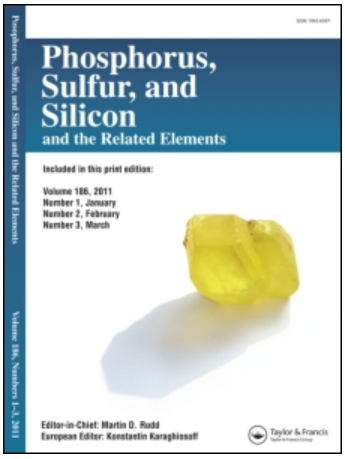

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

REACTION OF DIALKOXYTHIOXAPHOSPHORANESULFENYL CHLORIDES WITH DIALKYL TRIMETHYLSILYL PHOSPHITES. NEW STEREOSELECTIVE ROUTE TO THE UNSYMMETRICAL TETRAALKYL DITHIOPYROPHOSPHATES. PREPARATION OF DIASTEREOISOMERIC 2-TRIMETHYLSILYLOXY-4-METHYL-1,3,2-DIOXAPHOSPHORINANES

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To cite this Article Łopusiński, Andrzej , Michalski, Jan and Potrzebowski, Marek(1986) 'REACTION OF DIALKOXYTHIOXAPHOSPHORANESULFENYL CHLORIDES WITH DIALKYL TRIMETHYLSILYL PHOSPHITES. NEW STEREOSELECTIVE ROUTE TO THE UNSYMMETRICAL TETRAALKYL DITHIOPYROPHOSPHATES. PREPARATION OF DIASTEREOISOMERIC 2-TRIMETHYLSILYLOXY-4-METHYL-1,3,2-DIOXAPHOSPHORINANES', Phosphorus, Sulfur, and Silicon and the Related Elements, 28: 3, 299 — 305
To link to this Article: DOI: 10.1080/03086648608072821
URL: http://dx.doi.org/10.1080/03086648608072821

Phosphorus and Sulfur, 1986, Vol. 28, pp. 299–305
0308-664X/86/2803–0299/$15.00/0

REACTION OF DIALKOXYTHIOXAPHOSPHORANESULFENYL CHLORIDES WITH DIALKYL TRIMETHYLSILYL PHOSPHITES. NEW STEREOSELECTIVE ROUTE TO THE UNSYMMETRICAL TETRAALKYL DITHIOPYROPHOSPHATES. PREPARATION OF DIASTEREOISOMERIC 2-TRIMETHYLSILYLOXY-4-METHYL-1,3,2-DIOXAPHOSPHORINANES

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(*Received November 4, 1985; in final form December 18, 1985*)

Unsymmetrical dithiopyrophosphates $(RO)_2P(S)SP(O)(RO)_2$ **5** are formed in excellent yield and purity in reaction of dialkoxythioxaphosphoranesulfenyl chlorides **1** with trimethylsilylphosphites $Me_3SiOP(OR')_2$ **4**. The full stereospecificity of this reaction has been demonstrated with an aid of diastereoisomeric cis- and trans-2-trimethylsilyloxy-4-methyl-1,3,2-dioxaphosphorinanes **9** which react with **1** with full retention of configuration at the phosphorus center. Preparation of diastereoisomeric cis- and trans-**9** has been described and their configuration established.

This paper is a part of our studies on the chemistry of phosphoroorganic dicoordinate sulfur halogens RR'P(Y)SX (Y = S,O; X = Br,Cl). The development of such versatile strongly electrophilic reagents is promising, because they can be widely used in the synthesis of organophosphorus compounds.[1]

In earlier papers from this Laboratory a successful use of dialkoxyoxophosphoranesulfenyl chlorides $(RO)_2P(O)SCl$ **6** in the synthesis of symmetrical tetraalkylmonothiopyrophosphates $(RO)_2P(O)—S—P(O)(OR)_2$ has been demonstrated.[2]

Recently, a novel synthesis of dialkoxythioxaphosphoranesulfenyl chlorides **1** has been described, based on easy conversion of readily available dialkoxythioxaphosphoranesulfenyl bromides **2**, via the corresponding sulfenate ester **3**.[3]

$$\underset{\mathbf{2}}{(RO)_2P(S)-SBr} \xrightarrow[:B]{R'OH} \underset{\mathbf{3}}{(RO)_2P(S)SOR'} \xrightarrow[-BHCl]{Me_3SiCl} \underset{\mathbf{1}}{(RO)_2P(S)-SCl} \qquad (1)$$

The studies described in this paper demonstrate that the thioxaphosphoranesulfenyl chlorides **1** are very convenient reagents for the preparation of unsymmetrical tetraalkyldithiopyrophosphates **5**.[4]

$$(RO)_2\overset{\overset{S}{\|}}{P}\text{-}S\text{-}Cl + Me_3SiOP(OR')_2 \longrightarrow (RO)_2\overset{\overset{S}{\|}}{P}\text{-}S\text{-}\overset{\overset{O}{\|}}{P}(OR')_2 + Me_3SiCl \quad (2)$$

1 **4** **5**

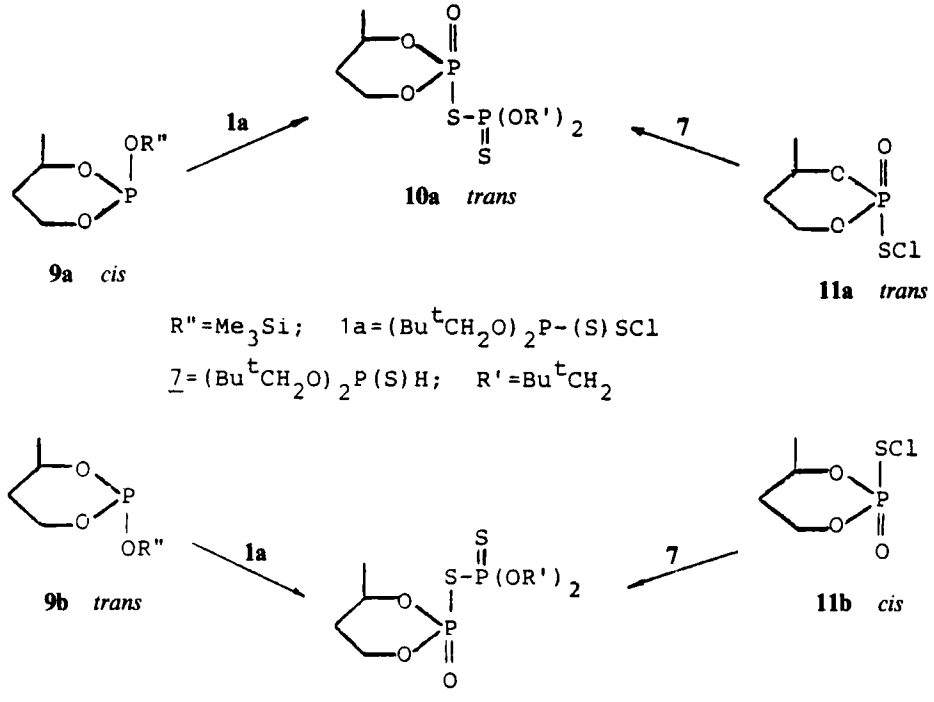
In spite of their availability the bromides **2** are less suitable, because of the side reactions involved.[5] This synthesis of the unsymmetrical dithiopyrophosphate system is alternative to the method worked out in this Laboratory involving the reaction of dialkoxyoxophosphoranesulphenyl chlorides **6** with dialkoxythiophosphites **7**.[7]

$$(RO)_2\overset{\overset{O}{\|}}{P}\text{-}S\text{-}Cl + H\text{-}\overset{\overset{S}{\|}}{P}(OR')_2 \xrightarrow[-HCl]{} \mathbf{5} \quad (3)$$

6 **7**

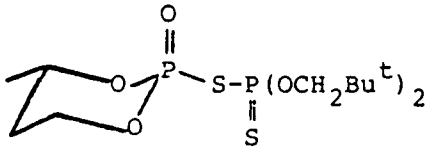
Other methods leading to the unsymmetrical dithiopyrophosphates are of limited applicability. The reaction shown in the equation (2) proceeds at low temperatures in neutral solvents like dichloromethane with almost quantitative yield affording the desired dithiopyrophosphate **5**. Compounds **5** exhibit a characteristic pattern in the ^{31}P NMR spectra. An illustration of the efficacy of the new reaction and its stereospecificity came from our studies performed with model trimethylsilylphosphites **9a**, **9b** derived from diastereoisomeric 2-hydrogen-2-oxo-4-methyl-1,3,2-dioxaphosphorinanes.[8,9] The synthesis of *cis*- and *trans*-2-trimethylsilyloxy-4-methyl-1,3,2-dioxaphosphorinanes **9a, b** is described in the second part of this paper.

We have found that the *cis*-2-trimethylsilyloxy-4-methyl-1,3,2-dioxaphosphorinane **9a** reacts smoothly at $-5°C$ in hexane solution with sulfenyl chloride **1** R = Bu^tCH_2 to give stable, crystalline *trans* dithiopyrophosphate **10a** with characteristic ^{31}P NMR chemical shift values: δ P(O) 2.72 (d); δ P(S) 77.02 (d), $^2J_{PSP}$ = 12 Hz. The structure of the compound **10a** was established by its independent synthesis from the *trans* oxophosphoranesulfenyl chloride **11a** and dineopentylthiophosphite **7**. Under the same conditions, the *trans*-2-trimethylsilyloxy-4-methyl-1,3,2-dioxaphosphorinane **9b** reacts with **1** to give the *cis* dithiopyrophosphate **11b**, which is undestillable oil: δ P(O) 5.63 (d); δ P(S) 77.09 (d), $^2J_{PSP}$ = 12 Hz. This compound is spectroscopically identical with the major component of the condensation reaction between *cis*-**11b** and **7**. Pure *cis*-**11b** is not available and is always contaminated with the *trans* isomer **11a**.[10] The ratio **11a/11b** was 73:23 as ascertained by the ^{31}P NMR spectroscopy. The reaction with the thiophosphite **7a** led to the 73:23 mixture of diastereoisomeric dithiopyrophosphates **10a** and **10b**. The reaction of sulfenyl chlorides **11a** and **11b** with the thiophosphite **7a** provides unambiguous structure assignments for **10a** and **10b**, since in this process no bond is broken around the chiral phosphorus atom. One can finally conclude that the reaction between silylesters **9a** and **9b** and sulfenyl chloride **1a** proceeds with full retention of configuration at the chiral phosphorus atom. Slow epimerisation of *cis*-**10b** into the thermodynamically more stable isomer *trans*-**10a** was observed in boiling hexane by ^{31}P NMR spectroscopy.

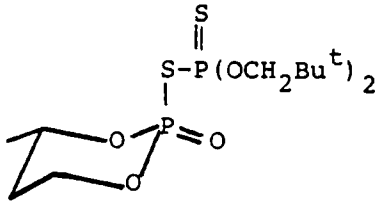


SCHEME 1

The ^{1}H NMR spectra of both diastereoisomeric dithiopyrophosphates **10a** and **10b** show that C-4 methyl protons are split by C-4 methine proton and additionally by the phosphorus nuclei with coupling constant values $^4J_{PH}$ = 1.60 Hz for *cis*-**10b** and $^4J_{PH}$ = 2.08 Hz for *trans*-**10a**. The observed magnitude of $^4J_{PH}$ coupling constant and lack of other splitting by C-5 axial methylene proton, which should be observed in the case of axial C-4 methyl group, suggests an equatorial position of this group.[11,12] The IR spectrum of the crystalline *trans* isomer **10a** shows a strong ν_{PO} band at 1246 cm^{-1}. On the other hand, the absorption ν_{PO} of the *cis* isomer **10b** is shifted to lower frequency 1220 cm^{-1}. This lower frequency value suggests the axial arrangement of P = O group in **10b**.[13] On this basis, the following conformations can be proposed for the diastereoisomers **10a** and **10b**.

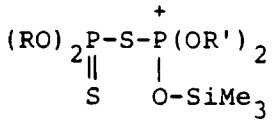


cis **10b**



trans **10a** m.p. 52°C

By analogy with the reactions between trialkyl phosphites and oxophosphorane-sulfenyl chlorides or benzenesulfenyl chloride, in which an Arbuzov-type intermediate was detected using ^{31}P NMR, a similar intermediate **12** may be formed in the reaction between silylphosphites **9** and sulfenyl chlorides **1**.[14]

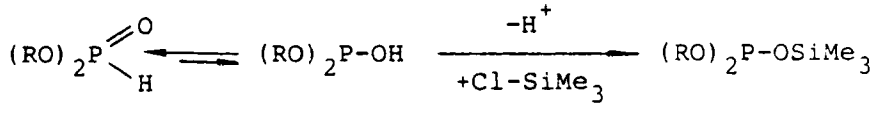


12

However, low temperature ^{31}P NMR studies failed to demonstrate the presence of that intermediate; it probably collapses very rapidly into final products, due to the high affinity of the chloride anion towards the silicon center.

Preparation of diastereoisomeric 2-trimethylsilyloxy-4-methyl-1,3,2-dioxaphosphorinans was undertaken in order to provide models for stereochemical studies described above.

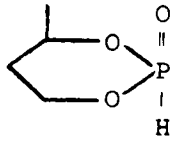
The phosphites and their structural analogues can be considered as "pseudotricoordinate" because of the tautomerism involved.



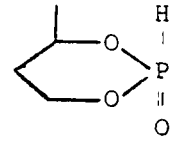
13 **9**

The anion derived from **13** is ambident with negative charge distributed between adjacent phosphorus and oxygen atoms. This anion undergoes P-alkylation, which is known as the Michaelis-Becker reaction, an important alternative to the Arbuzov reaction. O-Alkylations are exceptional but the silylating reagents react towards formation of oxygen-silicon bond yielding esters **9**, as described in the literature.[18] Optically active trimethylsilylphosphinates R'(RO)P—$OSiMe_3$ have been prepared in the reaction with the trimethylsilyl chloride with retention of configuration at the phosphorus atom.[15]

The cyclic systems derived from 4-methyl-1,3,2-dioxaphosphorinanes are of great merit in stereochemical studies as shown in excellent review by Maryanoff *et al.*[16] Nifant'ev and co-workers discovered the stereoselective synthesis of *cis*- and *trans*-2-hydrogen-2-oxo-4-methyl-1,3,2-dioxaphosphorinanes **13a** and **13b**.[8]

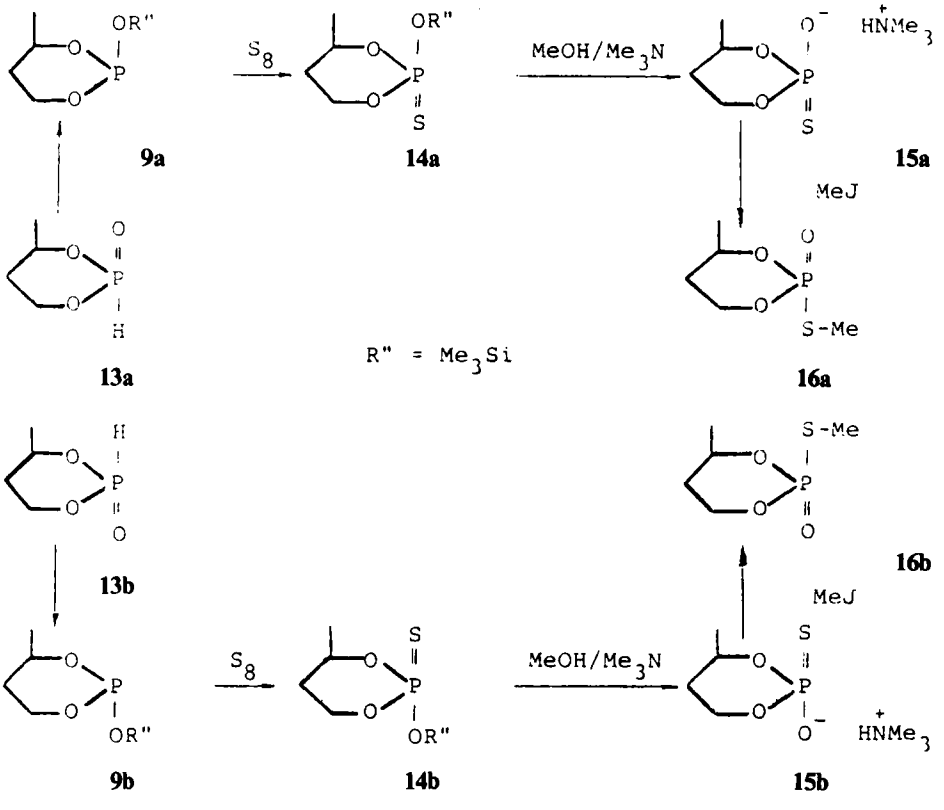


cis-**13a**



trans-**13b**

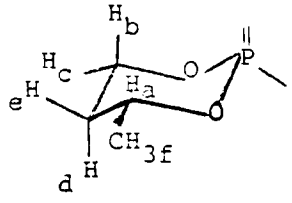
We have found that both diastereoisomers react smoothly with trimethylsilyl chloride in the presence of equivalent amount of trimethylamine at −10°C to give, in almost quantitative yield, the isomer **9a** with δ ^{31}P, 120.1 and **9b** with δ ^{31}P, 114.0. The relatively low temperature at which this reaction is performed, is essential in the case of the less stable isomer **9a**. Slow epimerisation of **9a** into **9b** was observed by ^{31}P NMR spectroscopy at 0°C in diethylether solution. This isomerisation was completed in one week.



The configuration of both diastereoisomers **9a** and **9b** was assigned on the basis of the following sequence of stereoselective reactions: addition of elemental sulfur to obtain trimethylsilylthionoesters **14a**, **14b**, which were treated with methanol-trimethylamine to form thioacids salts **15a**, **15b** and finally *S*-alkylation with methyl iodide to afford thioloesters **16a** and **16b** of known configuration.[17] It is evident that the salts **15a**, **15b** and silylesters **14a**, **14b** must have the same configuration as the thioloesters **16a**, **16b** since they are formed without bond breaking around the chiral phosphorus atom. It is well established that addition of elemental sulfur to the tricoordinate phosphorus compounds proceeds with retention of configuration at the phosphorus center. For this reason we were able to assign the cis configuration to the isomer **9a**, δ ^{31}P, 120.1 and the *trans* to the isomer **9b**, δ ^{31}P, 114.0. All the structural assignments were supported by ^{1}H NMR, I.R., M.S. data, and elemental analysis.

EXPERIMENTAL

All m.ps. and b.ps. are uncorrected. ^{1}H NMR were obtained on a Bruker[a] instrument (90 MHz) with $CDCl_3$ as an internal standard or Tesla[b] spektrometer (80 MHz) with TMS or benzene as internal standard. ^{31}P NMR were recorded on a Jeol C-60H instrument with 85% phosphoric acid as external standard. GPLC analysis were conducted with a Varian 10 gas chromatograph. Diastereomic purities were determined from integrated ^{1}H and ^{31}P NMR and GLPC analyses. Mass spectra were determined with a mass spectrometer at an ionizing voltage of 70 eV. The protons of dioxaphosphorinan rings are labeled as follows:



S-(diethoxyphosphoryl)dineopenthyl thiophosphate **5a**. To a solution containing 2.1 g (0.01 m) of diethyl trimethylsilylphosphite in 10 cm^3 dichloromethane at 0°C was added 3.05 g (0.01 m) dineopenthyl thioxaphosphorane sulfenyl chloride. The mixture was stirred for 10 min., when yellow colour from sulfenyl chloride disappeared. The solvent and trimethylchlorosilane were removed under reduced pressure. Yield 5.25 g, ^{31}P NMR δ 79.01 (P=S); δ 13.75 (P=O), $^2J_{P-P}$ = 15 Hz. Analysis: Found: C, 50.43; H, 6.50; P, 12.01; S, 11.84. Calc.: C, 50.95; H, 6.08; P, 11.79; S, 12.16.

S-(dimethoxyphosphoryl)diisopropyl thiophosphate **5b**. ^{31}P NMR δ 74.31 (P=S), δ 16.82 (P=O), $^2J_{P-P}$ = 15 Hz. Analysis: Found: C, 30.01; H, 6.15; P, 19.38. Calc.: C, 29.81; H, 6.21; P, 19.25.

Cis-2-trimethylsilyloxy-4-methyl-1,3,2-dioxaphosphorinan **9a**. To a stirred solution of 6.8 g (0.05 m) *cis* 2-hydro-4-methyl-1,3,2-dioxaphosphorinan **13a** in 50 m^3 dichloromethane and 5.1 g (0.05 m) anhydrous triethylamine 6.5 g (0.06 m) trimethylchlorosilane was slowly added at −10°C. The resulting solution was stirred at 0°C for 1 h. The solvent was removed under reduced pressure. The next 50 cm^3 of diethylether was added. The precipitated hydrochloride of triethylamine was filtered and solvent evaporated. The crude product was distilled B_p = 28°C/0.01 mmHg. Yield 8.3 g (80%), ^{31}P NMR δ 120.1, ^{1}H NMR[b] s($SiMe_3$) δ 0.19; d(H_f) δ 1.02; m(H_c) δ 1.29; m(H_d) δ 1.41; m(H_c) δ 2.91; m(H_b) δ 3.10; m(H_a) δ 3.18; $J_{da} = J_{ab}$ = 11 Hz, J_{fa} = 6.2 Hz; m/e = 208.

Trans-2-trimethylsilyloxy-1,3,2-dioxaphosphorinan **9b**. B.p. 28°C/0.01 mmHg. Yield 8 g (78%). ^{31}P NMR δ 114; ^{1}H NMR[a] s($SiMe_3$) δ 0.26; d(H_f) δ 1.20; m(H_c) δ 1.48; m(H_d) δ 1.64; m(H_c) δ 2.99; m(H_b) δ 3.68; m(H_a) δ 3.79; $J_{da} = J_{db}$ = 11 Hz, J_{fa} = 6.2 Hz, m/e = 208.

Trans-2-S-(dineopenthyloxythiophosphoryl)-2-oxo-4-methyl-1,3,2-dioxaphosphorinan **10a**. To a stirred solution of 2.08 g (0.01 m) of *cis* **9a** in 20 cm^3 of hexane at 0–5°C 3.05 g of dineopenthylthioxaphosphoranesulfenyl chloride dissolved in 10 cm^3 of hexane was added dropwise. Stirring was continued for 20 min. The solvent was evaporated under pressure of 5 mmHg. The product was crystallized from petrolum ether. M.p. 52–54°C. ^{1}H NMR[b] s(^{t}Bu) δ 0.80; dd(CH_3) δ 1.14; dd(—OCH_2—) δ 3.16; J_{H-CH_3} 6.3 Hz; J_{P-CH_3} 2.8 Hz. ^{31}P NMR δ 2.72 (P=O) δ 77.22 (P=S), $^2J_{P-P}$ = 12 Hz, m/e = 404. Analysis: Found: C, 40.32; H, 7.52; P, 15.57; S, 15.27. Calc.: C, 41.58; H, 7.42; P, 15.35; S, 15.14.

Cis-2-S-(dineopenthyloxythiophosphoryl)-2-oxo-4-methyl-1,3,2-dioxaphosphorinan **10b**. ^{1}H NMR s(^{t}Bu) δ 0.99; dd(CH_3) δ 1.48; dd(—OCH_2—) δ 3.87, J_{H-CH_3} 6.3 Hz, J_{P-CH_3} 1.6 Hz, ^{31}P NMR δ 5.64 (P=O), δ 77.22 (P=S), $^2J_{P-P}$ = 12 Hz, m/e = 404. Analysis: Found: C, 40.58; H, 7.25; P, 15.20; S, 15.46. Calc.: C, 41.58; H, 7.42; P, 15.35; S, 15.84.

Trans-2-thiono-2-trimethylsilyloxy-4-methyl-1,3,2-dioxaphosphorinan **14a**. To a solution containing 4.16 g (0.02 m) 9a in 25 cm^3 diethylether 0.64 g (0.02 m) of elemental sulphur was added at −50°C. The reaction was strongly exothermic. After stirring for 1 h the sulfur disappeared. The solvent was removed under reduced pressure and the product was distilled. Yield 4.6 g (96%). B.p. 55°C/0.01 mmHg. ^{1}H NMR[b] s($SiMe_3$) δ 0.21; dd(H_f) δ 0.85; m(H_c) δ 1.04; m(H_d) δ 1.14; m(H_c) δ 3.01; m(H_b) δ 3.32; m(H_a) δ 3.61; J_{da} = 11 Hz; J_{fa} = 6.2 Hz; J_{P-H_f} = 2 Hz. ^{31}P NMR δ 53.58, m/e = 240.

Cis-2-thiono-2-trimethylsilyloxy-4-methyl-1,3,2-dioxaphosphorinan **14b**. Yield 4.5 g (94%). B.p. 55°C/0.01 mmHg. ^{1}H NMR^b s(SiMe$_3$) δ 0.26; dd(H$_f$) δ 0.96; m(H$_c$) δ 1.08; m(H$_d$) δ 1.24; m(H$_e$) δ 3.12; m(H$_b$) δ 3.28; m(H$_a$) δ 3.38; $J_{da} = J_{db} = 11$ Hz, $J_{fa} = 6.2$ Hz, $J_{P-H_f} = 2$ Hz. ^{31}P NMR δ 47.53, m/e = 240.

Trans-2-thiono-2-hydroxy-1,3,2-dioxaphosphorinan trimethyl ammonium salt **15a**. To a solution 2.4 g (0.01 m) of **14a** in 20 cm^3 of diethylether 0.4 g (0.0125 m) of methanol and 0.59 g (0.01 m) of trimethylamine were dropped. The stirring was continued an 1 h, and the mixture was standing overnight. The white crystals were filtered and dried. ^{31}P NMR δ 56.01, m.p. = 122–124°C. Analysis: Found: C, 36.59; H, 8.02. Calc.: C, 37.0; H, 7.93.

Cis-2-thiono-2-hydroxy-1,3,2-dioxaphosphorinan trimethylammonium salt **15b**. ^{31}P NMR δ 58.6, m.p. = 115–118°C. Analysis: Found: C, 36.8; H, 7.73. Calc.: C, 37.0; H, 7.93.

This work was supported by the Polish Academy of Sciences, Research Project MR-I-12.

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