Synthesis of new organothiophosphorus insectoacaricides containing *N*-acylated amino acid fragments

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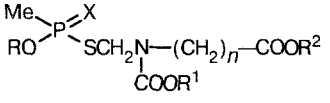
Methods for the synthesis of *O*-alkyl *S*-(*N*-acyl-*N*-alkoxycarbonylalkyl)aminomethyl (methyl)thio- and -dithiophosphonates based on the reaction between alkaline-metal salts of *O*-alkyl (methyl)thio- and -dithiophosphonates and *N*-alkoxycarbonyl-*N*-chloromethylglycine or -β-alanine esters and by treatment of *O*-alkyl (methyl)dithiophosphonoates and *N*-acylated amino acids or their esters with paraform in the presence of HCl were developed. The compounds obtained exhibit high insectoacaricide activity and selectivity.

Key words: (methyl)thiophosphonates; (methyl)dithiophosphonates; thiophosphorylated derivatives of amino acids; insectoacaricides.

Along with high activity against arthropod vermin, modern requirements for insectoacaricides include high selectivity, which results in lower hazards to humans and useful animals (including the predatory insects, entomophages), and ecological safety, that is, no accumulation of harmful and other abiogenic products of their decomposition in the environment.

As can be seen from an analysis of the literature data (for example, see Refs. 1—3) and our own data,[4—8] the selectivity of organophosphothio- and organophosphodithio-insectoacaricides is mainly determined by the differences in the ratios of the rates of the three types of metabolic reactions that occur in the organisms of mammals and arthropods: activation reactions resulting in the appearance of active metabolites capable of reacting with choline esterases, reactions of these metabolites with the esterases (inhibition) responsible for toxicity, and detoxication reactions resulting in nontoxic metabolites.



1a—p, 2a, b, d—f, j, o

1: X = S, **2**: X = O, **a—m**: n = 1, **n—p**: n = 2
a: R = R^1 = R^2 = Me; **b**: R = R^1 = Me, R^2 = Et;
c: R = R^2 = Me, R^1 = Pr^i; **d**: R = Et, R^1 = R^2 = Me;
e: R = R^2 = Et, R^1 = Me; **f**: R = Et, R^1 = Me, R^2 = Bu^i;
g: R = R^1 = Et, R^2 = Me; **h**: R = R^1 = R^2 = Et;
i: R = Et, R^1 = Pr^i, R^2 = Me; **j**: R = Et, R^1 = Bu^i, R^2 = Me;
k: R = Et, R^1 = CH_2Ph, R_2 = Me;
l: R = Et, R^1 = 3-MeC_6H_4, R^2 = Me;
m: R = Et, R^1 = 4-MeC_6H_4, R^2 = Me;
n: R = Et, R^1 = R^2 = Me ; **o**: R = R^2 = Et, R^1 = Me;
p: R = R^1 = R^2 = Et

Based on these concepts and our previous data[9,10] on the higher selectivity, in some cases, of (methyl)dithiophosphonates compared with similar dithiophosphates, we aimed at the synthesis and investigation of the insecticide properties of (methyl)thiophosphonates and (methyl)dithiophosphonates containing fragments of esters of *N*-alkoxycarbonylamino acid (glycine and β-alanine).

The premise of the potential selectivity of compounds **1** is that their activation during the oxidative desulfurization (that is, conversion into choline esterase inhibitors **2** under the action of monooxygenases) should occur faster in arthropods,[11,12] whereas detoxification during the hydrolysis by carboxylesterases (—$COOR^2$ → —COOH) should be faster in mammals.[13,14] The polar —C(O)N group favors the fixation of an inhibitor on the active surface of choline esterases and endows the phosphorus atom with electrophilicity sufficient for the optimal phosphorylating ability. Finally, compounds **1** are ecologically safe because their environmental decomposition gives only biogenic products: phosphoric acid (the C—P bond in methylphosphonates is easily cleaved by soil bacteria[15] with the formation of H_3PO_4) and amino acids.

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Table 1. Characteristics of compounds **1**, **2**, and **5**

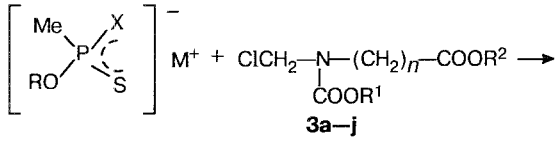
Compound	Method	Yield (%)	d_4^{20}	n_D^{20}	Found / Calculated (%)			Molecular formula
					C	H	P	
1a	*A*	88	1.2970	1.5334	—	—	10.37 10.28	$C_8H_{16}NO_5PS_2$
	B	90	—	1.5330	—	—	—	
1b	*A*	95	1.2574	1.5245	—	—	9.95 9.82	$C_9H_{18}NO_5PS_2$
	B	96	—	1.5240	—	—	—	
1c	*A*	96	1.2200	1.5152	—	—	9.21 9.40	$C_{10}H_{20}NO_5PS_2$
1d	*A*	93	1.2547	1.5247	—	—	9.54 9.82	$C_9H_{18}NO_5PS_2$
	B	97	—	1.5242	—	—	—	
1e	*A*	92	1.2248	1.5183	—	—	9.17 9.40	$C_{10}H_{20}NO_5PS_2$
	B	93	—	1.5181	—	—	—	
1f	*A*	90	1.1764	1.5086	—	—	8.53 8.66	$C_{12}H_{24}NO_5PS_2$
1g	*A*	88	1.2224	1.5155	—	—	8.95 9.40	$C_{10}H_{20}NO_5PS_2$
1h	*A*	96	1.1944	1.5103	38.27 38.47	6.54 6.46	8.75 9.02	$C_{11}H_{22}NO_5PS_2$
1i	*A*	97	1.1950	1.5103	—	—	8.84 9.02	$C_{11}H_{22}NO_5PS_2$
	B	95	—	1.5100	—	—	—	
1j	*A*	94	1.1752	1.5076	—	—	8.34 8.66	$C_{12}H_{24}NO_5PS_2$
1k	*B*	87	Viscous oil[a]		46.10 46.02	5.70 5.68	7.30 7.91	$C_{15}H_{22}NO_5PS_2$
1l	*B*	81[b]	Viscous oil		45.96 46.02	5.56 5.66	7.83 7.91	$C_{15}H_{22}NO_5PS_2$
1m	*B*	79	M.p. 64—65 °C[c]		45.91 46.02	5.80 5.66	7.81 7.91	$C_{15}H_{22}NO_5PS_2$
1n	*A*	90	1.2378	1.5240	—	—	9.24 9.40	$C_{10}H_{20}NO_5PS_2$
1o	*A*	89	1.2099	1.5176	—	—	8.65 9.02	$C_{11}H_{22}NO_5PS_2$
1p	*A*	93	1.1810	1.5120	—	—	8.52 8.66	$C_{12}H_{24}NO_5PS_2$
2a	*A*	93	1.3000	1.4943	—	—	10.67 10.86	$C_8H_{16}NO_6PS$
2b	*A*	91	1.2568	1.4870	—	—	10.45 10.35	$C_9H_{18}NO_6PS$
2d	*A*	78	1.2642	1.4905	—	—	10.29 10.35	$C_9H_{18}NO_6PS$
2e	*A*	86	1.2280	1.4855	—	—	9.81 9.89	$C_{10}H_{20}NO_6PS$
2f	*A*	96	1.1771	1.4804	—	—	9.10 9.07	$C_{12}H_{24}NO_6PS$
2j	*A*	93	1.1748	1.4790	—	—	8.55 9.07	$C_{12}H_{24}NO_6PS$
2o	*A*	69[b]	1.2076	1.4850	40.74 40.36	6.78 6.77	8.92 9.46	$C_{11}H_{22}NO_6PS$
5a	*B*	98	M.p. 79—81 °C[d]		32.04 31.89	5.37 5.35	10.21 10.28	$C_8H_{16}NO_5PS_2$
5b	*B*	83	M.p. 101—102 °C[c]		44.45 44.55	5.25 5.34	7.96 8.21	$C_{14}H_{20}NO_5PS_2$

Table 1. Continued

Compound	Method	Yield (%)	d_4^{20}	n_D^{20}	Found / Calculated (%) C	H	P	Molecular formula
5c	***B***	91	Viscous oil		38.97 38.59	6.43 6.48	7.72 8.29	$C_{12}H_{24}NO_4PS_3$
5d	***B***	31[b]	Viscous oil		30.90 31.11	4.97 5.22	8.85 8.91	$C_9H_{18}NO_3PS_4$
5e	***B***	24	1.2098	1.5314	38.27 38.33	6.31 6.43	9.81 9.88	$C_{10}H_{20}NO_4PS_2$
5f	***B***	50[b]	Viscous oil		31.15 30.93	5.78 5.77	9.13[e] 8.86	$C_9H_{20}NO_5PS_3$
5g	***B***	58	M.p. 56—58 °C[f]		41.05 40.86	5.52 5.39	7.30 7.53	$C_{14}H_{22}NO_5PS_3$
5h	***B***	74	M.p. 50—53 °C[f]		42.04 42.34	5.60 5.68	—[g]	$C_{15}H_{24}NO_5PS_3$
5i	***B***	87[b]	Viscous oil		29.95 29.66	5.78 5.81′	8.44[h] 8.50	$C_9H_{21}N_2O_5PS_3$
5j	***B***	93	Viscous oil		32.10 31.73	6.27 6.12	—[i]	$C_{10}H_{23}N_2O_5PS_3$
5k	***B***	83[b]	Viscous oil		32.27 31.78	5.76 5.67	9.96 10.24	$C_{16}H_{34}N_2O_8P_2S_5$
5l	***A***	61[b]	Viscous oil		34.22 33.67	5.77 5.65	10.70 10.85	$C_8H_{16}NO_4PS_2$
5m	***B***	83	1.2340	1.5220	—	—	9.44 9.40	$C_{10}H_{20}NO_5PS_2$
5n	***B***	86	Glassy mass[b]		—	—	10.06 9.82	$C_9H_{18}NO_5PS_2$

[a] Purified by column chromatography. Found (%): N, 3.68. Calculated (%): N, 3.58. [b] After purification by column chromatography. [c] From hexane with ether. [d] From benzene with hexane. Found (%): N, 4.66. Calculated (%): N, 4.65. [e] Found (%): S, 27.69. Calculated (%): S, 27.53. [f] From ether with pentane. [g] Found (%): S, 22.78. Calculated (%): S, 22.61. [h] Found (%): N, 7.61; S, 26.50. Calculated (%): N, 7.69; S, 26.39. [i] Found (%): N, 7.26; S, 25.08. Calculated (%): N, 7.40; S, 25.42.

Compounds **1** and **2** were synthesized by the reaction of potassium *O*-alkyl (methyl)dithiophosphonate or sodium *O*-alkyl (methyl)thiophosphonate with *N*-alkoxycarbonyl-*N*-chloromethylglycine or -β-alanine esters (**3a—j**) [method ***A***; Eq. (1), Table 1].

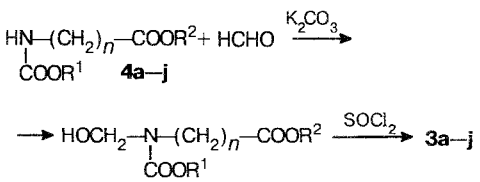


3a—j (1)

⟶ **1a—j, n—p; 2a, b, d—f, i, o**

X = O, S; M = K, Na; **3a—g**: n = 1, **3h—j**: n = 2
a: $R^1 = R^2$ = Me; **b**: R^1 = Me, R^2 = Et; **c**: R^1 = Me, $R^2 = Bu^i$; **d**: R^1 = Et, R^2 = Me; **e**: $R^1 = R^2$ = Et; **f**: $R^1 = Pr^i$, R^2 = Me; **g**: $R^1 = Bu^i$, R^2 = Me; **h**: $R^1 = R^2$ = Me; **i**: R^1 = Me, R^2 = Et; **j**: $R^1 = R^2$ = Et

Chloromethyl derivatives **3a—j** (Table 2) were obtained by reactions of *N*-alkoxycarbonylamino acid esters **4a—j** (synthesized by the previously described method;[16] the characteristics of the new compounds are given in Table 3) with formaline followed by chlorination of the hydroxymethyl derivatives with $SOCl_2$ [Eq. (2), Table 2; the designations for **4a—j** are the same as for **3a—j** in Eq. (1)].



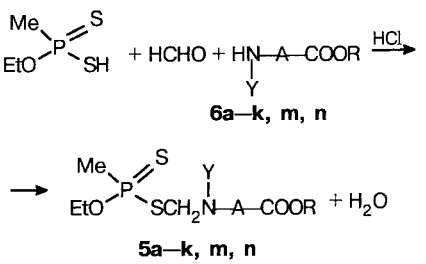
(2)

In addition, a simpler and technologically more efficient method for the synthesis of dithiophosphonates **1a,b,d,e,i—m** and their analogs (**5**) (method ***B***) was

Table 2. Characteristics of compounds **3**

Compound	Yield (%)	B.p./°C (*p*/Torr)	d_4^{20}	n_D^{20}	Found / Calculated (%) C	H	N	Molecular formula
3a	80	121—123(3)	1.2918	1.4622	37.14 36.84	5.12 5.15	6.95 7.16	$C_6H_{10}ClNO_4$
3b	79	89—90(0.5)	1.2328	1.4580	40.59 40.10	5.67 5.77	6.98 6.68	$C_7H_{12}ClNO_4$
3c	96	103—104(0.5)	1.1593	1.4550	—	—	5.96 5.89	$C_9H_{16}ClNO_4$
3d	79	118—119(1)	1.2294	1.4565	40.53 40.10	5.94 5.77	6.19 6.68	$C_7H_{12}ClNO_4$
3e	83	97—98(0.5)	1.1822	1.4530	42.86 42.96	6.38 6.31	6.15 6.26	$C_8H_{14}ClNO_4$
3f	71	98—99(0.5)	1.1780	1.4512	—	—	6.19 6.26	$C_8H_{14}ClNO_4$
3g	78	106—107(0.5)	1.1568	1.4548	—	—	6.25 5.89	$C_9H_{16}ClNO_4$
3h	73	95—96(0.5)	1.2511	1.4649	—	—	6.72 6.68	$C_7H_{12}ClNO_4$
3i	89	103—104(0.5)	1.2034	1.4607	—	—	5.96 6.26	$C_8H_{14}ClNO_4$
3j	84	116—117(2)	1.1651	1.4568	45.99 45.48	6.87 6.78	6.05 5.89	$C_9H_{16}ClNO_4$

developed. The method is based on a modification of the Mannich reaction found by us: the interaction of *O*-alkyl hydrogen (methyl)dithiophosphonates with derivatives of esters of amino acids **4a—j** or their analogs (**6**) and paraform in inert solvents ($CHCl_3$, CH_2Cl_2, ether, toluene) in the presence of gaseous HCl [Eq. (3), see Table 1].

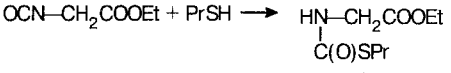


(3)

5a—l, 6a—l: A = —CH_2—
a: Y = —COOMe, R = H; **b**: Y = —$COOCH_2Ph$, R = H;
c: Y = —C(O)SPr, R = Et; **d**: Y = —C(S)SMe, R = Me;
e: Y = —Ac, R = Et; **f**: Y = —SO_2Me, R = Et;
g: Y = —SO_2Ph, R = Et; **h**: Y = —$SO_2C_6H_4Me$-4, R = Et;
i: Y = —SO_2NMe_2, R = Me; **j**: Y = —SO_2NMe_2, R = Et;
k: Y = —SO_2—, R = Et; **l**: Y = —CHO, R = Me;
m: Y = —COOMe, A = —CH(Me)—, R = Me;
n: Y = —COOMe, A = —CH_2CH_2—, R = H

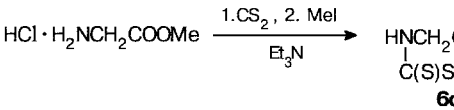
Method ***B*** simplifies the synthesis of compound **1** by eliminating three stages and permits one to prepare relatively pure compounds (96—98 % purity without additional purification) in good yields. In addition, this method is more general and makes it possible to synthesize derivatives of free amino acids **5a,b,n** (detoxification metabolites), derivatives of α-substituted amino acids **5m**, and to vary significantly the *N*-acyl substituents. Most of compounds **5** were obtained in good yields, but in some cases (compounds **5d—h**) the yields were lower due to the formation of side products in amounts greater than usual.

The starting compounds **6a,b,m,n**,[16,17] **6e**,[18] **6f**,[19] **6k**,[20] and **6l** [21] were obtained using the procedures described previously. Thiocarbamate **6c** was synthesized by the reaction of ethoxycarbonylmethylisocyanate[22] with propanethiol catalyzed by pyridine (see Table 3).



(4)

The similar dithiocarbamate **6d** was prepared by the reaction of a glycine ester with CS_2 and MeI in the presence of triethylamine (see Table 3).



(5)

Compounds **6i,j** were synthesized by the reaction of glycine ester hydrochlorides with dimethylchlorosul-

famide in the presence of an aqueous alkali (Eq. (6), see Table 3).

$$HCl \cdot H_2NCH_2COOR + ClSO_2NMe_2 \xrightarrow{NaOH} \underset{\displaystyle SO_2NMe_2}{\overset{\displaystyle |}{HNCH_2COOR}} \quad (6)$$

6i, j

The purity of the compounds was confirmed by TLC and elemental analysis. In most cases, the compounds **1**, **2**, and **5** obtained did not require further purification. If necessary, they were purified by chromatography on SiO_2.

The structures of the compounds obtained were confirmed by ^1H and $^{31}P-\{^1H\}$ NMR spectra. The observed multiplicity of the signals, along with usual couplings, is due to hindered rotation around the amide bond and the existence of the chiral phosphorus atom. For example, the spectrum of compound **1a** (C_6D_6) contains two doublets of the CH_3-P group at δ 1.68 and 1.75, J_{H-P} = 14.1 Hz (Δδ 0.07 ppm); two doublets of the CH_3O-P group at δ 3.22 and 3.23, J_{H-P} = 18.3 Hz (Δδ 0.01 ppm); a singlet of the amino acid ester group at δ 3.27; two singlets of the carbamate group at δ 3.27 and 3.22 (Δδ 0.05 ppm); and two singlets of the $N-CH_2-C(O)$ group at δ 4.01 and 4.19 (Δδ 0.18). The protons of the methylene group in $S-CH_2$ appear for one of the conformers as a doublet at δ 5.03, J_{H-P} = 15.2 Hz. For the other conformer, the diastereotopic protons form an ABX-system (where X is the phosphorus atom) with the center at δ 4.90 (δ_A 4.87, δ_B 4.94, J_{AB} = 13.9 Hz, J_{AX} = 15.4 Hz, J_{BX} = 15.4 Hz). The ^1H NMR spectrum of compound **1b** is similar to that of **1a** (C_6D_6), δ: 0.88 (t, 3 H, $\underline{CH_3}CH_2$, J_{H-H} = 7.0 Hz); 1.68 and 1.75 (Δδ 0.07 ppm) (both d, 3 H, CH_3-P, J_{H-P} = 14.0 Hz); 3.22 and 3.23 (Δδ 0.01 ppm) (both d, 3 H, CH_3O-P, J_{H-P} = 15.6 Hz); 3.28 and 3.32 (Δδ 0.04 ppm) (both s, 3 H, $CH_3OC(O)$); 3.86 (q, 2 H, $\underline{CH_2}CH_3$, J_{H-H} = 7.0 Hz); 3.99 and 4.16 (Δδ 0.17 ppm) (both s, 2 H, $NCH_2C(O)$); 4.89 (ABX-dd, δ_A 4.85, δ_B 4.92, J_{AB} = 14.3 Hz, J_{AX} = 15.3 Hz, J_{BX}= 15.3 Hz), and 5.00 (d, 2 H, SCH_2, J_{H-P} = 15.6 Hz). The $^{31}P-\{^1H\}$ NMR spectrum of compound **2d** (C_6D_6) contains two singlets at δ 50.89 and 51.66 (Δδ 0.77 ppm).

The toxicity of compounds **1**, **2**, and **5** (LD_{50}) was determined for white mice (orally) and for American cockroaches *Periplaneta americana* (integumentary application). The insecticide and acaricide contact activity (LC_{50}) for the imago of typhoid flies *Musca domestica*, rice weevils *Calendra oryzae*, black bean aphid *Aphis fabae*, grain aphid *Toxoptera graminum*, spider web tick *Tetranychus urticae*, and hawthorn tick *Tetranychus viennensis* were also determined. The data obtained for the most active compounds are given in Table 4. Compounds **1b**, **1d**, and **1e**, which are of the most interest, were investigated more thoroughly for various species of aphids, greenhouse white fly *Myzus persicae* and entomophages: podisus bug *Podisus maculiventris* and aphis lion *Chrysopa carnea* (Table 5). As can be seen from Tables 4 and 5, many compounds have high

Table 3. Characteristics of compounds **4** and **6**

Compound	Yield (%)	B.p./°C (*p*/Torr)	d_4^{20}	n_D^{20}	Found / Calculated (%)			Molecular formula
					C	H	N	
4c	79	134—135(1)	1.0853	1.4388	51.11 50.78	7.76 7.99	7.81 7.40	$C_8H_{15}NO_4$
4f	76	91—92(0.5)	1.1032	1.4363	—	—	8.39 8.00	$C_7H_{13}NO_4$
4g	87	100—101(0.5)	1.0870	1.4395	—	—	7.58 7.40	$C_8H_{15}NO_4$
4j	88	90—92(1)	1.0904	1.4412	50.87 50.78	7.94 7.99	—	$C_8H_{15}NO_4$
6c	85	125—126(1)	—	1.4862	47.14 46.81	7.20 7.36	—	$C_8H_{15}NO_3S$
6d	72	M.p. 51—52 °C[a]			33.59 33.50	5.10 5.06	—[b]	$C_5H_9NO_2S_2$
6g	51	M.p. 60—61.5 °C[c]			48.87 49.37	5.31 5.39	—[d]	$C_{10}H_{13}NO_4S$
6h	50	M.p. 59—61 °C[c]			51.37 51.35	5.89 5.88	5.27[e] 5.44	$C_{11}H_{15}NO_4S$
6i	29	135—136(2.5)	—	1.4598	—	—	14.05 14.28	$C_5H_{12}N_2O_4S$
6j	48	136—137(2)	—	1.4576	33.93 34.27	6.70 6.71	—	$C_6H_{14}N_2O_4S$

[a] From a hexane—ether mixture. [b] Found (%): S, 36.03. Calculated (%): S, 35.77. [c] From 50 % MeOH. [d] Found (%): S, 13.70. Calculated (%): S, 13.18. [e] Found (%): S, 12.37. Calculated (%): S, 12.46.

Table 4. Toxicity of compounds **1, 2,** and **5** for mice, insects, and ticks

Compound	LD_{50}/mg kg^{-1}	ЛД$_{50}$/μg g^{-1}	LC_{50} (%)				
	Mice	American cockroach	Typhoid fly	Rice weevil	Black bean aphid	Grain aphid	Spider web tick
1a	215	90	0.1	0.01	0.0013	—	0.00038
1b	150	32	0.08	0.01[a]	0.001	0.0016	0.00007
1c	180	—	0.04	0.008	0.003	—	—
1d	183	38	0.05	0.03	0.0012	0.0009	0.00028
1e	125	15.5	—	—	0.0021	0.002	0.00012[b]
1f	680	105	0.09	0.07	0.01	—	0.0022
1g	107	—	0.1	0.03	0.0024	—	0.001
1h	90	—	0.1	0.1	<0.01	—	0.05
1i	175	—	0.04	0.03	0.0035	—	—
1j	30	18.5	—	—	0.0037	—	0.00038
1n	—	—	[c]	[c]	—	—	0.017
1o	640	480	[c]	[c]	<0.01	—	0.0041[b]
1p	550	—	[c]	[c]	[c]	—	0.05
2a	[d]	6.7	0.09	0.0017	0.0001	0.0052	0.00003
2b	[d]	5.8	0.02	0.0023	0.00008	0.0036	0.00005
2d	[d]	15.5	0.02	0.01	—	0.0076	0.00012
2e	[d]	7	0.08	—	—	0.0084	0.00024[b]
2f	52	12	—	0.022	0.00015	0.0052	0.00002
2j	[d]	23	—	0.02	0.0012	0.0062	0.00029
2o	[d]	160	—	0.022	—	—	0.0078[b]
5d	—	—	—	—	0.01	—	0.0045
5e	115	30.5	—	—	—	—	0.00008
5f	—	—	—	—	0.004	—	0.002
5i	—	—	[c]	[c]	[c]	—	0.0008
5j	—	—	[c]	[c]	[c]	—	0.001
5l	—	—	[c]	0.02	0.01	—	0.004
5m	—	—	0.04	0.03	0.0018	—	0.005
Carbophos	400	—	—	—	0.002	0.002	—
Chlorophos	630	—	0.03	0.08	—	—	—
Rogor	140	—	—	—	0.0015	0.004	0.00074—0.0013
Metaphos	50	—	—	—	—	—	0.001

[a] For sugar-beet weevil, LC_{50} 0.019 % (Foxim, LC_{50} 0.012 %). [b] For hawthorn tick LC_{50} (%): **1e**, 0.00094; **1o**, 0.0175; **2e**, 0.00039; **2o**, 0.009 (Rogor, 0.0027). [c] Nontoxic in the cut-off concentration. [d] LD_{50} < 25 mg kg^{-1}.

Table 5. Toxicity of compounds **1b,d,e** for various species of aphid, greenhouse white fly, and podisus bug

Insect	LC_{50} (%)				
	1b	**1d**	**1e**	Carbophos	Rogor
Apple green aphid	0.0047	0.0025	0.0005	—	0.0004
Pea aphid	—	—	0.038	0.0011	—
Peach aphid (race R)	0.0029	0.00016	0.0072	0.0016	0.011
Cotton aphid	0.0014	0.002	0.00017	0.0005	0.0002
Plum aphid	—	—	0.0011	0.003	—
Woolly apple aphid	0.0015	0.0016	—	—	0.0012
Cabbage aphid	0.0014	0.0013	—	0.002	—
Large potato aphid	0.0025	0.0054	—	—	0.001
Greenhouse white fly*	—	0.0028	0.0022	0.002	—[a]
Greenhouse white fly**	—	—	0.0023	0.01	—
Aphis lion	0.014	0.017	—	—	0.02
Podisus bug	0.022	0.056	—	—	0.021

* Race S. ** Race R. [a] Aktellik, LC_{50} 0.016 %.

insectoacaricide activity, at the standard level or higher, including activity against organophosphorus insecticide-resistant races of insects. On the other hand, some of them (for example, compound **1d**) exhibit higher selectivity than rogor and metaphos, higher activity against various species of aphids and ticks, and lower toxicity for mice and podisus bugs.

Experimental

NMR spectra were recorded on a Bruker WP 200-SY spectrometer with HMDS (^1H) and 85 % H_3PO_4 (^{31}P) as internal standards.

Thin layer chromatography was carried out on SiO_2 Chemapol L, 100/160 μm in hexane : acetone, 3 : 2 (for derivatives of free amino acids **5a**,**b**,**h**, $CHCl_3$: MeOH, 10 : 1 was used). Purification of the compounds was carried out on a column with the same sorbent with a weight ratio compound : SiO_2 = 1 : 15 to 20 : 1; a mixture of hexane with acetone in ratios from 100 : 1 to 3 : 2 was used as the eluent. For compound **5n**, a mixture of $CHCl_3$ with ethyl acetate in ratios from 10 : 1 to 3 : 2 was used as the eluent.

***O*-Alkyl *S*-(*N*-alkoxycarbonyl-*N*-alkoxycarbonylalkyl)aminomethyl (methyl)dithiophosphonates (1).**

Method *A*. *O*-Ethyl *S*-(*N*-methoxycarbonyl-*N*-methoxycarbonylmethyl)aminomethyl (methyl)dithiophosphonate (1d). Ester **3a** (4.89 g, 25 mmol) in 5 mL of acetone was added dropwise with stirring to a solution of potassium *O*-ethyl (methyl)dithiophosphonate (5.25 g, 27 mmol) in 20 mL of dry acetone. The mixture was stirred for 3 h at 20 °C and filtered. The precipitate was washed with acetone, and the filtrate was concentrated *in vacuo*. The residue was dissolved in ether or benzene, washed with ice water, a chilled saturated solution of Na_2CO_3, and water (10 mL of each), and dried with Na_2SO_4. The solvent was distilled off *in vacuo* (finally, at 75—80 °C/1 Torr) to give 7.34 g (93 %) of dithiophosphonate **1d**.

Compounds **1a—c,e—j,n—p** and **5l** were obtained in a similar way (see Table 1).

***O*-Alkyl *S*-(*N*-acyl- (or *N*-alkoxycarbonyl)-*N*-alkoxycarbonylalkyl)aminomethyl (methyl)dithiophosphonates (1, 5).**

Method *B*. *O*-Ethyl *S*-(*N*-ethoxycarbonylmethyl-*N*-methoxycarbonyl)aminomethyl (methyl)dithiophosphonate (1e). A stream of dry HCl was rapidly passed through a mixture of *O*-ethyl hydrogen (methyl)dithiophosphonate (4.69 g, 0.03 mol), dry paraform (0.90 g, 0.03 mol), and *N*-methoxycarbonylglycine ethyl ester (**4b**) (4.83 g, 0.03 mol) in $CHCl_3$ (CH_2Cl_2, ether, or toluene) (30 mL) with vigorous stirring and cooling (the initial temperature in the bath was −20 to −30 °C) in such a way that the temperature of the reaction mixture was −5 to 0 °C until the precipitate dissolved completely and the mixture was saturated with HCl. To remove excess HCl, the mixture was concentrated *in vacuo* to remove one quarter of the solvent volume without heating. The residue was washed twice with ice water, twice with a cold saturated solution of $NaHCO_3$* and water (10 mL of each), and dried with Na_2SO_4. The solvent was distilled off *in vacuo* (finally, at 70—80 °C/1 Torr) to give 9.22 g (93 %) of dithiophosphonate **1e**.

* For amino acid derivatives **5a**,**b**,**n**, washing with $NaHCO_3$ was omitted.

Compounds **1a**,**b**,**d**,**i**,**k—m** and **5a—k**,**m**,**n** were obtained in a similar way (see Table 1).

The compounds prepared using methods *A* and *B* usually did not require further purification, but, if needed, they were purifired by column chromatography (see above).

***O*-Alkyl *S*-(*N*-alkoxycarbonyl-*N*-alkoxycarbonylalkyl)aminomethyl (methyl)thiophosphonates (2). *O*-Methyl-*S*-[(*N*-methoxycarbonyl-*N*-methoxycarbonylmethyl)aminomethyl]-(methyl)thiophosphonate (2a).** A solution of ester **3a** (1.96 g, 10 mmol) in acetone (2 mL) was added dropwise with stirring and cooling with ice water to a solution of sodium *O*-methyl (methyl)thiophophonate (1.63 g, 11 mmol) in dry acetone (10 mL) in such a way that the temperature of the mixture did not exceed 5 °C. The mixture was stirred for 1 h at 0 to 5 °C and for 2 h at 20 °C; the precipitate was filtered off and washed with acetone. The filtrate was concentrated *in vacuo*; the residue was dissolved in $CHCl_3$, washed with ice water, a cold saturated solution of $NaHCO_3$ and water (5 mL of each), and dried with Na_2SO_4. The $CHCl_3$ was removed *in vacuo* to give 2.71 g (93 %) of thiophosphonate **2a**.

Compounds **2b**,**d—f**,**j**,**o** were prepared in a similar way (see Table 1). If required, they were purifired by column chromatography (see above).

Esters of *N*-alkoxycarbonyl-*N*-chloromethylamino acids (3). *N*-Chloromethyl-*N*-methoxycarbonylglycine methyl ester (3a). A mixture of ester **4a** (14.72 g, 0.10 mol), 40 % aqueous formaline (11.26 g, 0.15 mol), and anhydrous K_2CO_3 (0.15 g) was stirred for 5—7 h on a boiling water bath. Then the mixture was cooled to 20 °C and extracted with $CHCl_3$ (3×20 mL). The extracts were washed with ice water (2×10 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The residue was dissolved in abs. $CHCl_3$ (35 mL), then a solution $SOCl_2$ (12.02 g, 0.101 mol) in $CHCl_3$ (10 mL) was added dropwise to the solution with vigorous stirring, so that the temperature of the mixture did not exceed 25 °C. The mixture was kept at 20 °C for 1 h and then boiled until the liberation of HCl and SO_2 ceased. The $CHCl_3$ was removed *in vacuo*, and the residue was distilled *in vacuo* to give 13.81 g (80 %) of ester **3a**.

Compounds **3b—j** were prepared in a similar way (see Table 2).

***N*-Chloromethyl-*N*-formylglycine methyl ester** was obtained according to the same procedure. The yield was 32 %, b.p. 120—121 °C (2 Torr), n_D^{20} 1.4818. Found (%): C, 36.56; H, 4.91; N, 9.09. $C_5H_8ClNO_3$. Calculated (%): C, 36.27; H, 4.87; N, 8.46.

***N*-Propylthiocarbonylglycine ethyl ester (6c).** A mixture of ethoxycarbonylmethylisocyanate (3.87 g, 0.703 mol), propanethiol (2.36 g, 0.031 mol), and 2 drops of abs. pyridine was boiled for 1 h (during this period, the temperature of the mixture increased from 70 to 130 °C). Subsequent distillation *in vacuo* afforded 5.24 g (85 %) of compound **6c** (see Table 3).

***N*-Methylthiothiocarbonylglycine methyl ester (6d).** Dry Et_3N (10.12 g, 0.10 mol) was added with cooling (4—6 °C) and stirring to a solution of glycine methyl ester hydrochloride (6.28 g, 0.705 mol) in dry MeOH (50 mL), then CS_2 (3.81 g, 0.05 mol) was added dropwise without cooling; after 30—40 min, CH_3I (7.24 g, 0.051 mol) was added dropwise at 20 °C. The mixture was kept overnight, the precipitate was filtered off, and the filtrate was concentrated *in vacuo*. The residue was dissolved in 50 mL of benzene, washed with ice water (2×15 mL), and dried with Na_2SO_4. The benzene was removed *in vacuo*, and the residue was recrystallized from a hexane—ether mixture to give 6.46 g (72 %) of compound **6d** (see Table 3).

***N*-Phenylsulfonylglycine ethyl ester (6g).** Et_3N (3.03 g, 30 mmol) was added with cooling (ice water) and stirring to a suspension of glycine ethyl ester hydrochloride (2.10 g, 15 mmol) in 30 mL of dry CH_2Cl_2, then phenylsulfonyl chloride (2.61 g, 15 mmol) was added portionwise. The reaction mixture was stirred at 20 °C until the odor of the chloride disappeared. The precipitate was filtered off, and the filtrate was concentrated *in vacuo*. Crystallization from 50 % MeOH afforded 1.85 g (51 %) of compound **6g** (see Table 3).

Compound **6h** was obtained in a similar way (see Table 3).

***N,N*-Dimethyl-*N'*-ethoxycarbonylmethylsulfamide (6j).** $(CH_3)_2NSO_2Cl$ (7.47 g, 52 mmol) and 10 *N* NaOH (5.2 mL) were added in small portions (alternately from two dropping funnels) at −5 to 0 °C (the temperature of the mixture) with vigorous stirring to a solution of 6.98 g (50 mmol) of glycine ethyl ester hydrochloride in 10 mL of water (after that, a solution of anhydrous Na_2CO_3 (2.90 g, 27.4 mmol) in 15 mL of water was added from the second funnel) in such a way that the last portion of chloride was added simultaneously with the last portion of the Na_2CO_3 solution. The mixture was kept for 45 min at 0 °C and for 1 h at 20—25 °C, extracted with $CHCl_3$, dried with Na_2SO_4, and concentrated. The residue was dissolved in ether, filtered, and concentrated. Distillation *in vacuo* gave 5.0 g (48 %) of compound **6j** (see Table 3).

Compound **6i** was obtained in a similar way (see Table 3).

Determination of the toxicity of compounds 1, 2, and 5 for mice and arthropods. The toxicity for mammals was studied using white mice of both sexes weighing 15—20 g. Various doses of the compounds were injected orally as emulsions in distilled water with a minimum amount of OP-7. Each dose was assayed with six animals. After 48 h, the death rate was registered. The surviving animals were observed for 14—30 days. The toxicity for American cockroaches was determined by applying 1 μL of acetone solutions of the compounds on the prothorax of the insect. Death rates were registered after 24 and 48 h. LD_{50} values for mice and cockroaches were calculated using the probit analysis method.[23]

For typhoid flies (three-day-old imago), 1 μL of solutions of the compounds in acetone were appled on the medibacks. Death rates were registered after 24 h. Rice weevil beetles were sprayed with ethanolic solutions of the compounds on Petri dishes (37 mL per 1 m^2). Death rates were registered after 48 h. Aphids were sprayed with water—ethanolic solutions of compounds on Petri dishes (5 μL per 1 cm^2). Death rates were registered after 48 h. Spider web ticks were put on round pieces of bean leaves which had been previously immersed for 3 s into water—ethanolic solutions of the compounds and then dried. Death rates were registered after 48 h. LC_{50} values for flies, weevils, aphids, and ticks were calculated using the previously described method.[24,25]

References

1. R. D. O'Brien, in *Toxic Phosphorus Esters,* Academic Press, New York—London, 1960.
2. M. Eto, in *Organophosphorus Pesticides: Organic and Biological Chemistry*, Boca Ration, CRC Press, Cleveland, Ohio, 1974, 387.
3. V. I. Rozengart and O. E. Sherstobitov, *Izbiratel'naya toksichnost' fosfororganicheskikh insektoakaritsidov* [*Selective Toxicity of Organophosphorus Insectoacaricides*], Nauka, Leningrad, 1978, 174 (in Russian).
4. I. L. Brik, Yu. E. Mandel'shtam, O. V. Sundukov, A. A. Rakitin, I. N. Sazonova, K. N. Savchenko, A. N. Fedin, A. E. Shipov, G. V. Zhdanova, T. A. Mastryukova, and M. I. Kabachnik, *Khimiya v sel'skom khozyaistve* [*Chemistry in Agriculture*], 1974, **12**, 33 (in Russian).
5. Yu. S. Kagan, E. A. Ershova, M. A. Klisenko, T. A. Mastryukova, A. E. Shipov, G. V. Zhdanova, A. P. Brestkin, I. L. Brik, Yu. E. Mandel'shtam, and M. I. Kabachnik, *Izv. Akad. Nauk SSSR, Ser. Biol.* [*Bull. Acad. Sci. USSR, Div. Biol. Sci.*], 1982, 242 (in Russian).
6. Yu. S. Kagan, E. A. Ershova, M. A. Klisenko, T. A. Mastryukova, A. E. Shipov, G. V. Zhdanova, A. P. Brestkin, I. L. Brik, Yu. E. Mandel'shtam, and M. I. Kabachnik, *Izv. Akad. Nauk SSSR, Ser. Biol.* [*Bull. Acad. Sci. USSR, Div. Biol. Sci.*], 1982, 461 (in Russian).
7. G. F. Makhaeva, V. L. Veselova, T. A. Mastryukova, A. E. Shipov, G. V. Zhdanova, and M. I. Kabachnik, *Bioorg. Khim.*, 1983, **9**, 920 [*Sov. J. Bioorg. Chem.*, 1983, **9** (Engl. Transl.)].
8. G. F. Makhaeva, V. L. Yankovskaya, G. A. Odoeva, N. N. Shestakova, A. E. Khovanskikh, T. A. Mastryukova, A. E. Shipov, G. V. Zhdanova, and M. I. Kabachnik, *Bioorg. Khim.*, 1985, **11**, 957 [*Sov. J. Bioorg. Chem.*, 1985, **11** (Engl. Transl.)].
9. T. A. Mastryukova, A. E. Shipov, E. B. Gorbenko, M. I. Kabachnik, Yu. S. Kagan, E. A. Ershova, M. P. Shabanova, and K. N. Savchenko, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1971, 2003 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1971, **20**, 1888 (Engl. Transl.)].
10. T. A. Mastryukova, Z. K. Emkuzheva, A. E. Shipov, Yu. S. Kagan, E. A. Ershova, K. N. Savchenko, S. A. Roslavtseva, N. A. Guseva, T. N. Kaluzhina, V. P. Golubeva, and M. I. Kabachnik, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1979, 637 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1979, **28**, 591 (Engl. Transl.)].
11. R. D. O'Brien, in *Toxic Phosphorus Esters,* Academic Press, New York, London, 1960.
12. V. I. Rozengart and O. E. Sherstobitov, in *Izbiratel'naya toksichnost' fosfororganicheskikh insektoakaritsidov* [*Selective Toxicity of Organophosphorus Insectoacaricides*], Nauka, Leningrad, 1978, 108, 120 (in Russian).
13. R. D. O'Brien, G. D. Thorn, and R. W. Fisher, *J. Econ. Entomol.*, 1958, **51**, 714.
14. M. Eto, in *Organophosphorus Pesticides: Organic and Biological Chemistry*, Boca Ration, CRC Press, Cleveland, Ohio, 1974, 164.
15. C. G. Daughton, A. M. Cook, and M. Alexander, *J. Agric. Food Chem.*, 1979, **27**, 1375.
16. E. Fisher and W. Axhausen, *Lieb. Ann.*, 1905, **305**, 138.
17. H. Leuchs, *Ber.*, 1906, **39**, 857.
18. F. Barrow and G. W. Ferguson, *J. Chem. Soc.*, 1935, 410.
19. B. Helferich and R. Mittag, *Ber.*, 1938, **71**, 1480.
20. T. Saito and T. Hiraoka, *Chem. Pharm. Bull.*, 1977, **25**, 792.
21. R. G. Jones, *J. Am. Chem. Soc.*, 1949, **71**, 644.
22. Yu. A. Davidovich, V. I. Butaeva, O. M. Galkin, T. N. Sentsova, and S. V. Rogozhin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1977, 1682 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1977, **26**, 1554 (Engl. Transl.)].
23. V. B. Prozorovskii, *Farmakologiya, toksikologiya* [*Pharmacology, Toxicology*], 1962, **25**, 115 (in Russian).
24. M. L. Belen'kii, *Elementy kolichestvennoi otsenki farmakologicheskogo effekta* [*The Elements of Quantitative Appraisal of Pharmacological Effects*], Izd. AN Latv. SSR, Riga, 1959 (in Russian).
25. P. V. Popov, *Khimiya v sel'skom khozyaistve* [*Chemistry in Agriculture*], 1965, **3**, 72 (in Russian).

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