Synthesis and pesticidal activity of some *O*-alkyl *O*-(2-alkoxyethyl) *O*-(1,5-di-R-6-oxo-1*H*-pyridazin-4-yl) thiophosphates

V. KONEČNÝ, Š. VARKONDA, and V. KUBALA

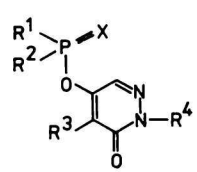
Research Institute of Agrochemical Technology, 810 04 Bratislava

Received 14 March 1978

Some *O*-alkyl *O*-(2-methoxyethyl, 2-ethoxyethyl) *O*-(1,5-di-R-6-oxo-1*H*-pyridazin-4-yl) thiophosphates were synthesized and tested for contact and systemic insecticidal, acaricidal, ovicidal, and fungicidal activities. The highest activity was found with *O*-ethyl *O*-(2-methoxyethyl) *O*-(5-methoxy-1-methyl-6-oxo-1*H*-pyridazin-4-yl) thiophosphate. The antipowdery mildew activity of this compound on *E. graminis* was several times higher than that of the used standard Chloraniformethane.

Были синтезированы некоторые *O*-алкил *O*-(2-метоксиэтил, 2-этоксиэтил) *O*-(1,5-ди-R-6-оксо-1*H*-пиридазин-4-ил) тиофосфаты и была испытана их контактная и системная инсектицидная, акарицидная, овицидная и фунгицидная активности. Самая высокая активность обнаружена для *O*-этил *O*-(2-метоксиэтил) *O*-(5-метокси-1-метил-6-оксо-1*H*-пиридазин-4-ил) тиофосфата и по отношению к мучнисторосым грибам *E. graminis* она в несколько раз превосходит активность использованного стандарта, Хлораниформетана.

Systematic investigation of 4-pyridazinyl organophosphates (*A*) led to the finding that the substituents R^1—R^4 and X greatly influence the contact and systemic insecticidal, acaricidal, ovicidal, and fungicidal activities [1—5].

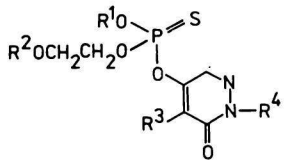


A

From the synthesized and biologically tested compounds the highest contact insecticidal, acaricidal, and ovicidal activities were obtained with those compounds where R^1 and R^2 were identical or different alkoxy groups, R^3 = alkoxy, R^4 = alkyl, cyclohexyl, phenyl, and benzyl, and X = sulfur was more advantageous than

X = oxygen in which case the compounds were generally less stable. Only few compounds exhibited higher fungicidal activity than the used standards. The fungicidal activity was selective on *E. graminis* at spraying. The most active compounds were those with R^1 = ethyl, ethoxy or dimethylamino, R^2 = ethoxy or dimethylamino, R^3 = chlorine, methoxy, and ethylthio, R^4 = methyl, phenyl, and X = oxygen or sulfur.

Continuing the investigation of the effect of the substituents R^1—R^4 and X on pesticidal activity, we synthesized a new group of 4-pyridazinyl thiophosphates of the formula (*B*).



B

The compounds listed in Table 1 were prepared by the reaction of *O*-alkyl *O*-(2-alkoxyethyl) chlorothiophosphate with sodium or potassium salt of 1,5-disubstituted 6-oxo-1*H*-pyridazin-4-ol in acetonitrile or acetone at the boiling temperature of the reaction mixture. The obtained products were purified by column chromatography and the purity was checked by t.l.c.

In contact insecticidal activity (Table 2) on *Musca domestica* and *C. granaria* the synthesized compounds were much less active than the used standard. Similar results were obtained in systemic insecticidal activity on *M. sanborni*. The compounds *X*, *XI*, *XIV*, and *XVI* showed good contact insecticidal activity on *A. fabae*. The obtained values could be compared to the activity of the standard Pirimikarb but were almost by an order lower than the activity of Propoxur. The compounds *XI* and *XIII* were most active on females of *T. urticae*. The observed activities were on the same level as the activity of the standard Acrex. In tests on eggs of *T. urticae* the effect of the synthesized compounds was by one or two orders lower than that of Acrex.

Fungicidal activity (Table 3) was observed with *O*-ethyl *O*-(2-methoxyethyl) *O*-(1,5-di-R-6-oxo-1*H*-pyridazin-4-yl) thiophosphates only; they acted selectively on *P. infestans* or *E. graminis*. The compound *X* was most active on *P. infestans* at spraying showing similar activity as the standard Mankozeb. Better results were obtained in antipowdery mildew activity on *E. graminis* at spraying. The compounds *XI* and *XIII* exhibited identical or even higher activity than Chloraniformethane. The compound *XI* was several times more active than the used standard.

From the synthesized 4-pyridazinyl thiophosphates *O*-ethyl *O*-(2-methoxyethyl) *O*-(5-methoxy-1-methyl-6-oxo-1*H*-pyridazin-4-yl) thiophosphate (*XI*) was

Table 1

Characterization of the synthesized compounds (*B*)

Compound	R^1	R^2	R^3	R^4	Formula	*M*	Calculated/found % P	Calculated/found % S	Yield %	n_D^{20}
I	CH_3	C_2H_5	Cl	CH_3	$C_{10}H_{16}ClN_2O_5PS$	342.71	9.04 8.83	9.35 9.63	58.1	1.5271
II	CH_3	C_2H_5	CH_3O	CH_3	$C_{11}H_{19}N_2O_6PS$	338.31	9.15 8.90	9.48 9.62	65.0	1.5201
III	CH_3	C_2H_5	C_2H_5S	CH_3	$C_{12}H_{21}N_2O_5PS_2$	368.30	8.41 8.43	17.41 17.38	70.7	1.5437
IV	CH_3	C_2H_5	Cl	$CH_2=CH—CH_2$	$C_{12}H_{18}ClN_2O_5PS$	367.74	8.40 8.90	8.70 8.90	69.2	1.5315
V	CH_3	C_2H_5	Cl	C_6H_{11}	$C_{15}H_{23}ClN_2O_5PS$	409.81	7.54 7.82	7.80 8.09	73.3	1.5329
VI	CH_3	C_2H_5	Cl	C_6H_5	$C_{15}H_{17}ClN_2O_5PS$	403.77	7.65 7.80	7.92 8.17	57.0	1.5441
VII	CH_3	C_2H_5	CH_3O	C_6H_5	$C_{16}H_{20}N_2O_6PS$	399.35	7.74 7.58	8.01 8.30	90.8	1.5599
VIII	CH_3	C_2H_5	C_2H_5O	C_6H_5	$C_{17}H_{22}N_2O_6PS$	413.37	7.47 7.70	7.74 8.01	86.2	1.5524
IX	CH_3	C_2H_5	C_2H_5S	C_6H_5	$C_{17}H_{22}N_2O_5PS_2$	429.43	7.20 7.25	14.90 14.72	65.5	1.5740
X	C_2H_5	CH_3	Cl	CH_3	$C_{10}H_{14}ClN_2O_5PS$	342.71	9.04 9.28	9.35 9.61	83.3	1.5278

Table 1 (Continued)

Compound	R^1	R^2	R^3	R^4	Formula	*M*	Calculated/found % P	Calculated/found % S	Yield %	n_D^{20}
XI	C_2H_5	CH_3	CH_3O	CH_3	$C_{11}H_{19}N_2O_6PS$	338.31	9.15 9.01	9.48 9.32	97.4	1.5192
XII	C_2H_5	CH_3	C_2H_5S	CH_3	$C_{12}H_{21}N_2O_5PS_2$	368.30	8.41 8.20	17.41 17.62	84.5	1.5478
XIII	C_2H_5	CH_3	C_2H_5O	CH_3	$C_{12}H_{21}N_2O_6PS$	352.33	8.80 8.91	9.09 8.94	81.0	1.5170
XIV	C_2H_5	CH_3	Cl	C_4H_9	$C_{13}H_{21}ClN_2O_5PS$	383.78	8.05 8.25	8.33 8.40	85.1	1.5180
XV	C_2H_5	CH_3	Cl	C_6H_{11}	$C_{15}H_{23}ClN_2O_5PS$	409.81	7.54 7.44	7.80 8.02	81.6	1.5319
XVI	C_2H_5	CH_3	CH_3O	C_6H_{11}	$C_{16}H_{26}N_2O_6PS$	405.39	7.62 7.58	7.89 7.88	90.4	1.5248
XVII	C_2H_5	CH_3	Cl	C_6H_5	$C_{15}H_{17}ClN_2O_5PS$	403.77	7.65 7.97	7.92 8.01	77.8	1.5640
XVIII	C_2H_5	CH_3	CH_3O	C_6H_5	$C_{16}H_{20}N_2O_6PS$	399.35	7.74 7.64	8.01 8.36	85.4	1.5630
XIX	C_2H_5	CH_3	C_2H_5O	C_6H_5	$C_{17}H_{22}N_2O_6PS$	413.37	7.47 7.66	7.74 8.08	86.3	1.5548
XX	C_2H_5	CH_3	C_2H_5S	C_6H_5	$C_{17}H_{22}N_2O_5PS_2$	429.43	7.20 6.98	14.90 15.10	83.8	1.5800
XXI	C_2H_5	CH_3	CH_3O	$C_6H_5CH_2$	$C_{17}H_{22}N_2O_6PS$	413.37	7.47 7.22	7.74 8.01	71.4	1.5510
XXII	C_2H_5	C_2H_5	CH_3O	CH_3	$C_{12}H_{21}N_2O_6PS$	352.33	8.79 9.01	9.01 9.21	94.8	1.5160
XXIII	$(CH_3)_2CH$	C_2H_5	CH_3O	CH_3	$C_{13}H_{23}N_2O_6PS$	366.35	8.45 8.60	8.75 8.90	74.0	1.5110

Table 2

Insecticidal, acaricidal, and ovicidal properties LD_{50} (%) of the synthesized compounds

Compound	Contact toxicity					Systemic toxicity
	Musca domestica	*Calandra granaria*	*Aphis fabae*	*Tetranychus urticae*		*Macrosiphoniella sanborni*
				Adults	Eggs	
I	0.275	>0.1	>0.1	>0.1	>0.5	>0.5
II	0.280	>0.1	0.070	>0.1	0.234	>0.5
III	>0.5	>0.1	>0.1	>0.1	>0.5	>0.5
IV	>0.5	>0.1	>0.1	>0.1	0.163	>0.5
V	>0.5	>0.1	>0.1	0.0325	>0.5	>0.5
VI	0.274	>0.1	0.0506	0.0365	0.0271	>0.5
VII	0.227	>0.1	0.0506	>0.1	>0.5	>0.5
VIII	0.274	>0.1	0.0610	0.0568	>0.5	>0.5
IX	0.474	>0.1	>0.1	>0.1	>0.5	>0.5
X	>0.5	>0.1	0.0085	>0.1	>0.5	>0.5
XI	0.424	0.065	0.0032	0.0030	0.177	>0.5
XII	>0.5	>0.1	0.0092	0.042	>0.5	>0.5
XIII	>0.5	0.055	0.042	0.0055	0.274	>0.5
XIV	>0.5	>0.1	0.0053	0.042	>0.5	>0.5
XV	>0.5	>0.1	0.100	0.036	>0.5	0.434
XVI	0.338	>0.1	0.0035	0.033	0.251	>0.5
XVII	>0.5	>0.1	>0.1	>0.1	>0.5	>0.5
XVIII	>0.5	>0.1	0.010	>0.1	>0.5	0.441
XIX	>0.5	0.10	0.034	0.058	>0.5	>0.5
XX	>0.5	>0.1	>0.1	>0.1	>0.5	0.166
XXI	0.426	>0.1	>0.1	0.051	>0.5	>0.5
XXII	>0.5	>0.1	>0.1	0.047	>0.5	>0.5
XXIII	>0.5	>0.1	0.10	>0.1	>0.5	>0.5
Fenitrothion	0.0038	0.0052	—	—	—	—
Propoxur	—	—	0.00057	—	—	—
Pirimikarb	—	—	0.0011	—	—	—
Dinobuton	—	—	—	0.0014	0.0022	—
Thiometon	—	—	—	—	—	0.0022

— not tested.

found to be the most active compound which acted selectively on *E. graminis* that is wide-spread at cultivation of cereals. Practical use of this compound, however, is not real because of its high oral toxicity on rats ($LD_{50} = 23.0$ mg/kg). It could be used perhaps after modification as microcapsules.

Table 3

Fungicidal properties (%) of some compounds

Compound	LD_{50}	
	Phytophthora infestans	*Erysiphe graminis*
X	32.4	500.0
XI	500.0	2.5
XII	500.0	34.8
XIII	500.0	16.6
XIV	112.0	500.0
XVI	500.0	82.1
XIX	311.0	500.0
XXII	500.0	73.5
Mankozeb	12.9	—
Chloraniformethane	—	15.1

— not tested.

Experimental

Physical constants and data on elemental analysis of the synthesized compounds are summarized in Table 1.

Thin-layer chromatography was performed on Silufol "R" plates without indicator (Lachema, Brno) in the system benzene—acetone (9 : 1). Detection was carried out with 0.5% DQC (2,6-dibromo-4-chloroimidoquinone) in petroleum ether at 120°C.

Column chromatography was performed on Silica gel 100/160 mesh (Lachema, Brno) activated for 6 h at 140°C before use. Benzene with the addition of acetone (0 to 2% according to the impurities present) was used as eluting agent. The course of separation was followed by t.l.c.

Substituted 4-pyridazinyl thiophosphates

To sodium or potassium salt of 1,5-disubstituted 6-oxo-1*H*-pyridazin-4-ol (0.055 mol) in acetonitrile or acetone (80 ml), *O*-alkyl *O*-(2-methoxyethyl, 2-ethoxyethyl) chlorothiophosphate (0.05 mol) was added at 18°C under stirring. The reaction mixture was stirred for 2—4 h under reflux and after cooling to 15°C, toluene (100 ml) was added. The reaction mixture was washed with water, 5% sodium carbonate, water and dried. Then toluene was distilled off under reduced pressure and the obtained product was purified by column chromatography.

Pesticidal activity

Contact insecticidal activity was followed on *Musca domestica* L., *Calandra granaria* L. using Fenitrothion (*O*,*O*-dimethyl *O*-(3-methyl-4-nitrophenyl) thiophosphate) as standard

and on *Aphis fabae* SCOP using Propoxur (2-isopropoxyphenyl *N*-methylcarbamate) and Pirimikarb (5,6-dimethyl-2-dimethylamino-4-pyrimidyl *N*,*N*-dimethylcarbamate) as standards. Systemic insecticidal activity was followed on *Macrosiphoniella sanborni* THEOB (the host plant was *Chrysanthemum indicum*) using Thiometon (*O*,*O*-dimethyl *S*-(2-ethylthioethyl) dithiophosphate) as standard. Acaricidal activity was followed on females of *Tetranychus urticae* KOCH, ovicidal activity on eggs of *T. urticae* using Acrex (2-*sec*-butyl-4,6-dinitrophenyl isopropyl carbonate) as standard. Insecticidal, acaricidal, and ovicidal activities were determined after [6, 7]. The obtained results are summarized in Table 2.

Fungicidal activity was determined by *in vitro* and *in vivo* methods. Inherent activity was followed on spores of *Sclerotinia fructicola* (WINT) by the method after Sharvell using Kaptan (3a,4,7,7a-tetrahydro-*N*-trichloromethanesulfenylphthalimide) as standard. Antipowdery mildew activity was followed on living plants of spring barley, sort Dunajský trh (*Erysiphe graminis* DC.) using Chloraniformethane (1-(3,4-dichloroanilino)-1-formylamino-2,2,2-trichloroethane) as standard, on cucumbers (*Erysiphe polyphaga* HAMMARLUND) using Dinokap (2,4-dinitro-6-octylphenyl crotonate + 2,6-dinitro-4-octylphenyl crotonate) as standard, and on tomatoes (*Phytophthora infestans* De BY) using Mankozeb (Zn(II) and Mn(II) salts of ethylenebis-dithiocarbamic acid in the ratio of 7 1) as standard. The plants were sprayed and the antipowdery mildew activity was determined after [8]. The activity on *Tilletia foetida* was determined by the zone method as follows: The Petri dishes were filled with fine sifted and sterilized (150°C for 2 h) soil (40 g) and moistened with distilled water (17 ml). The surface of the soil was infected with the suspension of spores of *T. foetida* (0.1 g spores in 1.5 ml/Petri dish) by an atomizer. The preparation (0.1 ml; concentration of the active compound 500 p.p.m.) was applied into the centre of the Petri dish. Then the cultures were incubated for 10 days at 10°C. Karbaxin (5,6-dihydro-2-methyl-1,4-oxathin-3-carboxanilide) was used as standard. The diameter of the formed zone was measured after incubation time.

Fungicidal activity on *Botrytis cinerea* and *Fusarium nivale* was determined by the zone method as follows: Onto certain places of the filtration paper, marked in advance, 3 μl of 1% acetone solutions (or wettable powders) were applied by micropipette. After drying the filtration paper was put into Petri dishes (20 cm diameter) containing agar medium (40°C) infected with *B. cinerea* and *F. nivale*, respectively (50 ml of 2% agar + 10 ml suspension of the conidia). When the medium became solid, the cultures were incubated in thermostat (20—21°C) approximately for 4 days. Kaptan was used as standard.

Systemic activity on *E. polyphaga* was determined as follows: Cucumber cotyledons were transplanted into vessels filled with gravel and irrigated with the Knopp nutrient solution. On the third or fourth day the plants were irrigated with the solution of the preparation (concentration of the active compound 500 p.p.m. in 10 ml/1 application) and on the fifth day they were infected with spores of *E. polyphaga* and put into a greenhouse chamber for incubation. Tridemorf (*N*-tridecyl-2,6-dimethylmorpholine) was used as standard.

Systemic activity on *P. infestans* was determined similarly by irrigation of tomatoes.

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Translated by A. Kardošová