Insecticidal and Acaricidal Activity of Certain *O,O*-Dialkyl *O*-3-Pyridazinyl Phosphorothioates†

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Received December 19, 1973

Forty-three 3-pyridazinyl phosphorothioates were evaluated for insecticidal and acaricidal activities against two-spotted spider mite, turnip aphid, smaller brown planthopper, mosquito larvae and American cockroach. Approximate acute oral toxicity of these compounds in mice was also examined. In general, the toxicity in mice was in parallel with the pesticidal activity, but a few compounds clearly showed a high degree of selectivity between pests and mice. Especially *O,O*-dimethyl *O*-(6-cyclohexyloxy-3-pyridazinyl)phosphorothioate showed substantially reduced mammalian toxicity but maintained high insecticidal and acaricidal activity.

It is generally pointed out that nitrogen-containing heterocycles are electronically similar to nitrobenzenes.

Fukuto and Metcalf¹⁾ reported that there was an excellent relationship between insecticidal activity of substituted phenyl phosphates and their physicochemical properties such as Hammett's sigma values. Therefore, it may be expected that the insecticidal and acaricidal activity of *O,O*-diethyl *O*-(3-pyridazinyl)phosphorothioate (**1**) is comparable with that of *O,O*-diethyl *O*-(4-nitrophenyl)phosphorothioate (Parathion).

It is widely known that a potent insecticide with low toxicity like Chlorthion or Fenitrothion has been produced by adding a second substituent on the nitrophenyl group of the Parathion. Accordingly, by adding various substituents on the pyridazine ring of **1**, phosphorothioates having high insecticidal activity and low mammalian toxicity may be obtained.

A literature research revealed that the synthesis of *O,O*-diethyl *O*-(6-chloro-3-pyridazinyl) phosphorothioate (**2**) is only one example of *O,O*-dialkyl *O*-(6-substituted-3-pyridazinyl) phosphorothioates ever described before our studies started. Moreover, **2** is

reported to be very unstable for practical use.²⁾

In this study, we have prepared many *O,O*-dialkyl *O*-(6-substituted-3-pyridazinyl) phosphorothioates containing ether or thioether groups on the 6-position of the heterocyclic ring, and investigated their insecticidal and acaricidal activity as well as their acute oral toxicity in mice.

MATERIALS AND METHODS

Syntheses of the phosphorothioates

Syntheses of most of *O,O*-dialkyl *O*-(6-subst.-3-pyridazinyl)phosphorothioates tested here are described in the previous paper,³⁾ or were conducted in the same way. The physical constants of new derivatives are listed in Table I.

O,O-Diethyl *O*-(6-chloro-3-pyridazinyl) phosphorothioate (**2**) was synthesized as reported by Du Breuil,²⁾ *O,O*-Diethyl *O*-(3-pyridazinyl)phosphorothioate (**1**) was

† Pyridazinyl Phosphorothioates. Part II. This paper was presented at Kanto Regional Meeting of Agricultural Chemical Society of Japan, Tokyo, October 7, 1972.

TABLE I. NEW *O,O*-DIALKYL *O*-(6-SUBST.-3-PYRIDAZINYL)PHOSPHOROTHIOATES

Compounds No.	R ¹	R ²	Mp (°C), or $n_D^{(C)}$
6	C ₂ H ₅	<i>n</i> -C ₄ H ₉ O	n_D^{24} 1.5006
7	"	<i>n</i> -C ₅ H ₁₁ O	28 ~ 30
9	"	(CH ₃) ₂ CHCH ₂ CH(CH ₃)O	n_D^{24} 1.4975
11	"	CH ₂ =CH-CH ₂ O	n_D^{28} 1.5115
15	<i>i</i> -C ₃ H ₇	C ₂ H ₅ O	n_D^{26} 1.4952
16	"	C ₂ H ₅ S	35
17	"	<i>n</i> -C ₄ H ₉ O	n_D^{28} 1.4912
19	C ₂ H ₅	4-Cl-C ₆ H ₄ O	67.5
20	"	4-Cl-C ₆ H ₄ S	76 ~ 76.5
23	"	4-CH ₃ -C ₆ H ₄ O	72 ~ 73
24	"	2,3-di-CH ₃ -C ₆ H ₃ O	82
25	"	2-(CH ₂ =CH-CH ₂)-C ₆ H ₄ O	n_D^{21} 1.5475
26	"	2-CH ₃ O-C ₆ H ₄ O	78 ~ 79
27	"	2-Cl-6-CH ₃ -C ₆ H ₃ O	56
28	"	2,6-di-Cl-C ₆ H ₃ O	82
31	"	<i>i</i> -C ₆ H ₁₁ O	n_D^{24} 1.4975
37	CH ₃	<i>n</i> -C ₄ H ₉ O	n_D^{28} 1.5082
38	"	(CH ₃) ₂ CHCH ₂ CH(CH ₃)O	n_D^{22} 1.5350
39	<i>i</i> -C ₃ H ₇	(CH ₃) ₂ CHCH ₂ CH(CH ₃)O	n_D^{26} 1.4856
43	"	CH ₂ =CH-CH ₂ O	n_D^{27} 1.5017

prepared as follows—A mixture of 3(2H)pyridazinone (4 g, 0.04 mole), *O,O*-diethyl phosphorothiochloridate (9.3 g, 0.05 mole), and KOH (2.35 g) in water (10 ml) was stirred for 4 hr at room temperature. The reaction mixture was extracted with toluene (10 ml × 3 times). The toluene and excess thiochloridate were evaporated below 60°C at 1 mmHg, and the residue was dissolved in benzene, and chromatographed over alumina column. Elution with benzene gave 1.7 g (16%) of **1**, n_D^{20} 1.5015. *Anal.* Calcd. for C₈H₁₃O₃N₂SP: C, 38.71; H, 5.28; N, 11.29; P, 12.48. Found: C, 38.54; H, 5.59; N, 11.13; P, 12.48%.

Acaricidal and insecticidal activity

The acaricidal and insecticidal activity of the compounds for the two-spotted spider mite (*Teranychus urticae*), the turnip aphid (*Lipaphis pseudobrassicae*), the smaller brown planthopper (*Laodelphax striatellus*), the mosquito larvae (*Culex pipiens molestus*) and the American cockroach (*Periplaneta americana*) were assayed by the method usually employed for the testings of insecticides.

All parts and percentages in the following experiments are by weight.

Experiment 1. Acaricidal activity against the two-spotted spider mite. A wettable powder was prepared

by homogeneously admixing and pulverizing each 10 parts of the test compounds, 3 parts of sodium dodecylbenzenesulfonate, 2 parts of polyvinyl alcohol and 85 parts of clay. The wettable powder thus prepared was diluted to the serial concentrations of 1000, 300, 100, 30 ppm . . . , respectively, with water containing 0.01% of a spreader (Shingramin).*

Leaves of cowpea (*Vigna sinensis*) with adult mites were dipped for 10 sec into the test solutions. After air-drying, the leaves were placed in petri-dishes and were kept at 25°C. After 24 hr, mortality of the mites (%) was recorded. The activity ratings were determined according to the following scale.

Ratings	Dilutions (ppm)					
	1000	300	100	30	10	3 1
0	×					
1	△	×				
2	○	△	×			
3	○	○	△	×		
4	○	○	○	△	×	
5	○	○	○	○	△	×
6	○	○	○	○	○	△ ×

×-----less than 30% mortality

△-----30% ~ 79% mortality

○-----80% or higher mortality

* Trade name of a spreader containing polyoxyethylene dodecyl ether, polyoxyethylene aryether sulfonic acid and abietic acid polyalcohol ester.

Experiment 2. Insecticidal activity against the turnip aphid. Seedlings of radish (*Raphanus sativus*) with aphids were dipped for 30 sec into the test solutions. After air-drying, the seedlings, which were put in a small bottle with water together with a cotton stopper, were placed into a glass cylinder, and were kept at 25°C. After 24 hr, mortality of the aphids (%) was determined as in Experiment 1.

Experiment 3. Insecticidal activity against the smaller brown planthopper. The test solutions prepared as in Experiment 1, were applied by spraying on rice plants which were planted in an unglazed pot with a diameter of 9 cm in an amount of 10 ml per pot. After air-drying, the plants were covered with a glass cylinder having a diameter of 7 cm and a height of 14 cm. Into each cylinder were placed 15 final instar nymphs of planthopper, and the upper opening of the cylinder was closed with a gauze lid. After the pot was kept at 25°C for 24 hr, mortality of the insects (%) was determined as in Experiment 1.

Experiment 4. Insecticidal activity against mosquito larvae. Twenty five milliliters of each test solutions prepared as in Experiment 1 were dispersed into 25 ml water in a 100 ml volume polyethylene cup in which 15 4th (final) instar larvae of mosquito were confined. After the cup was kept at 25°C for 24 hr, mortality of the larvae (%) was counted as in Experiment 1.

Experiment 5. Insecticidal activity against the American cockroach. The activity against 1st instar nymphs of the American cockroach was assayed by the method described in the previous reports,^{4,5} and the ratings were determined according to the following scale.

Ratings	Amounts of active substance						
	2~3mg	100 μ g	10 μ g	1 μ g	0.1 μ g	0.01 μ g	
0	×						
1	△						
2	○	×					
3	○	△					
4	○	○	×	△			
5	○	○	○	×	△		
6	○	○	○	○	×	△	
7	○	○	○	○	○	×	△

×-----0% mortality

△-----less than 100% mortality

○-----100% mortality

Mammalian toxicity

The toxicity of the compounds in mice (DDY-SLC mouse, body weight 25~32 g), was evaluated by the conventional method, and approximate acute oral LD₅₀ values for tested compounds were determined according to Litchfield-Wilcoxon method.

RESULTS AND DISCUSSION

The results for the testings of insecticidal and acaricidal activities along with acute oral toxicities in mice of numbers of *O,O*-dialkyl *O*-(6-subst.-3-pyridazinyl) phosphorothioates are shown in Figures 1~6.

O,O-Diethyl *O*-(3-pyridazinyl) phosphorothioate (**1**) showed a very high insecticidal activity, and its acute oral toxicity in mice was 6.43 mg/kg, while the corresponding value of Parathion is reported to be 9.80 mg/kg.⁶⁾

The compounds having alkyl, cycloalkyl, alkenyl and alkynyl groups of 1~6 carbon atoms as the 6-substituents (**3**~**12** in Fig. 1) were very effective, and they showed almost the same order of high activity as the compound **1** and the 6-chloro derivative (**2**) exhibited against spider mite and planthopper, but, at the same time these compounds showed high toxicity in mice. While, strikingly, the activity of **13** with a straight chain alkyl of 12 carbon atoms was very low, although its toxicity was also lower.

The results of the testings for mosquito larvae and the American cockroach are much interesting (Fig. 2). With the increase of the carbon chain length of the 6-substituents, the activity against the former insect becomes higher, whereas that against the American cockroach becomes lower. Even the compound **13** with a long chain substituent showed a high activity against mosquito larvae.

In the test for mosquito larvae, the chemicals were dispersed into the water. Therefore, it may be necessary for the chemicals to be lipophilic to some extent in order to exhibit larvicidal activity. Accordingly, it will be postulated that the phosphorothioates having longer substituents at the 6-position were more effective than those having shorter ones. In contrast, against the American cockroach the active principles were directly applied to insects, that is, contact activity was examined.

The phosphorothioates having thioether bonds on the 6-position of the pyridazine ring were slightly more effective than those having

spider mite ○
 planthopper +
 turnip aphid Δ

FIG. 1. Biological Activity of *O,O*-Diethyl *O*-(6-Alkoxy-, alkenyloxy-, and alkynyloxy-3-pyridazinyl)phosphorothioates.

FIG. 2. Biological Activity of *O,O*-Diethyl *O*-(6-Alkoxy-, alkenyloxy-, and alkynyloxy-3-pyridazinyl)phosphorothioates for Mosquito Larvae and American Cockroach.

ether bonds on the same position (Fig. 3).

The phosphorothioates with substituted or unsubstituted phenoxy groups on the 6-position of the pyridazine ring (19, 21~30 in Fig. 4) were very effective against two-spotted spider mite,

mosquito larvae and American cockroach, but were less effective against turnip aphid and brown planthopper. In contrast with the 6-alkoxy derivatives, these 6-phenoxy ones showed lower mammalian toxicity, although

Comp. No.	R ¹	X	R ²	Ratings	LD ₅₀ mice mg/kg
				0 1 2 3 4 5 6 7 8 9 10 11	
3	C ₂ H ₅	O	CH ₃		< 25
14	"	S	"		19.5
15	<i>i</i> -C ₃ H ₇	O	C ₂ H ₅		> 50
16	"	S	"		25-50
17	"	O	<i>n</i> -C ₄ H ₉		> 200
18	"	S	"		246
19	C ₂ H ₅	O	4-Cl-C ₆ H ₄		> 50
20	"	S	"		> 50

FIG. 3. Biological Activity of Certain 3-Pyridazinyl Phosphorothioates with Ether and Thioether Bonds at the 6-Position.

Symbols are the same as in Figs. 1 and 2.

Comp. No.	X	Ratings	LD ₅₀ mice mg/kg
		0 1 2 3 4 5 6 7 8 9 10 11 12 13	
21	H		25-50
22	2-CH ₃		> 50
23	4-CH ₃		50-200
24	2, 3-di-CH ₃		> 50
25	2-allyl		—
26	2-CH ₃ O		—
27	2-Cl, 6-CH ₃		> 50
19	4-Cl		> 50
28	2,6-di-Cl		> 50
29	2, 4, 6-tri-Cl		50-200
30	4-NO ₂		< 50

FIG. 4. Biological Activity of *O,O*-Diethyl *O*-(6-Phenoxy-3-pyridazinyl)phosphorothioates.

Symbols are the same as in Figs. 1 and 2.

the both series are *O,O*-diethyl derivatives. However compounds with an electron attracting group such as 4-nitro on the benzene ring (eg. compound 30 in Fig. 4) showed a high toxicity.

With respect to the substituents on the 4- or 5-position of the pyridazine ring, introduction of a 4-methyl group decreased the activity of

the original compounds (32 vs. 31, 33 vs. 21, 34 vs. 22 and 36 vs. 23 in Fig. 5). On the other hand, the 5-methyl compound, eg. *O,O*-diethyl *O*-(5-methyl-6-*o*-tolylloxy-3-pyridazinyl)-phosphorothioate (35) was almost as effective as the unsubstituted compound (22), although the relation between mammalian toxicity and the presence or absence of the 4- or 5-methyl

Comp. No.	R	X	Ratings												mice LD ₅₀ mg/kg
			0	1	2	3	4	5	6	7	8	9	10	11	12
31 32	H 4-CH ₃	<i>i</i> -C ₅ H ₁₁ O "													< 25 —
21 33	H 4-CH ₃	C ₆ H ₅ O "													25-50 —
22 34 35	H 4-CH ₃ 5-CH ₃	2-CH ₃ -C ₆ H ₄ O " "													> 50 > 50 < 50
23 36	H 4-CH ₃	4-CH ₃ -C ₆ H ₄ O "													50-200 —

FIG. 5. Relation between the 4- or 5-Methyl Substituents and the Biological Activity of *O,O*-Diethyl *O*-(6-Subst.-3-pyridazinyl)phosphorothioates.

Symbols are the same as in Figs. 1 and 2.

Comp. No.	R ¹	R ²	Ratings												mice LD ₅₀ mg/kg
			0	1	2	3	4	5	6	7	8	9	10	11	12
37 6 17	CH ₃ C ₂ H ₅ <i>i</i> -C ₃ H ₇	<i>n</i> -C ₄ H ₉ " "													— < 25 > 200
38 9 39	CH ₃ C ₂ H ₅ <i>i</i> -C ₃ H ₇	 " "													50-200 < 50 < 50
40 10 41	CH ₃ C ₂ H ₅ <i>i</i> -C ₃ H ₇	cyclo-C ₆ H ₁₁ " "													50-200 < 50 > 50
42 11 43	CH ₃ C ₂ H ₅ <i>i</i> -C ₃ H ₇	CH ₂ =CH-CH ₂ " "													< 50 < 50 > 50

FIG. 6. Relation between the Kinds of *O,O*-Dialkyl Groups and the Biological Activity of *O,O*-Dialkyl *O*-(6-Subst.-3-pyridazinyl)phosphorothioates.

Symbols are the same as in Figs. 1 and 2.

groups on the pyridazine ring is not so clear.

As for the effect of the kinds of *O,O*-dialkyl groups on the activity as well as mammalian toxicity, the relationship was quite as usual; namely, the *O,O*-diethyl compounds generally

showed the highest activity as well as toxicity. In contrast, *O,O*-dimethyl and *O,O*-diisopropyl compounds showed lower activity as well as lower toxicity (Fig. 6). Although, *O,O*-dimethyl *O*-(6-cyclohexyloxy-3-pyridazinyl)phos-

phorothioate (40) showed lower toxicity, it exhibited excellent insecticidal and acaricidal activity as well as the corresponding *O,O*-diethyl compound (10).

In conclusion, *O,O*-dialkyl *O*-(substituted-3-pyridazinyl)phosphorothioates showed various orders of activity and mammalian toxicity depending on the kinds and positions of the substituents, and a few compounds showed some degree of selection between toxicity for the pests and mouse.

Acknowledgements. The authors wish to express

their thanks to Messers T. Omino, S. Ohno and T. Mizuno for their help in conducting the biological tests.

REFERENCES

- 1) T. R. Fukuto and R. L. Metcalf, *J. Agr. and Food Chem.*, **4**, 930 (1956).
- 2) S. Du Breuil, *J. Org. Chem.*, **26**, 3382 (1961).
- 3) T. Jojima and H. Takeshiba, *Agr. Biol. Chem.*, **38**, 1169 (1974).
- 4) H. Tsuji and T. Mizuno, *Jap. J. Sanit. Zool.*, **22**, 1 (1971).
- 5) T. Mizuno and H. Tsuji, *ibid.*, **23**, 41 (1972).
- 6) Y. Nishizawa, K. Fujii, T. Kadota, J. Miyamoto and H. Sakamoto, *Agr. Biol. Chem.*, **25**, 605 (1961).