ON THE BIOLOGICAL ACTIVITY OF FIVE MEMBERED PHOSPHORUS-CONTAINING HETEROCYCLES

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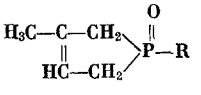
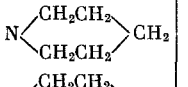
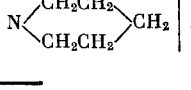
We had earlier reported on a method of synthesizing various derivatives of phosphacyclopentene [1], on the structure [2, 3] and an investigation of the biological activity of these substances [4, 5]. It was found that phosphacyclopentene derivatives, containing aryl, aroxyl, or alkoxyl groups at the phosphorus atom, possess low toxicity and exert a characteristic effect upon experimental animals, causing a loss of mobility, a change to the "side position," and a decrease in the reflex excitability [4]. These substances proved to be strong antispasmodic agents and manifested a protective effect when mice were poisoned by convulsive poisons with various mechanisms of action, including certain anticholinesterase organophosphorus compounds [5]. We were interested in determining the characteristic features of the molecular structure of compounds of the type studied, which are responsible for these specific properties, unusual for organophosphorus substances. We have begun investigations including the synthesis and study of the biological activity of various phosphacyclopentene derivatives with variation both of the structure of the ring and of the nature of the substituents at the phosphorus atom.

In this work we report on the synthesis and the results of a primary study of the biological activity of two new groups of compounds, containing a five-membered ring with the phosphorus atom. These are the P-amides of phosphacyclopentene-3 and P-esters of 1,2-oxaphosphacyclopentene-4. The formulas, constants, and analytical data of the substances synthesized are presented in Tables 1 and 2.

The synthesis of P-amides of 1-oxo-3-methylphosphacyclopentene-3 (see Table 1) was conducted in the following way. To a solution of equimolar amounts of the secondary amine and trimethylamine in absolute ether, a solution of the calculated amount of 1-bromo-1-oxo-3-methylphospholene [1] in an equal or half volume of anhydrous methylene chloride was added dropwise with ice cooling and mixing. The reaction mixture was mixed and then heated to the boiling point of the ether for several hours. After filtration of the triethylamine hydrobromide and removal of volatile products, the pure compounds were isolated by three fractional distillations.

P-Esters of 1,2-oxaphosphacyclopentene (see Table 2) were produced from 2-chloro-2-oxo-3,3,5-dimethyl-1,2-oxaphosphacyclopentene-4 [6] and the corresponding alcohols in the presence of diethylamine.

TABLE 1. Compounds of the Type 

No.	R	Yield, %	B.p., °C (p, mm Hg)	n_D^{20}	d_4^{20}	MR*	P*, %	N*, %	Growth formula
I	$N(C_4H_9)_2$	36,8	116—20 (0,017)	1,4832	0,9745	71,33 71,51	13,20 13,73	5,74 5,76	$C_{13}H_{26}NOP$
II		43,0	110—12 (0,013)	1,5200	1,0920	55,40 55,45	15,56 15,55	6,83 7,03	$C_{10}H_{18}NOP$
III†		22,0	140—1 (0,010)	1,5228	M.p. 52,3		15,50 15,55	7,32 7,03	$C_9H_{16}NO_2P$

* Top numbers – values found, bottom numbers – calculated.

† Found %: C 53.32; H 8.01. Calculated %: C 53.72; H 8.02.

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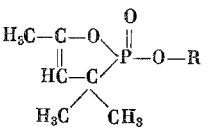
TABLE 2. Compounds of the Type 

No.	R	Yield, %	B.p., °C (p, mm Hg)	n_D^{20}	d_4^{20}	MR*	P*, %	C*, %	H*, %	Growth formula
IV	C_2H_5 †	58,2	72—3 (0,015)	1,4525	1,0796	47,56 47,34	16,41 16,29	50,24 50,52	8,06 7,95	$C_8H_{15}O_3P$
V	C_4H_9-*i*	18,0	78 (0,015)	1,4500	1,0359	56,61 56,58	14,48 14,19	54,54 55,04	8,84 8,77	$C_{10}H_{19}O_3P$
VI	C_6H_5	44,8	103—5 (0,22)	1,5172	1,1525	62,55 62,72	13,15 13,02	60,32 60,50	6,54 6,35	$C_{12}H_{15}O_3P$

* Top numbers – values found, bottom numbers – calculated.
† This compound was also synthesized by N. I. Rizpolozhenskii and F. S. Mukhametov.

TABLE 3. Results of Evaluation of the Biological Effects of the Compound

Compound	LD_{50} for mice, intraperitoneally, mg/kg	Maximum tolerable dose MTD, mg/kg	When MTD administered		% Inhibition of cholinesterase under 30 min influence of preparation in a concentration of 10^{-3} M	
			change to five positions	cholinergic symptoms	serum	brain
I	195±9	150	+	—	0	0
II	700±34	500	—	—	0	0
III	4400±555	2500	—	—	15	15
IV	490±35	200	—	+	82	93
V	87±7	40	—	+	90	99
VI	41±2	31	—	+	89	89

The reaction proceeds weakly in ether solution, and precipitation of triethylamine hydrochloride continues for several days. To accelerate the reaction, the ether was replaced by benzene and the reaction mixture heated to the boiling point of benzene for several hours, just as was done in the synthesis of amides of the analogous cyclic thionephosphonic acids [7]. This method led to an increase in the yield of the products and a reduction of the reaction time.

The results of a preliminary evaluation of the biological effects of these compounds are cited in Table 3. As can be seen from Table 3, only one preparation – the dibutylamide (I) – in the maximum tolerable dose caused a change of the mice to the side position. Injections of the esters (IV)-(VI) induced the characteristic syndrome of excitation of the cholinoreactive systems of the organism. By an evaluation of the effects of equimolar solutions of the compounds studied (concentration 10^{-3} M) on rabbit serum and brain cholinesterase, conducted according to the Hestrin method, demonstrated that the amides show no inhibiting effects upon the pseudocholinesterase (serum) and true cholinesterase (brain), whereas esters of oxaphospholine, more toxic substances, inhibited both enzymes to the same degree.

Our investigations indicate that such changes in the structure of phosphacyclopentene derivatives as replacement of the alkyl or alkoxyl group on the phosphorus atom by an amide group or replacement of one carbon atom in the ring by oxygen lead to a substantial change in the nature of the biological effects of these substances.

CONCLUSIONS

1. Five-membered heterocycles were synthesized: P-amides of 1-oxo-3-methylphosphacyclopentene-3 and P-esters of 2-oxo-3,3,5-trimethyl-1,2-oxaphosphacyclopentene-4.

2. A preliminary evaluation was made of the biological activity of the compounds obtained.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of the first issue of this year.
