SYNTHESIS AND STUDY OF PROPERTIES OF BIS(ALLYLOXYMETHYL)PHOSPHONIC ACID AND ITS ESTERS

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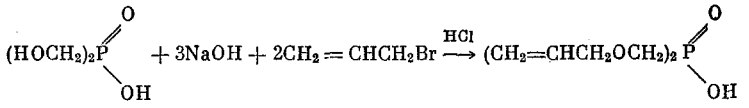
While studying the reactions of bis(hydroxymethyl)phosphonic acid with alkyl halides, we were successful in developing a fairly simple method of synthesis of bis(allyloxymethyl)phosphonic acids by the scheme



Treatment of this acid with trialkyl phosphites yielded the corresponding esters of bis(allyloxymethyl)phosphonic acid, the properties of which, together with those of the acids, are presented in Table 1. The obtained compounds can be copolymerized with vinyl monomers, for example, with methyl methacrylate to form lattice polymers (more detailed data on their polymerization and copolymerization will be reported later).

It appeared of interest to study the biological activity of the synthesized compounds, since they are similar in their structure to derivatives of diallylphosphonic acid [1], which possess spasmodic and antispasmodic activity [3]. Under the effect of toxic doses of the ethyl ester of bis(allyloxymethyl)phosphonic acid, a lowering of the rectal temperature by 8-10° and a sharply expressed depression are observed, and only in fatal doses did the investigated compound cause a forced side position in animals. LD_{50} for white mice is 625 mg/kg. The investigated ester noticeably depressed the orientation reaction in white mice, yielding in this relation by two time to an equivalent dose of Aminazine. Results of the experiment are presented in Fig. 1. The compound in doses of 40-100-200 mg/kg did not prevent and did not change the characteristic spasms caused by nicotine and corazol, and did not affect the group toxicity of phenamine for white mice.

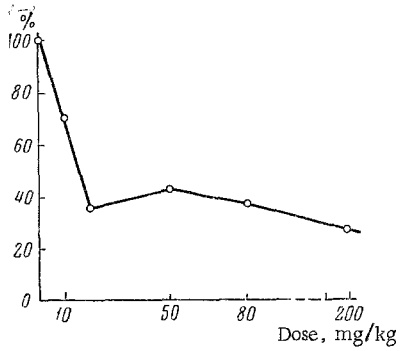


Fig. 1. Effect of the ethyl ester of bis(allyloxymethyl)phosphonic acid on the orientation reaction of white mice. On the ordinate axis is expressed the orientation reaction of the animals as a percentage in relation to the control taken as 100. On the abscissa axis is the dose of the investigated compound in mg/kg.

The combined effect of the investigated compound with chloral hydrate or Barbamyl was characterized by a significant increase of the time of the side position in animals. This effect was expressed most intensely upon combination with Barbamyl. Length of sleep of white mice increased by 23 times from a dose of 200 mg/kg, and by 11 times from 50 mg/kg.

The hypothermal effect from therapeutic doses of the compound was statistically reliable in the course of 5 h of observation. Simultaneous introduction of the studied compound with Aminazine and Barbamyl significantly increased the temperature lowering and slightly lengthened the time of hypothermia. The results of several experiments are presented in Fig. 2.

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TABLE 1. Properties of Synthesized Products of the General Formula

$(CH_2=CHCH_2OCH_2)_2P(=O)OR$

R	Yield, %	bp, °C (p, mm of Hg)	n_D^{20}	d_4^{20}	MR Found	MR Calculated	Found / Calculated, % P	Found / Calculated, % C	Found / Calculated, % H	Empirical formula
H	64,0	250 (1·10⁻³) *	1,4790	1,1535	50.69	51,12	15,73 / 15,02	44,90 / 46,59	7,31 / 7,33	$C_8H_{15}O_4P$
CH_3	62,0	90—92 (3·10⁻²)	1,4659	1,0940	55,51	56,19	13,40 / 14,09	48,83 / 48,60	7,90 / 7,65	$C_9H_{17}O_4P$
C_2H_5	66,9	93—95 (3·10⁻²)	1,4620	1,0670	60,57	60,28	8,13 / 8,12	51,00 / 51,28	13.50 / 13,24	$C_{10}H_{19}O_4P$
C_3H_7	67,3	98—100 (3·10⁻²)	1,4613	1,0450	65,11	65,09	12,46 / 12,50	52,60 / 53,22	8,68 / 8,46	$C_{11}H_{21}O_4P$
C_4H_9	62,0	105—110 (3·10⁻²)	1,4594	1,0301	69,55	70,05	12,05 / 11,70	54,87 / 54,96	9,02 / 8,70	$C_{12}H_{23}O_4P$
C_3H_5	50,0	98—100 (2,5·10⁻²)	1,4710	1,0627	64,56	64,63	12,78 / 12,60	54,01 / 53,60	7,56 / 7,72	$C_{11}H_{19}O_4P$

*Purification of the product was carried on a film distillation apparatus. The temperature of the spiral is given.

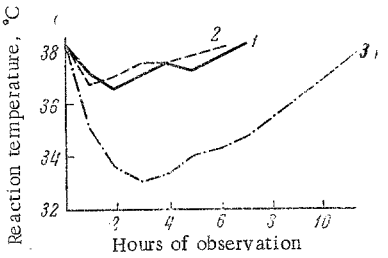

Fig. 2. Hypothermal effect of the ethyl ester of bis(allyloxymethyl)phosphonic acid and its combination with Aminazine and Barbamyl: 1) investigated compound in a dose of 50 mg/kg; 2) Aminazine, 5 mg/kg; 3) ethyl ester of bis(allyloxymethyl)phosphonic acid, 50 mg/kg + Aminazine, 5 mg/kg.

EXPERIMENTAL

bis(Allyloxymethyl)phosphonic Acid. We dissolved 90 g of bis(hydroxymethyl)phosphonic acid and 85.7 g of NaOH in 300 ml of water. To the obtained solution was added 224 g of allyl bromide, and the reaction mixture was heated with stirring and 70°C for 4 h. The upper layer was separated from the reaction mixture, and the lower layer was extracted with ether and acidified with 30 ml of conc. HCl. The upper layer formed during this is mainly bis(allyloxymethyl)-phosphonic acid. Water and the volatile fraction were distilled from the obtained product. During this, a residue precipitated which was filtered. Yield of crude bis(allyloxymethyl)phosphonic acid was 94 g (64%). Purification of the product was carried out with a film distillation apparatus. Constants of the obtained product are presented in Table 1.

Ethyl Ester of bis(Allyloxymethyl)phosphonic Acid. We mixed 20 g of bis(allyloxymethyl)phosphonic acid with 236 g of triethyl phosphite and heated the reaction mixture at 130° for 5 h. At the end of the reaction, diethylphosphorous and the excess triethyl phosphite were distilled from the reaction mixture; the residue was distilled in vacuum. Constants of the obtained ester are presented in Table 1. The remaining esters of bis(allyloxymethyl)phosphonic acid were obtained analogously.

The peak toxicity of the ester for white mice was determined upon intravenous introduction. LD_{50} was established by the punch-analysis graphic method of Miller and Teinter. The effect of the material on the orientation reaction of white mice was carried out by the method of [4]. The determined character and localization of the effect of the ester on the central nervous system was explained by the reaction of the first with soporific materials (chloral hydrate and Barbamyl). The effect of the material on the body temperature of animals in combination with Aminazine and Barbamyl was studied on white rats. The results of the experiment were treated statistically.

CONCLUSIONS

1. A method of preparation of bis(allyloxymethyl)phosphonic acid and its esters was developed.

2. The ethyl ester of bis(allyloxymethyl)phosphonic acid is a low-toxicity compound with expressed depressive effects on the central nervous system.

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