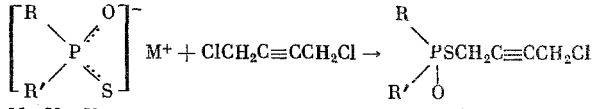
SYNTHESIS OF ω-SUBSTITUTED BUTYNYL ESTERS OF PHOSPHORUS THIOACIDS

N. N. Godovikov, L. A. Vikhreva,
T. A. Pudova, and M. I. Kabachnik

UDC 542.91:547.1'118

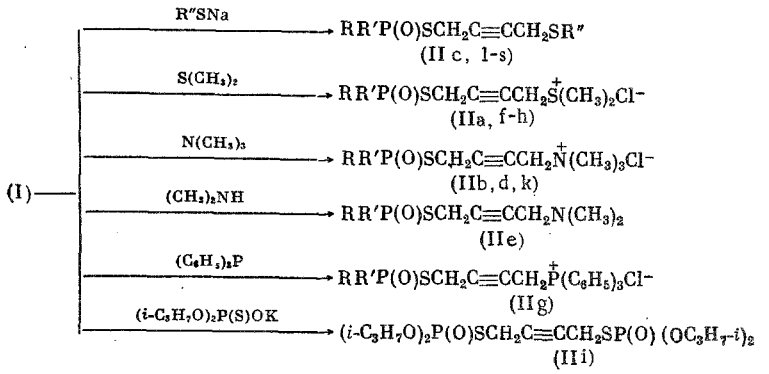
The anticholinesterase activity of the thioesters of pentavalent phosphorus acids is quite dependent on the structure of the "cleavable" portion of the inhibitor molecule and, in particular, on the presence of polar substituents in it, such as sulfide, sulfonium, amino, ammonium, and other groups [1]. The synthesis of P(V) acids, containing in the alkthiol radical, besides the indicated groupings, also an acetylene linkage, is of definite interest. The presence of such a "hard" fragment in the thioester radical can facilitate the manifestation of selectivity in the effect of organophosphorus inhibitors toward cholinesterases of different origin.

The synthesis of such compounds was accomplished as follows [2, 3]. First the reaction of the Na or K salts of the appropriate phosphorus monothioacids with excess 1,4-dichloro-2-butyne gave the ω-chlorobutynyl esters of phosphorus thioacids (I) (Table 1).



M=Na, K. (I)

Then the (I) compounds were reacted with various nucleophilic reagents to give the corresponding ω-substituted butynyl esters of phosphorus monothioacids (Table 2). As the nucleophilic reagents we used dimethyl sulfide, sodium alkyl mercaptides, trimethylamine, dimethylamine, triphenylphosphine, and potassium dialkyl thiophosphates.



The structure of the obtained compounds was confirmed by the IR and Raman spectral data. Thus, in all cases the IR spectra have bands in the vicinity of 1280 cm^{-1} (P=O) and, depending on the substituents, in the vicinity of 2220-2240 cm^{-1} (C≡C). The Raman spectra of these compounds have intense bands in the vicinity of 2220-2240 cm^{-1} (C≡C).

The structure of some of the synthesized (II) compounds was proved by counter synthesis. Thus, the alkylation of sodium O-alkyl methylthiophosphonate with (ω-chloro-2-butynyl) ethyl sulfide (III) gives O-alkyl S-(ω-ethylmercapto-2-butynyl) methylthiophosphonates. The starting sulfide (III) was obtained by reacting sodium ethyl mercaptide with a fivefold excess of 1,4-dichloro-2-butyne.

A. N. Nesmeyanov Institute of Heteroorganic Compounds, Academy of Sciences of the USSR, Moscow.
Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 11, pp. 2588-2594, November, 1980. Original article submitted January 11, 1980.

0568-5230/80/2911-1843$07.50

TABLE 1. ω-Chlorobutynyl Esters of Phosphorus Thioacids $RR'P(O)SCH_2C \equiv CCH_2Cl$

Compound	R	R′	mp, °C (0.001 mm)	d_4^{20}	n_D^{20}	Yield, %	Empirical formula	Found / Calculated, %		
								C	H	P
(Ia)	CH_3	C_2H_5O	122–123	1,2605	1,5283	72,5	$C_7H_{12}ClO_2PS$	36,72 / 37,09	5,23 / 5,29	13,50 / 13,60
(Ib)	C_2H_5O	C_2H_5O	127–130	1,2441	1,5080	56,5	$C_8H_{14}ClO_3PS$	37,13 / 37,43	5,45 / 5,46	12,11 / 12,09
(Ic)	C_6H_5	C_2H_5O	162–163	1,2593	1,5721	48	$C_{12}H_{14}ClO_2PS$	49,56 / 49,80	4,92 / 4,75	10,51 / 10,72
(Id)	C_6H_5	C_6H_5	*	–	–	78	$C_{16}H_{14}ClOPS$	60,10 / 59,91	4,49 / 4,37	9,84 / 9,67
(Ie)	i-C_3H_7O	i-C_3H_7O	118–120	1,1635	1,4940	52	$C_{10}H_{18}ClO_3PS$	42,06 / 42,09	6,33 / 6,31	10,46 / 10,86
(If)	CH_3O	CH_3O	128–130	1,3015	1,5163	45,5	$C_6H_{10}ClO_3PS$	31,35 / 31,45	4,50 / 4,40	12,47 / 13,50
(Ig)	CH_3	C_3H_7O	131–133	1,1918	1,5233	71,3	$C_8H_{14}ClO_2PS$	39,70 / 39,90	5,83 / 5,82	13,67 / 12,87

* mp, 63-64° C.

TABLE 2. ω-Substituted S-Butynyl Esters of Phosphorus Thioacids $RR'P(O)SCH_2C \equiv CCH_2X$

Compound	R	R′	X	Yield, %	mp, °C (0.001 mm)	d^{20}_4	n^{20}_D	Empirical formula	Found/Calculated, %		
									C	H	P
(IIa)	CH_3	C_2H_5O	$[(CH_3)_2\overset{+}{S}]Cl^-$	81	Oil	–	–	$C_9H_{18}O_2ClPS_2$	37,78 / 37,40	6,27 / 6,22	10,65 / 10,73
(IIb)	CH_3	C_2H_5O	$[(CH_3)_3\overset{+}{N}]Cl^-$	90	155–157*	–	–	$C_{10}H_{21}O_2ClNPS$	42,24 / 42,03	7,42 / 7,36	10,07 / 10,86
(IIc)	C_2H_5O	C_2H_5O	C_2H_5S	31	135–137	1,1548	1,5162	$C_{10}H_{19}O_3PS_2$	42,36 / 42,55	6,56 / 6,73	11,17 / 10,98
(IId)	C_2H_5O	C_2H_5O	$[\overset{+}{N}(CH_3)_3]Cl^-$	88	189–190*	–	–	$C_{11}H_{23}ClO_3NPS$	41,94 / 41,51	7,40 / 7,28	10,59 / 9,82
(IIe)	C_2H_5O	C_2H_5O	$(CH_3)_2N$	25	120–121	1,1045	1,4927	$C_{10}H_{20}O_3NPS$	45,10 / 44,95	7,87 / 7,48	N 5,78 / 5,27
(IIf)	C_2H_5O	C_2H_5O	$[(CH_3)_2\overset{+}{S}]Cl^-$	75	Oil	–	–	$C_{10}H_{20}O_3ClPS_2$	37,16 / 37,63	6,36 / 6,27	S 19,20 / 20,03
(IIg)	C_2H_5O	C_2H_5O	$[(C_6H_5)_3\overset{+}{P}]Cl^-$	71	105–108*	–	–	$C_{26}H_{29}O_3ClP_2S$	60,29 / 60,21	5,58 / 5,58	12,56 / 12,06
(IIh)	C_6H_5	C_2H_5O	$[(CH_3)_2\overset{+}{S}]Cl^-$	70	82–84*	–	–	$C_{14}H_{20}ClO_2PS_2$	47,83 / 47,88	5,70 / 5,68	8,83 / 8,83
(IIi)	$i\text{-}C_3H_7O$	$i\text{-}C_3H_7O$	$(i\text{-}C_3H_7O)_2P(O)S$	38	–	1,2390	1,4918	$C_{10}H_{32}O_6P_2S_2$	42,92 / 43,03	7,21 / 7,17	13,80 / 13,88
(IIk)	C_6H_5	C_6H_5	$[(CH_3)_3\overset{+}{N}]Cl^-$	79	129–132*	–	–	$C_{19}H_{23}ClNOPS$	59,87 / 60,09	6,07 / 6,06	8,07 / 8,27
(IIl)	CH_3O	CH_3O	C_2H_5S	25	122–124	1,2005	1,5245	$C_8H_{15}O_3PS_2$	37,15 / 37,70	5,95 / 5,92	11,23 / 12,23
(IIm)	C_6H_5	C_6H_5	C_2H_5S	85	–	–	1,6145	$C_{18}H_{19}OPS_2$	62,32 / 62,33	5,67 / 5,48	8,98 / 8,96
(IIn)	C_6H_5	C_2H_5O	C_2H_5S	78	–	–	1,5745	$C_{14}H_{19}O_2PS_2$	54,10 / 53,45	5,75 / 6,03	9,60 / 9,86
(IIo)	C_2H_5O	C_2H_5O	C_4H_9S	90	–	1,1110	1,5012	$C_{12}H_{23}O_3PS_2$	46,36 / 46,45	7,68 / 7,42	9,54 / 10,00
(IIp)	CH_3	C_2H_5O	C_2H_5S	24	125–130	1,1538	1,5335	$C_9H_{17}O_2PS_2$	42,21 / 42,89	6,56 / 6,75	12,16 / 12,31
(IIr)	CH_3	C_3H_7O	C_2H_5S	21	135–137	1,1319	1,5260	$C_{10}H_{19}O_2PS_2$	44,36 / 44,81	6,64 / 7,10	11,61 / 11,65
(IIs)	CH_3	C_4H_9O	C_2H_5S	20	140–145	1,1018	1,5198	$C_{11}H_{21}O_2PS_2$	47,08 / 47,21	7,48 / 7,51	11,07 / 11,07

* Melting point.

$$C_2H_5SNa + ClCH_2C \equiv CCH_2Cl \rightarrow C_2H_5SCH_2C \equiv \underset{(III)}{CCH_2Cl}$$

$$(III) + CH_3P(S)(OR)O^-Na^+ \rightarrow CH_3P(O)(OR)SCH_2C{\equiv}CCH_2SC_2H_5$$

(IIi-s)

It is interesting to mention that the alkylation of the S-(ω-ethylmercapto-2-butynyl) esters of methylthiophosphonic acid in excess CH_3I is accompanied by their cleavage. In all cases dimethylethylsulfonium iodide, probably formed by the scheme

$$CH_3P(O)(OR)SCH_2C{\equiv}CCH_2SC_2H_5 + CH_3I \rightarrow CH_3P(O)(OR)SCH_2C{\equiv}CCH_2\overset{+}{S}(CH_3)C_2H_5 \cdot I^-$$

$$[(CH_3)_2\overset{+}{S}C_2H_5]I \cdot \xleftarrow{CH_3I} C_2H_5SCH_3 + CH_3P(O)(OR)SCH_2C{\equiv}CCH_2I$$

was isolated from the cleavage products in nearly quantitative yield. The cleavage apparently proceeds in the same manner as the reaction of CH_3I with sulfides that contain either bulky or unsaturated radicals. Thus, it is known that the dibenzoyl and diallyl sulfides in excess CH_3I give trimethylsulfonium iodide [4].

EXPERIMENTAL

ω-Chlorobutynyl Esters of Phosphorus Thioacids (I). To 0.5 mole of 1,4-dichloro-2-butyne at ~ 20°C was added 0.1 mole of the K or Na salt of the appropriate phosphorus monothioacid in 200 ml of abs. alcohol. The mixture was refluxed for 2 h, the precipitate was filtered, the excess dichlorobutyne was vacuum-distilled and the residue was purified either by vacuum-distillation or by extraction with hexane. The constants, yields, and analysis data for the obtained compounds are given in Table 1.

Reaction of ω-Chlorobutynyl Esters of Phosphorus Thioacids with Sodium Alkyl Mercaptides. To 0.1 mole of O-O-diethyl S(ω-chloro-2-butynyl) thiophosphate in 50 ml of abs. alcohol at ~ 20° was added in 2 h 0.1 mole of EtSNa in 100 ml of alcohol. The mixture was refluxed for 2 h, the precipitate was separated, the solvent was evaporated, and the residue was purified either by vacuum-distillation or by extraction with hexane to give (IIc). Compounds (III-s) were obtained in a similar manner.

Reaction of ω-Chlorobutynyl Esters of Phosphorus Thioacids with Dimethyl Sulfide. A mixture of 0.02 mole of O-ethyl S-(ω-chloro-2-butynyl) methylthiophosphonate and a 10-fold excess of dimethyl sulfide was kept in the dark for 2 weeks at 20°. The excess dimethyl sulfide was distilled off and the residue was dried in vacuo to give (IIa). Compounds (IIf, h) were obtained in a similar manner.

O,O-Diethyl S-(ω-Dimethylamino-2-butynyl) Thiophosphate. To 0.22 mole of dimethylamine in 100 ml of ether at 20° was added 0.1 mole of (Ib). After 4 h the precipitate was filtered, the solvent was evaporated, and the residue was vacuum-distilled to give (IIe).

Reaction of ω-Chlorobutynyl Esters of Phosphorus Thioacids with Trimethylamine. A mixture of 0.02 mole of (I), 0.1 mole of Me_3N, and 50 ml of ether was left standing for 2 days at ~ 20°. The obtained precipitate was filtered, washed in succession with THF and ether, and dried in vacuo to give (IIb). Compounds (IId-k) were obtained in a similar manner.

Bis-[1,4-(S,S-diisopropylthiophosphoryl)]-2-butyne. To 0.2 mole of the K salt of diisopropyl thiophosphate in 100 ml of alcohol was added 0.1 mole of the dichlorobutyne. The mixture was refluxed for 2 h, the precipitate was filtered, the residue was extracted with hexane, and the latter was distilled off. We obtained (IIi).

O,O-Diethyl-ω-2-butynylthiophosphinyltriphenylphosphonium Chloride. To 0.0055 mole of O,O-diethyl S-(ω-chloro-2-butynyl) thiophosphate in 10 ml of benzene was added 0.0055 mole of Ph_3P, the mixture was kept for 24 h at ~ 20°, and the obtained crystals were separated, washed with benzene, and dried in vacuo to give (IIg).

(ω-Chloro-2-butynyl) Ethyl Sulfide (III). To 1 mole of 1,4-dichloro-2-butyne at 20° was added 0.2 mole of EtSNa in 100 ml of alcohol. The mixture was refluxed for 2 h, the NaCl was filtered, the solvent was evaporated, the dichlorobutyne was distilled off at 20 mm, and the residue was distilled to give 19.8 g (66.7%) of (III), bp 67-71° (2 mm), d_4^{20} 1.1140, n_D^{20} 1.5306. Found: C 48.42; H 5.99; S 21.46; Cl 24.29%. C_6H_9ClS. Calculated: C 48.48; H 6.06; S 21.55; Cl 23.91%.

O-Alkyl S-(ω-Ethylmercapto-2-butynyl) Methylthiophosphonates. To 0.1 mole of the Na salt of the O-alkylmethylthiophosphoric acid in 100 ml of alcohol at 20° was added 0.1 mole of (III). The mixture was refluxed for 2 h, the NaCl was filtered, the alcohol was distilled off, and the residue was vacuum-distilled. Compounds (IIp-s) were obtained. Infrared spectrum: 2230 (C≡C), 1280 cm^{-1} (P=O).

Reaction of O-Alkyl S-(ω-Ethylmercapto-2-butynyl) Methylthiophosphonates with Methyl Iodide. To 0.01 mole of the O-alkyl S-(ω-ethylmercapto-2-butynyl) methylthiophosphonate in 70 ml of abs. ether was added a fivefold excess of MeI. After 20 days the obtained precipitate was filtered and washed with ether to give dimethylethylsulfonium iodide as a hygroscopic powder in 90-95% yield. Found: C 21.70; H 5.05; I 57.68; S 15.16%. $C_4H_{11}IS$. Calculated: C 22.02; H 5.04; I 58.15; S 14.68%.

CONCLUSIONS

1. A number of ω-chlorobutynyl esters of phosphorus monothioacids were synthesized.

2. The reaction of the ω-chlorobutynyl esters of phosphorus monothioacids with nucleophilic reagents gave a number of ω-substituted S-butynyl esters of phosphorus monothioacids.

LITERATURE CITED

1. M. Ya. Mikhel'son and É. V. Zeimal, Acetylcholine [in Russian], Nauka, Leningrad (1970), p. 95.
2. L. A. Vikhreva, T. A. Pudova, I. B. Nemirovskaya, D. I. Lobanov, N. N. Godovikov, M. I. Kabachnik, S. A. Roslavtseva, and T. A. Spirina, Inventor's Certificate No. 607,414 (1979); Byull. Izobr., No. 26 (1979).
3. L. A. Vikhreva, T. A. Pudova, I. B. Nemirovskaya, D. I. Lobanov, N. N. Godovikov, M. I. Kabachnik, S. A. Roslavtseva, and T. A. Spirina, Inventor's Certificate No. 630,860 (1979); Byull. Izobr., No. 31 (1979).
4. E. H. Farmer and F. W. Shipley, J. Chem. Soc., 1519 (1947).

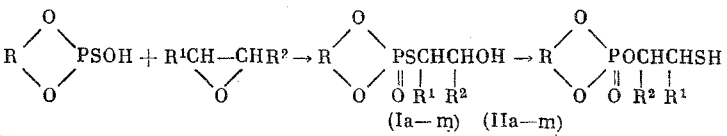
ISOMERIZATION OF S-2-HYDROXYALKYL ESTERS OF CYCLIC PHOSPHORUS THIOACIDS

O. N. Nuretdinova and F. F. Guseva

UDC 542.91:547.1'118

Previously it was shown that most S-2-hydroxyalkyl esters of dialkylthiophosphoric acids undergo rearrangement to give 2-mercapto derivatives [1]. An exception were the S-2-hydroxyalkyl esters of di-tert-butylthiophosphoric acid, which, probably due to steric hindrance, do not rearrange [2].

In order to establish if rearrangement can take place in the series of cyclic phosphorus thioacid derivatives and the relation between its occurrence and the ring size of the starting thioacid we studied the isomerization of some S-2-hydroxyalkyl esters of cyclic phosphorus thioacids, which were obtained by reacting these acids with alkylene α-oxides. The obtained S-2-hydroxyalkyl esters (I) were not isolated from the reaction mixture, since they are unstable and are rapidly converted to the O-2-mercaptoalkyl esters (II).



(Ia—m) (IIa—m)

R=$(CH_2)_3$, R^1=R^2=H (a); R^1=H, R^2=CH_3 (b); R^1=R^2=CH_3 (c); R=$CH_3CH(CH_2)_2$, R^1=H, R^2=CH_3 (d); R=$(CH_3)_2CCH_2CHCH_3$, R^1=H, R^2=CH_3 (e); R=$(CH_2)_4$, R^1=H, R^2=CH_3 (f); R^1=R^2=CH_3 (g); R=$CH_3CH(CH_2)_2$—$CHCH_3$, R^1=H, R^2=CH_3 (h); R^1=R^2=CH_3 (i); R=$CH_3CHCHCH_3$, R^1=H, R^2=CH_3 (k); R^1=R^2=CH_3 (l); R=$(CH_3)_2CC(CH_3)_2$, R^1=H, R^2=CH_3 (m).

A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Branch of the Academy of Sciences of the USSR.

Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 11, pp. 2594-2596, November, 1980. Original article submitted December 10, 1979.

0568-5230/80/2911-1847$07.50