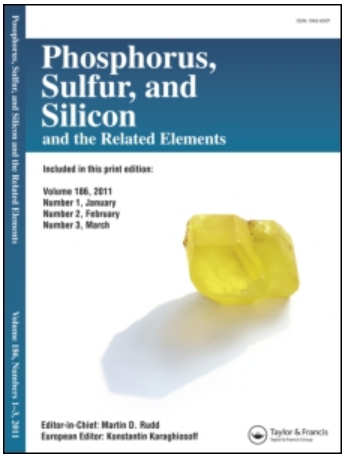


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS OF 1,2-O-ISOPROPYLIDENE GLYCERO-THIOLO-(DITHIOLO)-PHOSPHOHOMOCHOLINES. A NEW THION-THIOL ISOMERIZATION OF ALKYLENE PHOSPHOROTHIOATES

E. E. Nifantyev[a]; D. A. Predvoditelev[a]; E. N. Rasadkina[a]; A. R. Bekker[a]
[a] Department of Chemistry, V. I. Lenin Moscow State Pedagogical Institute, Moscow, U.S.S.R.

To cite this Article Nifantyev, E. E. , Predvoditelev, D. A. , Rasadkina, E. N. and Bekker, A. R.(1987) 'SYNTHESIS OF 1,2-O-ISOPROPYLIDENE GLYCERO-THIOLO-(DITHIOLO)-PHOSPHOHOMOCHOLINES. A NEW THION-THIOL ISOMERIZATION OF ALKYLENE PHOSPHOROTHIOATES', Phosphorus, Sulfur, and Silicon and the Related Elements, 34: 3, 109 — 117
To link to this Article: DOI: 10.1080/03086648708074314
URL: http://dx.doi.org/10.1080/03086648708074314

Phosphorus and Sulfur, 1987, Vol. 34, pp. 109–117
Photocopying permitted by license only

SYNTHESIS OF 1,2-O-ISOPROPYLIDENE GLYCERO-THIOLO-(DITHIOLO)-PHOSPHOHOMOCHOLINES. A NEW THION–THIOL ISOMERIZATION OF ALKYLENE PHOSPHOROTHIOATES

E. E. NIFANTYEV, D. A. PREDVODITELEV, E. N. RASADKINA, and A. R. BEKKER

V. I. Lenin Moscow State Pedagogical Institute, Department of Chemistry, Moscow 119882 (U.S.S.R.)

(Received October 29, 1986; in final form April 30, 1987)

A convenient method for thion–thiol isomerization of 1,3-alkylen-phosphorothioates under the action of phosphonium bromides is offered. The possibility of exo- and endo-cyclic isomerisation at the expense of a change of substituents on phosphorus atom is considered. Cyclic 1,2-O-isopropylideneglycerothiolo- and dithiolophosphates have been reacted with trimethylamine to yield in such a way 1,2-O-isopropylideneglycero-thiolo-(dithiolo)phosphohomocholines which are of interest for the synthesis of phospholipids.

Progress in organophosphorus compounds chemistry is increasingly used for the synthesis of natural compounds and their analogues. During recent years convenient methods for the preparation of variety of diacylglycerophosphates, -phosphonates, -amidophosphates and -thiophosphates have been developed.[1] The latter compounds attract a special attention since they possess many properties of natural phospholipids and besides, reveal some important features (see e.g. References 2–4). Thiophospholipids have not been studied to the equal extent: most papers are devoted to thion forms while thiol forms are studied insufficiently.[5–7] Phospholipids are meanwhile of significant interest for bioorganic chemistry because they are able to provide the transfer of phosphate groups to the nucleophilic conters of biomembranes or enzymes fixed on them due to a rupture of the reactive P–S bond.

The present paper describes a new method of the thiolphospholipids synthesis based on thion–thiol isomerization of readily accessible glyceroalkylenethionphosphates.[1,8] Such an isomerization has not previously been used in the lipid chemistry.

The thion–thiol isomerization of trialkylthionphosphates under the action of alkyl halides was first investigated by P. S. Pishchimuka[9] and later, in connection with the preparation of modern insecticides and their metabolites, it began to be studied widely for both acyclic and cyclic thionphosphates with the use of new catalysts.[10–13] For instance, French scientists[12] have thus studied an isomerizing action of nucleophiles (NMe_3, PPh_3) on 0,0-alkylenephosphates and showed that, in the presence of triphenylphosphine in acetonitrile or without a solvent, a slow conversion (3 days at 80°C) of 2-thiono-1,3,2-dioxyphosphorinanes to 2-oxo-1,3,2-

oxathiophosphorinanes occurs. Besides, it was found that the isomerization involved an intermediate formation of the phosphonium salt.

The same authors[13] used tetraethylammonium iodide as the isomerization catalyst and showed that, depending on the electrophility of carbon at the α-position with respect to the exocyclic ester group, the reaction may proceed in two directions with the formation of either endo- or exocyclic P–S bond.

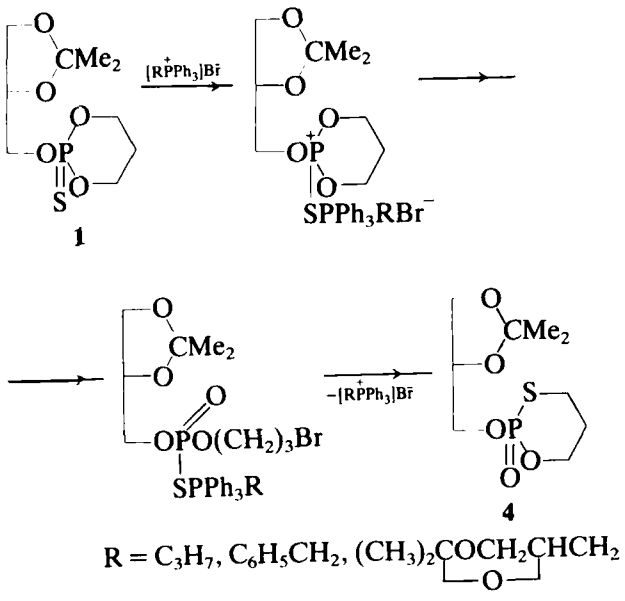
It was also found that prolonged heating of alkylenephosphonates caused the isomerization of alkylenephosphonates even without a catalyst; it was established that, if a partial positive charge on α-carbon atom of the radical was large enough, the formation of the exocyclic thiol isomer took place, otherwise dimerization and polymerization processes occurred.

Later some Polish authors[14,15] reported isomerization of cyclothionphosphates under the action of trifluoroacetic acid. In this case, the process occurs with the formation of the exocyclic P–S bond. It should be noted that the application of this catalyst for isomerization of alkylenephosphates containing 1,2-O-isopropylideneglyceryl radical cannot be performed since the isopropylidene protection is removed even in a weak acid medium.

The first stage of our work is devoted to synthesis of various types of models of thiolphosphohomocholines based on available 2-thiono-2-(1,2-O-isopropylidene-glycero)-1,3,2-dioxaphosphorinane **1**. Tentative experiments have shown the failure of the attempts to perform isomerization of this compound in the presence of usual catalysts, such as alkyl halides or triphenylphosphine at 90–100°C both in a solution of acetonitrile and without a solvent. We have found that phosphonium bromides obtained from triphenylphosphine and alkyl bromides (propyl bromide, benzyl bromide, bromodeoxyisopropylidenenglycerol) can be used as catalysts for the thion–thiol rearrangement. Both salts specially prepared as well as the unpurified salts formed in the reaction course were used. It was demonstrated that the heating of the starting thionphosphate 1 with propyltriphenylphosphonium bromide **2** or benzyltriphenylphosphonium bromide **3** at 85–95°C for 7–9 hours led to the formation of the thiol isomer **4** with sulfur in the cycle in yield 75–80%. It has been noted that isomerization in the presence of salt **3** preliminary obtained proceeds at somewhat greater rate.

The reaction involves the opening of the phosphorinano cycle with bromide ion. The reaction is completed by decomposition of the glycerophosphoalkyl bromide to separate the catalyst and to form the isomeric product **4** (see Scheme 1).

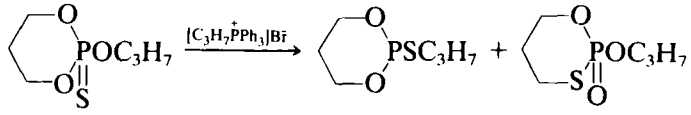
The optimum molar ratio of the phosphonium salt to alkylenethiophosphate is 0.25. An increase in catalyst amount does not result in an essential increase in the reaction rate while a rise of the temperature to 110°C decreases both the reaction time and the yield. Compound **4** was isolated by column chromatography on silica gel. It was shown by ^{31}P NMR method that unlike alkylenethionphosphate **1** ($\delta = 62$ ppm) its spectrum in benzene revealed two singlets (13.85 and 13.79 ppm), whereas spectra in acetone or chloroform show one singlet signal at 15.85 and 16.78 ppm, respectively. The two signals are caused by the fact that the molecule of this compound contains two chiral atoms (CH and P) and the product is formed as two diastereomeric pairs. A different multiplicity of the signals is explained by a specific features of anisochromism in different solvents.[1,16] The isomerization to a cycle was also confirmed by ^1H-NMR spectra.



SCHEME 1

The use of benzyltriphenylphosphonium chloride **5** led to a decrease of the thiolphosphate **4** yield to 20%, which is due to lesser nucleophility of chloride ion compared to that of bromide ion.

It was also demonstrated that replacement of the isopropylidene glyceryl radical by propyl (compound **6**) in initial thionphosphate and the use of propyltriphenylphosphonium bromide **2** as the catalyst resulted in the formation of two isomeric reaction products — one containing sulfur in the propyl radical (compound **7**) (30%) and another with sulfur in the ring (compound **8**) (71%)†). Such a course of the reaction is apparently related to the fact that, in the case of isopropylideneglyceryl radical, bromine cannot efficiently attack the carbon of glycerol residue due to steric hindrances while for the propyl radical it becomes possible.

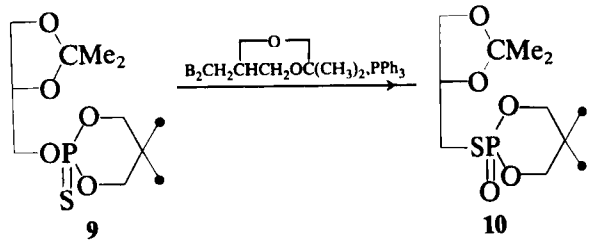


SCHEME 2

The hindrance of isomerization to the cycle by introduction of two methyl groups in position 5 of the phosphorinane ring (compound **9**), the use of a high-polar solvent (phosphorous acid hexamethyltriamide (hexametapol) and increase of the temperature (120°C) result in isomerization with the formation of

† Compounds **7** and **8** were not separated chromatographically; their ratio was determined by ^{31}P and ^{1}H NMR data (see the Experiment).

an exocyclic P–S bond (compound **10**) in low yield (10%). It should be pointed out that no isomerization took place if the reaction was run without a solvent.



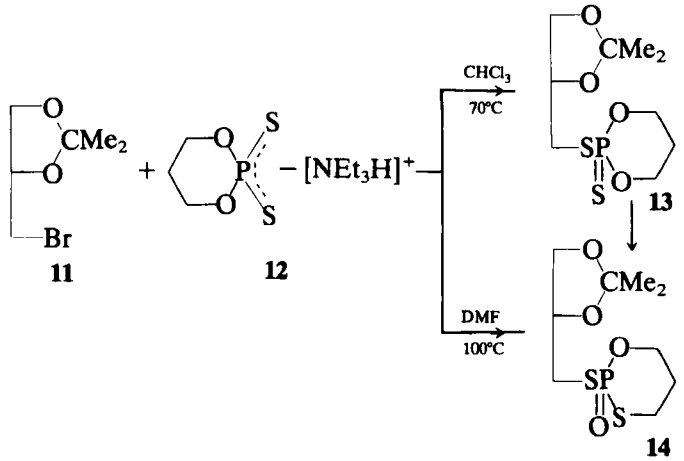
SCHEME 3

A similar reaction with thiophosphate **1** in hexametapol solution only led to the formation of compound **4** which confirmed once more that isomerization to a cycle proceeds readily.

The elaborated method of thion–thiol isomerization has also been used in the work with alkylenedithiophosphates. This made it possible to realize, on the basis of common key compounds, the synthesis of not only monothiolphospholipid models but also to prepare desirable compounds with two phosphorus-sulfur bonds. Such polysulfuric phospholipids are highly reactive and increase essentially the possibilities of ^{31}P NMR spectroscopy in investigations of biomembranes since the resonance field of their phosphorus nuclei differs considerably not only from that of natural phospholipids but also from monothiophospholipids.

The condensation of bromodeoxyisopropylideneglycerol **11** with a dithioacid triethylammonium salt **12** at 70°C in chloroform gave previously unknown dithiophosphate **13** in 52% yield. With dimethylformamide as the solvent, the reaction at 100°C led to isomer **14** in 53% yield. Its formation under these conditions is explained by isomerization of the initially formed phosphate **13** (see Scheme 4).

To confirm this suggestion, dithiophosphate **13** was isomerized to isomer **14** in up to 70% yield in dimethylformamide solution in the presence of an alkyl

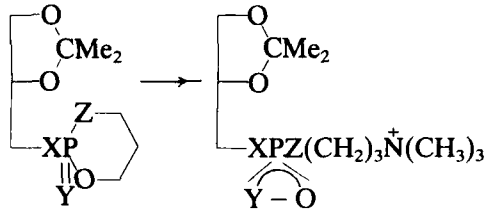


SCHEME 4

bromide. Thus, dimethylformamide plays the role of the electrophilic reagent in this reaction. Moreover, the thion–thiol isomerization of dithiophosphate **13** to **14** in good yield (69%) was accomplished using a raw phosphonium salt on the basis of alkyl bromide **11**. It is interesting, that in carrying out the reaction of salt **12** with alkyl bromide **11** with no solvent at 110–110°C isomerization of dithiophosphate **13** thereby formed is not completed, the reaction mixture containing approximately equal amounts of isomers **13** and **14**. It should be noted that, unlike monothiophosphate **1** conversion, with thiophosphate **13** by-processes occur more actively.

Dithiophosphates **13** and **14** were separated by column chromatography on silica gel. ^{31}P NMR spectrum of dithiophosphate **13** has a singlet at 91 ppm while that of **14** contains two singlets at 39.66 and 39.47 ppm which is related to the presence of two diastereomeric pairs in this product.

The preparation of O,S- and S,S-alkylenethionphosphonates opened the way to the synthesis of previously unknown thiol- and dithiophosphohomocholines by means of alkylation with phosphates (**4**, **13** and **14**) of trimethylamine (see for relative reactions of cyclic phosphates and thiophosphates[1]).



4, 13, 14 **15–17**

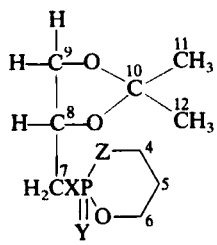
SCHEME 5

In the case of thionphosphate **4**, the reaction was run in benzene during 20 hours at 90–100°C, with a yield of thiolphosphohomocholine **15** 52%. Its purity and structure were confirmed by ^{31}P (singlet at 15.58 ppm) and ^{1}H NMR spectra (see Table). Alkylation of trimethylamine with phosphates **13** and **14** proceeds under milder conditions in comparison with phosphate **4** (85–90°C, 6 hours). The yields of homocholines **16** and **17** are 50% and 55%, respectively. ^{31}P NMR spectrum of compound **16** reveals two singlets with chemical shifts 74.87 and 74.82 ppm (chloroform-methanol) which shows that phosphorus in compound **13** is converted from a prochiral to chiral state. A similar increase in multiplicity for thionphosphatidylcholine has been noted earlier. The reverse phenomenon has been observed in the reaction of dithiophosphate **14** with trimethylamine: chiral phosphorus converted to achiral and ^{31}P NMR spectrum having revealed only one singlet at 38.58 ppm (chloroform-methanol).

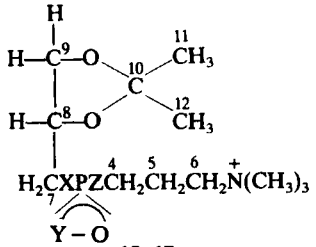
^{1}NMR spectra of compound obtained (**1**, **4**, **13–17**) see Table I. The introduction of exo- or endocyclic sulfur atoms (X, Z) linked with phosphorus in molecules of compounds (**4**, **13**, **14**, **15–17**) resulted in the upfield shift of S-methylene protons in comparison with the oxygen analogues ($\Delta\delta$ 1.3 ppm), which made it possible to identify these compounds by ^{1}H NMR spectra. It is interesting to note that coupling constants for CH_2-4 and CH_2-7 protons have

TABLE I

^{1}H NMR spectral data for compounds 1,14,13–17



1, 4, 13, 14



15–17

No.	X,Y,Z	Chemical shifts, δ, ppm								Coupling constants J, Hz	
		11-CH_3	12-CH_3	9-CH_2	8-CH	7-CH_2	4-CH_2	5-CH_2	6-CH_2	7H-P	4H-P
1	X = Z = O Y = S	1.35	1.42	3.83 4.09	4.36	4.09	4.45	1.80 2.28	1.45	(*)	(*)
4	X = Y = O Z = S	1.27	1.34	3.72 3.79 4.04	4.29	4.42	2.82 3.02	1.87 2.08	4.01	15.6	(*)
13	X = Y = S Z = O	1.34	1.43	3.78 4.11	4.38	3.16	4.49 4.43	1.83 2.30	4.43 4.49	16.8	(*)
14	X = Z = S Y = O	1.34	1.43	3.72 3.79 4.12	4.41	3.09	3.09	2.00 2.18	4.50	15.8	(*)
15	X = Y = O Z = S	1.31	1.38	3.80 4.04	4.29	3.88	2.75	2.17	3.56	12.0	14.7
16	X = Y = S Z = O	1.28	1.36	3.74 4.07	4.31	2.86 2.97	3.97	2.10	3.58	13.2	15.0
17	X = Z = S Y = O	1.06	1.13	3.51 3.84	4.15	2.70	2.70	1.94	3.21	13.0	13.0

* Not determined

similar values — $^3J_{(P-H)}12 + 17$ Hz. It should also be noted that for some compounds with two asymmetric centers (CH and P) (**4, 14**), a slight difference in chemical shifts of some proton signals was observed which corresponded to two pairs of diastereomers, e.g. $\delta = 3.72$ and 3.79 ppm for one of protons of CH_2-9 group and $\delta = 1.27$, 1.26 and 1.34, 1.35 ppm for hem-dimethyl protons. A similar behaviour was observed also in the ^{13}C NMR spectrum of compound **4** where two doublets were detected ($\delta = 73.50$ and 73.77 ppm) for CH-8 carbon nuclei and two singlets ($\delta = 109.35$ and 109.59 ppm) for C-10 nuclei. Such an increase in multiplicity in the ^{1}H and ^{13}C NMR spectra of the diastereomeric mixture has been already discussed previously for phosphoglyceric structures.[16,18]

EXPERIMENTAL

^{1}H NMR spectra of solutions of compounds **1**, **4**, **13**, **14**, in deuterochloroform, of compounds **15**, **16** in a deuterochloroformdeuteromethanol mixture and of compound **17** in deuteromethanol were recorded on a BRUKER WH-360 spectrometer. The proton signals were assigned with the aid of the double magnetic resonance. ^{31}P {^{1}H} NMR spectra of compounds **4**, **13**, **14** in benzene, of **4**, **13**, **15** in chloroform, of **4** in acetone and of **16**, **17** in a chloroform-methanol mixture were recorded on a VARIAN FT-80A instrument (32.2 MHz) using 85% phosphoric acid as an external standard. ^{13}C NMR spectrum of compound **4** in deutero-chloroform was recorded on a BRUKER WM-250 spectrometer (62.89 MHz).

Adsorption chromatography was performed on a column packed with silica gel 100/400 mμ, TLC—on Silufor UV-254 (Czechoslovakia) with a benzene–dioxane (3:1) mixture (A) and methanol (B).

To determine the compounds on Silufol plates, 1% aqueous solution of silver nitrate and "molybdene blue" were used.[19]

Glycerothionphosphate **1** was synthesized according to,[8] phosphonium salts from propyl bromide **2** and benzyl bromide **3** according to,[20] **5** from benzyl chloride.[21] Thionphosphate **6**, bromodeoxyisopropylideneglycerol **11** and dithioacid salt **12** were obtained according to,[13,22,23] respectively. The compounds used had the constants cited in the literature. Glycerothionphosphate on the basis of neopentyleneglycol **9** was prepared similarly to compound **1**, b.p. 135°C (10^{-4} mm Hg), n_D^{20} 1.4822.

2-Oxo-2-(1,2-O-isopropylideneglycero)-1,3,2-oxathiophosphorinane **4**.

(a) A mixture of 1.0 g of thionphosphate **1** and 0.41 g of benzyltriphenylphosphonium bromide **3** was heated for 7 hours at 85–90°C and thiolphosphate **4** was isolated on a silica gel column with benzene. The column was washed with benzene and the product was eluted with a benzene-dioxane (5:1) mixture. After removing the solvent and drying the residue for 1 h at 50°C in vacuo (1 mm Hg), 0.8 g (80%) of **4** was obtained, n_D^{20} 1.4907, R_f 0.48 (A). ^{1}H NMR data are presented in Table I.

^{13}C NMr (δ, ppm): 24.85 s, 26.37 s (2C, $(\underline{C}H_3)_2C$), 26.05 d (1C, SCH_2, $^2J_{(C-P)}$ 6.29 Hz), 27.55 s (1C, $SCH_2\underline{C}H_2CH_2O$), 65.55 d (1C, $\underline{C}H_2OP$, $^2J_{(C-P)}$ 11.9 Hz), 66.68 s (1C, $\underline{C}H_2OC$), 71.81 d (1C, $CH_2\underline{C}H_2OP$, $^2J_{(C-P)}$ 5.6 Hz), 73.51 d, 73.77 d (1C, $CH_2\underline{C}H$, $^3J_{(C-P)}$ 7.55 Hz), 109.35 s, 109.59 s (1C).

^{31}P NMR (δ, ppm): 13.85 s, 13.79 s (benzene), 15.85 s (acetone), 16.78 s (chloroform). Found %: C 39.85, H 6.21, P 11.25. Calcd. for $C_9H_{17}O_5PS$%: C 40.29, H 6.38, P 11.54.

In a similar way, from 1.0 g of thionphosphate **1** and 0.36 g of propyltriphenylphosphonium bromide for 8 hours was obtained 0.75 g (75%) of thiolphosphate **4**. n_D^{20} 1.4906.

Similarly, from 1.0 g of thionphosphate **1** and 0.37 g of benzyltriphenylphosphonium chloride **5** during 7 hours 0.2 g (20%) of thiolphosphate **4** was prepared. n_D^{20} 1.4907.

b) A mixture of 0.18 g bromodeoxyisopropylideneglycerol **11**, 0.24 g of triphenylphosphine and 1.0 g of thionphosphate **1** was heated for 10 hours at 85–95°C. Thiolphosphate **4** (0.85 g, 85%) was isolated as described in a). n_D^{20} 1.4905.

A similar treatment of a mixture of 0.16 g of benzyl bromide 0.24 g of triphenylphosphine and 1.0 g of thionphosphate **1** during 8 hours yielded 0.8 g (80%) of **4**. n_D^{20} 1.4907.

Similarly, 0.75 g (75%) of thiolphosphate **4** was obtained from 0.11 g of propyl bromide, 0.23 g of triphenylphosphine and 1.0 g of thionphosphate **1** during 9 hours. n_D^{20} 1.4906.

In a similar way, 0.4 g (40%) of thiolphosphate **4** was obtained from 1.0 g of thionsphosphate **1**, 0.18 g of bromodeoxyisopropylideneglycerol **11** and 0.24 g of triphenylphosphine in 1.5 ml of hexametapol during 8 hours at 100°C. n_D^{20} 1.4907.

2-Oxo-2-propyl-1,3,2-oxathiaphosphorinane **8** *and 2-oxo-2-S-propyl-1,3,2-dioxaphosphorinane* **7**.

1.0 g of thionphosphate **6** and 0.48 g of phosphonium salt **2** were heated for 36 hours at 85°C. Thiolphosphates **7** and **8** formed were isolated as described for **4**, the yield 0.5 g (50%), R_f 0.45 (A).

^{1}H NMR spectrum (δ, ppm): 1.0 ppm (6H, CH_3), 1.77 m (4H, $CH_3\underline{C}H_2$), 1.97 m 2.15 m (4H, $CH_2\underline{C}H_2CH_2O$), 2.90 m (2H, $CH_3CH_2\underline{C}H_2S$, $^3J_{(P-H)}$ 14.77 Hz), 3.01 m (2H, $PSCH_2$, $^3J_{(P-H)}$ 16.71 Hz), 4.10 m (2H, $CH_3CH_2\underline{C}H_2O$), 4.45 m (6H, $PO\underline{C}H_2CH_2CH_2O$, $PO\underline{C}H_2CH_2CH_2S$).

^{31}P NMR spectrum (δ, ppm): 21.64 s (30%), 15.58 s (70%) (chloroform). Found %: C 36.62, H 6.53, P 15.65. Calcd. for $C_6H_{13}O_3PS$ % C 36.73, H 6.63, P 15.81.

2-Oxo-2-(1,2-S-isopropylideneglycero)-5,5-dimethyl-1,3,2-dioxaphosphorinane **10**.

To a solution of 1.0 g of thionphosphate **9** in 1.5 ml of hexametapol were added 0.16 g of bromodeoxyisopropylideneglycerol **11** and 0.22 g of triphenylphosphine followed by heating the

mixture for 14 hours at 120°C. Thiolphosphate **10** formed was isolated as described for compound **4**, yield 0.1 g (10%), R_f 0.54 (A). ^{1}H NMR spectrum (δ, ppm): 0.99 s, 1.25 s (6H, $CH_2C(CH_3)_2CH_2$), 1.30 s, 1.43 s (6H, $OC(CH_3)_2O$), 3.07 m (2H, CH_2SP, $^3J_{(P-H)}$ 14.7 Hz), 3.79 m (2H, $COCH_2$), 4.13 m (4H, $POCH_2$), 4.39 m (1H, CH). Found %: C.44.41, H 7.13, P 10.39. Calcd. for $C_{11}H_{21}O_5PS$ %: C 44.59, H 7.09, P 10.47.

2-Thio-2-(1,2-S-isopropylideneglycero)-1,3,2-dioxaphosphorinane **13**.

A solution of 0.5 g of bromodeoxyisopropylideneglycerol **11** and 0.63 g of triethylammonium salt **12** in 3 ml of chloroform was heated for 10 hours at 70°C; chloroform was removed under reduced pressure and ether was added to the residue. Triethylammonium bromide was filtered off, the ether was evaporated and the product thus obtained was purified on a column with silica gel by eluting with benzene. Benzene was removed in vacuo and the residue was dried at 40°C (1 mm Hg) for 1 hour to yield **13** (0.46 g, 54%), n_D^{20} 1.4875, R_f 0.71 (A). ^{1}H NMR data are listed in Table I. ^{31}P NMR spectrum (δ, ppm): 91.02 s (benzene), 88.03 s (chloroform), found %: C 37.91, H 5.98, P 10.92. Calc. for $C_9H_{17}O_4PS_2$%: C 38.01, H 6.02, P 10.89.

2-Oxo-2-(1,2-S-isopropylideneglycero)-1,3,2-oxathiophosphorinane **14**.

a) A solution of 0.5 g of bromodeoxyisopropylideneglycerol **11** and 0.63 g of triethylammonium salt **12** in 3 ml of dimethylformamide was heated for 3 hours at 95–100°C. Dimethylformamide was removed *in vacuo* and ether was added to the residue. The triethylammonium hydrobromide precipitate was filtered, the ether was evaporated and the product obtained was purified on a column with silica gel by eluting with benzene. The column was washed with benzene and eluted with benzene-dioxane mixture (5:1) to obtain 0.45 g (53%) of **14**, n_D^{20} 1.4728, R_f 0.40 (A). ^{1}H NMR data are presented in Table I.

^{31}P NMR spectrum (δ, ppm): 39.47 s, 39.66 s (chloroform). *Analysis*: Found %: C 38.12, H 6.09, P 10.78. Calcd. for $C_9H_{17}O_4PS_2$ %: C 38.01, H 6.02, P 10.89.

b) 0.2 g of dithiophosphate **13**, 0.034 g of bromide **11** and 0.049 g of triphenylphosphine were heated during 6 hours at 90°C. Dithiolphosphate **14** (0.138 g, 69%) was isolated on a column by following the technique described in (a). n_D^{20} 1.4726.

c) To a solution of 0.2 g of dithiophosphate **13** in 2 ml of dimethylformamide was added 0.034 g of bromide **11** and the mixture was heated for 5 hours at 95–100°C. The alkyl bromide was vacuum removed and isomeric phosphate **14** in thus formed was isolated by column chromatography as above. The yield of **14** was 0.136 g (68%). n_D^{20} 1.4727.

1,2-O-Isopropylideneglycero-3-thiolphosphohomocholine **15**.

A solution of 0.5 g of thiolphosphate **4** and 0.56 g of trimethylamine in 5 ml of benzene was heated in a sealed ampoule during 20 hours of 110°C. Colourless crystals precipitated were filtered, washed consequently with benzene and ether and dried at 40°C at 1 mm Hg for 1 hour. The yield of **15** was 0.32 g (51.6%), m.p. 225–226°C, R_f 0.1 (B). ^{1}H NMR data are given in Table I. ^{31}P NMR spectrum (δ, ppm): 15.58 s (chloroform).

Analysis: Found %: C 42.31, H 7.61, P 8.92. Calcd. for $C_{12}H_{26}NO_5PS$ %: C 42.7, H 7.71, P 9.20.

1,2-S-Isopropylideneglycero-3-thiophosphohomocholine **16**.

A solution of 0.25 g of dithiophosphate **13** and 0.40 g of trimethylamine in 4 ml of benzene was heated in a sealed ampoule for 6 hours at 90°C. Colourless crystals thus formed were filtered and washed with benzene and acetone. After drying for 2 hour at 40°C (1 mm Hg) the yield of **16** was 0.15 g (50%), m.p. 145–146°C, R_f 0.25 (B). ^{1}H NMR data are presented in Table I.

^{31}P NMR (δ, ppm): 74.87 s, 74.62 s (chloroform-methanol). *Analysis*: Found %: C 41.75, H 7.61, P 8.95. Calcd. for $C_{12}H_{26}NO_4PS_2$ %: C 41.98, H 7.58, P 9.03.

1,2-S-Isopropylideneglycero-3-thiolphosphohomocholine **17**.

Similarly to synthesis of **16**, the reaction of 0.25 g of dithiophosphate **14** with 0.40 g of trimethylamine gave dithiolhomocholine **17** (0.165 g, 55%), m.p. 196–197°C, R_f 0.12 (B). ^{1}H NMR data are presented in Table I.

^{31}P NMR spectrum (δ, ppm): 36.83 s (chloroform-methanol). *Analysis*: Found %: C 41.82, H 7.51, P 8.97. Calcd. for $C_{12}H_{26}NO_4PS_2$ %: C 41.98, H 7.58, P 9.03.

REFERENCES

1. E. E. Nifantyev and D. A. Predvoditelev, *Bioorg. Khim.*, **7,** 1285 (1981).
2. V. V. Chupin, I. A. Vasilenko, D. A. Predvoditelev, G. A. Serebrennikova and R. P. Evstigneeva, *Dokl. Akad. Nauk SSSR,* **248,** 235 (1979).
3. K. Bruzik, S. M. Gupta and Ming-Daw Tsai, *J. Am. Chem. Soc.*, **104,** 4862 (1982).
4. G. A. Orr, C. F. Brewer and G. Heney, *Biochemistry,* **21,** 3202 (1982).
5. D. A. Predvoditelev, Kh. Kh. Alarkon and E. E. Nifantyev, *Bioorg. Khim.*, **6,** 1087 (1980).
6. G. A. Serebrennikova and R. P. Evstigneeva, *Bioorg. Khim.*, **10,** 970 (1984).
7. B. Mlotkowska and A. Markowska, *Liebigs Ann. Chem.* **1984,** 1.
8. E. E. Nifantyev, D. A. Predvoditelev and Kh. Kh. Alarkon, *Zh. Org. Khim.*, **14,** 163 (1978).
9. P. S. Pishchimuka, *Zh. Russ. Fiz.-Khim. Obshch.*, **44,** 1406 (1912).
10. H. Teichmann and G. Hilgetag, *Chem. Ber.*, **98,** 856 (1965); 864 (1965).
11. N. N. Mel'nikov, V. A. Khaskin and I. K. Shvetsova-Shilovskaya, *Zh. Obshch. Khim.*, **33,** 2456 (1963); **34,** 40 (1964).
12. H. P. Nguyen, N. T. Thuong and P. Chabrier, *C.R. Acad. Sci., Ser. C,* **271,** 1465 (1970).
13. N. P. Nguyen, N. T. Thuong and P. Chabrier, *C.R. Acad. Sci., Ser. C,* **272,** 1145 (1971); 1588 (1971).
14. W. J. Stec, B. Uznanski, K. Bruzik and J. Michalski, *J. Org. Chem.*, **41,** 1291 (1976).
15. K. Bruzik and W. J. Stec, *Pol. J. Chem.*, **56,** 753 (1982).
16. G. Zon and K. Mislov, *Topics in Current Chemistry,* **19,** 61 (1971).
17. K. Bruzik, Ru-Tai Jiang and Ming-Daw Tsai, *Biochemistry,* **22,** 2478 (1983).
18. E. N. Rasadkina, D. A. Predvoditelev, M. V. Smirnov and E. E. Nifantyev, *Zh. Org. Khim.*, **20,** 38 (1964).
19. J. C. Dittmer and R. L. Lester, *J. Lipid. Res.*, **5,** 126 (1964).
20. F. Kröhnke, *Chem. Ber.*, **83,** 291 (1950).
21. K. Friedrich and H. G. Henning, *Chem. Ber.*, **92,** 2156 (1959).
22. P. P. Bird and J. S. Chadha, *Tetrahedron Lett.*, **1966,** 4541.
23. D. A. Predvoditelev, D. N. Afanasyeva and E. E. Nifantyev, *Zh. Obshch. Khim.*, **44,** 2629 (1974).