyl O-aryl phosphoramidothioates were prepared by the method described above (Table 3).

O,O-Dimethyl O-(2,6-dichloro-4-methylphenyl) phosphate (**43**) was prepared according to Steinberg.[9]

O,S-Dimethyl O-(2,6-dichloro-4-methylphenyl) phosphorothiolate (**44**)

To a solution of **14** (6.0 g) in methanol (30 ml) potassium *N,N*-dimethyldithiocarbamate (3.5 g) was added at 20–25°C while stirring. The reaction was continued at 25–30°C for 5 hr. To the mixture, methyl iodide (5.0 g) was added and the resultant mixture was refluxed for 1 hr. After cooling, the mixture was concentrated *in vacuo* to remove methanol and extracted with toluene. The toluene solution was successively washed with water, 2% sodium carbonate solution and water, and concentrated *in vacuo*. The residue was chromato-

graphed over silica gel. Elution with hexane–acetone (2 : 1, v/v) gave 4.3 g (71%) of **44**.

O,S-Dimethyl O-(2,6-dichloro-4-mehtylphenyl) phosphorothionothiolate (**45**) was prepared by modifying the method of Malatesta and Pizzotti[10] as follows.

Potassium hydroxide (2.8 g) dissolved in water (2.8 g) was diluted with methanol (50 ml). To the solution, hydrogen sulfide gas was introduced until saturation and then *O*-(2,6-dichloro-4-methylphenyl) phosphorodichloridothioate (5.2 g) was added at 25–33°C. The reaction was continued at 50–55°C for 1 hr. After cooling, methyl iodide (5.0 g) was added and the mixture was refluxed for 1 hr. The precipitate produced was filtered off and the filtrate was concentrated *in vacuo*. The residue was directly chromatographed over silica gel. Elution with hexane–acetone (14 : 1, v/v) gave 0.6 g (20%) of **45**.

2-(2,6-Dichloro-4-methylphenyl)-1,3,2-dioxaphospholan-2-sulfide (**50**) was prepared according to Tolkmith and Britton.[11]

3. *Antifungal Activity against R. solani*

Antifungal activity was determined by using the agar dilution method similar to that reported earlier.[14] The ED_{50} value of each tested compound was based on the molar concentration for a 50% reduction of the mycelial growth of *R. solani*. The activity is also expressed as $-\log ED_{50}$, as listed in each Table.

4. *Structure-Activity Correlations*

The structure-activity correlations for a series of *O,O*-dimethyl *O*-(4-substituted-2,6-dichlorophenyl) phosphorothioates and *O*-alkyl *O*-methyl *O*-(2,4,6-trichlorophenyl) phosphorothioates were analyzed with the multiple regression technique.[15] The hydrophobic π, hydrogen bonding HB, Hammett σ, Taft E_s and Verloop STERIMOL parameters were used in the analyses. Their values were taken from Ref. 16) and some of them are listed in Tables 2 and 4. The levels of significance of correlations and terms were examined by t and F tests.

RESULTS

1. *Synthesis of Compound*

The methylation of 2,6-dichlorohydroquinone with methyl iodide occurs predominantly between the chlorine atoms.[6] In fact, an attempt to prepare 2,6-dichloro-4-alkoxyphenol by alkylation of 2,6-dichlorohydroquinone with alkyl iodide resulted in poor yield (<5%). Thus we felt it necessary to devise an alternative method for the preparation of 2,6-dichloro-4-alkoxyphenol in quantity. This was achieved in good yield by selective demethylation of 2,6-dichloro-4-alkoxy-1-methoxybenzene with a mixture of 48% hydrobromic acid and acetic acid.

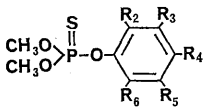
Phosphorylation of phenols with *O,O*-dialkyl phosphorochloridothioates proceeded smoothly by using finely powdered potassium carbonate as a base in the presence of a catalytic amount of copper (I) chloride.

2. *Relationships between Chemical Structure and Antifungal Activity against R. solani*

Position isomers of the trichlorophenyl phosphorothioates were prepared and their antifungal activities were examined in order to test the effect of substitution positions on benzene ring. As shown in Table 1, the degree of activity decreased in the following order: 2,4,6- > 2,4,5- > 2,3,6- > 2,3,4- > 3,4,5- > 2,3,5-position.

The replacement of chlorine atoms at the 2,4,6-position of compound **3** by bromine atom, nitro group or methyl group caused significant change in activity. For instance, compounds **14**, **15**, **19** and **21** in Table 1 were found to be more effective than **3** was particularly interesting. The increase of activity seen for **14** and the effect of substituents at the 4-position on the benzene ring was examined in more detail. For this purpose the structure-activity correlation for a series of *O,O*-dimethyl *O*-(4-substituted-2,6-dichlorophenyl) phosphorothioates is analyzed with the multiple regression technique.[15] As a result, we derived Eq. (4) for a series of 22 derivatives with the STERIMOL parameters L^2 and L, and the hydrophobic parameter squared π^2.

Table 1 Synthesis and antifungal activity against *R. solani* for a series of *O,O*-dialkyl *O*-aryl phosphorothioates.



No.	R_2	R_3	R_4	R_5	R_6	Yield(%)	mp(°C) or n_D^{20}	ED_{50} (μM)	$-\log ED_{50}$
5	Cl	Cl	Cl	H	H	85	1.5672	18.0	4.74
6	Cl	Cl	H	Cl	H	88	1.5630	180.0	3.74
7	Cl	Cl	H	H	Cl	86	1.5670	11.8	4.93
3	Cl	H	Cl	H	Cl	92	97–98[a]	0.83	6.08
8	Cl	H	Cl	Cl	H	90	38–40[b]	4.60	5.33
9	H	Cl	Cl	Cl	H	92	1.5630	46.0	4.33
10	CH_3	H	CH_3	H	CH_3	45	1.5190[c]	5.90	5.23
11	CH_3	H	CH_3	H	Cl	63	1.5395	1.35	5.87
12	CH_3	H	Cl	H	CH_3	53	1.5443[d]	3.60	5.44
13	CH_3	H	Cl	H	Cl	75	1.5562[e]	1.65	5.78
14	Cl	H	CH_3	H	Cl	90	79–79.5	0.31	6.51
15	Cl	H	CH_3	H	NO_2	65	78–79	0.11	6.96
16	NO_2	H	CH_3	H	NO_2	28	97–98	15.0	4.82
17	Br	H	CH_3	H	Br	92	81–83	1.27	5.90
18	Br	H	CH_3	H	NO_2	55	73–74	0.79	6.10
19	Cl	H	Cl	H	NO_2	48	1.5567	0.48	6.32
20	H	H	CH_3	H	Br	86	1.5318	1.80	5.74
21	Cl	H	CH_3	H	Br	85	73–74	0.36	6.44
22	CH_3O	H	CH_3	H	Cl	38	64–65	5.00	5.30

[a] Ref. 5), 59–60°C. Our sample (**3**) has shown extremely high melting point in comparison with that of Ref. 5). The structure of **3** was cofirmed on the basis of its elementary analysis and spectrometric data. [b] Ref. 12), 40°C. [c] Ref. 13), $n_D^{23.5}$ 1.5165. [d] Ref. 13), n_D^{25} 1.5432. [e] Ref. 13), n_D^{25} 1.5514.

$$-\log ED_{50} = -0.557L + 6.710 \quad (1)$$
$$(0.300)\quad(0.681)$$
$$n=22,\ s=0.628,\ r=0.655,\ F_{1,20}=15.00$$

$$-\log ED_{50} = -0.157L^2 + 6.365 \quad (2)$$
$$(0.061)\quad(0.393)$$
$$n=22,\ s=0.530,\ r=0.769,\ F_{1,20}=28.89$$

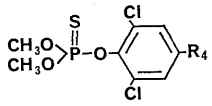
$$-\log ED_{50} = -0.356L^2 + 0.864L + 5.601 \quad (3)$$
$$(0.197)\quad(0.819)\quad(0.810)$$
$$n=22,\ s=0.485,\ r=0.821,\ F_{2,19}=19.68$$

$$-\log ED_{50} = -0.405L^2 + 1.103L$$
$$(0.194)\quad(0.821)$$
$$-0.287\pi^2 + 5.529 \quad (4)$$
$$(0.327)\quad(0.770)$$
$$n=22,\ s=0.457,\ r=0.852,\ F_{3,18}=15.91$$

In these and equations described later, n is the number of compounds included in the correlation, s is the standard deviation, r is the correlation coefficient and F_{ν_1,ν_2} is the F ratio of the correlation where $\nu_1=m$ and $\nu_2=n-m-1$: m is the number of independent variables used in the correlation. The figures in parenthesis are the 95% confidence intervals of the corresponding constants. In Eq. (4), both the L^2 and the intercept were justified by t test at levels of more than 99.5%, while the L and the π^2 terms were justified at levels of more than 97.5% and 90.0%, respectively. The compound (**23**) was used as a reference so as to make $L(H)=0$ and $\pi(H)=0$. A further improvement was obtained in Eq. (5) by using the same parameters described above, if such substituents as ethyl, cyano and formyl group were omitted because of their large deviation.

$$-\log ED_{50} = -0.372L^2 + 0.936L$$
$$(0.116)\quad(0.489)$$
$$-0.296\pi^2 + 5.679 \quad (5)$$
$$(0.191)\quad(0.445)$$
$$n=19,\ s=0.258,\ r=0.952,\ F_{3,15}=48.16$$

Table 2 Synthesis and antifungal activity against *R. solani* for a series of *O,O*-dimethyl *O*-(4-substituted-2,6-dichlorophenyl) phosphorothioates.



No.	R_4	Yield (%)	mp(°C) or n_D	ED_{50} (μM)	L^2	L	π^2	Obsd.	$-\log ED_{50}$ Calcd.[a]	$-\log ED_{50}$ Calcd.[b]
23	H	85	51–54	3.20	0.00	0.00	0.00	5.50	5.53	5.68
24	F	89	52–53	1.10	0.35	0.59	0.02	5.96	6.03	6.10
3	Cl	92	97–98	0.83	2.13	1.46	0.50	6.08	6.13	6.10
25	Br	90	103–105	2.40	2.13	1.77	0.74	5.62	6.00	5.95
26	I	82	95–96	5.20	4.17	2.17	1.25	5.20	5.66	5.58
14	CH_3	90	79–79.5	0.31	0.88	0.94	0.31	6.51	6.12	6.14
27	C_2H_5	90	1.5500 (18)[c]	0.23	4.20	2.05	1.04	6.64	5.79	(5.72)[d]
28	*i*-C_3H_7	88	1.5491 (25)[c]	4.50	4.20	2.05	2.34	5.35	5.42	5.34
29	*n*-C_3H_7	81	1.5589 (22)[c]	28.0	8.94	2.99	2.40	4.55	4.52	4.44
30	OCH_3	73	1.5581 (22)[c]	0.77	3.69	1.92	0.00	6.11	6.15	6.10
31	OC_2H_5	79	1.5510 (25)[c]	4.90	8.18	2.86	0.14	5.30	5.33	5.27
32	CH_2OCH_3	67	1.5473 (26)[c]	6.00	8.12	2.85	0.61	5.22	5.21	5.14
33	SCH_3	80	1.5920 (26)[c]	1.30	5.02	2.24	0.37	5.89	5.86	5.80
34	SC_2H_5	82	1.5834 (26)[c]	27.0	10.11	3.18	1.14	4.56	4.61	4.55
35	CH_2SCH_3	76	1.5752 (26)[c]	46.0	11.22	3.35	0.08	4.34	4.65	4.61
36	CN	73	110–111	0.17	4.71	2.17	0.32	6.77	5.92	(5.86)[d]
37	CHO	46	72–74	9.0	2.16	1.47	0.42	5.04	6.15	(6.12)[d]
38	$COCH_3$	67	1.5622 (26)[c]	0.68	4.00	2.00	0.30	6.17	6.03	5.97
39	COC_2H_5	56	49–50	18.5	8.94	2.99	0.00	4.74	5.20	5.15
40	$COOC_2H_5$	48	1.5440 (24)[c]	115.0	15.21	3.90	0.26	3.90	3.60	3.59
41	CF_3	87	60–61	1.00	1.54	1.24	0.77	6.00	6.05	6.04
42	NO_2	72	54–55	0.20	1.90	1.38	0.08	6.69	6.26	6.24

[a] Calculated by using Eq. (4). [b] Calculated by using Eq. (5). [c] The figures in parenthesis show the temperature measured. [d] Not included in the correlation.

In Eq. (5), all terms were justified at levels of more than 99.5% by t test. The $-\log ED_{50}$ values of each compound calculated by using Eqs. (4) and (5) are summarized in Table 2, together with the observed values. The use of other physicochemical parameters did not afford any significant improvement.

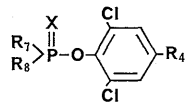
As shown in Table 3, the substitution of P=S (**14**) to P=O (**43**) caused a drastic reduction in activity against *R. solani*. A similar result was obtained in the case between phosphorothiolates **44** and **45**. The phosphoramidothioates **51**, **52** and **53** were less effective than **3**. The change of dimethoxyphosphinothioyl group of compound **14** to other dialkoxyphosphinothioyl group resulted in a marked decrease in the degree of activity (Nos. **46**, **47**, **48** and **49**). The cyclic compound (**50**) were also found to possess only a low antifungal activity.

On the other hand, a good correlation was derived in a series of *O*-alkyl *O*-methyl *O*-(2,4,6-trichlorophenyl) phosphorothioates as shown in the following equation.

$$-\log ED_{50} = -1.420\pi + 7.000 \quad (6)$$
$$(0.464) \quad (0.856)$$
$$n=6,\ s=0.292,\ r=0.973,\ F_{1,4}=72.19$$

In Eq. (6), all terms were justified at levels of more than 99.5% by t test. The $-\log ED_{50}$ values of each compound calculated by using Eq. (6) are listed in Table 4, together with the observed values. The antifungal activity for this series was not correlated well by σ, E_s and L.

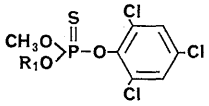
Table 3 Synthesis and antifungal activity against *R. solani* for a series of *O,O*-dialkyl *O*-aryl phosphorothioates and related compounds.



No.	R_7	R_8	X	R_4	Yield (%)	mp(°C) or n_D^{20}	ED_{50} (μM)	$-\log ED_{50}$
43	CH_3O	CH_3O	O	CH_3	85	1.5277	105.0	3.98
14	CH_3O	CH_3O	S	CH_3	90	79–79.5	0.31	6.51
44	CH_3O	CH_3S	O	CH_3	71	1.5590 (25)[a]	15.5	4.81
45	CH_3O	CH_3S	S	CH_3	20	52–53	2.5	5.60
46	C_2H_5O	C_2H_5O	S	CH_3	67	1.5409 (26)[a]	145.0	3.84
47	n-C_3H_7O	n-C_3H_7O	S	CH_3	70	1.5310	220.0	3.66
48	n-C_4H_9O	n-C_4H_9O	S	CH_3	75	1.5070	>500.0	—[b]
49	$CH_3OCH_2CH_2O$	$CH_3OCH_2CH_2O$	S	CH_3	56	1.5280	380.0	3.42
50	$-OCH_2CH_2O-$		S	CH_3	32	88–90	76.0	4.12
51	CH_3O	NH_2	S	CH_3	60	82–83	15.0	4.80
52	CH_3O	CH_3NH	S	Cl	67	78.5–79.5	7.0	5.15
53	CH_3O	$(CH_3)_2N$	S	Cl	73	1.5733	>500.0	—[b]
54	CH_3O	C_6H_5	S	Cl	60	1.6186 (21.5)[a]	43.0	4.37

[a] The figures in parenthesis show the temperature measured.
[b] Not calculated.

Table 4 Synthesis and antifungal activity against *R. solani* for a series of *O*-alkyl *O*-methyl *O*-(2,4,6-trichlorophenyl) phosphorothioates.



No.	R_1	Yield (%)	mp(°C) or n_D^{20}	ED_{50} (μM)	π	$-\log ED_{50}$	
						Obsd.	Calcd.[a]
3	CH_3	92	97–98	0.83	0.54	6.08	6.23
55	C_2H_5	33	49–50	1.90	1.08	5.72	5.47
56	n-C_3H_7	36	1.5518	12.0	1.62	4.92	4.70
57	n-C_4H_9	28	1.5423	135.0	2.16	3.87	3.93
58	i-C_4H_9	39	1.5510	210.0	2.03	3.70	4.12
59	n-C_5H_{11}	42	1.5390	470.0	2.70	3.33	3.17

[a] Calculated by using Eq. (6).

DISCUSSION

The trichlorophenyl phosphorothioates appeared suitable as position isomers for testing qualitatively the effect of substitution positions on benzene ring, because they could be conveniently prepared. Consequently, the substituents at 2-, 4-, and 6-positions on benzene ring was found to be essential for enhancing the antifungal activity against *R. solani*.

In a series of *O,O*-dimethyl *O*-(4-substituted-2,6-dichlorophenyl) phosphorothioates, the antifungal activity can be represented by Eq. (1)–(4) or, preferably, by Eq. (5), though the precise reason for the large deviation observed in such substituents as ethyl, cyano and formyl group is still not clear. These correlations indicate that the change in the activity is paraborically related to the variation in both the length and the hydrophobicity of sub-

stituents. Moreover, according to Eq. (6), the degree of the activity for a series of *O*-alkyl *O*-methyl *O*-(2,4,6-trichlorophenyl) phosphorothioates decreased with an increase in the hydrophobicity of the alkyl group. The substitution of P=S to P=O as well as the change of dimethoxyphosphinothioyl group to other dialkoxyphosphinothioyl group in the phosphorothioates was also shown to cause a drastic reduction in the antifungal activity against *R. solani*.

In complete contrast to the above results, it has been reported that in a series of *O,O*-dialkyl *O*-aryl phosphorothioates having an insecticidal activity the activity is greatly influenced by the electronic factor of benzene ring substituents and the inhibitory potency of anticholinesterase is activated by the metabolic oxidation of P=S to P=O.[17] Therefore, the results of the present study suggest that the mode of antifungal action may not be related to esterase inhibition, considering that the effect of substituents for the antifungal activity is quite different from that for the structurally similar organophosphorus insecticide.

It is known that certain trialkyl esters of phosphorothioic acids are effective against *R. solani*. Thus, *O,O*-diethyl *S*-methyl phosphorothiolothionate[18] and *O,O*-diethyl *S*-ethylthiomethyl phosphorothiolothionate[19] are good fungicides, while *O,O,O*-trimethyl phosphorothioate[20] is almost ineffective against *R. solani*. In this context, it is worth noting that the methoxyphosphinothioyl moiety for this series of compounds studied is essential for enhancing the antifungal activity.

Although compounds having higher antifungal activity than **14** were obtained as shown in Tables 1 and 2, *O,O*-dimethyl *O*-(2,6-dichloro-4-methylphenyl) phosphorothioate (tolclofos-methyl, **14**) is the most promising fungicide among all of *O,O*-dialkyl *O*-aryl phosphorothioates examined for controlling soil borne diseases caused by *R. solani* on the base of both the efficacy of antifungal activity and the ease of preparing in a high yield. Already, mode of action,[21] metabolism in rats and mice,[22] and photodegradation in water and on soil surface[23] of **14** have been reported elsewhere. Practical methods of use were established in Europe.[24]

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要　　約

O,O-Dialkyl *O*-aryl phosphorothioates および関連化合物の合成と抗菌活性*

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提題化合物の *Rhizoctonia solani* に対する抗菌活性を寒天培地希釈法を用いて検討した．抗菌活性を高めるためには，methoxyphosphinothioyl 部とベンゼン環の 2,4,6-置換様式が必須であった．*O,O*-dimethyl *O*-(4-substituted-2,6-dichlorophenyl) phosphorothioates では，抗菌活性は，パラ置換基の長さと疎水性とに放物線的に相関することが判明した．また，*O*-alkyl *O*-methyl *O*-(2,4,6-trichlorophenyl) phosphorothioates では，抗菌活性はアルキル基部分の疎水性の増加とともに低下した．これらは，本系統類似の殺虫剤とはその作用発現に対する置換基効果がまったく異なるものであった．抗菌活性の強さおよび高収率で合成できる容易さから，*O,O*-dimethyl *O*-(2,6-dichloro-4-methylphenyl) phosphorothioate (tolclofos-methyl, **14**) が実用性のある殺菌剤として選抜された．

* 有機リン殺菌剤の研究（第2報）