Synthesis and pesticidal activity of *O*,*S*-dialkyl *O*-(1-R^4-5-R^3-6-oxo-1*H*-pyridazin-4-yl) thiophosphates

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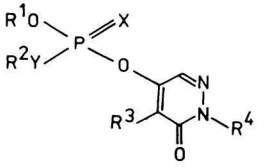
The synthesis of *O*,*S*-dialkyl *O*-(1-R^4-5-R^3-6-oxo-1*H*-pyridazin-4-yl) thiophosphates (R^4 = alkyl, phenyl; R^3 = alkoxy, alkylthio, chlorine) is described. All the prepared compounds were tested for contact and systemic insecticidal, acaricidal, and ovicidal activities. The pesticidal activity and toxicity of the mostly active compounds against warm-blooded organisms were compared to the activities of the corresponding *O*,*O*,*O*-esters.

Описывается синтез *O*,*S*-диалкил *O*-(1-R^4-5-R^3-6-оксо-1*H*-пиридазин-4-ил) тиофосфатов (R^4 = алкил, фенил; R^3 = алкокси, алкилтио, хлор). Все приготовленные соединения были испытаны на контактную и системную инсектицидную, акарицидную и овицидную активности. Пестицидная активность и токсичность наиболее активных соединений по отношению к теплокровным организмам была сравнена с активностью соответствующих *O*,*O*,*O*-сложных эфиров.

Continuing the study of the synthesis and pesticidal activity of 4-pyridazinyl organophosphates, we synthesized and spectrally characterized a new group of compounds *I*—*XXV* (Table 1) of the given formula (see p. 823).

We examined the prepared compounds as well as the analogous *O*,*O*-dialkyl *O*-(5-alkoxy-1-phenyl- and -methyl-6-oxo-1*H*-pyridazin-4-yl) thiophosphates *XXVI*—*XXXIV* (see the formula) described in [1, 2] for insecticidal activity and toxicity against warm-blooded organisms with the aim of finding out if this group of compounds is similarly so highly active and low toxic as were the *O*,*S*-dialkyl *O*-aryl thiophosphates [3—9]. The spectral methods were applied for the determination of the structures of the synthesized compounds *XII* and *XXII* (Table 2) in accordance with [10].

The synthesized compounds *I*—*IX*, *XIX*—*XXI*, and *XXV* did not exhibit significant activities in tests for contact (*M. domestica, C. granaria,* and *A. fabae*) and systemic *(A. fabae)* insecticidal, acaricidal *(T. urticae),* and ovicidal *(T.*



I—XXV X = O, Y = S, R^1—R^4 see Table 1
XXVI—XXXIV X = S, Y = O, $R^2 = C_2H_5$

	R^1	R^3	R^4
XXVI	C_2H_5	CH_3O	CH_3
XXVII	C_3H_7	CH_3O	CH_3
XXVIII	$(CH_3)_2CH$	CH_3O	CH_3
XXIX	C_2H_5	CH_3O	C_6H_5
XXX	C_3H_7	CH_3O	C_6H_5
XXXI	$(CH_3)_2CH$	CH_3O	C_6H_5
XXXII	C_2H_5	C_2H_5O	C_6H_5
XXXIII	C_3H_7	C_2H_5O	C_6H_5
XXXIV	$(CH_3)_2CH$	C_2H_5O	C_6H_5

urticae) activities and therefore were not included in Table 3. None of the synthesized *O,S*-esters was so much active on *M. domestica* in contact insecticidal tests as the *O,O*-esters. On *C. granaria* the compound *X* was partly active however, its activity was by an order lower than that of the analogous *O,O*-dialkyl derivative *XXVI*. On *A. fabae* the compounds *XII* and *XXII* were partly active but by two orders less than the *O,O*-dialkyl derivative *XXVIII*. In acaricidal activity on *T. urticae* several compounds were active; the most active was the compound *XII*, the compound *XI* was by an order less active. On the whole, none of the synthesized compounds showed so high activity as the *O,O*-dialkyl derivatives. In ovicidal tests on eggs of *T. urticae* both the synthesized *O,S*-dialkyl and the compared *O,O*-dialkyl derivatives were only slightly active.

It can be stated unambiguously that the synthesized *O,S*-dialkyl derivatives as well as the *O,O*-dialkyl derivatives prepared earlier are much less active than the *O,S*-dialkyl *O*-aryl thiophosphates. It was shown further that the *O,S*-dialkyl *O*-pyridazinyl thiophosphates are much less stable than the corresponding *O,O*-dialkyl derivatives.

The toxicity of the *O,S*-dialkyl derivatives against male rats (peroral, Table 3) was much lower than that of the corresponding *O,O*-dialkyl derivatives proving the assumption about the lower toxicity of *O,S*-dialkyl derivatives against warm--blooded organisms.

Table 1

Characterization of the prepared compounds

Compound	R^1	R^2	R^3	R^4	Formula	M	Calculated/found % P	Calculated/found % S	Yield %	n_D^{20}
I	C_2H_5	C_2H_5	Cl	CH_3	$C_9H_{14}ClN_2O_4PS$	312.69	9.90 10.11	10.25 10.36	69.4	1.5309
II	C_2H_5	C_3H_7	Cl	CH_3	$C_{10}H_{16}ClN_2O_4PS$	326.71	9.42 9.60	9.81 9.91	61.8	1.5326
III	C_2H_5	$(CH_3)_2CH$	Cl	CH_3	$C_{10}H_{16}ClN_2O_4PS$	326.71	9.42 9.76	9.81 10.07	90.2	1.5311
IV	C_2H_5	C_2H_5	Cl	C_6H_5	$C_{14}H_{16}ClN_2O_4PS$	374.76	8.26 8.60	8.55 8.86	27.8	1.5699
V	C_2H_5	C_3H_7	Cl	C_6H_5	$C_{15}H_{18}ClN_2O_4PS$	388.78	7.97 8.12	8.25 8.61	48.6	1.5730
VI	C_2H_5	$(CH_3)_2CH$	Cl	C_6H_5	$C_{15}H_{18}ClN_2O_4PS$	388.78	7.97 8.12	8.25 8.61	46.2	1.5721
VII	C_2H_5	C_2H_5	Cl	C_6H_{11}	$C_{14}H_{22}ClN_2O_4PS$	380.81	8.13 7.98	8.42 8.69	41.4	1.5324
VIII	C_2H_5	C_3H_7	Cl	C_6H_{11}	$C_{15}H_{24}ClN_2O_4PS$	394.83	7.84 8.16	8.12 8.41	42.6	1.5341

Table 1 (Continued)

Compound	R^1	R^2	R^3	R^4	Formula	*M*	Calculated/found % P	Calculated/found % S	Yield %	n_D^{20}
IX	C_2H_5	$(CH_3)_2CH$	Cl	C_6H_{11}	$C_{15}H_{24}ClN_2O_4PS$	394.83	7.84 7.68	8.12 8.00	49.6	1.5336
X	C_2H_5	C_2H_5	CH_3O	CH_3	$C_{10}H_{17}N_2O_5PS$	308.28	10.05 9.85	10.40 10.73	58.4	1.5270
XI	C_2H_5	C_3H_7	CH_3O	CH_3	$C_{11}H_{19}N_2O_5PS$	322.30	9.61 9.64	9.95 10.14	62.8	1.5212
XII	C_2H_5	$(CH_3)_2CH$	CH_3O	CH_3	$C_{11}H_{19}N_2O_5PS$	322.30	9.61 9.80	9.95 10.26	76.2	1.5299
XIII	C_2H_5	C_2H_5	CH_3O	C_6H_5	$C_{16}H_{21}N_2O_5PS$	370.34	8.35 8.49	8.66 8.87	78.5	1.5650
XIV	C_2H_5	C_3H_7	CH_3O	C_6H_5	$C_{17}H_{23}N_2O_5PS$	384.36	8.06 8.09	8.34 8.24	69.6	1.5662
XV	C_2H_5	$(CH_3)_2CH$	CH_3O	C_6H_5	$C_{17}H_{23}N_2O_5PS$	384.36	8.06 8.13	8.34 8.76	76.9	1.5644
XVI	C_2H_5	C_2H_5	C_2H_5O	C_6H_5	$C_{17}H_{23}N_2O_5PS$	384.36	8.06 8.00	8.34 8.43	69.5	1.5639

Table 1 (Continued)

Characterization of the prepared compounds

Compound	R^1	R^2	R^3	R^4	Formula	M	Calculated/found % P	Calculated/found % S	Yield %	n_D^{20}
XVII	C_2H_5	C_3H_7	C_2H_5O	C_6H_5	$C_{18}H_{25}N_2O_5PS$	398.38	7.77 7.55	8.05 8.45	65.2	1.5588
XVIII	C_2H_5	$(CH_3)_2CH$	C_2H_5O	C_6H_5	$C_{18}H_{25}N_2O_5PS$	398.38	7.77 8.03	8.05 8.16	78.5	1.5532
XIX	C_2H_5	C_2H_5	C_2H_5S	CH_3	$C_{11}H_{19}N_2O_4PS_2$	338.37	9.15 9.12	18.95 19.05	47.2	1.5489
XX	C_2H_5	C_3H_7	C_2H_5S	CH_3	$C_{12}H_{21}N_2O_4PS_2$	352.39	8.79 8.53	18.20 18.40	56.2	1.5460
XXI	C_2H_5	$(CH_3)_2CH$	C_2H_5S	CH_3	$C_{12}H_{21}N_2O_4PS_2$	352.39	8.79 8.49	18.20 18.47	87.5	1.5401
XXII	$(CH_3)_2CH$	C_2H_5	CH_3O	CH_3	$C_{11}H_{19}N_2O_5PS$	322.30	9.61 9.86	9.95 9.98	75.0	1.5199
XXIII	$(CH_3)_2CH$	C_2H_5	CH_3O	C_6H_5	$C_{16}H_{21}N_2O_5PS$	370.34	8.35 8.48	8.66 8.78	84.0	1.5645
XXIV	$(CH_3)_2CH$	C_2H_5	C_2H_5O	C_6H_5	$C_{17}H_{23}N_2O_5PS$	384.36	8.06 8.16	8.34 8.44	88.2	1.5566
XXV	$(CH_3)_2CH$	C_2H_5	C_2H_5S	CH_3	$C_{11}H_{19}N_2O_4PS_2$	338.37	9.15 9.31	18.95 19.16	81.2	1.5491

Table 2

Spectral data of chosen compounds

Compound	IR, cm^{-1}			UV, nm		^{1}H-NMR, δ(p.p.m.)					
	ν(C=O)	ν(C=N)	ν(P=O)	λ_{max}	(log ε)	CH_3CH_2, $(CH_3)_2CH$	CH_3N	CH_3O	CH_2	CH	=CH—
XII	1658	1619	1271	212 (4.55)	289 (3.82)	1.40[a] m	3.79 s	4.20[b] s	3.90[a] m	4.35[a] m	7.92 s
XXII	1659	1620	1269	213 (4.51)	287 (3.77)	1.35[a] m	3.65 s	4.10 s	3.69 q	4.85[a] m	7.81 s

s — singlet, q — quartet, m — multiplet.

a) Undistinguishable multiplet.

b) The signal of CH_3O protons is overlapped by the signal of CH_2 protons.

Table 3

Insecticidal, acaricidal, and ovicidal activities (ED_{50} in %) and toxicity (LD_{50} in mg/kg) of some synthesized compounds

Compound	*Musca domestica*	*Calandra granaria*	*Aphis fabae*	*T. urticae*		Toxicity
				Females	Eggs	
X	>0.5	0.086	0.1	0.040	>0.5	16.1
XXVI	0.0092	0.0066	0.00079	0.00010	>0.5	2.5—5
XI	>0.5	>0.1	0.084	0.0066	>0.5	37.0
XXVII	0.0051	0.050	0:00044	0.00023	0.018	8.0
XII	0.10	0.10	0.050	0.00064	0.48	50.0
XXII	0.10	>0.1	0.031	0.10	>0.5	35.0
XXVIII	0.0040	0.0048	0.00035	0.000022	0.055	5.4
XIII	>0.5	>0.1	>0.1	>0.1	>0.5	55.0
XXIX	0.0084	>0.1	0.028	0.016	0.50	2.0
XIV	>0.5	>0.1	>0.1	0.066	>0.5	81.0
XXX	0.11	>0.1	0.0010	>0.1	0.083	31.0
XV	0.10	>0.1	>0.1	0.032	>0.5	90.0
XXIII	>0.5	>0.1	>0.1	0.016	0.42	74.0
XXXI	0.0033	0.0051	0.0022	0.0086	0.052	14.0
XVI	>0.5	>0.1	>0.1	>0.1	>0.5	120.0
XXXII	0.0019	>0.1	0.0045	0.0021	>0.5	13.0
XVII	>0.5	>0.1	>0.1	0.026	>0.5	160.0
XXXIII	0.12	>0.1	0.052	>0.1	0.048	23.0
XVIII	>0.5	>0.1	>0.1	0.017	>0.5	160.0
XXIV	>0.5	>0.1	>0.1	0.021	>0.5	125.0
XXXIV	0.0031	0.0083	0.0082	0.0052	0.35	19.0
Malathion	0.017	0.0056	0.0046	—	—	—
Fenitrothion	0.0021	0.00053	0.0017	—	—	—
Karbofenthion	—	—	—	0.000081	0.0025	—

Experimental

The starting 5-R^3-1-R^4-6-oxo-1*H*-pyridazin-4-ols were prepared after [11], *O*,*S*-dialkyl chlorothiophosphates after [12].

The i.r. spectra were measured on a UR-20 spectrophotometer (Zeiss, Jena) in the region of 700—3700 cm^{-1} in chloroform solutions (concentration 0.02—0.06 M; cell thickness 0.089 mm). The apparatus was calibrated by polystyrene foil.

The u.v. spectra were taken on a Specord UV VIS spectrometer in methanol (concentration 1.0×10^{-4}—2.0×10^{-5} M; cell thickness 1.0 cm).

^{1}H-N.m.r. spectra were measured on a Tesla BS 487 C apparatus (80 MHz) in $CDCl_3$ in the presence of internal standards TMS and HMDS. The spectral data are presented in Table 2.

Contact insecticidal activity was followed on *Musca domestica* L., *Calandra granaria* L., and *Aphis fabae* SCOP using Malathion (*O*,*O*-dimethyl *S*-1,2-(diethoxycarbonyl)ethyl dithiophosphate) and Fenitrothion (*O*,*O*-dimethyl *O*-(3-methyl-4-nitrophenyl) thiophosphate) as standards. Systemic insecticidal activity was followed on *A. fabae* using Thiometon (*O*,*O*-dimethyl *S*-(2-ethylthioethyl) dithiophosphate) as standard. Acaricidal activity was followed on females of *Tetranychus urticae* KOCH and ovicidal activity on eggs of *T. urticae* using Karbofenthion (*O*,*O*-diethyl *S*-(4-chlorophenylthiomethyl) dithiophosphate) as standard. The methods for the determination of insecticidal, acaricidal, and ovicidal activities were published in [13, 14].

The acute oral toxicity was determined on male rats (130—150 g), race Wistar, after the method described in [1]. The results are presented in Table 3.

O,S-Dialkyl O-(1-R^4-5-R^3-6-oxo-1H-pyridazin-4-yl) thiophosphates (I—XXV)

To sodium or potassium 1,5-disubstituted 6-oxo-1*H*-pyridazin-4-ol (0.11 mol) in ethyl methyl ketone (100 ml) *O*,*S*-dialkyl chlorothiophosphate (0.1 mol) was added under stirring. Stirring was continued for 3 h at 60°C, then the mixture was cooled and benzene (100 ml) was added. After washing the solution with water, 5% sodium carbonate solution, and water the mixture was dried and benzene was distilled off under reduced pressure. The residue was purified by column chromatography (SiO_2) using benzene with the addition of acetone (0—10%) as eluting agent. Characterization of compounds is presented in Table 1.

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