ORGANOPHOSPHORUS COMPOUNDS

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ORGANOPHOSPHORUS COMPOUNDS WITH LOW TOXICITY

Since the discovery of the toxic properties of organic phosphorus derivatives, a large number of investigators have been engaged in the synthesis and study of the biological action of compounds of this class. The opinion arose that the physiological activity of organophosphorus compounds is based on their ability to interact with cholinesterase, and the aim of most work was to obtain toxic agents, insecticides, and medicinal substances whose mechanism of action would be based on the inactivation of this enzyme. And although in some studies a discrepancy was noted between the level of toxicity and the degree of cholinesterase inhibition (^1), organophosphorus compounds with low anticholinesterase activity long failed to attract the attention of investigators.

By the present time a sufficient body of information has accumulated indicating that the biological activity of organophosphorus compounds is not exhausted by their ability to inactivate cholinesterase. Among derivatives of this class, preparations have been found that possess antimicrobial (^2, ^3) and antiblastomic action (^4, ^5), as well as insecticides that do not exhibit anticholinesterase activity (^6). The ability of organic phosphorus derivatives to exert both excitatory and blocking action directly on cholinoreactive systems has been established (^1, ^7, ^8). Organophosphorus compounds have been synthesized (^9) that are antagonists of the strong organophosphorus cholinesterase inhibitors—armin and nibufin (^10). The narcotic action of weak anticholinesterase agents from the class of organophosphorus compounds is mentioned in the reports of I. A. Frankov (^11, ^12). In 1957, Vandekar (^13), describing the anesthetic action of sublethal doses of low-toxic esters of phosphoric and thiophosphoric acids that do not exhibit anticholinesterase activity, suggested that in stronger cholinesterase inhibitors the anesthetic effect is not revealed because of their high toxicity.

It may be assumed that cholinesterase inhibition, which causes the rapid death of animals, masks the diverse mechanisms by which synthetic organophosphorus compounds act on the organism. From this point of view, it seems expedient to

us to synthesize and study the biological activity of organic phosphorus derivatives with low anticholinesterase activity and low toxicity.

In a previous work it was reported (^14) that certain low-toxic derivatives of phosphacyclopentane induce in animals a state resembling narcosis. To study the relationships between structure and biological action in compounds of this series, new derivatives of phosphacyclopentane were synthesized, information on which is given in Table 1. All the substances obtained are colorless liquids, soluble in water and in ordinary organic solvents. All esters were obtained from 1-oxo-1-bromo-3-methylphosphacyclopentane (^15) and the corresponding alcohols in ether solution in the presence of triethylamine. Amide XIII was obtained from the same bromoanhydride and a twofold amount of diethylamine.

In the biological studies, both newly synthesized compounds and compounds described earlier (^14) were used. As a

The criteria of physiological activity adopted were the mean lethal dose (LD_{50}), the duration of the lateral position of mice upon administration of the maximum tolerated doses (MTD) of the preparations, and their effect on the action of an absolutely lethal dose of Corazol, a typical antagonist of narcotic substances.

Table 1

No.	Compound of the type $CH_3-C(=O)-CH_2-P(-R)-CH_3$, where $R =$	Yield, %	B.p., °C (mm Hg)	n_D^{20}	d_4^{20}	MR_D^*	P, %†
III	OC_3H_7-iso	17.5	111–112 (8)	1.4700	1.0494	46.2646.22	18.0417.80
V	OC_4H iso **	36.5	72–73 (0.02)	1.4696	1.0297	50.9650.84	16.2016.46
VI	OC_5H_{11}-iso	41.3	72–74 (0.03)	1.4716	1.0182	55.5755.45	14.9915.34
IX	OC_6H_{13}-n	46.8	138–40 (0.06)	1.4718	1.0062	60.0960.03	14.5714.35
XII	$O(CH_2)_2C_6H_5$	31.9	147 (0.07)	1.5392	1.1256	65.7065.71	13.4613.13
XIII	$N(C_2H_5)_2$	19.36	86–86.5 (0.02)	1.4910	1.0271	52.7253.03	16.7916.57
XIV	OCH_2CH_2Cl ***	25.4	105 (0.09)	1.5015	1.2372	46.3546.46	16.2415.90

No.	Compound of the type $CH_3-C(=O)-CH_2-P(=O)(R)-R$, where $R =$	Yield, %	B.p., °C (mm Hg)	n_D^{20}	d_4^{20}	MR_D^*	P, %†
XV	OC_6H_5	50.4	120–22 (0.03)	1.5500	1.1745	56.48 56.47	14.87 14.69

* Upper figures are found values; lower figures are calculated.
** Found, %: C 37.04, H 9.01; calculated, %: C 37.44, H 9.10.
*** Found, %: Cl 18.18; calculated, %: Cl 18.25.

The results of the experiments presented in Table 2 permit the following conclusions:

1. All the alkoxy derivatives of phosphacyclopentene studied, in maximum tolerated doses, cause depression of the central nervous system of mice of varying duration—their transition into a lateral position. Administration of amide XIII leads to a certain increase in motor activity and an increase in reflex excitability.
2. For most compounds with unbranched hydrocarbon radicals, the duration of the lateral position decreases with increasing length of this radical and increasing toxicity. The exception is the methyl ether.
3. Upon administration of iso-compounds (III, V, VII), the duration of the lateral position of mice decreases somewhat in comparison with the isomers containing unbranched ether radicals.
4. The duration of the lateral position in most cases is parallel to the ability of the preparations to reduce the toxic action of Corazol (prevention of death or increase in the life span of the animals).

Comparison of the toxicity and the duration of the lateral position of the animals shows that the maximum discrepancy between these quantities is exhibited by 1-ethoxy-1-oxo-3-methylphosphacyclopentene-3 (II), which we selected for further, more detailed study. Of particular interest was the investigation of the anticholinesterase activity of this compound, which showed the greatest selectivity of action. Experiments carried out by Hestrin' s method showed that, to suppress enzyme activity *in vitro* by 50% (Y_{50}), very high concentrations of the preparation are required: for cholinesterase of rabbit brain, $2.50 \cdot 10^{-1}$ mol/l; for cholinesterase of rabbit blood serum, $1.87 \cdot 10^{-1}$ mol/l.

Table 2

No.	Compound $CH_3-C-CH_2\backslash\overset{O}{P}-R$, $HC-(CH_2)_2$ where R =	LD_{50}	DMT	Duration of lateral position, min, upon administration of DMT	Effect of 1/2 DMT on the action of corazole LD_{100}: convulsions	Effect of 1/2 DMT on the action of corazole LD_{100}: death (%)	Effect of 1/2 DMT on the action of corazole LD_{100}: life prolongation (% of control)
I	OCH_3	3250*	2500*	273*	–	0	
II	OC_2H_5	2290*	2000*	532*	–	0	
III	OC_3H_7-*iso*	1375	1000	117	+	60	730
IV	OC_3H_7-*n*	1080*	875*	195*	+	10	1260
V	OC_4H_9-*iso*	475	400	53	+	90	400
VI	OC_4H_9-*n*	545*	375*	88*	+	90	400
VII	OC_5H_{11}-*iso*	440	300	85	+	90	600
VIII	OC_5H_{11}-*n*	375*	300*	136*	+	90	700
IX	OC_6H_{13}-*n*	175	100	7	+	100	1300
X	OC_6H_{11}-*cis*	417*	350*	32*	+	100	390
XI	$OCH_2C_6H_5$	400*	350*	104*	+	80	800
XII	$O(CH_2)_2C_6H_5$	263	200	18	+	80	300
XIII	$N(C_2H_5)_2$	1030	500	–	+	70	240

* These data were published earlier (14); they are given here for comparison.

Table 3

Convulsant poison	Doses in mg/kg: LD_{100} of the convulsant poison	Doses in mg/kg: 1/2 DMT of compound II	Convulsions	Salivation	Dead mice (%)	Life prolongation (% of control)
Corazole	150	–	+++	+	100	
Corazole	150	1000	–	–	0	
Nibufin	13.3	–	+++	+	100	
Nibufin	13.3	1000	–	–	0	
Strychnine	2	–	+++	–	100	
Strychnine	2	1000	+	–	0	
Picrotoxin	10	–	+++	+	100	
Picrotoxin	10	1000	+	+	0	
Cordiamine	416	–	+++	+	100	
Cordiamine	416	1000	+	–	30	380
Armin	0.83	–	+++	+	100	
Armin	0.83	1000	+	+	80	760
Chlorophos	1000	–	+++	+	100	
Chlorophos	1000	1000	–	–	80	770
Caffeine	1250	–	+++	+	100	
Caffeine	1250	1000	+++	–	100	850
Nicotine	100	–	+++	+	100	
Nicotine	100	1000	+	–	100	300
Eserine	2	–	+++	+	100	
Eserine	2	1000	–	–	100	170

Table 3 presents the results of experiments investigating the influence of compound II on the action of absolutely lethal doses of certain analeptics and cholinomimetic agents. All these substances, in toxic doses, cause severe convulsions as a result of excitation of various parts of the central nervous system. An aqueous solution of the preparation was administered to mice subcutaneously 15 min before the subcutaneous injection of the convulsant poisons. From the data in Table 3 it is evident:

1. Preliminary administration of 1-ethoxy-1-oxo-3-methylphosphacyclopentene-3 completely prevents the death of animals upon administration of absolutely lethal doses of corazole, nibufin, strychnine, and picrotoxin, and protects from death 70% of animals poisoned with cordiamine.
2. The average lifespan of mice that received absolutely lethal doses of cordiamine, caffeine, nicotine, armin, and chlorophos, against the background of preparation II, increases 3–8-fold.
3. The preparation completely eliminates or significantly weakens convul-

sions caused by the administration of all the substances studied, except caffeine.

4. Prophylactic administration of preparation II prevents the salivation that occurs upon administration of lethal doses of corazol, cordiamine, caffeine, nicotine, nibufin, and chlorophos, but does not affect the appearance of this symptom in poisoning with picrotoxin, eserine, and armin.

The results obtained indicate that the compounds studied exhibit a specific depressant action on the central nervous system of animals, not associated with inactivation of cholinesterase.

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