SYNTHESIS OF SOME O,O-DIETHYLPHOSPHORIC ACID THIOESTERS

Ya. L. Yarv, A. A. Aaviksaar, D. I. Lobanov, and N. N. Godovikov

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Organophosphorus compounds of type $(C_2H_5O)_2P(O)SX$ (I), with electronegative substituents X = $(CH_2)_nSC_2H_5$ and $(CH_2)_n\overset{+}{S}(CH_3)C_2H_5$ in the cleaved portion, are of interest as irreversible inhibitors of serine esterases for studying the structure of the active surface and the mechanism of the action of these enzymes. In contrast to the previously studied series $(C_2H_5O)(CH_3)P(O)SX$ (II), with the same X groups [1], the diethyl phosphonates do not contain asymmetric phosphorus. This circumstance simplifies the analysis and interpretation of the kinetic data on the antienzymatic action of (I) when compared with (II), since the serine esterases exhibit variable stereoselectivity toward an asymmetric phosphorus atom in the reaction center [2-4].

The synthesis and antiacetylcholinesterase activity of the series (I) inhibitors, with n = 1-3, were described in [5-9]. The series (I) inhibitors with n = 4-6 were synthesized in the present paper, and the synthesis of the compounds, where n = 1-3, was also repeated. The O,O-diethyl thiophosphates were obtained by reacting diethyl chlorophosphate with the appropriate sodium mercaptides in benzene.

$$(C_2H_5O)_2P(O)Cl + NaS(CH_2)_nSC_2H_5 \rightarrow (C_2H_5O)_2P(O)S(CH_2)_nSC_2H_5 + NaCl$$

According to [10], the thus obtained inhibitors can contain highly active impurities, which greatly distort the results of the kinetic measurements of their antienzymatic activity, in particular, in the reaction with the acetylcholinesterase of bovine erythrocytes. In view of this, special attention was given in the present paper to the purification of the synthesized compounds. Instead of vacuum-distillation, we used the more selective method of liquid chromatography on silica gel [11] to isolate the inhibitors from the reaction mixture.

The alkylation of the O,O-diethyl S-(ω-ethylmercaptoalkyl)phosphates with dimethyl sulfate gave the corresponding methyl methosulfates.

$$(C_2H_5O)_2P(O)S(CH_2)_nSC_2H_5 + (CH_3)_2SO_4 \rightarrow (C_2H_5O)_2P(O)S(CH_2)_n\overset{+}{S}(CH_3)C_2H_5 + CH_3SO_4^-$$

Together with the methyl methosulfates, which have an asymmetric sulfonium group, the alkylation of the inhibitors with diethyl sulfate also gave a number of ethyl ethosulfates that lack a center of asymmetry in the molecule.

The mercaptans $C_2H_5S(CH_2)_nSH$, where n = 2-6, were obtained by alkylating the corrsponding α,ω-alkyldithiols with ethyl bromide. The compound $C_2H_5SCH_2SH$ was obtained from chloromethyl ethyl sulfide.

EXPERIMENTAL METHOD

Mercaptomethyl Ethyl Sulfide. With stirring, to 27 g (0.35 mole) of thiourea in 50 ml of abs. alcohol was added 37 g (0.33 mole) of chloromethyl ethyl sulfide [12], and the mixture was heated at 80° for 3 h. The thiuronium salt that deposited on cooling was washed with abs. ether and recrystallized from abs. alcohol. The yield of the thiuronium salt was 36 g (0.19 mole). With heating, the obtained salt was dissolved in 50 ml of water, and to the stirred solution was added 75 ml of 3.0 M NaOH solution, after which the mixture was kept at 45° for 1 h. The hydrolysis of the thiuronium salt, as well as all of the subsequent

Institute of Heteroorganic Compounds, Academy of Sciences of the USSR, Moscow. Tartu State University, Institute of Cybernetics, Academy of Sciences of the Estonian SSR, Tallin. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 2, pp. 426-428, February, 1976. Original article submitted June 30, 1975.

TABLE 1. O,O-Diethyl S-(ω-Ethylmercaptoalkyl) Thiophosphates $(C_2H_5O)_2P(O)S(CH_2)_nSC_2H_5$

n	Yield,* %	n_D^{20}	d_4^{20}	Found, %				Empirical formula	Calculated, %			
				C	H	O	P		C	H	O	P
1	53	1,5043	1,1506	34,2	6,9	19,6	12,5	$C_7H_{17}O_3PS_2$	34,4	7,0	19,6	12,6
2†	56	1,4985	1,1333	37,2	7,3	18,6	12,1	$C_8H_{19}O_3PS_2$	37,2	7,4	18,6	12,0
3	37	1,4904	1,1128	39,8	7,8	17,5	11,1	$C_9H_{21}O_3PS_2$	39,7	7,8	17,6	11,4
4	43	1,4842	1,0890	41,8	8,1	16,6	10,6	$C_{10}H_{23}O_3PS_2$	41,9	8,1	16,8	10,8
5	48	1,4770	1,0723	44,0	8,3	15,9	10,1	$C_{11}H_{25}O_3PS_2$	44,0	8,4	16,0	10,3
6	45	1,4740	1,0500	45,7	8,5	15,1	10,0	$C_{12}H_{27}O_3PS_2$	45,8	8,7	15,3	9,8

*Yield of product after chromatographic purification.
†Compare with data given in [5, 7, 9].

TABLE 2. Alkyl Alkosulfates of O,O-Diethyl S-(ω-Ethylmercaptoalkyl) Thiophosphates $[(C_2H_5O)_2P(O)S(CH_2)_nS(C_2H_5)R]^+ \cdot RSO_4^-$

n	R	Yield, %	n_D^{20}	Found, %			Empirical formula	Calculated, %		
				C	H	O		C	H	O
1	CH_3	82	1,5180	31,6	6,9	33,2	$C_9H_{23}O_7PS_3$	31,9	6,9	33,1
2	CH_3	93	1,5120*	31,2	6,7	29,3	$C_{10}H_{25}O_7PS_3$	31,2	6,6	29,1
3	CH_3	87	1,5072	33,0	7,0	28,0	$C_{11}H_{27}O_7PS_3$	33,1	6,8	28,1
4	CH_3	80	1,5006	34,7	6,9	27,2	$C_{12}H_{29}O_7PS_3$	34,9	7,1	27,2
5	CH_3	85	1,4945	36,9	7,0	26,3	$C_{13}H_{31}O_7PS_3$	36,6	7,3	26,2
6	CH_3	91	1,4892	38,6	8,0	24,9	$C_{14}H_{33}O_7PS_3$	38,2	7,6	25,4
1	C_2H_5	70	1,5100	33,0	6,9	27,8	$C_{11}H_{27}O_7PS_3$	33,1	6,9	28,1
2	C_2H_5	65	1,5036	35,2	7,0	27,0	$C_{12}H_{29}O_7PS_3$	34,9	7,1	27,2
4	C_2H_5	63	1,4907	35,2	7,0	25,0	$C_{14}H_{33}O_7PS_3$	38,1	7,6	25,4
6	C_2H_5	72	1,4792	40,9	8,1	23,5	$C_{16}H_{37}O_7PS_3$	41,0	8,0	23,9

* cf. [5].

steps of the synthesis, was carried out in an argon atmosphere. After cooling, the excess alkali was neutralized with dilute H_2SO_4 solution, 10 g of NaCl was added, and the product was extracted with ether. The ether extract was washed with water, dried over Na_2SO_4, the ether was evaporated, and the residue was vacuum-distilled. The yield was 10 g (28%), bp 46° (11 mm), n_D^{20} 1.5348; d_4^{20} 1.0505. The purity of the compound was verified by TLC on Silufol UV-254 plates, R_f 0.61, and the eluent was 1:8 acetone–hexane.

O,O-Diethyl S-(ω-Ethylmercaptoalkyl) Thiophosphates. To a stirred suspension of 2.3 g (0.1 mole) of sodium in 50 ml of benzene was carefully added a solution of 0.15 mole of the mercaptan in 50 ml of benzene. After adding all of the mercaptan the mixture was refluxed until the test for the formation of sodium mercaptide was negative, after which it was cooled to 5° and 17.4 g (0.1 mole) of diethyl chlorophosphate was added in drops. To complete the reaction the mixture was heated for 6 h at 45° and then let stand overnight. The reaction mixture was treated several times with water, dried over Na_2SO_4, and the solvent was removed in vacuo. The obtained product was purified on a silica gel column [11].

The constants, yields, and analysis data for the obtained compounds are given in Table 1; their purity was checked by TLC on Silufol UV-254 plates, using 1:1 acetone–heptane as the eluent.

Methyl Methosulfates and Ethyl Ethosulfates of O,O-Diethyl S-(ω-Ethylmercaptoalkyl) Thiophosphates. To a stirred mixture of 0.03 mole of freshly distilled dialkyl sulfate and 0.025 mole of the O,O-diethyl S-(ω-ethylmercaptoalkyl) thiophosphate was added 2 ml of abs. ether, and the mixture was kept at ~20° until the mixture ceased to stratify. The lower layer was separated, reprecipitated several times from abs. ethanol solution with abs. ether, and kept for several hours in vacuo. The constants, yields, and analysis data are given in Table 2.

CONCLUSIONS

We synthesized a number of O,O-diethyl S-(ω-ethylmercaptoalkyl) thiophosphates, and their methyl methosulfates and ethyl ethosulfates.

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