SYNTHESIS AND DETERMINATION OF ABSOLUTE CONFIGURATION OF R-α-AMINO-BENZYLPHENYLPHOSPHINIC ACID

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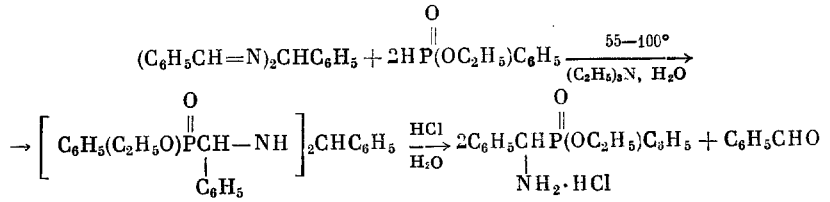
In a number of their properties, α-aminophosphinic and α-aminophosphonic acids are close to the natural α-aminocarboxylic acids, which is largely responsible for the growing interest in them [1, 2]. In contrast to the α-aminophosphonic acids [3-5], the α-aminophosphinic acids have not been described in the optically active form. In the present paper we synthesized ethyl α-aminobenzylphenylphosphinate (EABPP), established the absolute configuration of its C(R),P(S)-isomer, obtained R-α-aminobenzylphenylphosphinic acid, and synthesized some asymmetric ionites with C(R),P(S)-EABPP and R-α-aminobenzylphenylphosphinic acid groupings.

EABPP was synthesized by the addition of ethyl phenylphosphinate to the double bonds of hydrobenzamide and subsequent decomposition of the bis(phenylethoxyphosphoryl)tetrahydrohydrobenzamide with HCl.



Like in the synthesis of diethyl α-aminobenzylphosphonate [4], the catalytic properties of triethylamine are manifested only in the presence of moisture. At 100°C a time of 2 h is sufficient to complete the reaction. Bis(phenylethoxyphosphoryl)tetrahydrohydrobenzamide decomposes very easily. The quite pure EABPP hydrochloride is isolated in up to 85% yield. The proposed method for the synthesis of EABPP (and evidently of many other similar phosphinates) is much more convenient and productive than those described in [6, 7].

The stereospecificity of the reaction is conveniently studied by the PMR method on the basis of the absorption intensity of the methyl groups of the EABPP diastereomers. The spectrum of a benzene solution of EABPP, synthesized at 100°, has two triplets (δ_1 1.0, δ_2 0.8 ppm) of equal intensity, which testifies to the presence of both diastereomeric racemic modifications of EABPP in equal concentration. The ratio of the EABPP diastereomers can be changed by lowering the temperature either in the first step of the reaction to 55-60° or in the step of decomposing the bis(phenylethoxyphosphoryl)tetrahydrohydrobenzamide with insufficient acid. In the first case the ratio of the diastereomers δ_1:δ_2 reaches 1:2, while in the second case the δ_1 diastereomer is isolated after additional recrystallization.

The optical resolution of EABPP was run by repeated recrystallization of the dibenzoyl-d-tartrate of the mixed EABPP diastereomers (δ_1:δ_2 = 1:1) from ethanol. After seven recrystallizations the melting point and optical activity of the salt remain constant. The δ_1-isomer of EABPP isolated from this salt has $[\alpha]_D^{20}$ +14.0 (ethanol).

To establish the absolute configuration of the asymmetric centers of the isolated EABPP enantiomer we made an x-ray structure study of its hydrochloride. Within the limits of accuracy, the principal valence angles in both independent ammonium cations A and B have identical values (Table 1). The structure of the cation, with the principal bond lengths, is shown in Fig. 1.

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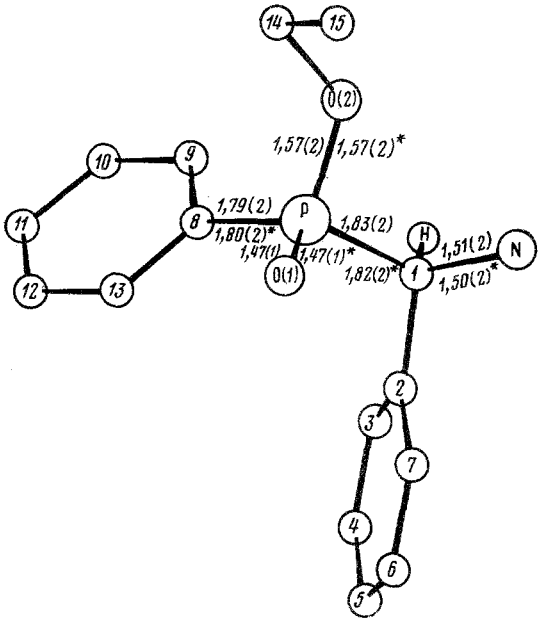

Fig. 1. Geometry of EABPP cation with principal bond lengths (marked with an asterisk for cation B).

TABLE 1. Principal Valence Angles (deg) in Cations A and B of Ethyl α-Aminobenzylphenylphosphinate

Angle	A	B	Angle	A	B
O^1PO^2	116,8(8)	116,4(8)	PC^1N	111(1)	111(1)
O^1PC^1	114,4(8)	115,0(8)	PC^1C^2	111(1)	112(1)
O^1PC^8	111,5(8)	111,0(9)	C^2C^1N	112(1)	112(1)
O^2PC^1	99,5(8)	98,5(8)	$C^1C^2C^3$	120(2)	121(2)
O^2PC^8	106,8(8)	107,4(9)	$C^1C^2C^7$	121(2)	120(2)
C^1PC^8	106,7(8)	107,5(9)	PC^8C^9	122(1)	120(2)
PO^2C^{14}	118(1)	120(1)	PC^8C^{13}	119(1)	122(2)

The P atom has a distorted tetrahedral coordination, typical for tetracoordination organophosphorus compounds of type RR'P(=X)Y [8]. Thus, the valence angles RPY and R'PY are smaller (average for both cations: O^2PC^1 99°, O^2PC^8 107°, and C^1PC^8 107°), whereas the angles XPR and XPY, formally involving the P=X double bond (O^1PO^2 116.6°, O^1PC^1 114.7, and O^1PC^8 111.3°) are larger than the ideal tetrahedral values, which is in agreement with the mutual repulsion of the electrons of the double bond and the valence electrons of the P—R(R') and P—Y bonds. The lengths of the P—O^1 double bond (1.47 Å) and the P—O^2 single bond (1.57(1) Å) are usual (for example, in the hydroxyoxaphosphafluorene molecule $C_{12}H_8P(=O)OH$ [9] they are equal to 1.481 and 1.553 Å). In harmony with the different character of the hybridization of the carbon atoms of C^1—sp^3 and C^8—sp^2, the length of the P—C^1 bond [1.83(2) Å] is somewhat greater than that of the P—C^8 bond (1.80(2) Å). The phenyl rings are planar, with an average C—C bond length of 1.38(3) Å.

Each $C_6H_5CH(\overset{+}{N}H_3)P(O)(OC_2H_5)C_6H_5$ cation has three ammonium H atoms, which are capable of forming H bonds. In harmony with this, 6 H bonds exist in the structure, in which connection they are all of the type N—H...Cl, and each Cl^- anion takes part in three such bonds (Table 2). The H bonds have a length of 3.10-3.21 Å, which is somewhat shorter than the usual value of 3.3 Å [10], i.e., these bonds are quite stable. Cation A forms two hydrogen bonds with the Cl(A) anions, connected by translation (relay) c. In a similar manner, cation B is bonded to two Cl(B) anions. As a result, the chainlets ...Cl(A)...H—N(A)—H... and ...Cl(B)...H—N(B)—H... arise along bond c. The remaining bonds N(A)—H...Cl(B) and N(B)—H...Cl(A) of these chainlets contract to ribbons, which are also parallel to the c axis.

R-α-Aminobenzylphenylphosphinic acid was obtained by cleaving the ester groups of C(R),P(S)-EABPP with HBr [11] in glacial CH_3COOH. The reaction is quite rapid and the half-

TABLE 2. Hydrogen Bonds N–H...Cl

Bond	Length, Å	Angle	ω, deg
N(A)...Cl(A)	3,10(1)	Cl(A)N(A)Cl(B)	93(1)
N(A)...Cl(A)(z–1)	3,15(1)	Cl(A)N(A)Cl(A)(z–1)	127(1)
N(A)...Cl(B)	3,16(1)	Cl(B)N(A)Cl(A)(z–1)	91(1)
N(B)...Cl(B)	3,21(1)	Cl(A)N(B)Cl(B)	91(1)
N(B)...Cl(B)(z+1)	3,18(1)	Cl(B)N(B)Cl(B)(z+1)	122(1)
N(B)...Cl(A)	3,12(1)	Cl(A)N(B)Cl(B)(z+1)	91(1)

reaction time is ∿1 h. With excess dealkylating agent, the following values of the first-order reaction rate constants (sec^{-1}) were obtained at 15, 25, 35, and 45°: $k_{15} = 3.83 \cdot 10^{-5}$, $k_{25} = 1.88 \cdot 10^{-4}$, $k_{35} = 4.30 \cdot 10^{-4}$, and $k_{45} = 12.65 \cdot 10^{-4}$. The values of the energy of activation, preexponent, and entropy of activation, calculated from these data, are: E = 20 kcal/mole, log A = 11.14 and $\Delta S^{\neq} = -12.2$ eu.

Sorbents with C(R),P(S)-EABPP and R-α-aminobenzylphenylphosphinic acid groupings were obtained as described in [12], by aminating the chloromethylated cross-linked styrene copolymer with the indicated phosphinate and subsequent cleavage of the ester groups of the sorbent. The latter asymmetric sorbent can be used for the ligand-exchange chromatography of the enantiomers of complexing compounds.

EXPERIMENTAL

EABPP Hydrochloride. The HCl salt was synthesized as described in [4] from 79.3 g of hydrobenzamide [13], 114 g of freshly distilled ethyl phenylphosphinate [14], 41 ml of Et_3N, and 0.6 ml of water at 55-100°. The reaction course was checked by TLC. Slight heating up of the mixture is observed at the start of reaction. The crude EABPP·HCl salt has mp 166-169°, 170-172° after recrystallization from EtOH, and 183-184° after a second recrystallization. Found: C 57.5; H 6.2; N 4.5; P 9.8%. $C_{15}H_{19}NPO_2Cl$. Calculated: C 57.8; H 6.1; N 4.5; P 9.95%.

The yield of the EABPP hydrochloride reaches 85% and depends on the purity of the ethyl phenylphosphinate, the reaction temperature, and the amount of water in the mixture. A deficiency of water leads to isomerization of the hydrobenzamide to amarin as described in [4]. Excess water facilitates the formation of a by-product, which, in contrast to bis-(phenylethoxyphosphoryl)tetrahydrohydrobenzamide, is insoluble in ethanol–ether mixture, but is readily soluble in water. The product gives a positive ninhydrin test, and evolves ammonia when alkali is added; mp ∿183°. These data permit assuming that the by-product is the ammonium salt of phenylphosphinic acid. Found: C 44.7; H 5.9; N 8.6; P 19.6%. $C_6H_{10}NPO_2$. Calculated: C 45.3; H 6.3; N 8.8; P 19.5%. The partial saponification of phosphorus-containing components is also observed when aminophosphinates and aminophosphonates are synthesized by the Fields–Kabachnik–Medved method [6, 15].

C(R),P(S)-EABPP. Synthesized as described in [4] by the repeated recrystallization of the acid salt, obtained from a mixture of the diastereomeric racemic modifications of EABPP and the monohydrate of dibenzoyl-d-tartaric acid (DBTA) [16] (Table 3). After seven and more recrystallizations the salt has mp 160° and $[\alpha]^{20}$ (λ, nm): −79.5° (589), −83.8° (578), −97.5° (546), −193° (436), −370° (365) (C 1, methanol). Found: C 62.2; H 4.9; N 2.1; P 4.9%. $C_{33}H_{32}NPO_{10}$. Calculated: C 62.6; H 5.1; N 2.2; P 4.9%.

The EABPP, isolated from the salt in 85% yield [16], is an oil that crystallizes rapidly on standing, mp 85-89°, $[\alpha]^{20}$ (λ, nm): +14.0°(589), +14.3°(578), +16.2°(546), +26.3°(436), +36.7°(365) (C 5.2, EtOH).

Racemic α-Aminobenzylphenylphosphinic Acid. The acid was obtained by keeping for 3 days a solution of 0.64 g of mixed diastereomeric racemates of EABPP in 10 ml of glacial AcOH, saturated with dry HBr. After working up the solution as described in [16] we isolated 0.29 g (47%) of α-aminobenzylphenylphosphinic acid monohydrate. After recrystallization from 50% EtOH, mp 234-235°. Found: C 58.5; H 6.3; N 5.2; P 11.3%. $C_{13}H_{14}NPO_2 \cdot H_2O$. Calculated: C 58.9; H 6.0; N 5.2; P 11.7%.

R-α-Aminobenzylphenylphosphinic Acid. The acid was obtained from 0.59 g of C(R),P(S)-EABPP as indicated above. We isolated 0.19 g (33.5%) of the compound. After recrystalliza-

TABLE 3. Recrystallization of Acid Salt of EABPP and DBTA from Ethanol

Taken for recrystallization		Salt, isolated after recrystallization			
salt, g	EtOH, ml	g	%	mp, °C	$[\alpha]_D^{20}$ (c 1, MeOH)
59,1 EABPP + +71,0 DBTA·H_2O	50 EtOH+ +500 ether	93,0	78	–	–57,9
92,8	100 MeOH+ +200 ether	42,0	45	~145	–62,1
42,0	125	26,4	63	154–156	–
26,4	85	21,0	80	154–156	–68,1
21,0	72	17,2	82	156–158	–70,8
17,2	85	12,9	75	156–158	–73,6
12,8	62	10,8	88	159–160	–76,1
10,6	62	8,7	82	160	–79,1
8,7	60	6,9	79	160	–79,4
6,6	55	5,3	80	160	–79,5

TABLE 4. Amination of Styrene Copolymer with EABPP

Time of removing sample after start of reaction, h	Found, %		Time of removing sample after start of reaction, h	Found, %	
	N	P		N	P
15	3,5	–	50	5,7	–
30	5,4	–	65	5,8	–
40	5,7	2,5	100	5,5	2,5

TABLE 5. Coordinates of Atoms of EABPP Hydrochloride (for Cl, P, O, and N·10^4, for C·10^3; A and B are independent cations and anions)

	A			B		
atom	X	Y	Z	X	Y	Z
Cl	6651(3)	0	5911(8)	5850(3)	1827(4)	821(9)
P	8634(3)	1300(4)	–598(9)	3938(3)	316(4)	4112(10)
O^1	8650(7)	1053(7)	–3113(20)	3870(8)	545(8)	1598(21)
O^2	8099(8)	2007(8)	–33(25)	4597(8)	–298(8)	4703(26)
N	7233(7)	583(8)	975(24)	5225(7)	1172(8)	5827(24)
C^1	816(1)	64(1)	146(3)	431(1)	103(1)	616(3)
C^2	858(1)	–11(1)	131(3)	382(1)	174(1)	597(3)
C^3	910(1)	–34(1)	310(3)	390(1)	222(1)	404(4)
C^4	952(1)	–101(1)	293(4)	342(1)	288(1)	394(4)
C^5	941(1)	–145(1)	102(4)	286(1)	304(1)	576(4)
C^6	888(1)	–124(1)	–75(4)	276(1)	256(1)	763(4)
C^7	845(1)	–58(1)	–64(4)	324(1)	192(1)	776(3)
C^8	966(1)	148(1)	54(3)	296(1)	0(1)	521(4)
C^9	980(1)	185(1)	270(3)	225(1)	17(1)	400(5)
C^{10}	1060(1)	200(1)	347(3)	148(2)	–4(2)	463(6)
C^{11}	1125(1)	177(1)	213(5)	142(2)	–38(2)	674(7)
C^{12}	1112(1)	138(1)	5(4)	204(3)	–58(2)	813(6)
C^{13}	1034(1)	124(1)	–74(3)	288(2)	–33(2)	734(5)
C^{14}*	821(2)	271(2)	–169(6)	450(2)	111(2)	344(6)
$C^{14'}$*	–	–	–	474(4)	–88(4)	327(9)
C^{15}*	755(2)	263(2)	–301(6)	515(2)	–107(2)	151(7)

*Atoms of disordered C_2H_5 groups, refined isotropically; the C^{15} occupies one position, while the C^{14} atom occupies two positions, $-C^{14}$ and $C^{14'}$, in which connection the $C^{14'}$ position could not be detected in cation A, while in cation B the populations of the positions are respectively equal to 0.7 and 0.3.

TABLE 6. Anisotropic Temperature Factors (·10) as T = $\exp[-1/4(B_{11}h^2a^{*2} + \ldots + 2B_{12}hka^*b^*\ldots)]$

	A						B					
atom	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Cl	38(2)	48(2)	36(2)	5(2)	−1(2)	1(2)	43(2)	55(3)	41(3)	8(2)	6(2)	3(2)
P	40(2)	31(2)	31(3)	−1(2)	3(2)	0(2)	39(3)	34(2)	39(3)	4(2)	−2(2)	2(2)
O^1	56(6)	42(7)	21(6)	−9(5)	5(5)	−2(5)	64(7)	46(7)	31(6)	−7(6)	−1(6)	1(6)
O^2	60(7)	38(7)	62(8)	16(6)	10(6)	−4(7)	64(8)	43(8)	63(9)	8(7)	−16(7)	−15(7)
N	23(6)	36(7)	33(7)	8(5)	6(5)	1(6)	30(6)	33(8)	38(7)	−1(6)	5(5)	3(7)
C^1	43(10)	34(9)	17(7)	7(8)	0(7)	3(7)	38(10)	30(8)	24(9)	−4(7)	1(7)	3(7)
C^2	33(8)	32(10)	20(8)	4(7)	5(7)	1(8)	31(10)	30(10)	36(10)	7(8)	−3(8)	−1(9)
C^3	48(11)	43(10)	31(10)	12(9)	−5(9)	−2(9)	46(11)	44(11)	34(11)	−9(9)	7(9)	−4(9)
C^4	47(12)	54(12)	58(13)	16(11)	−19(10)	10(11)	53(12)	35(10)	58(13)	−11(10)	−3(11)	−13(10)
C^5	49(11)	40(10)	39(12)	11(9)	−9(10)	−3(10)	27(9)	56(12)	58(13)	−8(9)	1(9)	12(11)
C^6	66(13)	35(11)	36(12)	5(9)	13(10)	−10(9)	45(10)	57(13)	46(12)	11(9)	19(9)	−9(11)
C^7	40(10)	38(11)	50(12)	2(8)	−6(9)	2(10)	31(9)	45(11)	43(10)	5(9)	11(8)	9(9)
C^8	45(10)	24(9)	29(9)	−9(7)	−2(8)	6(7)	57(11)	40(10)	33(11)	−11(10)	−3(9)	1(10)
C^9	60(13)	47(11)	29(10)	22(11)	15(9)	−5(9)	35(9)	45(14)	90(17)	−2(10)	5(11)	25(12)
C^{10}	69(12)	40(12)	25(10)	24(11)	−5(9)	−16(10)	58(18)	98(22)	99(22)	−6(17)	−2(17)	20(21)
C^{11}	53(11)	43(14)	55(15)	6(10)	−8(11)	−25(13)	77(16)	78(26)	94(25)	−16(17)	0(17)	−25(21)
C^{12}	51(12)	50(12)	65(14)	−5(11)	8(10)	−4(12)	111(31)	116(31)	66(19)	−44(28)	45(22)	19(19)
C^{13}	38(9)	47(11)	43(10)	−3(9)	11(9)	−8(10)	59(21)	94(24)	49(16)	−58(19)	−4(15)	26(16)
C^{14}	135(9) *						103(12) *					
$C^{14'}$							122(32) *					
C^{15}	146(9) *						133(12) *					

*B_{iso}, Å²·10.

tion from 50% EtOH, mp 232°, $[\alpha]^{20}$ (λ, nm): −28.8° (589), −30.2° (578), −35.0°(546), −67.0° (436), −122° (365) (C 0.9, HCl, 1:1).

The hydrolysis rate of EABPP was studied polarimetrically in 4.5% EABPP solution (in glacial AcOH), enriched with the C(R),P(S)-isomer ($[\alpha]^{20}_{578}$ = +3.3°, ethanol). The equation for a first-order reaction was used to calculate the reaction rate constants (integral method) [17].

The sorbent with R-α-aminobenzylphenylphosphinic acid groupings was obtained as described in [12], by aminating at 40° the chloromethylated macroreticular styrene polymer, crosslinked with 5% p-xylylene dichloride and 0.5% divinylbenzene [18], with EABPP ($[\alpha]^{20}_{578}$ = +3.3°, ethanol) and subsequent cleavage of the ester groups of the sorbent using HBr and either alkaline or acid hydrolysis [16] (checked via the IR spectrum). The reaction is complete (Table 4) in 40 h. From the elemental analysis data, the capacity of the anionite reaches 1.8 mg-equiv/g.

Crystal and Molecular Structure of (+)-EABPP. The experiment was run on a 4-circle Hilger–Watts automatic diffractometer using λ Cu radiation (graphite monochromator), $2° \leq 2\theta \leq 120°$, $\theta/2\theta$ scan, 1500 reflections with $F^2 \geq 3\sigma$. The structure was deciphered by the direct method and was refined by the method of least squares as the full-matrix anisotropic approximation (the C^{14} and C^{15} atoms of the disordered C_2H_5 groups were refined isotropically). The position and isotropic heat parameters (B_{iso} 5.0 Å^2) of the H atoms of the phenyl rings and the C^1 atom, arranged in the calculated positions, were fixed during the refining process. All of the calculations were made on an Eclipse S/200 minicomputer based on Syntex-EXTL programs. The final value was R 0.058, R_w 0.059. The absolute configuration of the cation (R for the C atom and S for the P atom) was determined by the Hamilton test [19], taking into account the anomalous corrections for the Cl, P, and O atoms (for the inverted structure R 0.067, R_w 0.070).

The crystals of the EABPP hydrochloride are monoclinic, a = 16.119 (2), b = 18.010 (2), c = 5.581 (1) Å, β = 90.61 (2)°, V = 1620.0 (4) Å^3, d_{meas} = 1.27, d_{calc} = 1.28 g/cm^3, Z = 4, space group $P2_1$, and each cell has two independent cations and anions. The coordinates of the atoms and their temperature factors are given in Tables 5 and 6.

CONCLUSIONS

1. A convenient method was proposed for obtaining ethyl α-aminobenzylphenylphosphinate from hydrobenzamide and ethyl phenylphosphinate. It was found that this reaction is stereospecific as regards the configuration of the C and P atoms.

2. The first members of α-aminophosphinic acids, and specifically α-aminobenzylphenylphosphinic acid and its ethyl ester, were obtained in the optically active form, and the absolute configurations of the asymmetric C and P atoms were determined.

3. The rate of hydrolyzing ethyl α-aminobenzylphenylphosphinate by dry HBr was studied.

4. Sorbents of the polystyrene type, containing the groupings of R-α-aminobenzylphenylphosphinic acid and its ethyl ester, were obtained for the first time.

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SYNTHESIS, REACTION WITH ESTERASES, AND TOXICITY OF O-ALKYL S-(CARBALKOXYMETHYLMERCAPTO)METHYL METHYLTHIOPHOSPHONATES

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Previously [1] we had described the synthesis and physiological activity of compounds of general formula $CH_3(RO)P(S)S(CH_2)_nSCH_2COOR'$ (I) (R = CH_3, C_2H_5; R' = CH_3, C_2H_5, i-C_3H_7, i-C_4H_9; n = 1, 2), among which are included active insecticides and acaricides with a moderate toxicity toward warm-blooded animals. It was shown that the physiological activity of the (I) compounds depends to a large degree on the structure of the R and R' substituents. In this connection it was interesting to follow the effect of the R and R' groups on the ability of the monothio analogs of the (I) compounds to inhibit the esterases of warm-blooded animals and arthropoda and compare the obtained data with the toxicity of these compounds. In addition, it was previously established [2] that an increase in the size of the alkyl in the alkoxyl group on the phosphorus atom enhances (due to the hydrophobic interactions with the environment of the active center) the ability of methylthiophosphonates to inhibit the cholinesterases of warm-blooded animals. Consequently, it also seemed interesting to ascertain to what degree this relationship extends to the esterases of arthropoda.

We synthesized a number of O-alkyl S-(carbalkoxymethylmercapto)methyl methylthiophosphonates:

$$CH_3(RO)P(O)SCH_2SCH_2COOR' \text{ (II)} - \text{(XIV)}$$

R = CH_3, C_2H_5, C_3H_7, C_4H_9, i-C_4H_9, C_5H_{11}, C_6H_{13}, C_7H_{15}, C_8H_{17}; R' = CH_3, C_2H_5, i-C_4H_9.

These compounds were obtained by the reaction of sodium O-alkyl methylthiophosphonates with carbalkoxymethyl chloromethyl sulfides. The constants of the obtained compounds and their elemental analysis data are given in Table 1.

To estimate the antienzymatic activity of compounds (II)-(XIV) we determined the bimolecular rate constants (k_2) of the reactions of these compounds with the acetylcholinesterase of human erythrocytes (ACE), the butyrylcholinesterase of horse serum (BuCE), the cholinesterase (CE_t) and carboxylesterase (CBE) of the nerve tissue of the American cockroach (Periplaneta americana L.), and also the I_{50} values for the cholinesterase of housefly heads (Musca domestica L.) (CE_m). The toxicity of the compounds was characterized by the LD_{50} values.

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