SYNTHESIS AND BIOLOGICAL ACTIVITY OF FIVE-MEMBERED ORGANOPHOSPHORUS HETEROCYCLES

1-OXO-1-ALKOXY-2- (AND 3-) PHOSPHOLENES

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The opinion has previously been advanced that the anticholinesterase activity of many organophosphorus compounds masks other possible mechanisms for their action on the organism. Therefore the suggestion was made of the desirability of biological studies of synthetic organophosphorus compounds with low toxicity and low anticholinesterase activity [1]. This approach led to the detection of new biological effects which are not typical of anticholinesterase organophosphorus compounds. Among these are hypothermal activity, ability to reduce oxygen requirement, and antagonism with anticholinesterase substances [2, 3].

In the phospholene derivative series, compounds were found which exerted a depressive action on experimental animals, displayed anticonvulsive properties, or were antagonists to cholinomimetic substances [1]. Thanks to successes in the field of synthesis [4, 5] and separation of isomeric products [6], we had the opportunity to study the effect of such fine structural factors as the position of the double bond in the ring on the biological properties of 1-oxo-1-alkoxyphospholenes. Since a shift of the double bond in the ring shows up in the polar characteristics of molecules [7], it could have been expected that the isomeric products would differ also in biological properties. For the more complex phospholene derivatives containing a nitrophenyl substituent, such a difference has been noted in a single pair of isomers [8]. It was of interest to examine this question in more detail in very simple phospholene derivatives.

With this objective we synthesized five pairs of isomeric ethers with different alkoxy radicals. The pure isomers of 1-oxo-1-chloro-2-phospholene (I) and 1-oxo-1-chloro-3-phospholene (VII) (Table 1) served as starting materials for their preparation. Structures of all the compounds prepared were confirmed by IR spectra (Figs. 1 and 2). In the spectrum of I, the following bands characteristic of a cis-disubstituted double bond were observed (in cm^{-1}): 3067 (w), $\nu_{=C-H}$; 1580 (m), $\nu_{C=C}$; 1329 (s), $\delta_{=C-H}$; 685 (s), $\delta_{=C-H}$; and the following were observed for the phosphoryl group: 1244 (s), $\nu_{P=O}$; 520 (s), $\delta_{P=O}$; 465, ν_{P-Cl}. In the spectrum of VII, the following bands of a cis-disubstituted double bond are present (in cm^{-1}): 3057 (w), $\nu_{=C-H}$; 1610 (w), $\nu_{C=C}$; 650 (s), $\delta_{=C-H}$; and the following were observed for the phosphoryl group: 1260 (s), $\nu_{P=O}$; 498 (s), $\delta_{P=O}$; 465 (s), ν_{P-Cl}.* The 1215 cm^{-1} band in the spectrum of this compound, which attracts attention by its high intensity, can be assigned to one of the ring vibrations. On transition from the acid chlorides to the ethers, characteristics are displayed which are inherent to P–O–alkyl groups [9]. Among the new bands, the most intense is the band for C–O vibrations close to 1000 cm^{-1}. As the substituent becomes more complex, it is shifted somewhat to the long wavelength region and becomes more complex. The appearance and increase in size of the radicals also shows up in the C–H valence stretching bands in the 2800-3000 cm^{-1} region.

*Abbreviations: s) band strong in intensity; m) medium; w) weak.

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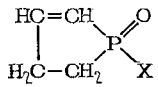
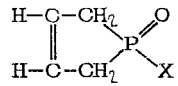
TABLE 1. 1-Oxo-2- (and 3-) Phospholene Derivatives



I - VI



VII - XII

Compound	X	Yield, %	bp (deg)	n_D^{20}	d_4^{20}	Found				Empirical formula	Calc.			
						C	H	P	MR		C	H	P	MR
						%					%			
I	Cl	43	84—6 (0,02)	1,5244	1,3304	31,42	22,16	35,35	4,62	C_4H_6ClOP	35,20	4,42	22,60	31,34
II	OCH_3	61	68—70 (0,04)	1,4948	1,2010	32,04	23,08	44,96	6,81	$C_5H_9O_2P$	45,46	6,87	23,44	32,36
III	OC_2H_5	70	84—6 (0,04)	1,4861	1,1380	36,80	20,78	49,20	7,85	$C_6H_{11}O_2P$	49,31	7,58	21,20	36,98
IV	OC_3H_7-n	75	83—6 (0,03)	1,4821	1,0983	41,57	18,87	52,94	8,30	$C_7H_{13}O_2P$	52,49	8,18	19,34	41,60
V	OC_3H_7-iso	72	72—3 (0,04)	1,4779	1,0910	41,54	19,07	52,20	8,18	$C_7H_{13}O_2P$	52,49	8,18	19,34	41,60
VI	OC_8H_{17}-n	78	116—20 (0,04)	1,4740	1,0024	64,55	13,87	62,51	10,23	$C_{12}H_{23}O_2P$	62,58	10,07	13,45	64,69
VII	Cl	84	68—70 (0,02)	1,5196	1,3349	31,06	23,16			C_4H_6ClOP*	—	—	22,60	31,34
VIII	OCH_3	72	54—8 (0,04)	1,4900	1,1904	32,08	23,36	45,67	7,13	$C_5H_9O_2P$	45,46	6,87	23,44	32,36
IX	OC_2H_5	72	75—7 (0,04)	1,4800	1,1310	36,70	20,71	48,91	7,60	$C_6H_{11}O_2P$	49,31	7,58	21,20	36,98
X	OC_3H_7-n	81	71—2 (0,02)	1,4773	1,0906	41,51	19,72	52,61	8,08	$C_7H_{13}O_2P$	52,49	8,18	19,34	41,60
XI	OC_3H_7-iso	85	68—70 (0,03)	1,4727	1,0825	41,46	19,15	52,76	8,34	$C_7H_{13}O_2P$	52,49	8,18	19,34	41,60
XII	OC_8H_{17}-n	85	110—12	1,4711	0,9982	64,47	13,47	62,70	9,86	$C_{12}H_{23}O_2P$	62,58	10,07	13,45	64,69

* Found, %: Cl 25.89. Calc., %: Cl 25.97. Residual pressure (in mm) indicated in parentheses.

TABLE 2. Biological Properties of 1-Oxo-1-alkoxy-2- (or 3-) Phospholenes

Compound	Toxicity			Side position, min	Hypothermal effect, deg	Corazole antagonism (animals, % survived)	Cholinesterase depression	
	MLD	LD_{50}	LD_{100}				brain	serum
	mg/kg							
II	5000	6700±290	8000	0	4,5±0,3	20	0	0
VIII	3000	5300±330	7000	153±37	4,8±0,2	80	0	0
III	3000	4200±162	5000	44±11	3,7±0,3	30	0	0
IX	2500	300±75	3500	262±37	4,8±0,4	100	0	0
V	2000	3100±83	4000	74±6	3,8±0,3	100	0	0
XI	1500	2380±65	3500	69±9	2,5±0,2	70	0	0
IV	1600	2220±126	3200	272±52	6,7±0,4	100	0	0
X	1000	1500±75	2000	131±27	5,6±0,4	100	0	0
VI	125	155±7	200	29±1	4,2±0,3	0	100	100
XII	100	150±7	200	0	3,8±0,3	0	100	100

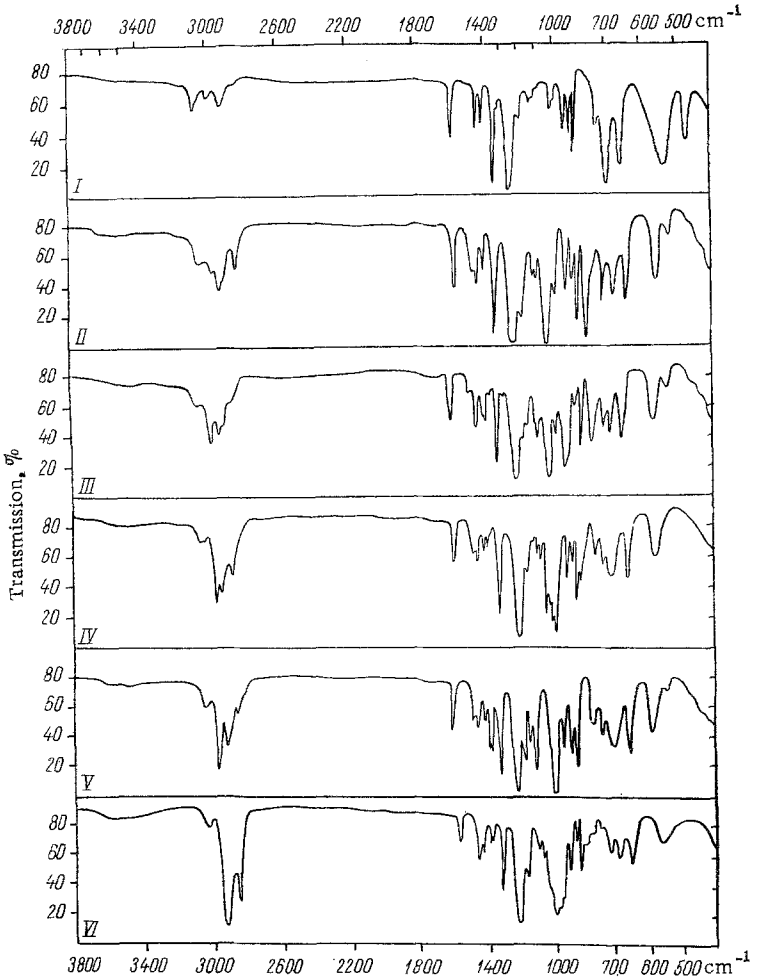


Fig. 1. IR spectra of 1-oxo-2-phospholene derivatives.

In the biological experiments (Table 2) the following relationships were observed. In all cases the 3-phospholenes are more toxic than the 2-phospholenes, the toxicity of the compounds rising with lengthening of the chain in the radicals. As the radicals become larger, the difference between the isomeric compounds decreases.

The effect of the position of the double bond on motor activity of animals (duration of the "side position"), hypothermal action, and also on antagonism with corazole, including the anticonvulsive effect, depends on the length of the chain in the ether radical, and bears a diverse character. In the methyl and ethyl ethers, the Δ^3-isomers are the more active; in the propyl ethers, the position of the double bond shows up to a smaller degree; and of the octyl ethers, the Δ^2-isomer is somewhat the more active, although neither octyl derivative prevents the death of mice from a lethal dose of corazole.

TABLE 3. Distribution of III and IX in the Rat Organism

Object of study	Content, mg %		Ratio
	IX	III	IX : III
Starting solution	14 611±443	5509±382	2,7
Plasma	18,3±1,0	3,9±0,1	4,8
Erythrocytes	25,2±5,0	11,2±2,0	2,3
Liver	37,0±2,0	12,7±1,0	3,0
Kidney	37,0±4,0	13,9±2,0	2,7
Spleen	29,6±3,0	9,6±1,0	3,1
Heart	46,7±9,0	15,5±3,0	3,0
Muscle	38,0±3,0	11,2±1,0	3,4
Lungs	33,6±3,0	9,1±1,0	3,7
Thymus	28,0±4,0	11,3±2,0	2,5
Pancreas	42,7±4,0	8,9±1,0	4,7
Adrenal glands	54,9±6,0	17,9±2,0	3,0
Testicle	27,4±4,0	11,2±2,0	2,5
Hemispheres	37,4±6,0	14,2±2,0	2,6
Brain cord	34,0±3,0	9,9±2,0	3,3
Cerebellum	19,5±0,4	8,7±0,3	2,2
Duodenum	43,4±10,0	12,9±3,0	3,5
Large intestine	43,0±6,0	13,9±3,0	3,3
Contents of small intestine	40,0±6,0	10,4±2,0	1,4
Urine	835±275	102,2±15,0	4,8

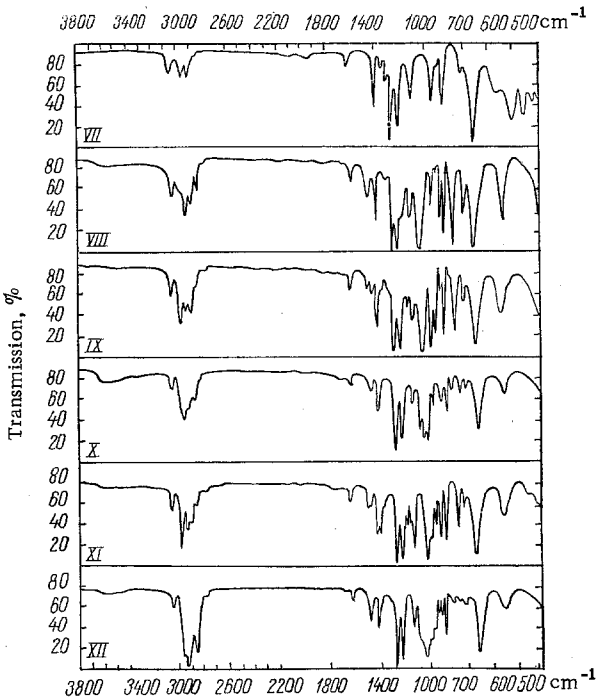


Fig. 2. IR spectra of 1-oxo-3-phospholene derivatives.

The character of the contractions of isolated sections of gut and the activity of serum and rabbit brain cholinesterase are not changed under the influence of compounds II-V and VIII-XI at a concentration of 10^{-3} mole/liter. In the same concentration the octyl ethers exert a depressive action on gut contractions, completely suppressing peristaltic, rhythmic contractions and decreasing tone. They completely inactivate serum or brain cholinesterase. Since the suppression of enzyme activity is not accompanied by symptoms of cholinergic excitation and is observed only when compounds with large hydrocarbon radicals (VI and XII) are used, it may be suggested that it is nonspecific and is connected with an increased lipoidophilicity of these substances.

Considering that the 2- and 3-phospholenes differ rather appreciably in their biological properties, we considered it of interest to evaluate the distribution of the isomers in the various organs of experimental animals. The content of the isomeric ethyl ethers III and IX in the blood, urine, feces, and organ homogenates of rats is shown in Table 3. The larger amount of the preparations in the urine than in the intestinal contents indicates that the main route of their elimination from the organism is via the kidneys. The fluctuation of isomer ratio in the various organs indicates specificity of their sorption. The maximum concentrations of both isomers are recorded in the adrenal gland, the heart, and the intestines. It is interesting to note that for most of the organs a tendency is observed to a shift of the ratio between isomers in favor of IX, which is also the more active with respect to a number of biological characteristics.

EXPERIMENTAL

1-Oxo-1-chloro-2-phospholene (I) and 1-Oxo-1-chloro-3-phospholene (VII). These were synthesized [10] and purified [6] by procedures which have been described.

Ethers II-V and VIII-XI. These were synthesized by the reaction of equimolar amounts of the appropriate chlorophospholenes and alcohols in diethyl ether medium in the presence of triethylamine. The octyl ethers VI and XII were prepared by adding the acid chlorides I and VII to an excess of octyl alcohol with

cooling and subsequent removal of the hydrogen chloride formed by the procedure described for preparing acyclic phosphonates [11].

A drop of the appropriate substance was squeezed between plates of potassium bromide to take the IR spectra. The instrument was a UR-10, slot program 4.

Toxicity was determined on mice 18 to 24 g in weight upon one-time intraperitoneal injection of the preparations. Compounds II-V and VIII-XI were used in the form of aqueous solutions; VI and XII, in the form of emulsions. Experimental results were treated by the Behrens procedure. "Side position" was evaluated by the time from the moment of complete loss of motor activity of the mice, caused by introduction of a MLD of the preparations, to their "arousal." The hypothermal effect was determined by the difference between the temperatures measured 5 min before introduction and 1 h after introduction of a MLD of the preparations. Temperature was measured on the skin of the animal by a TSM-2 electrical thermometer. Corazole antagonism was characterized by the percent of mice which survived, having received 1/2 MLD of the preparation 15 min before injection of an absolutely lethal dose of corazole, and also by the prevention of convulsions. The effect on contracting activity of an isolated section of gut was studied by the Magnus method at a concentration of the preparations of 10^{-3} mole/liter. Anticholinesterase activity was evaluated in vitro by the method of [12] on a homogenate of brain gray matter and rabbit blood serum. The final concentration of the preparations was 10^{-3} mole/liter.

Evaluation of the distribution of III and IX in the rat organism was carried out 1 h after injecting a 20% solution of a mixture of the isomers in a dose of 2000 mg/kg. The ratio of III to IX was 1 : 2.7. The blood was stabilized with heparin and the plasma was separated from the erythrocytes. Homogenates were prepared from the organs at a 1 : 3 dilution with water. The content of both isomers was determined simultaneously by gas chromatography. A direct chromatographing of the homogenates was employed, rather than the usually adopted organic solvent extraction of the compounds being determined. The water served as an internal standard thereupon. Since the sensitivity with respect to water was not constant, a calibration was carried out just before each analysis. The chromatograph was an Rue-104 instrument with a differential flame ionization detector. The column was glass, 1.5 m long, containing QF-1 fluorinated silicone supported in an amount of 3% on "gas-chrom Q" solid carrier. The thermostat temperature was 110°.

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