NEW TYPE OF SELECTIVELY ACTING ORGANOPHOSPHORUS INSECTICIDES AND ACARICIDES

COMMUNICATION 2. METHYLDITHIOPHOSPHONIC ACID DERIVATIVES

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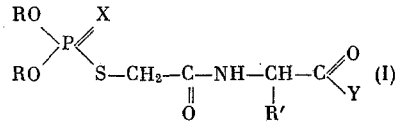
UDC 541.69:661.718.1

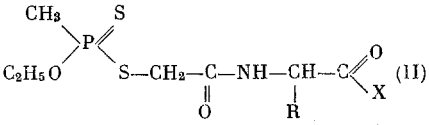
In a previous paper [1] we discussed a new type of selectively acting insecticides and acaricides, namely derivatives of the mono- and dithiophosphoric acids, containing the moieties of amino acids, their esters and methylamides (I)



(I)

X=O or S; Y=OH, OC_2H_5 or $NHCH_3$; R=CH_3, C_2H_5 or i-C_3H_7; R′=H, CH_3, i-C_3H_7, n-C_3H_7, i-C_4H_9, $CH_2C_6H_5$, $CH_2C_6H_4OH$, $CH_2CH_2SCH_3$, etc.

The obtained compounds belong to the type of anticholinesterase substances, in which connection their toxicity and also their selectivity of action are strongly dependent on the nature of the amino acids that enter into the molecule. Included among the described compounds were effective selective insecticides and acaricides with either a low or moderate toxicity toward warm-blooded animals. Since it is known that phosphonic acid derivatives, when compared with phosphates, are frequently stronger cholinesterase inhibitors, it was interesting to investigate the analogous series of methyldithiophosphonates of general formula (II)



(II)

R=H, CH_3, i-C_3H_7, i-C_4H_9, $CH_2CH_2SCH_3$; X=OH or OC_2H_5

These compounds were obtained by us by reacting the appropriate chloroacetyl derivatives of amino acids or their esters [2-6] with ammonium O-ethyl methyldithiophosphonate according to the scheme

$$CH_3(C_2H_5O)P(S)SNH_4 + ClCH_2C(O)NHCH(R)COX \rightarrow CH_3(C_2H_5O)P(S)\text{-}SCH_2C(O)NHCH(R)COX + NH_4Cl$$

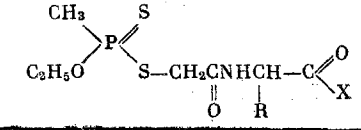
The constants of the obtained compounds, the yields, and the elemental analysis data are given in Table 1. In all cases the purity of the compounds was checked by thin-layer chromatography.

As was to be expected, the compounds of this series proved to be more toxic when compared with the corresponding dithiophosphates, both toward arthropoda and toward warm-blooded animals. Analogous to the dithiophosphates, the least toxic compounds were those containing a free carboxyl group. Thus, for example, for EG-22 the LD_{50} (per os on white mice) was 380 mg/kg. For the corresponding esters the LD_{50} varied in the range 50-140 mg/kg.

The results of studying the insecticidal and acaricidal activity of the obtained compounds are given in the last two columns in Table 1. The acaricidal activity is more characteristic for compounds of this

Institute of Heteroorganic Compounds, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 9, pp. 2003-2005, September, 1971. Original article submitted December 9, 1969.

TABLE 1.



Laboratory code	R	X	Yield, %	Mp, °C	Found, %				Calc., %				R_f of hexane–acetone (3:2) $SiO_2 \cdot 10\% H_2O$	CK_{50}	
					C	H	N	P	C	H	N	P		greenbug*	spider mite†
EG-21	H	OH	40	63—64	31,0 31,2	5,1 5,2		11,3 11,2	31,0	5,2		11,4	0,14	0,017	0,0068
EG-22	*i*-C_3H_7	OH	70	79—81	38,4 38,5	6,2 6,2		9,1 9,4	38,3	6,4		9,9	0,45	0,2	0,09
EG-25	*i*-C_4H_9	OH	86	66—67	40,1 40,4	7,0 6,9	4,3 4,5		40,4	6,8	4,3		0,49		
EG-36	‡	OH	82	Oil	33,8 33,6	5,8 6,1	5,2 5,2		33,7	5,6	4,8		0,12		
EG-20	H	OC_2H_5	82	"				10,1 10,4				10,3	0,44	0,0005	0,0003
EG-32	CH_3	OC_2H_5	80	"	38,8 38,9	6,7 6,7			38,3	6,4			0,47	0,0027	0,00084
EG-27	*i*-C_3H_7	OC_2H_5	87	"	42,8 42,8	7,2 7,0		8,9 9,2	42,2	7,1		9,1	0,61	0,004	0,0011
EG-26	*i*-C_4H_9	OC_2H_5	80	"				8,5 8,6				8,7	0,61	0,01	0,0012
EG-39	**	OC_2H_5	80	"	42,1 42,3	7,3 7,4	3,7 4,0		42,2	7,1	4,1		0,56		
III-187	‡	OC_2H_5	80	"				9,7 9,7				9,9		0,0027	0,007
EG-30	$C_2H_4SCH_3$	OC_2H_5	90				4,0 3,9				3,8		0,59	0,015	0,0043
	Thiophos													0,001—0,008	0,003—0,006

*Read on the second day.
†Read on the third day.
‡β-Alanine derivative.
** Isovaline derivative.

TABLE 2

Laboratory code	Compound	LD_{50} for mice	LD_{50}^{I} / LD_{50}^{II}	LC_{50} for greenbug	LC_{50}^{I} / LC_{50}^{II}	LC_{50} for spider mite	LC_{50}^{I} / LC_{50}^{II}
III-120	$(C_2H_5O)_2P(S)SCH_2C(O)NHCH_2COOC_2H_5$	750	5,3	0,015	30	0,012	40
EG-20	$CH_3(C_2H_5O)P(S)SCH_2C(O)NHCH_2COOC_2H_5$	140		0,0005		0,0003	
III-141	$(C_2H_5O)_2P(S)SCH_2C(O)NHCH(C_3H_7\text{-}i)COOC_2H_5$	90	1,8	0,17	42	0,0019	1,7
EG-27	$CH_3(C_2H_5O)P(S)SCH_2C(O)NHCH(C_3H_7\text{-}i)COOC_2H_5$	50		0,004		0,0011	

series, in which connection they, as a rule, are more active insecticides and acaricides than the corresponding phosphates. However, it should be mentioned that the selectivity of their action on arthropoda is expressed more weakly than in the case of the dithiophosphates, probably due to their higher overall physiological activity. Thus, a selective acaricidal action is observed only for the compounds EG-21, EG-26, and EG-30.

Different relationships are observed when the action of these two groups of substances on arthropoda and warm-blooded animals is compared. Here the methyldithiophosphonates exhibit a greater selectivity. From the data in Table 2 it can be seen that compounds EG-20 and EG-27, which belong to the type of methyldithiophosphonates, are 1.8-5.3 times more toxic toward warm-blooded animals than are the corresponding dithiophosphates (III-120, III-141), whereas they are 30-42 times more effective as insecticides. It might be reasoned that compounds, characterized by an even greater selectivity of action, will be found in the new group of insecticides and acaricides containing peptide linkages.

EXPERIMENTAL METHOD

A solution of 0.02 mole of the chloroacetyl derivative of the amino acid or of the amino acid ester and 0.022 mole of ammonium O-ethyl methyldithiophosphonate in 30-40 ml of absolute alcohol was heated, with stirring, at 60-65° for 2.5-3 h. The precipitate of ammonium chloride was filtered, the filtrate was evaporated in vacuo, and the oily residue was dissolved in either ether or chloroform, washed with ice water, and dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was analyzed by the method of thin-layer chromatography on KSK silica gel, containing 10% of water, in the system hexane –acetone (3:2). Compounds EG-21, EG-22, and EG-25 crystallized when cooled and rubbed with hexane. They are purified by recrystallization from a mixture of hexane and either benzene or ether. In the case of the oily substances their purification was effected by freezing them out of solution in a mixture of ether and hexane at –78°.

CONCLUSIONS

1. A number of methyldithiophosphonates, containing the moieties of amino acids, and their esters, were obtained.

2. Among the obtained compounds exist active insecticides and acaricides, which possess a moderate toxicity for warm-blooded animals.

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