Synthesis and physiological activity of new organophosphorus pesticides of 1,3,2-oxazaphosphorinane series

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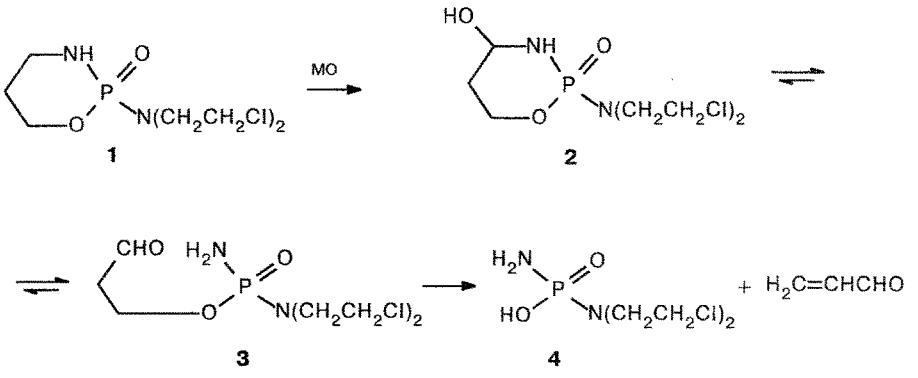
Methods for the synthesis of 2-aryloxy(arylthio)- and 2-alkoxy(alkylthio)-2-thio(oxo)-1,3,2-oxazaphosphorinanes and their *N*-substituted derivatives based on the reactions of the corresponding dichlorophosphates, dichlorothio-, and dithiophosphates with 3-aminopropan-1-ol or its substituted derivatives in the presence of Et_3N or aqueous alkali under phase transfer catalysis conditions, as well as by the reaction of the tetramethylammonium salt of 2-hydroxy-2-thio-1,3,2-oxazaphosphorinane with alkyl- and acyl halides, by that of 2-chloro-2-thio-1,3,2-oxazaphosphorinane with sodium thiolates, and by other methods, were developed. The compounds obtained exhibit high nematocide activity but low toxicity for mammals. Some active synergists for permethrine were found among these compounds.

Key words: derivatives of 2-thio-1,3,2-oxazaphosphorinane, derivatives of 2-oxo-1,3,2-oxazaphosphorinane, insectoacaricides, nematocides, synergists for permethrine.

Our previous works devoted to the search for selective insectoacaricides[1–3] were based on the assumption that the influence of the ratio of oxidative activation (desulfuration) rates upon the action of monooxygenases (MO) and of hydrolytic detoxication upon the action of carboxyl esterases during metabolism in mammals and arthropods could be the basis of prerequisites for the selectivity of action. These assumptions were confirmed by investigations of the metabolism and mechanism of action of the compounds obtained.[4–6] Some compounds synthesized on the basis of this concept are of practical interest as selective insectoacaricides.

The present work describes compounds synthesized for verifying a new hypothesis based on the well studied metabolism of carcinolytic cyclophospamide, 2-[di(2-chloroethyl)amino]-2-oxo-1,3,2-oxazaphosphorinane (**1**).[7,8] The main direction of cyclophosphamide metabolism (Scheme 1) is the transformation upon the action of monooxygenases (MO) to semiaminal (**2**), which is in equilibrium with the aldo-form (**3**). The equilibrium is shifted by spontaneous decomposition of compound **3** affording diamidophosphate (**4**), an active cytotoxic metabolite, and acrolein. Cyclophosphamide **1** itself is practically non-cytotoxic and serves as a

Scheme 1



1 **2** **3** **4**

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 2241—2249, November, 1995.

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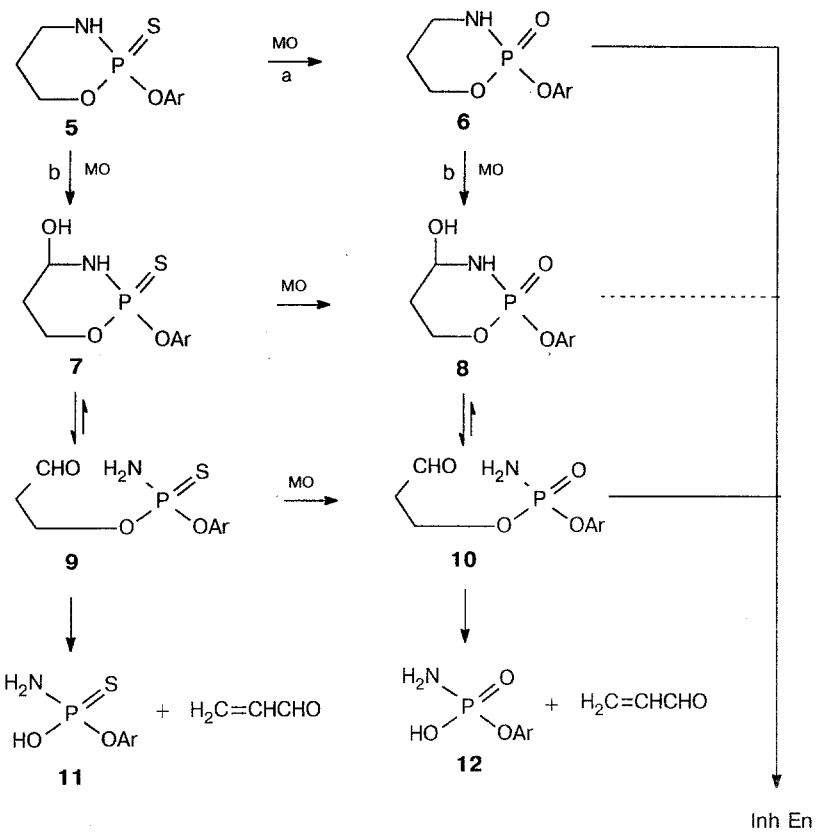
Scheme 2

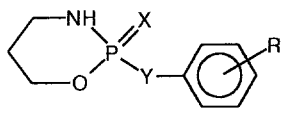


Inh En is the inhibited enzyme

transport form that delivers metabolite **4** to the site of action.

We proposed that 1,3,2-oxazaphosphorinane derivatives, whose molecules contain groups typical of insecticides, *e.g.* OAr (compounds **5**, Scheme 2), instead of the nitrogen mustard residue, would undergo similar transformations. In this case, oxidative desulfuration (activation), which transforms compounds **5** into potential inhibitors of chlolinesterases (**6**) (Scheme 2, path *a*), should proceed faster in arthropoda,[9] whereas hydroxylation (Scheme 2, path *b*), affording products of detoxication **11** and **12** through compounds **7—10**, is more typical of mammals.[8,9] In our opinion, the difference in the ratio of the rates of these metabolic processes in both these organisms can be prerequisites for selectivity of action.

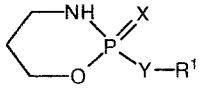
In view of this, we prepared and studied a series of 1,3,2-oxazaphosphorinane derivatives (**13—21**).



13a—s; 14a,f,k,l; 15a—c,f,l,t—v; 16a

13: X = S, Y = O; **14**: X = Y = O; **15**: X = Y = S; **16**: X = O, Y = S

	R		R		R
a	H	**i**	2,4,6-Br_3	**q**	3-Me, 4-MeS
b	4-Me	**j**	2-NO_2	**r**	3-Me, 4-MeS(O)
c	3,4-Me_2	**k**	3-NO_2	**s**	3-Me, 4-$MeSO_2$
d	2-Cl	**l**	4-NO_2	**t**	3-MeO
e	3-Cl	**m**	2-NO_2, 5-Me	**u**	2,5-Cl_2
f	4-Cl	**n**	4-CN	**v**	4-F
g	4-Br	**o**	4-MeC(O)		
h	2,4,5-Cl_3	**p**	2-Pr^iOOC		



17a—c,e,g—l; 18a—d,k—n; 19b,e,f,m,n

17: X = Y = S; **18**: X = O, Y = S; **19**: X = S, Y = O

	R^1		R^1		R^1
a	Me	**f**	Bu^t	**k**	CH_2CH_2SEt
b	Et	**g**	C_5H_{11}	**l**	CH_2COOMe
c	Pr	**h**	C_6H_{13}	**m**	COOMe
d	Pr^i	**i**	C_7H_{15}	**n**	COOEt
e	Bu	**j**	CH_2Ph		

Table 1. Characteristics of compounds **13—21**

Compound	Method	Yield (%)	M.p. °C	Found / Calculated (%)					Empirical formula
				C	H	P	N	S	
13a	A	66	[a]	—	—	13.37 13.51	—	—	$C_9H_{12}NO_2PS$
13b	A	84	69—71	48.88 49.37	5.94 5.80	—	5.95 5.76	—	$C_{10}H_{14}NO_2PS$
13c	A	47	92—93	51.40 51.30	6.40 6.32	11.85 12.00	—	12.50 12.04	$C_{11}H_{16}NO_2PS$
	B	62	92—93						
13d	A	47	64—66	—	—	11.74 11.74	5.52 5.31	—	$C_9H_{11}ClNO_2PS$
13e	A	83	61—63	41.04 40.99	4.53 4.20	—	5.16 5.31	—	$C_9H_{11}ClNO_2PS$
13f	A	80	74—76	41.08 40.99	4.24 4.20	—	5.20 5.31	—	$C_9H_{11}ClNO_2PS$
13g	A	63	84—85	35.09 35.07	3.55 3.59	—	4.78 4.55	—	$C_9H_{11}BrNO_2PS$
13h	A	61	116—118	—	—	9.34 9.31	4.16 4.21	—	$C_9H_9Cl_3NO_2PS$
13i	A	61	191—193	23.18 23.25	1.97 1.95	6.70 6.66	2.82 3.01	—	$C_9H_9Br_3NO_2PS$
13j	A	45	98—100	39.41 39.40	4.36 4.04	11.13 11.30	—	11.70 11.69	$C_9H_{11}N_2O_4PS$
13k	A	60	81—83	39.30 39.42	4.10 4.14	—	9.92 10.21	—	$C_9H_{11}N_2O_4PS$
13l	A	67	99—101[b]	—	—	—	—	—	$C_9H_{11}N_2O_4PS$
13m	A	45	138—140	41.30 41.67	4.50 4.54	10.25 10.74	—	11.70 11.12	$C_{10}H_{13}N_2O_4PS$
13n	A	40	109—111	47.22 47.23	4.59 4.36	11.43 12.18	10.98 11.02	—	$C_{10}H_{11}N_2O_2PS$
13o	A	50	110—111	48.73 48.70	5.27 5.20	11.40 11.42	11.43 11.82	—	$C_{11}H_{14}NO_3PS$
13p	A	26	Oil[c]	49.98 49.52	5.80 5.75	9.64 9.82	—	—	$C_{13}H_{18}NO_4PS$
13q	A	65	112—114[c]	44.99 45.66	5.70 5.57	10.67 10.70	—	22.14 22.16	$C_{11}H_{16}NO_2PS_2$
13r	E	29	133—135[c]	42.87 43.27	4.70 5.28	10.13 10.14	4.40 4.58	—	$C_{11}H_{16}NO_3PS_2$
13s	A	50	122—124[c]	41.14 41.11	4.99 5.02	9.43 9.64	—	20.15 19.96	$C_{11}H_{16}NO_4PS_2$
14a	A	56	63—65	50.42 50.71	5.55 5.67	—	6.78 6.57	—	$C_9H_{12}NO_3P$
14f	A	61	103—105	43.64 43.65	4.37 4.48	—	5.58 5.66	—	$C_9H_{11}ClNO_3P$
14k	A	45	103—105	42.18 41.86	4.50 4.29	12.04 12.00	—	—	$C_9H_{11}N_2O_5P$
14l	A	71	122—124	41.68 41.86	4.40 4.29	—	10.42 10.85	—	$C_9H_{11}N_2O_5P$
15a	A	80	48—49[c]	—	—	12.44 12.62	—	26.98 26.14	$C_9H_{12}NOPS_2$
15b	A	46	105—106[c]	—	—	11.79 11.94	—	25.04 24.72	$C_{10}H_{14}NOPS_2$
15c	A	20	84—85[c]	—	—	11.20 11.33	5.45 5.14	—	$C_{11}H_{16}NOPS_2$
15f	A	46	89—90[c]	—	—	11.04 11.07	—	23.22 22.92	$C_9H_{11}ClNOPS_2$

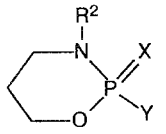
Table 1 (*continued*)

Compound	Method	Yield (%)	M.p. °C	Found / Calculated (%) C	H	P	N	S	Empirical formula
15l	A	25	121—122[c]	37.27 37.22	3.80 3.82	10.57 10.67	9.69 9.69	—	$C_9H_{11}N_2O_3PS_2$
15t	A	71	76—77[c]	— —	— —	11.14 11.25	— —	23.79 23.29	$C_{10}H_{14}NO_2PS_2$
15u	A	50	114—115[c]	34.46 34.40	3.41 3.21	— —	4.23 4.48	20.53 20.41	$C_9H_{10}Cl_2NOPS_2$
15v	A	40	67—68[c]	— —	— —	— —	— —	24.39 24.35	$C_9H_{11}FNOPS_2$
16a	A	57	84—85[c]	— —	— —	14.26 13.51	6.45 6.15	—	$C_9H_{12}NO_2PS$
17a	A	60	[d]	— —	— —	16.94 16.90	— —	35.08 34.99	$C_4H_{10}NOPS_2$
17b	A	70	[d]	— —	— —	15.59 15.70	— —	32.51 32.50	$C_5H_{12}NOPS_2$
17c	A	70	[d]	— —	— —	14.43 14.60	— —	30.66 30.59	$C_6H_{14}NOPS_2$
17e	A	75	[d]	— —	— —	13.69 13.73	— —	28.44 28.45	$C_7H_{16}NOPS_2$
17g	A	30	[d]	— —	— —	— —	5.61 5.61	—	$C_8H_{18}NOPS_2$
17h	A	61	[d]	45.31 45.57	8.40 8.44	—	5.55 5.91	—	$C_9H_{20}NOPS_2$
17i	A	34	[d]	— —	— —	11.16 11.58	5.53 5.24	23.85 23.98	$C_{10}H_{22}NOPS_2$
17j	A	50	[d]	— —	— —	11.89 11.94	— —	24.91 24.72	$C_{10}H_{14}NOPS_2$
17k	D	16	[d]	— —	— —	11.85 12.03	— —	37.34 37.37	$C_7H_{16}NOPS_3$
17l	D	28	[d]	29.81 29.87	5.16 5.19	12.97 12.84	— —	26.65 26.58	$C_6H_{12}NO_3PS_2$
18a	C	55	[e]	— —	— —	— —	— —	— —	$C_4H_{10}NO_2PS$
18c	C	34	[f]	37.22 36.91	7.51 7.23	15.75 15.86	— —	— —	$C_6H_{14}NO_2PS$
18j	C	70	[d]	— —	— —	13.20 13.40	— —	— —	$C_{10}H_{14}NO_2PS$
18k	C	71	[g]	34.58 34.84	6.64 6.68	12.84 12.83	— —	— —	$C_7H_{16}NO_2PS_2$
18l	C	75	[d]	31.72 32.00	5.30 5.37	13.70 13.75	— —	— —	$C_6H_{12}NO_4PS_2$
18m	C	7	[d]	— —	— —	14.97 14.67	— —	— —	$C_5H_{10}NO_4PS$
18n	C	9	[d]	32.30 32.00	5.53 5.37	13.61 13.75	— —	— —	$C_6H_{12}NO_4PS$
19b	A D	30 59	[h] [i]	— —	— —	— —	— —	— —	$C_5H_{12}NO_2PS$
19e	A	50	[d]	40.11 40.18	7.68 7.71	14.62 14.80	— —	15.42 15.32	$C_7H_{16}NO_2PS$
19f	D	50	[d]	40.37 40.18	7.75 7.71	14.96 14.80	— —	— —	$C_7H_{16}NO_2PS$
19m	C	14	[d]	— —	— —	14.35 14.67	— —	— —	$C_5H_{10}NO_4PS$
19n	C	40	[d]	32.12 32.00	5.48 5.37	13.53 13.75	— —	— —	$C_6H_{12}NO_4PS$
20a	A	30	[d]	— —	— —	19.56 20.50	— —	— —	$C_4H_{10}NOPS$
20b	A	55	81—83	50.51 50.70	5.84 5.67	14.39 14.53	— —	15.18 15.04	$C_9H_{12}NOPS$
20c	A	60	49—51	42.40 41.67	4.79 4.54	10.59 10.74	— —	10.99 11.12	$C_{10}H_{13}N_2O_4PS$
20d	A	31	68—69[c]	45.56 46.32	5.84 5.44	11.95 11.94	5.41 5.40	25.23 24.73	$C_{10}H_{14}NOPS_2$

Table 1 (*continued*)

Compound	Method	Yield (%)	M.p. °C	Found / Calculated (%) C	H	P	N	S	Empirical formula
20f	A	28	104—105[c]	50.40 50.14	6.57 6.31	10.88 10.78	5.01 4.89	22.30 22.31	$C_{12}H_{18}NOPS_2$
20g	A	45	42—43	45.30 45.56	5.51 5.42	—	8.53 8.86	—	$C_{12}H_{17}N_2O_4PS$
20h	A	30	54—58[c]	—	—	10.21 10.27	—	20.99 21.27	$C_{13}H_{20}NOPS_2$
20i	A	50	82—84[c]	53.72 53.65	6.48 6.43	9.70 9.88	4.43 4.47	20.52 20.46	$C_{14}H_{20}NOPS_2$
20j	A	20	122—123[c]	54.94 55.11	6.81 6.77	9.60 9.46	4.39 4.30	19.70 19.58	$C_{15}H_{22}NOPS_2$
20k	A	25	79—80[c]	57.11 57.28	5.85 5.41	9.98 9.23	4.09 4.19	18.86 19.11	$C_{16}H_{18}NOPS_2$
20l	A	40	80—90[c]	58.79 58.43	6.23 5.77	8.88 8.86	3.94 4.01	18.11 18.35	$C_{17}H_{20}NOPS_2$
20m	A	43	117—118	59.13 59.00	5.49 5.28	9.98 10.14	4.60 4.59	—	$C_{15}H_{16}NO_2PS$
20n	A	50	91—92	60.11 60.17	5.37 5.68	9.71 9.70	4.81 4.39	—	$C_{16}H_{18}NO_2PS$
20p	A	57	108—109	53.03 53.02	4.45 4.50	9.18 9.12	4.27 4.50	—	$C_{15}H_{15}ClNO_2PS$
20q	A	54	102—104	51.53 51.43	4.28 4.32	—	7.81 8.00	—	$C_{15}H_{15}N_2O_4PS$
21e	A	50	[j]	44.94 45.55	8.44 8.50	12.70 13.05	—	—	$C_9H_{20}NO_2PS$
21g	A	45	54—55	48.00 48.00	5.95 5.71	—	9.20 9.33	—	$C_{12}H_{17}N_2O_5P$
21m	A	54	66—67	62.64 62.28	5.50 5.58	10.72 10.71	4.95 4.84	—	$C_{15}H_{16}NO_3P$
21n	A	47	89—90	63.52 63.36	5.94 5.98	10.22 10.21	4.24 4.62	—	$C_{16}H_{18}NO_3P$
21o	A	68	58—59	55.55 55.65	4.42 4.67	—	4.42 4.33	—	$C_{15}H_{15}ClNO_3P$
21p	A	40	80—82	55.73 55.65	4.66 4.67	9.50 9.57	4.55 4.33	—	$C_{15}H_{15}ClNO_3P$
21r	A	60	[d]	53.14 53.12	6.65 6.69	11.23 11.42	5.17 5.16	—	$C_{12}H_{18}NO_2PS$

[a] Oil purified by chromatography on SiO_2, n_D^{20} 1.5855, d_4^{20} 1.2987; literature data[11]: 37 % yield. [b] Literature data[10]: 32 % yield, m.p. 101—103 °C. [c] Purified by chromatography on SiO_2. [d] Viscous oil purified by chromatography on SiO_2. [e] n_D^{20} 1.5387; literature data[20]: n_D^{24} 1.5360. [f] n_D^{20} 1.5202, d_4^{20} 1.2239. [g] n_D^{20} 1.5561, d_4^{20} 1.2673. [h] B.p. 104—106 °C (0.03 Torr), n_D^{20} 1.5188, d_4^{20} 1.2356; literature data[12]: b.p. 109—110 °C (0.04 Torr), n_D^{20} 1.5156, d_4^{20} 1.2303. [i] n_D^{20} 1.5224, d_4^{20} 1.2394. [j] Purified by chromatography on SiO_2, n_D^{24} 1.4982.



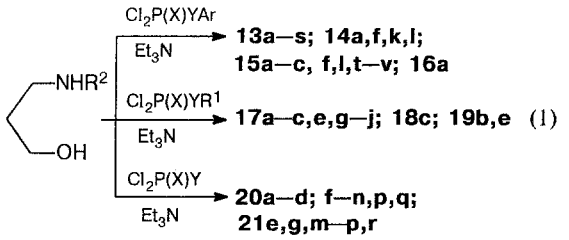
20a—d; f—n,p,q; 21e,g,m—p,r

20: X = S, **21**: X = O

R^2, Y	R^2, Y	R^2, Y
a H, Me	**g** Pr^i, 3-$NO_2C_6H_4O$	**m** Ph, PhO
b H, Ph	**h** Bu^s, PhS	**n** Ph, 4-$MeOC_6H_4O$
c Me, 3-$NO_2C_6H_4O$	**i** cyclo-C_5H_9, PhS	**o** Ph, 2-ClC_6H_4O
d Me, PhS	**j** cyclo-C_6H_{11}, PhS	**p** Ph, 3-ClC_6H_4O
e Pr^i, PrS	**k** $PhCH_2$, PhS	**q** Ph, 3-$NO_2C_6H_4O$
f Pr^i, PhS	**l** Ph(Me)CH, PhS	**r** Ph, PrS

Three of these compounds, **13a, 1**, and **19b**, were prepared earlier for other purposes by the reaction of 2-chloro-2-thio-1,3,2-oxazaphosphorinane with ethanol and 4-nitrophenol in the presence of Et_3N[10] or with sodium phenoxide,[11] as well as by addition of sulfur to 2-ethoxy-1,3,2-oxazaphosphorinane.[12]

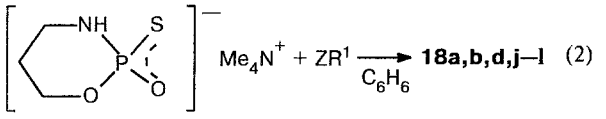
A general method affording higher yields of compounds was used to synthesize the majority of compounds **13—21**, *i.e.*, the reaction of dichlorothio-[13,14] and dithiophosphates[15,16] or dichlorophosphates[17] with 3-aminopropan-1-ol or its *N*-substituted derivatives[18,19] in the presence of Et_3N (method A, equation (1), Table 1).



(1)

This reaction can also be carried out in the presence of aqueous alkali under phase transfer catalysis conditions (method B, Table 1).

2-Alkyl(or substituted alkyl)thio-2-oxo-1,3,2-oxazaphosphorinanes were also obtained by alkylation of the tetramethylammonium salt of 2-hydroxy-2-thio-1,3,2-oxazaphosphorinane (**22**)[20] with alkyl halides in C_6H_6 (method C, equation (2), Table 1).



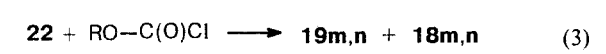
(2)

22

Z = Cl, Br, I;
R^1 = Me, Pr^i, $PhCH_2$, CH_2CH_2SEt, CH_2COOMe

Only thiol esters are formed upon alkylation, except in the reaction with $PhCH_2Br$. In the latter case, the products of S- and O-alkylation (TLC, ^{31}P NMR) in a *ca.* 100 : 1 ratio were obtained.

Acylation of salt **22** with methyl- and ethylchlorocarbonates affords a mixture of thione and thiol isomers in a 5 : 1 ratio, according to ^{31}P NMR (method C, equation (3), Table 1).

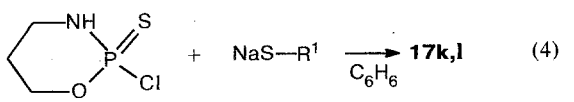


(3)

The isomers were isolated in a pure state using SiO_2 column chromatography.

Thus, alkylation and acylation of salt **22** in benzene generally occurs in a similar way to those of sodium salts of acyclic phosphorus thioacids in alcohol and dioxane.[21,22]

2-Alkylthio-2-thio-1,3,2-oxazaphosphorinane derivatives with functionally substituted alkyl groups were prepared by the reaction of 2-chloro-2-thio-1,3,2-oxazaphosphorinane[10] with the corresponding sodium thiolates in benzene (method D, equation (4), Table 1).



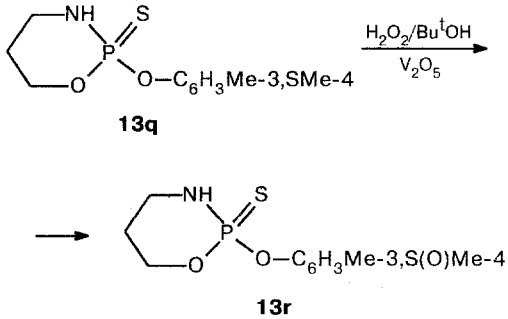
(4)

Table 2. Toxicity of compounds **13—15** and **17—20** to mice, aphids, and mites

Compound	LD_{50} mg kg^{-1} Mice	Death percent at a cut-off concentration (LC_{50} (%)) Black beet aphids 0.01 %		Spider mite 0.05 %	
13d	>2000	—		100	(0.013)
13g	>1500	5		0	
13h	>3500	0		100	(0.002)
13i	>4000	10		0	
13k	>1000	20		0	
13l	>1000	40		24	
14l	<1000	20		14	
15a	700	100	(0.002)	0	
15v	—	95		0	
17c	—	0		100	(0.04)
18a	—	90		0	
18b	—	80		0	
18c	150	—		100	(0.006)
19b	—	25		5	
20j	—	—		30	
20k	—	—		22	
20q	—	15		100	(0.0012)
Carbophos	400	100	(0.002)	—	
Metaphos	50	—		100	(0.001)

It should be noted that when this reaction is carried out with 2-(ethylthio)-ethane-1-thiol in EtOH and even in Bu^{t}OH, the corresponding 2-alkoxy-2-thio-1,3,2-oxazaphosphorinanes **19b,f** are unexpectedly formed as the main products, instead of the 2-(2-ethylthioethylthio)-derivative (**17**), and the yield of dithiophosphate **17k** is only 3—5 %, according to ^{31}P NMR.

2-(3-Methyl-4-methylsulfinylphenoxy)-2-thio-1,3,2-oxazaphosphorinane **13r** was obtained by oxidation of the corresponding 4-methylthio-derivative **13q** with anhydrous hydrogen peroxide catalyzed by V_2O_5 in Bu^{t}OH[23] (method E, equation (5), Table 1).



(5)

The structure of compounds obtained was confirmed by spectral data (IR, ^{31}P NMR). The purity of the compounds was confirmed by TLC and elementary analyses. In some cases, chromatography on SiO_2 was used for purification or separation of the products.

Table 3. Nematocide activity of compounds **13—15**, **18**, **20**, and **21**

Compound	LD_{50} mg kg^{-1} Mice	LC_{50} (%) (*in vitro*)			Reduction of gall-formation (%) at a given concentration (g/kg of soil)	
		Stem potato nematode	Rice aphelenchoid	Alfalfa aphelenchoid cyst-forming nematode		
13k	>1000	0.00083	—	—	87 88	(0.08) (0.096)
13o	—	0.00028	—	—	47	(0.096)
13r	—	0.00025	—	—	43	(0.096)
14k	55	0.00016	0.00027	[a]	92	(0.08)
15a	700	0.0033	0.0033	—	96[b]	
18c	150	—	—	—	93	(0.08)
20g	625	0.00017	0.00028	0.0039	88	(0.096)
21g	260	0.00025	0.00034	[a]	82	(0.096)
Heterophos	30	—	—	0.0039	77—93; (0.08)	84—99 (0.096)
Ethaphos	300	0.00015	0.00021	[a]	—	

[a] Non-toxic. [b] Saprogenous nematode at 0.00027 g/kg of soil (100 % heterophos).

For the compounds obtained, we determined the toxicity (LD_{50}) to white mice (orally) and studied the contact insecticide activity for housefly imagoes *Musca domestica*, rice weevil beetles *Calendra oryzae*, and black beet aphids *Aphis fabe*, the contact acaricide activity for spider mite *Tetranychus urticae* (% of deaths at a cut-off concentration and LC_{50}*), the nematocide activity *in vitro* (LC_{50}) for stalk potato nematodes *Ditylenchus destructor*, rice aphelenchoids *Aphelenchoides besseyi*, and lucerne cystogenous nematodes *Heterodera medicaginis*, as well as the nematocide activity in vegetative experiments in soil (reduction of gall-formation as a % of control at a given concentration of compounds in soil) for gall nematodes *Meloidogyne incognita*, *Meloidogyne arenaria*, and saprogenous nematode *Panagrellus red.* The corresponding data are given in Tables 2 and 3. As can be seen from the Tables, most of the compounds, as could be expected, have a low toxicity to mice. The compounds were found to be weak insecticides, they are not active with respect to houseflies and rice weevil beetles and only slightly more active with aphids, and **15a** is the only compound which is close to the standard (see Table 2). The compounds are somewhat more active as acaricides, but only compounds **13h**, **18b**, and **20q** are close to the standard (see Table 2). However, the highest activity (at a standard level) exhibited by these compounds was the activity against gall and stem nematodes (see Table 3). Compounds **13k**, **14k**, **20g**, and **21g** are particularly active, and their effectiveness is comparable to the significantly more toxic heterophos.

* LC_{50} is the concentration of a compound (%) that causes the death of 50 % of the organisms.

Thus, the structure of 1,3,2-oxazaphosphorinane favors decreasing the toxicity of compounds for mammals as compared with acyclic analogs and causes some change in the spectrum of pesticide activity. The compounds exhibit high selectivity of action, which is the most pronounced in the case of 1,3,2-oxazaphosphorinane derivatives with nematocide activity.

Compounds **13—21** were also tested as synergists for permethrine for houseflies (SRS race) and German cockroaches *Blattella germanica* (the synergistic activity is expressed as joint action coefficients, JAC). The majority of compounds tested exhibit synergistic activity, and some of them exceed the standards, piperonylbutoxide (PPB) and *S,S,S*-tributyltrithiophosphate (TBTP), particularly for cockroaches. The corresponding data are given in Table 4.

Experimental

IR spectra were obtained on a UR-20 spectrophotometer from KBr pellets or thin layers without a solvent. $^{31}P-\{^1H\}$ NMR spectra were recorded on Bruker HX-90 and Bruker WP 200-SY spectrometers in $CDCl_3$, MeCN, Me_2CO, CH_2Cl_2, and DMF using 85 % H_3PO_4 as the standard.

Thin-layer chromatography was carried out on Chemapol L 100/160 μm SiO_2 in hexane—acetone, 4 : 1 and 3 : 2. Purification and isolation of compounds were carried out on a column with the same carrier but with mass ratio compound : SiO_2 = 1 : 15; hexane—acetone mixtures, 100 : 1 to 3 : 2, were used as eluents.

Derivatives of 2-thio(oxo)-1,3,2-oxazaphosphorinanes and 2-thio(oxo)-3-alkyl(phenyl)-1,3,2-oxazaphosphorinanes (13—21). Method A. A mixture of the corresponding 3-aminopropan-1-ol (55 mmol) and Et_3N (111 mmol) in CH_2Cl_2 (25 mL) was added dropwise with stirring over a period of 3 h to a solution of the phosphoryl, thiophosphoryl,

Table 4. Synergistic activity coefficients for compounds **13** and **15—20** mixed with permethrine in a 10 : 1 ratio

Compound	JAC[a]	
	Flies, SRS race	German cockroaches
13a	1.3	2.3
13b	2.1	2.8
13d	2.3	1.5
13m	1.0	1.6
15a	2.3	2.8
16a	1.5	1.5
17b	1.7	3.9
17c	1.0	4.2
17e	1.8	5.2
17g	1.0	3.7
17h	0.7	1.8
17i	1.0	1.8
17j	1.2	2.0
18c	0.8	1.2
19b	1.6	1.5
19e	1.0	1.0
20a	2.8	1.3
20b	0.9	3.0
PPB	2.1	1.0
TBTP	2.0	4.0

[a] Confidence intervals were ±0.1—0.2 for flies and ±0.1—0.3 for cockroaches.

dithiophosphoryl, or thiophosphonyl dichloride (55 mmol) in dry CH_2Cl_2 (60 mL) in such a way that the temperature of the mixture did not exceed 20 °C (5—10 °C for aryl dichlorophosphates). The mixture was kept at 20 °C for 12 h, the precipitate was filtered off, the filtrate was washed with cold water (3 × 20 mL; in the case of 3-phenyl-1,3,2-oxazaphosphorinane derivatives, the filtrate was additionally washed twice with dilute HCl (1 : 10), saturated $NaHCO_3$, and water (15 mL each)), dried with Na_2SO_4, and the solvent was finally distilled off *in vacuo* (75—80 °C/1 Torr at the end of distillation). The residue was purified by crystallization or chromatography on SiO_2. If required, the product can be additionally purified by boiling with active carbon in $CHCl_3$. Compounds **13a—s**, **14a,f,k,l**, **15a—c,f,l,t—v**, **16a**, **17a—c,e,g—j**, **18c**, **19b,e**, **20a—d,f—n,p,q**, and **21e,g,m—p,r** were obtained using this method (see Table 1).

Compounds 13, **19**, and **20c,g,n,p,q**. IR, KBr or thin layer without a solvent, ν/cm^{-1}: 3360—3420 (NH, absent for compounds **20**); 1200—1220 (P—O—C(aryl), absent for compounds **19**); 1050—1060 (P—O—C(alkyl)); 630—660, 690—710 (P=S). ^{31}P—{^1H} ($CDCl_3$, MeCN, DMF, δ: 58—67.1 (s); **16a** (Me_2CO): 20.2 (s); **18c** ($CDCl_3$): 27.07 (s).

Compounds 14 and **21g,m—p**. IR, KBr, ν/cm^{-1}: 3200—3250 (NH involved in an H-bond, absent for compounds **21**); 1250—1265 (P=O); 1210—1220 (P—O—C(aryl)); 1050—1060 (P—O—C(alkyl)). ^{31}P-{^1H} of **21p**, CH_2Cl_2, δ: −5.29 (s).

^{31}P—{^1H} NMR of compounds **15** (except **15v**), **17a—s,e,g—j**, and **20d—f,i—k**, Me_2CO, δ: 76—86 (s); **15v**: 79.5 (d, J_{P-F} = 5 Hz); **20h**: 83.2 (s), 84.4 (s) (Δδ 1.2); **20l**: 83.9 (s), 84.1 (s) (Δδ 0.2).

Method B. 2-(3,4-Dimethylphenoxy)-2-thio-1,3,2-oxazaphosphorinane (13c). A solution of 3-aminopropan-1-ol in CH_2Cl_2 (5 mL) and 50 % aqueous NaOH were added at 0—5 °C with vigorous stirring over a period of 2 h to a mixture of *O*-(3,4-dimethylphenyl) dichlorothiophosphate (1.82 g, 7 mmol) and triethylbenzylammonium chloride (0.16 g, 0.7 mmol) in CH_2Cl_2 (15 mL). The addition was performed in small portions, alternately from two dropping funnels, so that the content of both funnels was consumed simultaneously. After 2 h at 0—5 °C, the solution was decanted, washed twice with ice water, and dried with Na_2SO_4. The solvent was distilled off *in vacuo* (75—80 °C/1 Torr at the end of the process), and the residue was extracted many times with ether at 20 °C. The ethereal extract was concentrated *in vacuo*, and the residue was crystallized from EtOH to give 1.12 g (62 %) of compound **13c**, m.p. 92—93 °C.

Method C. 2-(Methoxycarbonylmethylthio)-2-oxo-1,3,2-oxazaphosphorinane (13l). A mixture of compound **22** (3.44 g, 15 mmol) and methyl bromoacetate (2.18 g, 14 mmol) in dry C_6H_6 (35 mL) was refluxed with stirring for 6 h and filtered. The filtrate was washed with cold water (3 × 20 mL) and dried with Na_2SO_4. The C_6H_6 was removed *in vacuo* (75—80 °C/1 Torr at the end of the process). The residue was purified by chromatography on SiO_2 to afford 2.43 g (75%) of **18l** (see Table 1). ^{31}P—{^1H} NMR, $CDCl_3$, δ: 22.03 (s).

The same procedure was used for the preparation of compounds **18a** (from MeI), **18b** (from EtI), and **18d** (from Pr^{i}I). ^{31}P—{^1H} NMR, $CDCl_3$, δ: 25—27.4 (s).

Compound **18j** was obtained from $PhCH_2Br$ (1 h at 20 °C and 0.5 h at 45 °C). ^{31}P—{^1H} NMR, $CDCl_3$, δ: 26.30 (s), 68.86 (s) (the ratio of integral intensities was ~100 : 1).

Compound **18k** was obtained from $ClCH_2CH_2SEt$ (refluxing for 30 h). IR (without a solvent), ν/cm^{-1}: 3230 (NH involved in H-bonds), 1250 (P=O), 1050 (P—O—C). ^{31}P—{^1H} NMR, $CDCl_3$, δ: 26.43 (s).

2-Ethoxycarbonyloxy-2-thio (19n) and 2-ethoxycarbonylthio-2-oxo-1,3,2-oxazaphosphorinanes (18n). Ethyl chlorocarbonate (1.63 g, 15 mmol) was added with stirring to a solution of **22** (3.59 g, 16 mmol) in dry C_6H_6 (35 mL), and the mixture was refluxed for 6 h. The precipitate was filtered off, and the filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$, washed with ice water (2 × 15 mL), and dried with Na_2SO_4. Removal of $CHCl_3$ *in vacuo* afforded a mixture of **19n** and **18n** (2.53 g, 75 %). ^{31}P—{^1H} NMR, $CDCl_3$, δ: 58.62 (s), 15.42 (s), ratio of integral intensities 5 : 1. The mixture was separated using chromatography on SiO_2 to give 1.34 g (40 %) of **19n**. [IR, ν/cm^{-1}: 3380 (NH), 1765 (C=O), 1050 (P—O—C). ^{31}P—{^1H} NMR, $CDCl_3$, δ: 58.60 (s)] and 0.30 g (9 %) of **18n** [^{31}P—{^1H} NMR, $CDCl_3$, δ: 15.45 (s) (see Table 1)].

2-Methoxycarbonyloxy-2-thio- (19m) and 2-methoxycarbonylthio-2-oxo-1,3,2-oxazaphosphorinanes (18m). A mixture of compounds **19m** and **18m** was obtained in a similar way in 50 % yield; ^{31}P—{^1H} NMR, $CDCl_3$, δ: 58.39 (s), 15.16 (s) (ratio of integral intensities 5 : 1). Chromatography on SiO_2 afforded 14 % **19m** and 7 % **18m** (see Table 1).

Method D. 2-(Methoxycarbonylmethylthio)-2-thio-1,3,2-oxazaphosphorinane (17l). Methyl mercaptoacetate (2.65 g, 25 mmol) was added to MeONa prepared from Na (0.53 g, 23 mg-atom) in MeOH (15 mL). MeOH was totally removed *in vacuo*, and dry C_6H_6 (20 mL) was added to the residue. 2-Chloro-2-thio-1,3,2-oxazaphosphorinane (3.43 g, 20 mmol) was added to the suspension obtained, and the mixture was refluxed with stirring for 6 h. The mixture was then washed with cold water (2 × 20 mL) and dried with Na_2SO_4. The C_6H_6 was distilled off *in vacuo*, and the residue was purified by chromatography on SiO_2 to afford 1.35 g (28 %) of product **17l**. ^{31}P—{^1H} NMR, $CDCl_3$, δ: 82.90 (s) (see Table 1).

2-(2-Ethylthioethylthio)-2-thio-1,3,2-oxazaphosphorinane (17k) (0.85 g, 16 %) was obtained under similar conditions

from 2-(ethylthio)ethane-1-thiol (3.06 g, 25 mmol). $^{31}P-\{^1H\}$ NMR, $CDCl_3$, δ: 84.08 (s) (see Table 1).

2-Ethoxy-2-thio-1,3,2-oxazaphosphorinane (19b) was isolated in 59 % yield as the only product when the reaction described above was carried out in EtOH. $^{31}P-\{^1H\}$ NMR, $CDCl_3$, δ: 67.10 (s) (see Table 1).

2-*tert*-Butoxy-2-thio-1,3,2-oxazaphosphorinane (19f) was isolated in 50 % yield when the reaction was carried out in Bu^tOH. $^{31}P-\{^1H\}$ NMR, $CDCl_3$, δ: 58.37 (s) (see Table 1).

Method E. 2-(3-Methyl-4-methylsulfinylphenoxy)-2-thio-1,3,2-oxazaphosphorinane (13r). A solution of 8.5 % H_2O_2 (1.6 g) in Bu^tOH (0.136 g, 4 mmol H_2O_2),[23] in which V_2O_5 (0.005 g) was preliminarily diluted, was added in small portions at 20 °C to a solution of **13q** (1.16 g, 4 mmol) in a mixture of Bu^tOH (16 mL) and CH_2Cl_2 (10 mL). Each subsequent portion of the H_2O_2 solution was added after the previous portion discolored. After H_2O_2 addition was completed, the mixture was kept at 20 °C for 2.5—3 h. TLC was used to monitor the course of the reaction. If needed, one or two portions of the same H_2O_2 solution (but without V_2O_5) were added. The criterion of reaction completion was the observation that decolorization of the reaction mixture no longer occurred and the TLC spot of the starting **13g** disappeared. The mixture was diluted with CH_2Cl_2, washed twice with cold water, and dried with Na_2SO_4, and the solvents were distilled off *in vacuo*. The residue (0.80 g) was purified by chromatography on SiO_2 to give 0.35 g (29 %) of compound **13r**, m.p. 133—135 °C (see Table 1). $^{31}P-\{^1H\}$ NMR, CH_2Cl_2, δ: 61.37 (s).

Determination of toxicity to mice and arthropoda was described in detail previously.[3]

Determination of toxicity to nematodes. In the *in vitro* laboratory experiments, the toxicity was determined by sinking nematodes (30—40 species) into working solutions of compounds (or into distilled water for control). After 7 days, alive and dead nematodes were calculated using a binocular microscope. LC_{50} was calculated as described previously.[24]

In vegetative experiments with gall nematodes, the compounds were introduced into a soil invasioned with gall nematode larvae, in the form of sand granulate (prepared by mixing 30 g of sand and a solution of a compound followed by removal of the solvent) by uniform mixing 5 days before seeding a cucumber culture. The efficiency of action was estimated 25 days after seeding by estimation of reduction in gall-formation on the plantule roots as compared with control. The percent of reduction in gall-formation was calculated by the formula $T = (a - b) \cdot a^{-1} \cdot 100$, where a is the mean value of galls in the control, and b is the mean value of galls under experimental conditions.

Determination of the synergistic activity. The toxicity of permethrine, compounds under study, and their mixtures for insects was determined by topical application of 1 μL of acetone solutions with different concentrations on mesonotum of imago of houseflies (SRS race) and prothorax of German cockroaches. The degree of toxicity was determined by calculating LD_{50} (μg/g).[24] The joint action coefficients (JAC) were calculated as described previously.[25]

This study was financially supported in part by the International Science Foundation (Grant Nos. NDO 000 and NDO 300) and by the Russian Foundation for Basic Research (Grant No. 93-03-0451). The authors are grateful for this support.

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Received April 20, 1995