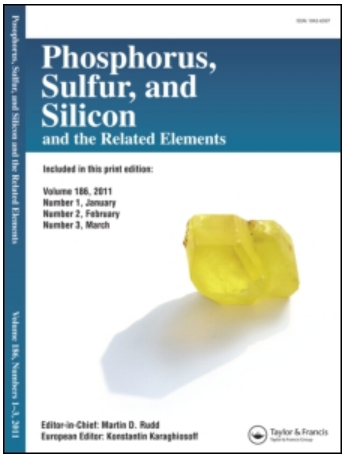

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SYNTHESIS, BIOLOGICAL ACTIVITY AND MECHANISM OF ACTION OF 1,3,2-OXAZAPHOSPHORINANE DERIVATIVES

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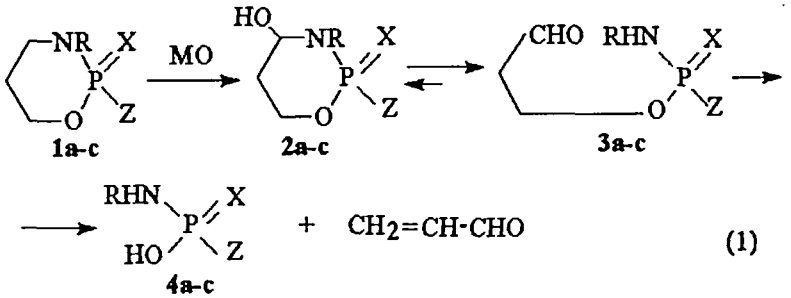
Abstract The title compounds were obtained by the reaction of the corresponding phosphorodichloridates with 3-aminopropanol-1 in the presence of an organic base or under phase transfer conditions, and by some other methods. They are highly active nematocides and sinergists to permethrin with low toxicity to mammals. Some peculiarities of mechanism of action of the compounds were established.

The searching for selective pesticides among the derivatives of 1,3,2-oxazaphosphorinane is founded on the new hypothesis, based on the well-studied metabolism of cancerolitic cyclophosphamide (**1a**) [1] (equation 1).



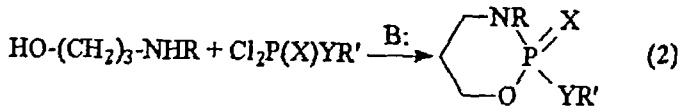
a: R = H, X = O, Z = $N(CH_2CH_2Cl)_2$; **b**: R = H, Alkyl, Ph, X = S, Z = YR';

c: R = H, Alkyl, Ph, X = O, Z = YR'; Y = O, S; R'= Ar, Alkyl.

We suggested, that thioderivatives **1b** with typical for insecticides leaving groups (Z= =YR') insted of the nitrogen mustard residue of **1a** would undergo analogous metabolic transformations. In this case oxydative desulfuration (activation) of **1b** to **1c**, involving the formation of cholinesterase inhibitors, should occur faster in arthropoda,

whereas *hydroxylation* to **2b,c** under the action of monooxygenases, leading eventually to the detoxication products **4b,c** is more typical for mammals. The differences in the rates ratios of these metabolic reactions in arthropoda and mammals could be a factor of selectivity.

The most general method of synthesis of the title compounds is presented by the equation (2):



(2)

where B: - Et_3N or aqueous NaOH (CH_2Cl_2, phase transfer conditions). Some of monothioderivatives were obtained by the reaction of tetramethylammonium salt of 2- oxy-2-thio-1,3,2-oxazaphosphorinane [2] with alkyl halides (only S-products were formed) and with alkyl chlorocarbonates (O- and S-isomers in the ratio 5:1 were obtained). Dithioderivatives (**1b**; Z = SR'), where R' is a substituted alkyl group, were synthesized by the reaction of 2-chloro-2-thio-1,3,2-oxazaphosphorinane with sodium mercaptides.

Most of the compounds **1b** have a low toxicity for mice (LD_{50} 1000-3500 mg/kg, orally) and possess a weak insecticidal activity - only the compound **1b** (R = H, Z = SPh; LC_{50} 0.002%) as aphicide against black been aphids is at the llevel of malathion (LC_{50} 0.002%). As acaricides the compounds are more active, but only **1b** (R = H, Z = 2,4,5-$Cl_3C_6H_2O$; LC_{50} 0.002%) and **1c** (R = H, Z = PrS; LC_{50} 0.006%) against spider mites are near the level of parathion-methyl (LC_{50} 0.001%). Many of the compounds **1b,c** are active nematocides at the level of ethaphos and geterophos: potato stalk nematodes - LC_{50} 0.00016-0.00083% (ethaphos, LC_{50} 0.00015%); rice aphelenchoides - LC_{50} 0.00027-0.00034% (ethaphos, LC_{50} 0.00021%); lucerne cystogenous nematodes (**1b**; R = i-Pr, Z = 3-$NO_2C_6H_4O$) - LC_{50} 0.00039% (geterophos, LC_{50} 0.00039%). The compounds, where Z = 3-$NO_2C_6H_4O$ (**1b**, R = H, LD_{50} >1000 mg/kg; **1b**, R = i-Pr, LD_{50} 625 mg/kg and **1c**, R = i-Pr, LD_{50} 260 mg/kg) are active against gall nematodes in soil, providing 88% reduction of gall formation at the concentration 0.096 g/kg of soil, that is at the level (84-99%) of considerably more toxic geterophos (LD_{50} 30 mg/kg).

Some peculiarities of the compounds **1b,c** biological action were also observed. In toxicological experiments on mice the compounds show a typical clinical picture of

poisoning by cholinesterase inhibitors. However, the oxones **1c** possess an extremely low, compared to acyclic analogs, ability to inhibit human acetyl cholinesterase (AChE) and american cockroach cholinesterase (ChE). Some of the compounds **1c** are active inhibitors of american cockroach carboxyesterase (CE). For the compounds **1c** (R = H) Z and rate constants of inhibition (k_2, $M^{-1}.min^{-1}$) for AChE, ChE and CE are given: 4-ClC_6H_4O, $6.7.10^1$, $1.2.10^1$, $1.1.10^4$; 3-$NO_2C_6H_4O$, $2.4.10^2$, no inhibition, $5.4.10^4$; 4-$NO_2C_6H_4O$, $3.7.10^3$, $1.4.10^3$, $2.2.10^4$ (paraoxon, $3.7.10^5$, $4.3.10^5$, -); $EtSCH_2CH_2S$, $7.3.10^1$, no inhibition, $6.3.10^2$ (isosistox, $6.4.10^3$, -, -). A low anticholinesterase activity of the compounds **1c** was explained by one of us on the basis of the molecular mechanics calculations [3]. It was shown to be caused by steric hindrances, indused by the cyclic part of molecule, to a nucleophilic reaction of inhibitors with serine hydroxyl group.

However, a low inhibitory activity of the oxone **1c** (R = H, Z = 3-$NO_2C_6H_4O$) does not explain its high toxicity (LD_{50} 55 mg/kg) compared to that of the corresponding thione **1b** (LD_{50} >1000 mg/kg). It means, that this oxone can transformate *in vivo* to a more active cholinesterase inhibitor. This bioactivation was confirmed by the interaction of this oxone with the mixture of AChE and mice liver monooxygenase (MO) in the absence and in the presence of coenzyme NADPH. The results are given in Fig. 1

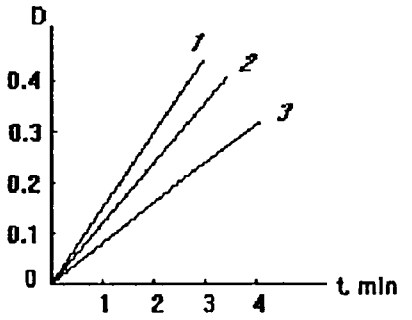


FIGURE 1. The Ellman kinetics of acetyl thiocholine iodide hydrolysis.

(the Ellman kinetics of acetyi thiocholine iodide hydrolysis, which is measured by an increase in optical density (*D*) over time (*t*)), where the line *1* presents an initial activity of AChE and MO mixture. The decreas of AChE activity in this mixture after 27 min incubation with the oxone (line *2*) is due to inhibition only by this compound because in the absence of NADPH MO is inactive. In the presence of NADPH the residual activity

is significantly lower (line *3*). It is a direct evidence of the formation of a more active inhibitor, which is very likely to be the compound **3c** (R = H, Z = 3-NO_2- C_6H_4O).

Since the compounds **3c** by analogy with the corresponding metabolite of cyclophosphamide **3a** can be unstable, we synthesized closely related in structure, but stable model compounds $H_2N(EtO)P(O)Z$ (**5**). They are actually considerably more active inhibitors of AChE, ChE and CE, than their cyclic analogs (Z and k_2 for AChE, ChE and CE are given): 4-ClC_6H_4O, $2.4.10^4$, $7.0.10^2$, $7.5.10^5$; 3-$NO_2C_6H_4O$, $4.4.10^5$, $1.1.10^5$, $1.3.10^7$.

Furthermore, the thione **1b** (R = H, Z = 3-$NO_2C_6H_4O$) does not desulfurate to the oxone **1c**, and suppresses desulfuration of insecticide dichlorone - $(EtO)_2P(S)SCH_2Cl_2$, that is the thiones **1b** inhibit MO. Hence, a low toxicity of thiones **1b** may be partially due to self-inhibition of desulfuration (activation), and a high toxicity of the oxones **1c** is due to metabolic convertion to more active AChE inhibitors.

Due to the ability of the compounds **1b** to inhibit MO, and their metabolites **1c** and **3c** - to inhibit CE - the both enzymes, detoxicating pyrethroids in insects, the thiones **1b** can be synergists to these preparations. In fact, the compounds **1b** in the mixture with permethrine (10:1) was shown to possess a high synergetic activity towards houseflies and german cockroaches with synergy coefficients (SC) being close to that of piperonyl butoxide (PB) conserning houseflies (**1b**, SC 1.2-2.4; PB - 2.1) and considerably higher conserning cockroaches (**1b**, SC 1.5-5.2; PB - 1.1).

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