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Abstract

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Synthesis and Some Properties of Phosphacyclopentene Derivatives

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In 1955 the first publication by McCormack appeared on the synthesis of phosphacyclopentene derivatives ([1,2]), to which insecticidal properties were attributed. In 1956 Daem ([3]) proposed insecticides which apparently ([4]) contain the phosphacyclopentene grouping. Somewhat later Perner ([5]) expressed the idea of the possibility of obtaining insecticides based on products of analogous structure, but containing, in the five-membered ring, in addition to the phosphorus atom, one oxygen atom. In 1962 a group of researchers ([6]) published data on the synthesis and screening biological examination of certain P-amides containing the 4-oxaphosphacyclopentene grouping.

Table 1

Compound*	Solubility in water	LD_{50}, mg/kg, upon single intraperitoneal administration	Maximum tolerated dose, mg/kg	Duration of lateral position upon administration of the maximum tolerated dose, min
I	insol.	7000	4000	–
II	insol.	3250	2500	273
III	insol.	2290	2000	533
IV	insol.	1080	875	195
V	insol.	545	375	88
VI	1 : 73	375	300	136
VII	1 : 3200	–	–	–
VIII	insol.	840	700	83
IX	insol.	615	500	76
X	1 : 100	400	350	104
XI	1 : 50	417	350	32
XII	insol.	680	250	–

Compound*	Solubility in water	LD_{50}, mg/kg, upon single intraperitoneal administration	Maximum tolerated dose, mg/kg	Duration of lateral position upon administration of the maximum tolerated dose, min
XIII	1 : 2	750	250	–
XIV	1 : 17	430	200	–

* See Table 2.

The limited information on physiological activity, as well as the availability of phosphacyclopentene derivatives based on the method for their preparation developed by some of us ([7–9]), prompted us to synthesize and begin studying the biological action of preparations of this type.

According to the previously developed procedure ([7,8]), by reaction of 1-oxo-1-bromo-3-methylphosphacyclopentene-2 with the corresponding alcohols in the presence of triethylamine in ether solution, esters of cyclophosphinic acid were synthesized (II–VII, X, XI). The acids (XIII and XIV) were obtained by saponification of the corresponding bromohydrides and recrystallized from acetone. The sodium salt (I) was prepared from equimolar amounts of acid XIII and sodium hydroxide in aqueous solution. Purification was carried out by reprecipitation with acetone from alcohol. Phosphine oxide (VIII) was obtained by McCormack' s method ([1]). The phenyl ester (IX) was synthesized by the method of B. A. Arbuzov and L. A. Shapshinskaya ([10]). The methyl ester (XII) was prepared by the reaction of 2-oxo-2-chloro-3,3,5-trimethyl-1-oxa-2-phosphacyclopentene-4 ([11,12]) with methanol in the presence of triethylamine. Data on the products obtained are given in Table 2.

The toxicity of the compounds was determined by the Behrens method upon single intraperitoneal administration to white mice. The LD_{50} values are presented in Table 1. For ester VII it was not possible to determine the toxicity because of its limited solubility in water. Most of the compounds listed in Table 1 gave a uniform picture of poisoning, similar to the action of narcotic substances. On the analogous action of organophospho-

Table 2

No.	Compound	Yield, %	M.p., °C	B.p., °C (mm Hg)	n_D^{20}	d_4^{20}	MR_D^*	P, %*	C, %*	H, %*
I	$CH_3-C\equiv C-CH_2-P(=O)ONa$	61	Decomposes above 320°	—	—	—	—	19.99	20.10	—
II	$CH_3-C\equiv C-CH_2-P(=O)(OC_2H_5)_2$	75	—	117–119 (10)	1.4827	1.0343	56.9136	12.96	52.22	7.59
III	$CH_3-C\equiv C-CH_2-P(=O)(OC_3H_7)_2$	77	—	118–119 (9)	1.4786	1.0085	61.6941	11.60	54.19	8.18
IV	$CH_3C-C\equiv C-CH_2-P(=O)(OC_4H_9)_2$	28.5	—	123–124 (8)	1.4723	0.9584	66.1646	10.72	58.01	7.80
V	$CH_3C-C\equiv C-CH_2-P(=O)(OC_5H_{11})_2$	61	—	136–137 (8)	1.4732	0.9353	70.9550	9.84	61.53	7.36
VI	$CH_3C-C\equiv C-CH_2-P(=O)(OC_6H_{13})_2$	69.8	—	146–147 (8)	1.4725	0.9201	75.4955	9.16	64.58	7.48
VII	$CH_3C-C\equiv C-CH_2-P(=O)(OC_8H_{17})_2$	53	—	125–128 (0.02)	1.4693	0.9043	84.0668	7.72	68.41	8.70
VIII	$CH_3C\equiv C-CH_2-P(=O)C_6H_5$	78.5	65–67	154–156 (0.60)	—	—	—	16.25	61.12	—
IX	$CH_3C\equiv C-CH_2-P(=O)C_6H_5$	48.1	56–57	158–159 (1.0)	1.5581	1.1805	56.8856	14.75	55.14	5.88
X	$CH_3C-C\equiv C-CH_2-P(=O)(C_6H_5)_2$	48.6	—	154–139 (0.06)	1.5465	1.1065	65.0157	11.36	69.52	6.68
XI	$CH_3C-C\equiv C-CH_2-P(=O)(C_6H_{11})_2$	45.5	—	124–126 (0.02)	1.4990	0.9850	87.9157	8.60	64.68	10.27
XII	$H-C-C(CH_3)_2-C\equiv C-CH_2-P(=O)(OC_3H_7)_2$	40	—	160–162 (0.06)	1.4573	1.0168	72.9842	9.72	58.32	8.44
XIII	$CH_3C\equiv CH_2-P(=O)(OC_6H_{13})_2$	30	116–117	174–176 (0.02)	1.5120	1.2165	32.7032	22.25	43.23	5.45

No.	Compound	Yield, %	M.p., °C	B.p., °C (mm Hg)	n_D^{20}	d_4^{20}	MR_D^*	P, %*	C, %*	H, %*
XIV	$CH_3-C-CH_2-P(=O)OH$	92	122-3	168-169 (0.05)				21.27 21.20		–

* Upper numbers are found values; lower numbers are calculated.

There is mention of such compounds in the report of I. A. Frankov (13). However, the author does not give the formulas of the substances acting in this way. Lethal doses of the compounds studied by us caused sharp depression and cessation of respiration. From the data in Table 1 it is seen that the toxicity of the esters in series II–VII and IX–X increases with increasing length of the hydrocarbon radical. The duration of the "lateral position" of the mice upon administration of the maximum tolerated doses of the preparations, adopted as a criterion for assessing the strength of their action, proved not to be parallel to toxicity and was maximal for the ethyl ester of cyclophosphinic acid III. The action of the preparations was reversible and, after the mice were awakened, did not affect their general condition. Upon administration of the free acids XIII and XIV, as well as of salt I, no phase changes in the condition of the animals were observed; preparation XII likewise produced such an effect only in lethal doses.

The action of the preparations *in vitro* was investigated on 7 species of pathogenic microbes. Most of the compounds were studied at dilutions of 1 : 100 and 1 : 1000. 250 million microbial bodies of daily agar cultures were placed in 1 ml of a solution of the sterilized preparation and incubated for 1 and 24 hours at 37°. Then, with a standard loop, inoculations were made onto solid nutrient media. The action of the preparations was evaluated by the character of microbial growth after incubation in a thermostat for 3 days. The results are given in Table 3. As is evident from the table, the broadest range of anti–

Table 3

Compound	Staphylococcus aureus	C. diphtheriae	S. typhi (Ty 4446)	S. typhi murium	B. coli O –111	Shigella flexneri	Shigella sonnei	Bact. proteus vulgaris
I	—	—	—	—	—	—	—	—
II	—	—	—	—	—	—	—	—

Compound	Staphylococcus aureus	C. diphtheriae	S. typhi (Ty 4446)	S. typhi murium	B. coli O –111	Shigella flexneri	Shigella sonnei	Bact. proteus vulgaris
III	—	–1 : 100	—	–1 : 100	–1 : 100	1 : 1001 : 1000	–1 : 100	—
IV	–1 : 100	–1 : 100	–1 : 100	–1 : 100	–1 : 100	—	–1 : 100	—
V	–1 : 100	1 : 100*1 : 100	1 : 1001 : 100	—	—	1 : 1000*1 : 1000	1 : 100*1 : 100	—
VI	1 : 100*1 : 100	1 : 1001 : 100	1 : 10001 : 1000	1 : 1001 : 100	1 : 100*1 : 100*	1 : 100*1 : 1000*	1 : 100*1 : 1000*	—
VII	1 : 35001 : 3500	1 : 35001 : 3500	—	1 : 3500*1 : 3500	—	—	1 : 35001 : 3500	—
VIII	—	—	—	—	—	—	—	—
IX	—	—	–1 : 100	–1 : 100	–1 : 100	–1 : 100	—	—
X	–1 : 100*	1 : 1001 : 100	1 : 1001 : 100	1 : 1001 : 100	1 : 1001 : 100	1 : 100*1 : 100	1 : 100*1 : 100	—
XI	–1 : 100	1 : 1001 : 100	1 : 1001 : 100	–1 : 100	1 : 1001 : 100	1 : 100*1 : 100	1 : 1001 : 100	—
XII	1 : 100*1 : 100	1 : 10001 : 1000	1 : 1000*1 : 1000	1 : 1001 : 1000	–1 : 1000	1 : 1001 : 1000*	1 : 1001 : 1000	—
XIII	–1 : 1000	1 : 1001 : 1000	1 : 10001 : 1000	1 : 1001 : 1000	1 : 1001 : 1000	1 : 1001 : 1000*	1 : 1001 : 1000	—
XIV	1 : 1001 : 1000	1 : 10001 : 1000	1 : 1000*1 : 1000	1 : 1001 : 1000	1 : 1001 : 1000	1 : 1001 : 1000	1 : 10001 : 1000	—

Note. The upper numbers are the bactericidal dilutions of the preparations at one-hour exposure; the lower numbers, at 24-hour exposure. A dash indicates the absence of bactericidal and bacteriostatic action of the preparations. An asterisk marks cases of bacteriostatic action of the preparations.

microbial action is possessed by acids XIII and XIV, as well as by esters XII and VII. Sodium salt I, phosphine oxide VIII, and the lower aliphatic esters did

not show bactericidal properties.

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Note: Figure translations are in progress. See original paper for figures.