

SYNTHESES, SPECTRAL PROPERTIES AND PESTICIDE ACTIVITY
OF O-ETHYL-S-PROPYL-O-(1-ALKYL, PHENYL-5-CHLORO,
ALKOXY-6-OXO-1H-PYRIDAZINE-4-YL) ESTERS
OF DITHIOPHOSPHORIC ACID

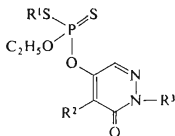
Václav KONEČNÝ, Štefan VARKONDA and Vojtech KUBALA

Research Institute of Agrochemical Technology, 810 04 Bratislava

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Syntheses of O-ethyl-S-propyl-O-(1-alkyl, phenyl-5-chloro, alkoxy-6-oxo-1H-pyridazine-4-yl) esters of dithiophosphoric acid are described. The compounds were investigated for their IR and UV spectra and for their contact and system activities as insecticides, acaricides, ovicides, fungicides and herbicides. Some of the compounds proved efficient acaricides; compound VIII also had an insecticide activity.

Out of the pyridazine-4-yl esters of organophosphoric acids hitherto synthesized, the most efficacious pesticides were O,O-dialkyl-O-(1,5-disubstituted-6-oxo-1H-pyridazine-4-yl) esters of thiophosphoric acid. However, their high insecticide,



(A)

No	R ¹	R ²	R ³
I	C ₃ H ₇	Cl	CH ₃
II	(CH ₃) ₂ CH	Cl	CH ₃
III	C ₃ H ₇	Cl	C ₂ H ₅
IV	C ₃ H ₇	Cl	C ₄ H ₉
V	C ₃ H ₇	Cl	CH ₂ -CH=CH ₂
VI	C ₃ H ₇	Cl	C ₆ H ₅
VII	C ₃ H ₇	Cl	C ₆ H ₁₁
VIII	C ₃ H ₇	CH ₃ O	CH ₃
IX	(CH ₃) ₂ CH	CH ₃ O	CH ₃
X	C ₃ H ₇	CH ₃ O	C ₆ H ₅
XI	C ₃ H ₇	CH ₃ O	C ₆ H ₁₁
XII	C ₃ H ₇	C ₂ H ₅ O	CH ₃
XIII	C ₃ H ₇	C ₂ H ₅ O	C ₆ H ₅

acaricide and ovicide activities are accompanied by toxicity to warm-blooded animals. They can be used as soil insecticides, but their toxicity limits their use in the spray form. In an attempt to eliminate this detrimental factor we have synthesized new pyridazine-4-yl esters of dithiophosphoric acid (formula (A)). With the view of reducing toxicity to warm-blooded organisms, and preserving the insecticide, acaricide and

TABLE I

O-Ethyl S-Propyl O-(1-Alkyl, phenyl-5-alkoxy, chloro-6-oxo-1*H*-pyridazine-4-yl)Phosphorodithioates

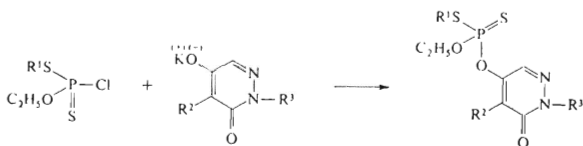
Compound	Formula (m.wt.)	Calculated/Found			n_D^{20} (yield, %)
		% P	% S	% N	
<i>I</i>	C ₁₀ H ₁₆ ClN ₂ O ₃ PS ₂ (342·8)	9·03	18·70	8·17	1·5711
		9·26	19·11	8·22	(48·6)
<i>II</i>	C ₁₀ H ₁₆ ClN ₂ O ₃ PS ₂ (342·8)	9·03	18·70	8·17	1·5689
		8·89	18·81	8·21	(60·0)
<i>III</i>	C ₁₁ H ₁₈ ClN ₂ O ₃ PS ₂ (356·8)	8·70	17·97	7·85	1·5610
		8·95	19·18	8·17	(57·4)
<i>IV</i>	C ₁₃ H ₂₂ ClN ₂ O ₃ PS ₂ (384·8)	8·05	16·66	7·28	1·5540
		8·23	17·01	7·11	(62·7)
<i>V</i>	C ₁₂ H ₁₈ ClN ₂ O ₃ PS ₂ (368·8)	8·40	17·39	7·60	1·5630
		8·50	17·19	7·87	(50·0)
<i>VI</i>	C ₁₅ H ₂₄ ClN ₂ O ₂ PS ₂ (394·9)	7·84	16·24	7·09	1·6078
		7·95	16·19	7·12	(70·9)
<i>VII</i>	C ₁₅ H ₃₀ ClN ₂ O ₂ PS ₂ (400·9)	7·73	15·99	6·99	1·5669
		7·91	16·01	7·10	(80·3)
<i>VIII</i>	C ₁₁ H ₁₉ N ₂ O ₄ PS ₂ (338·4)	9·15	18·75	8·28	1·5565
		9·29	19·12	8·23	(90·1)
<i>IX</i>	C ₁₁ H ₁₉ N ₂ O ₄ PS ₂ (338·4)	9·15	18·95	8·28	1·5541
		9·39	19·28	8·48	(72·5)
<i>X</i>	C ₁₆ H ₂₁ N ₂ O ₄ PS ₂ (400·5)	7·73	16·01	6·99	1·5950
		7·90	16·28	7·06	(71·4)
<i>XI</i>	C ₁₆ H ₂₇ N ₂ O ₄ PS ₂ (406·6)	7·62	15·77	6·89	1·5559
		7·89	16·04	7·02	(91·0)
<i>XII</i>	C ₁₂ H ₂₁ N ₂ O ₄ PS ₂ (352·5)	8·79	18·19	7·95	1·5508
		9·08	18·25	7·99	(84·2)
<i>XIII</i>	C ₁₇ H ₂₃ N ₂ O ₄ PS ₂ (414·6)	7·47	15·47	6·76	1·5876
		7·65	15·56	7·01	(83·2)

ovicide activities, we have substituted sulphur for the oxygen (RS-for the RO-group) bound to the phosphorus atom. This approach is known from the literature¹⁻⁷; it concerns mainly O-ethyl-S-propyl-S-aryl dithiophosphates, which, compared to O,O-dialkyl-O-aryl thiophosphates, are less toxic to warm-blooded organisms while retaining the insecticide and acaricide activities. Also included in the tests

TABLE II
Spectral Data of the Synthesized Compounds

Compound	IR, cm ⁻¹ CCl ₄ /CHCl ₃					UV λ _{max} nm, (log ε)				
	ν(C=O)	ν(C=N)	ν(POAr)	ν(P-O-C)	ν(P=S)					
<i>I</i>	1 673	1 607	964	1 023	1 078	1 178	675	640	219	297
	1 663	1 608	966	1 020	1 080	1 178	674	640	(4·20)	(3·60)
<i>II</i>	1 671	1 608	965	1 022	1 080	1 176	672	642	218	296
	1 652	1 608	966	1 020	1 080	1 177	671	642	(4·28)	(3·31)
<i>III</i>	1 666	1 603	966	1 023	1 083	1 170	679	637	213	296
	1 650	1 603	966	1 109	1 081	1 172	666	639	(4·00)	(3·23)
<i>IV</i>	1 664	1 602	966	1 024	1 084	1 170	681	536	213	297
	1 648	1 503	966	1 021	1 087	1 172	670	638	(4·42)	(3·67)
<i>V</i>	1 668	1 602	966	1 021	1 093	1 168	692	636	213	295
	1 655	1 602	967	1 019	1 074	1 169	664	641	(4·42)	(4·42)
<i>VI</i>	1 688	1 618	967	1 023	1 080	1 145	677	635	215	312
	1 675	1 615	966	1 019	1 080	1 147	676	633	(4·11)	(3·80)
<i>VII</i>	1 665	1 605	966	1 022	1 073	1 165	698	647	214	298
	1 650	1 604	967	1 020	1 075	1 164	698	645	(4·42)	(3·75)
<i>VIII</i>	1 662	1 623	963	1 024	1 118		683	662	220	286
	1 649	1 624	965	1 022		1 120	682	661	(4·13)	(3·68)
<i>IX</i>	1 663	1 625	963	1 025		1 121	688	664	212	287
	1 649	1 621	963	1 019		1 120	684	663	(4·31)	(3·70)
<i>X</i>	1 674	1 632	966	1 027	1 068	1 158	689	664	211	297
	1 663	1 628	964	1 022	1 067	1 165	687	661	(4·29)	(3·87)
<i>XI</i>	1 651	1 622	963	1 026	1 093	1 135	705	662	217	290
	1 646	1 622	966	1 020	1 095	1 137	700	654	(4·32)	(3·71)
<i>XII</i>	1 653	1 613	969	1 023		1 119	691	668	213	286
	1 641	1 614	968	1 019		1 118	690	668	(4·37)	(3·71)
<i>XIII</i>	1 662	1 618	964	1 022	1 064	1 130	692	666	212	287
	1 651	1 618	964	1 621	1 065	1 132	693	671	(4·40)	(3·80)

of insecticide, acaricide and ovicide activities and tests of toxicity has been one of the most efficacious compounds thus far known, viz O-ethyl-O-isopropyl-O-(5-methoxy-1-methyl-6-oxo-1*H*-pyridazine-4-yl) thiophosphate (XIV).



SCHEME 1

The compounds were synthesized by reaction of O-ethyl-S-propylchlorodithiophosphate with potassium salt of 1-alkyl, phenyl-5-chloro, alkoxy-6-oxo-1*H*-pyridazine-4-ol in acetonitrile (Scheme 1). The products were purified by column chromatography; the purity was tested by thin-layer chromatography (Table I). The IR spectra of the compounds had a very strong stretching vibration band $\nu(\text{C}=\text{O})$

TABLE III
Insecticide, Acaricide and Ovicide Activities (LD_{50} , %) of Compounds Synthesized

Compound	Insecticide activity			<i>T. urticae</i>	
	<i>M. domestica</i>	<i>C. granaria</i>	<i>A. fabae</i>	females	eggs
I	>0.5	>0.1	>0.1	0.085	0.10
II	>0.5	>0.1	>0.1	0.019	0.040
III	>0.5	>0.1	>0.1	0.024	>0.5
IV	>0.5	>0.1	>0.1	0.51	0.10
V	>0.5	>0.1	>0.1	0.081	0.41
VI	>0.5	>0.1	>0.1	>0.1	0.48
VII	>0.1	>0.1	>0.1	0.052	0.086
VIII	>0.5	>0.1	0.00076	0.00021	0.011
IX	>0.5	0.024	>0.1	0.00024	0.050
X	>0.5	>0.1	0.10	0.091	0.076
XI	>0.5	>0.1	>0.1	0.024	0.058
XII	0.39	>0.1	>0.1	0.00019	0.41
XIII	>0.5	>0.1	>0.1	0.0021	0.071
XIV	0.0040	0.0043	0.000095	0.000032	0.028
Carbofenthion	—	—	0.00034	0.00010	0.0024
Fenitrothion	0.0021	0.00046	0.0012	—	—

in CCl_4 at $1651-1674\text{ cm}^{-1}$, in CHCl_3 at a lower wave number of $1641-1675\text{ cm}^{-1}$. The highest values were measured with phenyl as R^3 . The stretching vibration $\nu(\text{C}=\text{N})$ gave a medium intensity band at $1602-1632\text{ cm}^{-1}$, the difference in wave numbers due to the use of different solvents being very small. This accords with the lower polarity of the $\text{C}=\text{N}$ band compared to the $\text{C}=\text{O}$ band. The stretching vibration $\nu(\text{P}-\text{O}-\text{C}_2\text{H}_5)$ was characterized by two to three medium-intensity bands, occurring in the range $1019-1178\text{ cm}^{-1}$. In CHCl_3 the values were 2 to 6 cm^{-1} lower in the lowest region, whereas the other bands, apart from unimportant exceptions, had the same values. The bands at $963-969\text{ cm}^{-1}$, of medium intensity, can be assigned to the stretching vibration $\nu(\text{P}-\text{O}-\text{C pyrid.})$, which is independent of the solvent employed. The stretching vibration $\nu(\text{P}=\text{S})$ had two low-intensity bands, one at $664-705\text{ cm}^{-1}$ and the other at $633-668\text{ cm}^{-1}$; the presence of two bands may be due to the existence of two conformations. The ultraviolet spectra of the synthesized compounds had two peaks; one at $211-220\text{ nm}$, probably due to a $\pi\rightarrow\pi^*$ transition, and the other at $286-312\text{ nm}$ can be assigned to an $n\rightarrow\pi^*$ transition (Table II).

In evaluating the insecticide effects on *Aphis fabae* none of the compounds was efficient enough in the first screening to be investigated further. The contact insecticide effects on *Musca domestica* and *Calandra granaria* were similar. Exceptions were compounds *XII* and *IX*, but still, these were weaker than the standard. With *A. fabae* only compound *VIII* was effective. It was stronger than the standard Fenitrothion, but somewhat weaker than the standard Carbofenthothion and compound *XIV*. The strongest effects were observed with females of the mites *Tetranychus urticae*; all the compounds except *VI* were subjected to refining tests. In these the strongest was compound *XII*, next came compounds *VIII* and *IX*. These compounds were not much weaker than the standard Carbofenthothion, but were nearly an order of magnitude weaker than compound *XIV*. In the ovicide effect on eggs of *T. urticae* all compounds except *III* were more or less active, but the activities of most of them were about a tenth of that of the standard. Compound *VIII* was stronger than *XIV*, but compounds *II*, *VII*, *IX*, *X*, *XI* and *XIII* were also satisfactory (Table III).

None of the compounds synthesized as potential fungicides and herbicides was selected for the refining tests. Comparison of the pesticide activities has revealed that replacement of oxygen in the RO-group on phosphorus by sulphur brings about a marked decrease in the insecticide, acaricide and ovicide activities. The compounds with S-propyl were more effective than those with S-isopropyl, in analogy to the comparison of O-propyl and O-isopropyl compounds.

In determining the toxicities by peroral administration to rat males compounds *VIII* (LD_{50} $15-25\text{ mg kg}^{-1}$) and *X* (LD_{50} $300-400\text{ mg kg}^{-1}$) proved less toxic than their O-propyl analogues, LD_{50} being 8.0 and 31.0 mg kg^{-1} , respectively.

EXPERIMENTAL

Methods

The infrared spectra ($400\text{--}2200\text{ cm}^{-1}$) were measured with an apparatus Zeiss IR Specord 75. The wave number calibration was carried out using the spectrum of a polystyrene foil. The spectra in CCl_4 and CHCl_3 were measured in a 0.1 mm cell (concentration $\sim 10^{-2}$). The UV spectra were measured in methanol with Unicam SP 8000 ($2 \cdot 10^{-5}$ to $5 \cdot 10^{-5}\text{ M}$ solutions in 1 cm cells were measured). Thin-layer chromatography was run on Silufol aluminium plates "R" without an indicator (Lachema, Brno) in a system benzene-acetone (9:1 \rightarrow 8:2). The spots were detected with a 0.5% solution of 1,6-dibromoquinone-4-chloroimide in light petroleum at 120°C . Column chromatography was carried out on Silicagel L 100/160 mesh (Lachema, Brno). Prior to use the silicagel was activated by heating at 140°C for 6 h. The eluant was toluene with an admixture of acetone, 0 to 5%, depending on the nature of the impurity. The course of separation was followed by TLC.

O-Ethyl-S-propylisopropyl chlorodithiophosphates were synthesized as previously described¹. The syntheses of 1-alkyl, phenyl-5-alkoxy, chloro-6-oxo-1*H*-pyridazine-4-ols were also effected according to a reported procedure⁸.

O-Ethyl-S-propyl-O-(1-alkyl,phenyl-5-alkoxy,chloro-6-oxo-1*H*-pyridazine-4-yl)
Esters of Dithiophosphoric Acid

To 0.07 mol of potassium salt of 1-alkylphenyl-5-alkoxy,chloro-6-oxo-1*H*-pyridazine-4-ol in 100 ml of acetonitrile was added 0.065 mol of O-ethyl-S-propyl chlorodithiophosphate and the mixture was refluxed for 3 to 5 h. After cooling down, 100 ml of toluene was added and the mixture was washed with water, a 5% solution of sodium carbonate and water. Then it was dried and the toluene was distilled off *in vacuo*. The residue was purified by column chromatography.

Pesticide Activity and Toxicity

Contact insecticide activities were examined on *Musca domestica* L., *Calandra granaria* L. and *Aphis fabae* SCOP, with fenitrothion, *i.e.* O,O-dimethyl-O-(3-methyl-4-nitrophenyl) thiophosphate, as standard. Systemic insecticide activities were tested on *A. fabae* with thiometon, *i.e.* O,O-dimethyl-S-(2-ethylthioethyl) dithiophosphate as standard. Acaricide activities were tested on females *Tetranychus urticae* KOCH, and ovicide activities on eggs of mites *T. urticae* with Carbofenothion, *i.e.* O,O-diethyl-S-(4-chlorophenylthiomethyl) dithiophosphate as standard. The methods for assessing the insecticide, acaricide and ovicide activities were described previously^{9,10}. The results are given in Table III.

The fungicide activities were determined *in vitro* and *in vivo*. The inherent activities were examined on spores of the fungus *Sclerotinia fructicola* (WINT.) by Sharvell's method, with captan, *i.e.* 3a,4,7,7a-tetrahydro-N-trichloromethanesulphenylphthalimide, as standard.

The activity against powdery mildew was followed by spraying growing barley (the variety Dunajský trh, *Erysiphe graminis* DC), with the use of chloraniformethane (1-(3,4-dichloroaniline)-1-formamino-2,2,2-trichloroethane) as standard, cucumbers (*Erysiphe polyphaga* HAMMARLUND) with dinoceop (2,4-dinitro-6-octylphenylcrotonate-2,6-dinitro-4-octylphenylcrotonate) as standard, and tomatoes (*Phytophthora intestans* DE BY) with mancozeb as standard (manganous and zinc salts of ethylenebisdithiocarbamide acid in a ratio of 7:1) according to ref.⁹.

The system effects on cucumbers *E. polyphaga* and on tomatoes *P. intestans* were investigated by irrigation¹¹, with the use of tridemorph (N-tridecyl-2,6-dimethylmorpholine) as standard. The effects on *Tilletia foetida*, *Botrytis cinerea* and *Fusarium nivale* were investigated by the zone method¹¹ with the use of captan as standard. The herbicide activity was assessed by preemergence application (in the soil) and postemergence application (on the leaves); the tests were carried out on *Avena sativa*, *Polygonum persicaria*, *Fagopyrum sagittatum* and *Sinapis alba* according to reported procedures¹².

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