SYNTHESIS OF SOME O-ETHYL S-ALKYL ALKYLTHIOPHOSPHONATES

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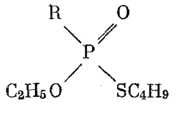
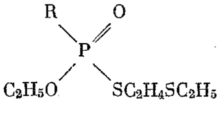
Previously it was shown [1-5] that the anticholinesterase activity of the O-alkyl S-alkyl methylthiophosphonates increases strongly with increase in the length and degree of branching of the O- and S-alkyl radicals.

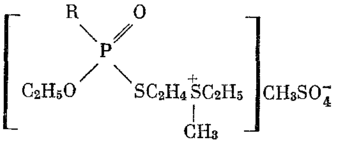
However, the effect of an alkyl radical, attached to the phosphorus atom, on the physiological activity of these compounds has not been studied. For this purpose we synthesized in the present paper some O-ethyl S-butyl alkylthiophosphonates (I), O-ethyl S-(β-ethylmercaptoethyl) alkylthiophosphonates (II), and O-ethyl S-(β-ethylmercaptoethyl) alkylthiophosphonate methyl methosulfonates (III).



(I)

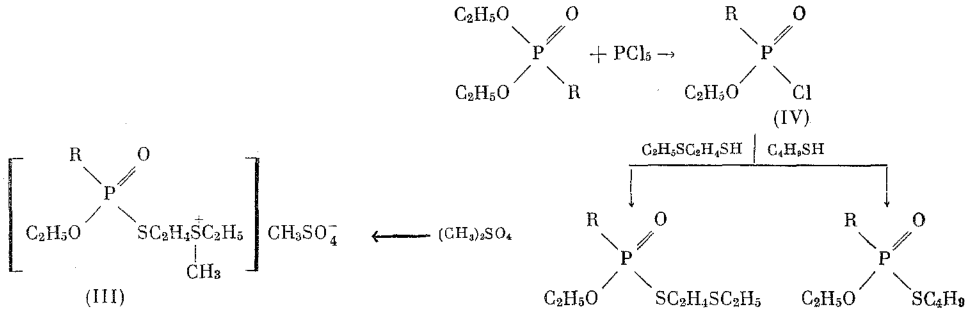


(II)



(III)

The starting compounds for the synthesis of the above-indicated compounds were diethyl phosphite [6, 7] and the O,O-diethyl alkylphosphonates [8]. Reaction of the latter with PCl_5 gave the acid chlorides of the O-ethylalkylphosphinic acids (IV), which when reacted with butyl mercaptan and β-mercaptoethyl ethyl sulfide respectively gave (I) and (II)



R = C_2H_5; n-C_3H_7; n-C_4H_9

The reaction of dimethyl sulfate with (II) gave the methyl methosulfonates (III). The constants and yields of the obtained compounds are given in Tables 1 and 2.

EXPERIMENTAL METHOD

The O,O-diethyl alkylphosphonates were obtained by the previously described procedure [6-8].

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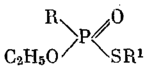
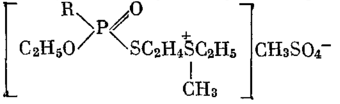
TABLE 1. O-Ethyl S-Alkyl Alkylthiophosphonates



R	R¹	Yield %	Bp, °C (p, mm of Hg)	n_D^{20}	d_4^{20}	R_f	MR found	MR calc.	Found, % C	Found, % H	Found, % P	Empirical formula	Calculated, % C	Calculated, % H	Calculated, % P
C_2H_5	C_4H_9	30	72—73 (1)	1,4729	1,0065	0,56	57,47	57,00	45,94	9,40	14,49	$C_8H_{19}PO_2S$	45,68	9,04	14,78
C_2H_5	$C_2H_5SC_2H_4$	66	112 ($5 \cdot 10^{-1}$)	1,5032	1,1051	0,50	64,49	65,01	39,76	8,12	12,32	$C_8H_{19}PO_2S_2$	39,66	7,85	12,81
C_3H_7	C_4H_9	46,4	82—87 ($3,5 \cdot 10^{-1}$)	1,4715	1,0109	0,66	61,93	61,85	48,84	9,38	13,69	$C_9H_{21}PO_2S$	48,21	9,37	13,84
C_3H_7	$C_2H_5SC_2H_4$	54	110—112 ($3,5 \cdot 10^{-1}$)	1,5005	1,0861	0,41	69,33	69,63	42,11	8,75	12,34	$C_9H_{21}PO_2S_2$	42,18	8,20	12,10
C_4H_9	C_4H_9	40	91,5-92,5 ($3,5 \cdot 10^{-1}$)	1,4760	1,000	0,54	66,73	66,46	50,20	9,65	12,74	$C_{10}H_{23}PO_2S$	50,42	9,66	13,02
C_4H_9	$C_2H_5SC_2H_4$	40,7	126 ($4 \cdot 10^{-1}$)	1,4919	1,0692	0,43	73,75	74,24	44,28	9,14	12,00	$C_{10}H_{23}PO_2S_2$	44,44	8,51	11,5

TABLE 2. O-Ethyl S-(β-Ethylmercaptoethyl) Alkylthiophosphonate Methyl Methosulfonates



R	Yield, %	n_D^{20}	Found P, %	Empirical formula	Calc. P, %
C_2H_5	Quantitative	1,5088	7,96	$C_{11}H_{25}PO_6S_3$	8,42
n-C_3H_7	"	1,5090	7,80	$C_{12}H_{27}PO_6S_3$	8,06
n-C_4H_9	90	1,5050	7,41	$C_{13}H_{29}PO_6S_3$	7,82

Acid Chloride of O-Ethylethylphosphonic Acid. To a solution of 14.5 g of $C_2H_5PO(C_2H_5O)_2$ in 33 ml of absolute CCl_4 was slowly added 15.3 g of PCl_5 (mole ratio 1.19 : 1) and then the mixture was allowed to stand overnight. The mixture was evaporated, and the residue was vacuum-distilled. We obtained 11.8 g (90%) of the acid chloride of O-ethylethylphosphonic acid, bp 82-84° (11 mm); n_D^{20} 1.4374.

Acid Chloride of O-Ethylpropylphosphonic Acid. To 49 g of PCl_5, contained in a three-necked flask equipped with a reflux condenser, with vigorous stirring, was added 43 g of O,O-diethylpropylphosphonate. Marked warming up of the reaction mixture was observed. The mixture was heated at 90-95° for 4 h and then allowed to stand overnight. Fractional distillation in vacuo gave 36 g (87.5%) of the acid chloride of O-ethylpropylphosphinic acid, bp 58° (1 mm); n_D^{20} 1.4440.

The acid chloride of O-ethylbutylphosphinic acid was obtained in similar manner in 84% yield; bp 69-70° (1 mm); n_D^{20} 1.4430; d_4^{20} 1.1373. Found: C 38.77; H 8.75; P 17.13%; MR 42.99. $C_6H_{14}PO_2Cl$. Calculated: C 39.04; H 7.61; P 16.81%; MR 43.36.

O-Ethyl S-(β-Ethylmercaptoethyl) Ethylthiophosphonates. To a suspension of 1.14 g of Na in 30 ml of absolute benzene was added 6.1 g of $C_2H_5SC_2H_4SH$, after which the mixture was heated at 80-85° for 3 h. To the cooled mixture was added 7.8 g of the acid chloride of O-ethylethylphosphinic acid in small portions, after which the mixture was heated at 85° for 8 h. The mixture was dissolved in a little water and then repeatedly extracted with benzene, after which the extract was dried over Na_2SO_4, the benzene was removed by distillation, and the residue was vacuum-distilled.

The O-ethyl S-n-butyl alkylthiophosphonates and O-ethyl S-(β-ethylmercaptoethyl) alkylthiophosphonates were obtained in a similar manner.

O-Ethyl S-(β-Ethylmercaptoethyl) Alkylthiophosphonate Methyl Methosulfonates. To 0.05 M of the O-ethyl S-(β-ethylmercaptoethyl) alkylthiophosphonate, dissolved in a little benzene, was added 0.05 M of dimethyl sulfate, after which the mixture was refluxed in a flask equipped with a reflux condenser and a calcium chloride tube. Then the solvent was distilled off, and the residue was shaken with a little ether and allowed to stand overnight. The ether solution was separated, while the residual viscous mass was dried in vacuo (1 mm) for 2 h at 60°.

CONCLUSIONS

A number of new O-ethyl S-alkyl alkylthiophosphonates were synthesized.

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