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NUCLEOPHILIC SUBSTITUTION AT
PHOSPHORUS:PHOSPHOROTHIOATES

By

YUH-GENG TSAY

This thesis is approved as a creditable and independent investigation by the candidate for the degree, Master of Science, and is acceptable as meeting the thesis requirements for this degree, but without implying that the conclusions reached by the candidate are necessarily the conclusions of the major department.

William M. Edwards
Thesis Adviser

4/25/73
Date

A thesis submitted
in partial fulfillment of the requirements for the
degree Master of Science, Major in
Chemistry, South Dakota
State University

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Date

1973

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NUCLEOPHILIC SUBSTITUTION AT

PHOSPHORUS:PHOSPHOROTHIOATES

The author wishes to express his special appreciation and gratitude to Prof. William S. Wadsworth Jr., his adviser, for his constant encouragement and advice through the whole work and his patience in reading and commenting on the entire writing.

He also wishes to thank all his friends who have made valuable contributions to this research.

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Thesis Adviser /

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Head, Chemistry Department

Date

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The author wishes to express his special appreciation and gratitude to Prof. William S. Wadsworth Jr., his adviser, for his constant encouragement and advice through the whole work and his patience in reading and commenting on the entire writing.

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this objective, a series of 2-substituted-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinans were prepared and employed as substrates. The stereochemical consequences due to a change in the basicity of nucleophiles, stability of leaving groups, polarity of solvents and added salts was determined. A comparison of the effects upon thio-phosphates and phosphates was made.

INTRODUCTION

The stereochemistry of nucleophilic substitutions at phosphorus has been a subject of intense study. Most studies have made use of optically active reactants and products and have been hampered by the ambiguities normally associated with such systems. In our laboratory, we introduced a new diagnostic tool which enables us to distinguish between possible stereochemical pathways. The tool, 2-substituted-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, allows us to study substitutions at phosphorus without resorting to optically active substrates. The object of our study was to determine the mechanism of nucleophilic substitutions at thiophosphoryl centers. To accomplish this objective, a series of 2-substituted-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinans were prepared and employed as substrates. The stereochemical consequences due to a change in the basicity of nucleophiles, stability of leaving groups, polarity of solvents and added salts was determined. A comparison of the effects upon thio-phosphates and phosphates was made.

Studies done by M. Green and R. F. Hudson⁶ indicated that a thio-pyrophosphate with one asymmetric phosphorus atom when treated with aqueous alkali solution gave the initial acid with almost zero activity. Since the displacement can occur with equal probability at either thio-

HISTORICAL

The stereochemistry of nucleophilic substitutions at a thiophosphoryl center has been the subject of systematic investigations ever since the successful resolution of asymmetric phosphorus thioacids¹⁻³ and phosphonium salts.⁴ Both substitution by retention and inversion has been detected and pathways have been advanced to explain results. Basically, most studies have made use of optically active reactants and products.⁵⁻⁸ Their usefulness has been limited by their rapid racemization, poor optical purity and low optical rotation.

Herbert S. Aaron et al.⁵ in their pioneering work reported that the reaction of phosgene with the sodium salt of an O-alkyl alkylphosphonothioic acid occurs with overall inversion of configuration. To account for the stereospecificity, intermediate, 1, which cyclizes to 2, before decomposing to the phosphonochloridate was suggested.

Scheme 1

Studies done by M. Green and R. F. Hudson⁶ indicated that a thio- higher than that of phosphorothioates, the nucleophiles will tend to pyrophosphate with one asymmetric phosphorus atom when treated with aqueous alkali solution gave the initial acid with almost zero activity. Since the displacement can occur with equal probability at either thio-

phosphoryl center, the formation of racemic O-ethyl methylphosphonothioic acid demonstrated the absence of a retention mechanism, (Scheme 1).

Scheme 1

In a similar study, it was reported⁹ that the alkaline hydrolysis of (+)-diethyl pyromethylphosphonothioate and (+)-S-methyl ethylphenylphosphinothiolate proceeds almost exclusively (at least 99%) by inversion of configuration. As the reactivity of phosphonothioates is higher than that of phosphorothioates,¹⁰ the nucleophiles will tend to attack the electrophilic phosphorus atom containing the C-P bond. It was found that reaction of (+)-pyrophosphonodithioate with hydroxide anion involves mainly inversion at the asymmetric thiophosphoryl

center¹¹ accompanied by some racemization.

The preparation of optically active O-ethyl ethylphosphono-chloridothioate, $\text{Et}(\text{EtO})\text{P}(\text{S})\text{Cl}$, 4, by the chlorination of O-ethyl ethylphosphonothioic acid with phosphorus pentachloride provides a convenient model for the mechanistic study of the reaction of phosphorus pentachloride with phosphorus thio acids. It was found by J. Michalski and M. Mikolajczyk^{8,12} that the reaction involves an inversion of configuration. The degree of optical purity of the (-)-chloride, 4, could be deduced from its reaction with sodium O-ethyl ethylphosphonate. The properties of (+)-diethyl ethylpyrophosphonothioate, 5, formed are compared with those of compound 5, prepared by condensation of (-)-sodium O-ethyl ethylphosphonothioate with racemic O-ethyl ethylphosphonochloridate, (Scheme 2). Since the 5 prepared by route (b-c) has a specific optical rotation equal to that obtained from reaction (a), it must have a configuration identical to that of (-)-acid, 3. This may be explained by assuming either subsequent inversions or retentions during the reaction (b-c). The former possibility which is consistent with results of alkaline hydrolysis of (-)-chloride, 4, to (-)-acid,⁸ 3, appears to be valid in this case.

Scheme 2

As proved by thin layer chromatography, O-ethyl ethylphosphonochloridate is not formed in reaction (b).¹³ The attack of phosphorus pentachloride is directed entirely on the oxygen atom. The possible phosphonium type intermediate is decomposed by nucleophilic attack of the chloride anion co-linear with the leaving group. A possible transition state for this displacement requires a bipyramidal structure similar to an Sn2 transition state with axial bonds, pd, weaker than the sp² bonds in the basal plane.¹⁴

Synthesis of optically active O-ethyl ethylphosphonochloridothionate¹⁹ was achieved by treating (+)-O-ethyl ethylphosphonochloridothionic acid with triethylphosphine dibromide (C₂H₅)₃PBr₂.

In order to extend the results of nucleophilic substitutions at thiophosphoryl centers¹¹ to other leaving groups and nucleophiles, a study of chloride-chloride exchange at the thiophosphoryl center was undertaken by J. Michalski et al.¹⁵. Their method successfully applied to carbon chemistry^{16,17} was extended to phosphorus.¹⁸ Direct proof of inversion at the thiophosphoryl center was provided by the demonstration that the rate of exchange between radioactive chloride anion and the active O-ethyl ethylphosphonochloridothionate is equal to the rate of inversion, e.g. to half the rate of racemization, (Scheme 3).

Scheme 3

Synthesis of optically active O-ethyl ethylphosphonobromido-thioate¹⁹ was achieved by treating (+)-O-ethyl ethylphosphonothioic acid with triphenylphosphine dibromide, $(C_6H_5)_3PBr_2$. For determination of its optical purity and relative configuration, the (+)-bromide was hydrolyzed by 2.85 N KOH in dioxane-water to the (+)-thiophosphonic acid. Comparison of the rotation of the acid obtained by alkaline

of its optical purity and relative configuration, the (+)-bromide was hydrolyzed by 2.85 N KOH in dioxane-water to the (+)-thiophosphonic acid. Comparison of the rotation of the acid obtained by alkaline hydrolysis with that of the starting material showed that the (+)-bromide had an optical purity of at least 94%. If we assume that the steric effect of the neopentyl glycol group^{9,10} (Scheme 4). The alkaline hydrolysis of 6 leads to the formation of the acid, 8, with the same optical purity as the original acid, but with a reversed configuration.

Thiopyrophosphate systems are quite suitable for stereochemical studies of phosphoric acid substitution reactions, for they can be used successfully to demonstrate chemically induced inversion at the thiophosphoryl center during alkaline hydrolysis. The thiophosphoryl center P(9) in the anhydride, 6, should be prone to attack by nucleophilic reagents both as a result of the electronic effect of substituting the ethyl group by an ethyl group, and of the known steric effect of the neopentyl glycol group^{9,10} (Scheme 4). The alkaline hydrolysis of 6 leads to the formation of the acid, 8, with the same optical purity as the original acid, but with a reversed configuration. It is remarkable that the reactions of the acid with phosphorus pentachloride^{8,12} and triphenylphosphine dibromide occur in stereochemically

identical ways.

The synthesis of optically active chloride¹² and its alkaline hydrolysis²⁰ form a cycle of two reactions, each of which proceed with inversion of configuration at the thiophosphoryl center and which together lead to the acid of original configuration. The stereochemical interpretation is confirmed by studies of the stereochemistry

of alkaline hydrolysis of optically active thio- and dithiopyrophosphonates.¹¹

Thiopyrophosphate systems are quite suitable for stereochemical studies of nucleophilic substitution reactions,^{11,21} for they can be used successfully to demonstrate chemical inversion of configuration at the thiophosphoryl center during alkaline hydrolysis. The thiophosphoryl center P(S) in the anhydride, 6, should be prone to attack by nucleophilic reagents both as a result of the electronic effect of substituting the ethoxyl group by an ethyl group, and of the known steric effect of the neopentyl glycol group, (Scheme 4). The alkaline hydrolysis of 6 leads to the formation of the acid, 8, with the same optical purity as the original acid, but with a reversed configuration. Taking into account the fact that reaction in which the anhydride, 6,

Scheme 4

is formed occurs without inversion of configuration at the chiral phosphorus atom, the formation of the thioacid, 8, with the opposite optical rotation and the same optical purity as the original thioacid proves full Walden inversion and selective attack of the hydroxide anion on the thiophosphoryl center.²² Analogous reactions were carried out to give the same result. This work, which is consistent with the results obtained from alkaline hydrolysis at a thiophosphoryl center by Hudson and Green, is evidence that inversion of configuration is a result of attack by hydroxide anion on thiophosphoryl centers.

Most investigations have shown that inversion occurs during the attack of nucleophilic reagents on thiophosphoryl centers^{8,11,12,20,21,23} and a transition state in the shape of a trigonal bipyramid in which

bonds are made and broken synchronously was assumed. The formation of a trigonal bipyramid intermediate followed by pseudorotation in those cases where racemization occurs might also be expected.²⁴⁻²⁷

Because of the inescapable importance²⁸ and great biochemical significance,²⁹ organophosphate esters have received much attention since the first esterification of phosphoric acids by Lassaigne in 1820.³⁰ In recent years, such interest has been generated over the stereochemistry of nucleophilic substitution reactions at phosphorus.³¹ The mechanism by which nucleophiles attack phosphorus leading to substitution have been postulated on the basis of both bimolecular, $S_N2(P)$, with and without inversion and in a few cases monomolecular, $S_N1(P)$ kinetics. Stereochemical pathways have been advanced³¹ to explain results.

It is now generally accepted that, in spite of numerous analogies, there are many important differences between the organic chemistry of phosphorus and carbon.^{31a} In the case of phosphorus compounds the essential complicating factor is the influence of phosphorus 3d orbitals which may or may not be a factor in the mechanism of nucleophilic substitutions.

It was expected that considerable information could be obtained by examining the stereochemistry of optically active chiral phosphorus compounds. Most mechanism studies have proposed an inversion of configuration at the phosphorus atom, and a pentacovalent intermediate in the shape of a trigonal bipyramid as the transition state characteristic of $S_N2(P)$ reactions. Racemization may also be expected as a result of pseudorotation of the trigonal bipyramid

RESULTS

Because of the insecticidal importance²⁸ and great biochemical significance,²⁹ organophosphate esters have received much attention since the first esterification of phosphoric acids by Lassaigne in 1820.³⁰ In recent years, much interest has been generated over the stereochemistry of nucleophilic substitution reactions at phosphorus.³¹ The mechanism by which nucleophiles attack phosphorus leading to substitution have been postulated on the basis of both bimolecular, $S_N2(P)$, with and without inversion and in a few cases monomolecular, $S_N1(P)$ kinetics. Stereochemical pathways have been advanced³¹ to explain results.

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intermediate.²⁴⁻²⁷

In order to eliminate those ambiguities usually associated with optically active substrates, we introduced a diagnostic tool³² which enables us to distinguish between possible stereochemical pathways. The tool involves an analysis of the configurational change at the five position of various 2-substituted-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinans.

Treatment of cis-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane with a nucleophile gives rise to substitution products whose configuration can be determined simply by observing the nmr chemical shift of methyl or chloromethyl hydrogens at the fifth position.

In expanding the usefulness of this technique to the stereochemistry of nucleophilic substitutions at a thiophosphoryl center,

we have been able to prepare and purify a number of 2-substituted-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinans, 9 and 10. The

(9) Cis(10) Trans

$R = -Cl, -OC_6H_5, -OC_6H_4NO_2, -OC_6H_4Br, -OC_6H_3(NO_2)_2$, etc.

designation of cis and trans is assigned according to the arrangement of the thiophosphoryl sulfur at position 2 in relation to the chloromethyl group at position 5.

In all cases only the single conformers of the two isomers are detected and isolated, although it was reported by O. A. Raevskii et al.³³ that via an IR spectra study some 2-thiono-1,3-dioxo-2-phosphorinans can exist as a mixture of conformers dependent upon temperature, solvent polarity, dielectric constant and ring substituents. Heating cis-2-(2,4-dinitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan and cis-2-(p-bromophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan at an elevated temperature of 190° provided no change in their nmr spectra. Thus the compounds are stable geometrical isomers and conformational mobility, if it does exist in solution should not be a hindrance in the determination of isomer ratios.

The configuration of the isomers at the five position can be determined by nmr analysis, Figure 1. The hydrogens of an axial chloromethyl group are shifted downfield from those of an equatorial chloromethyl group due to deshielding by the ring oxygens. Likewise, the methyl hydrogens when axial are shifted downfield relative to those of an equatorial methyl group found in the cis isomers, Table 1.

The configuration about the phosphorus atom in the two isomers has not been directly determined. However, single crystal X-ray analysis gives reliable evidence that in the case of cyclic 2-oxo-phosphorinan esters,³⁴⁻³⁶ the phosphoryl oxygen prefers an equatorial position, whereas the phosphoryl oxygen prefers an axial position in the case of phosphoramidates.^{37,38} Single crystal X-ray analysis of a cyclic 2-thio-phosphorinan ester is still under study in our laboratory.

As reported by A. W. Herriott,³⁹ oxidation of menthyl methyl-phenylphosphinothioate, 11, with m-chloroperoxybenzoic acid proceeded with a high degree of retention at phosphorus to give a phosphinate, 12.

The absolute configuration of 11 was determined by comparing its nmr spectrum with that of the corresponding phosphinate 12. To elucidate the configuration at the thiophosphoryl center in our system, a similar

Table 1: Chemical Shifts of 2-Substituted-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinans.^a

R	CH ₃	CH ₂ Cl
-Cl	1.43	3.37
-OC ₆ H ₄ OCH ₃	1.17	3.39
-OC ₆ H ₄ CH ₃	1.18	3.39
-OC ₆ H ₅	1.20	3.39
-OC ₆ H ₄ Br	1.20	3.40
-OC ₆ H ₄ NO ₂	1.29	3.47
-OC ₆ H ₃ (NO ₂) ₂	1.38	3.42

R	CH ₃	CH ₂ Cl
-Cl	1.01	3.74
-OC ₆ H ₄ OCH ₃	0.96	3.76
-OC ₆ H ₄ CH ₃	0.96	3.77
-OC ₆ H ₅	0.97	3.89
-OC ₆ H ₄ Br	0.98	3.76
-OC ₆ H ₄ NO ₂	1.01	3.81
-OC ₆ H ₃ (NO ₂) ₂	1.02	3.79

^a Measured with a Varian A-60A spectrometer at room temperature using CDCl₃ as solvent. In parts per million downfield from TMS as an external standard.

oxidation of cis-2-phenoxy-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan was attempted. Unfortunately, oxidation did not occur.

From our substitution studies, we find that thiophosphates behave much the same as phosphates in many respects. It leads us to assume that as in the case of the cyclic 2-oxo-phosphorinan esters, the thiophosphoryl sulfur in thiophosphates prefers an equatorial position while in the case of thiophosphoramidates the thiophosphoryl sulfur prefers an axial position.

2-Chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan, 13 and 14, which is the starting point of this research was prepared from thiophosphoryl chloride and 1-chloromethyl-1,1-dihydroxymethyl-ethane. The isomers were separated by means of repeated

recrystallization from a mixture of hexane and chloroform. The trans

isomer, the least soluble, was obtained in pure form, Figure 1.

To aid in our investigation a number of phenyl esters were also prepared. Treatment of an acetonitrile solution of 13 and 14 with sodium p-nitrophenoxide gave a mixture of isomers

The mixture of isomers was recrystallized from a mixture of carbon tetrachloride and acetonitrile to give the least soluble pure *cis* isomer, Figure 2. Isomers of 2-(p-bromophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinane were prepared from chloridate 13 and 14 and sodium p-bromophenoxide.

The pure *cis* isomer was obtained by repeated recrystallization of the

isomers from carbon tetrachloride, Figure 3. Isomers of 2-(2,4-dinitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan were prepared from sodium 2,4-dinitrophenoxide and chloridate 13 and 14.

The mixture of isomers was recrystallized from a mixture of carbon tetrachloride and acetonitrile to give the least soluble pure cis isomer, Figure 4. Treatment of an acetonitrile solution of sodium phenoxide with chloridate 13 and 14 gave a mixture of isomers.

The mixture was repeatedly recrystallized from a mixture of carbon tetrachloride and hexane to give the pure cis isomer, Figure 5.

In those cases where a charged nucleophile was employed, the stereochemical outcome of substitution at a thiophosphoryl center appeared to depend primarily upon the basicity of the attacking nucleophile. The role of the basicity of the nucleophile in the stereochemistry of the displacement was investigated by treating trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan, 14, with various nucleophiles in acetonitrile. To a stirred solution of acetonitrile and the sodium salt was added the trans-chloridate, 14. The mixture was stirred at room temperature for two days and water added to precipitate the product. The precipitate was washed well with water and dried under reduced pressure. The inversion-retention product ratio was obtained from nmr peak integration. Results indicate that the inversion-retention ratio is influenced by the basicity of the nucleophiles with retention favored by increased basicity, Table 2.

A sample of trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan was dissolved in deuterated acetonitrile. Isomerization of this pure isomer was followed by observing the change of its nmr spectrum. After ten days, it was found that there was no isomerization of this isomer. Pure cis-2-(p-methylphenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan, Figure 6, was separated from its isomer mixture by repeated recrystallization from a mixed solvent of hexane and carbon tetrachloride. Isomerization of this pure isomer was studied at room temperature in deuterated acetonitrile saturated with sodium p-methylphenoxide. Analysis of nmr spectra showed no isomerization after standing for fifteen days. Isomerization

Table 2: Treatment of Trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with Various Nucleophiles in Acetonitrile.

R				% Trans (retention)	% Cis (inversion)
-OCH ₃				50.0	50.0
-CH ₃				40.0	60.0
-Br				23.7	76.3
-NO ₂				5.1	94.9

of cis-p-nitrophenoxy ester in deuterated acetonitrile in the presence of added sodium p-nitrophenoxide was extremely slow. A solution of the cis-2,4-dinitrophenoxy ester in dimethylformamide did isomerize slowly in the presence of added sodium 2,4-dinitrophenoxide at 65° with pyrophosphate as a byproduct. The same ester did not isomerize when dissolved in deuterated acetonitrile and the solution heated at 65° for five months. Thus evidence is provided that all substitutions, Table 2, are kinetically controlled. Substitution of chloride ion is fast. Starting material does not isomerize under the reaction condition nor do the products.

Sodium p-methylphenoxide was found due to its better stability and greater ease in product purification to be a very favorable reactant. We have made use of this salt as a nucleophile for most of our mechanism studies.

It was found that the mode of substitution is also dependent upon the stability of leaving groups. Various cis-2-substituted-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinans were added separately to a stirred solution of acetonitrile and sodium p-methylphenoxide. The mixtures were stirred at room temperature for two days and water was added to precipitate the product. The precipitate was washed well with water and dried under reduced pressure. Analysis of nmr spectra indicated that inversion was aided by an increase in stability of leaving groups, Table 3.

In contrast to results obtained when various phenyl esters were employed as substrates, the chloridate 14 gave a quite different

Table 3: Treatment of Various Cis-2-substituted-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinans^a with Sodium p-Methylphenoxide in Acetonitrile.

$\xrightarrow{\text{NaOC}_6\text{H}_4\text{CH}_3}$	+		% <u>Cis</u> (retention)	% <u>Trans</u> (inversion)
$\text{R} =$ ^b $-\text{C}_6\text{H}_5$ $-\text{C}_6\text{H}_4\text{Br}$ $-\text{C}_6\text{H}_4\text{NO}_2$ $-\text{C}_6\text{H}_3(\text{NO}_2)_2$	98.5	1.5		
	97.4	2.6		
	95.2	4.8		
	— ^c	—		

^a When trans-chloridate was treated with $\text{NaOC}_6\text{H}_4\text{CH}_3$, a retention-inversion ratio of 40 to 60 was obtained. ^b In contrast to other substitutions which

proceeded to completion, substitution in this case was only 50% complete.

^c A side reaction took place in this case.

apparent that the nitro groups on the benzene ring have weakened the C-O bond thereby diverting the reaction. Treatment of an acetonitrile solution of sodium p-methylphenoxide with trans-chloridate 14 gave an inversion-retention ratio

14

of 60 to 40, (percentage). The increase in inversion when chloride ion is the leaving group may be due to the ability of the cation (Na^+) equivalent of tetramethylammonium chloride was added to the reaction mixture, the added salt and sodium p-methylphenoxide precipitated to inversion. The phenyl groups on the other hand are not capable of coordinating with a cation and retention predominates.

When the 2,4-dinitrophenoxy ester was used as a substrate, the reaction proceeded entirely by C-O bond cleavage to produce an aromatic ether, $\text{CH}_3\text{C}_6\text{H}_4\text{OC}_6\text{H}_3(\text{NO}_2)_2$, Figure 7. In this case, no products

resulting from substitution at phosphorus could be detected. It is

apparent that the nitro groups on the benzene ring have weakened the C-O bond thereby diverting the reaction.

We have also noted pronounced solvent effects on nucleophilic substitutions at a thiophosphoryl center. Trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan, 14, was added to sodium p-methylphenoxide solvent mixtures, Table 4. It was also found that the addition of tetramethylammonium chloride or lithium perchlorate changed the retention-inversion product ratios. These results show that the solvent effects on isomer ratios are actually a function of the solubility of the salt, NaCl, produced as byproduct. The salt is more soluble in dimethylformamide than in acetonitrile. When an equivalent of tetramethylammonium chloride was added to the reaction mixture, the added salt and sodium p-methylphenoxide precipitated sodium chloride to give acetonitrile soluble tetramethylammonium p-methylphenoxide. Its effect was to divert the substitution predominately to inversion. Added lithium perchlorate had an effect opposite to added tetramethylammonium chloride. The added lithium perchlorate evidently does not ionize appreciably in acetonitrile and its effect is to reduce the solubility of the sodium ion thereby diverting the substitution to predominate retention.

Data obtained with the thiophosphorochloridate prompted us to look at substrates with a leaving group other than chloride ion. Due to its ease of formation, purification and substitution cis-2-(p-nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan was selected. As with the thiophosphorochloridate, 14, the ratio of isomers obtained

Table 4: Percentage of CIs and Trans Isomers Obtained by Treating Trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with Sodium p-Methylphenoxide in Various Solvents.

Solvent	% Trans (retention)	% Cis (inversion)	
$\text{CH}_3\text{CN} + 1 \text{ eq. LiClO}_4$	87.5 ^a	12.5	
CH_3CN	40.0	60.0	
$\text{CH}_3\text{CN} + 1 \text{ eq. } (\text{CH}_3)_4\text{N}^+\text{Cl}^-$	6.2	93.8	
$\text{HCN}(\text{CH}_3)_2$	5.7	94.3	
$\text{HCN}(\text{CH}_3)_2 + 1 \text{ eq. } (\text{CH}_3)_4\text{N}^+\text{Cl}^-$	5.1	94.9	

^a Isomer ratios (%) were obtained by integration of NMR spectra obtained in CDCl_3 by means of a Varian A-60A spectrometer using TMS as an external standard.

by treating the p-nitrophenoxy ester with sodium p-methylphenoxide varied with the solvent and was influenced by added salts, Table 5.

Analysis of nmr spectra of various reaction products gave no evidence of reactant which is indicative that reactions had gone to completion. A sample of pure cis-2-(p-nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan was dissolved in deuterated acetonitrile at room temperature. In the presence of added sodium p-methylphenoxide, isomerization of the pure isomer was followed by observing the change in nmr peak ratios. The mixture gave a cis/trans ratio of 20 to 3 after sixteen days and had not reached equilibrium. The very slow isomerization of the pure cis isomer in the presence of added anion showed that product ratios are kinetically controlled. Products, which are formed rapidly, are not in equilibrium with reactants.

Although in the case of p-nitrophenoxy ester the added tetramethylammonium chloride increased the inversion product ratio, in all cases the retention product was the predominant one. In contrast the inversion product was the predominant one in most of the reactions using thiophosphorochloridate as the substrate. Also tetramethylammonium chloride had less of an effect upon diverting the substitution to inversion with p-nitrophenoxy ester as the substrate than it did with thiophosphorochloridate as the substrate. As mentioned in the study of the effect of stability of leaving groups on substitution at a thiophosphoryl center, the electrophilic cation may complex with chloride ion thereby aiding its departure. Such an effect would not be

Table 5: Treatment of Cis-2-(p-nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinane with Sodium p-Methylphenoxide in Various Solvents.

Solvent	% Cis (retention)	% Trans (inversion)	
BENZENE	a	-	
CH ₃ CN	95.2	4.8	
CH ₃ CN + 1 eq. (CH ₃) ₄ N ⁺ Cl ⁻	80.0	20.0	
$\text{HCN}(\text{CH}_3)_2$	87.1	12.9	
$\text{HCN}(\text{CH}_3)_2 + 1 \text{ eq. } (\text{CH}_3)_4\text{N}^+\text{Cl}^-$	76.2	23.8	

^a No reaction was observed in Benzene as solvent.

expected in the case where p-nitrophenoxide ion is the leaving group.

Unlike charged nucleophiles, neutral nucleophiles such as piperidine react with the trans-thiophosphorochloridate, 14, to give thiophosphoramidates predominately by inversion even without the influence of added salt. Treatment of a solution of acetonitrile and phosphates occur by anything but an associative mechanism. A change

excess piperidine with trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinane, 14, gave an inversion-retention ratio of 82.8 to 17.2, (percentage), Figure 8. Due to the assumed preference of sulfur for the axial position in thiophosphoramidates, substitution must proceed predominately by inversion of configuration at phosphorus.

Scheme 5

In the absence of complex formation caused by extraneous cations, it appears from our data that substitution could perhaps proceed

DISCUSSION

In accordance with conclusions drawn by others,^{40,41} on related systems, there is no evidence that substitutions at phosphorus in thio-phosphates occur by anything but an associative mechanism. A change in stereochemistry with added salts would suggest two separate mechanisms for substitution, one for inversion and one for retention (Scheme 5).

Scheme 5

In the absence of complex formation caused by extraneous cations, it appears from our data that substitution would perhaps proceed

predominately by retention whereas if complex formation were complete, substitution would proceed predominately by inversion. In the presence of a cation, equilibrium may be established between complexed thiophosphate and uncomplexed thiophosphate. The equilibrium would be dependent upon the concentration of the cation and the strength of the complex formed.

According to the "Polarity rule,"^{42,43} a charged nucleophile would be expected to attack the uncomplexed phosphate from a side opposite the thiophosphoryl sulfur, a position of minimum electron density. This stereochemical pathway would lead to a pentacovalent intermediate^{44,45} in the shape of a trigonal bipyramid. Nucleophiles are assumed to enter and leaving groups depart from apical positions. The intermediate would, therefore, undergo a pseudorotation^{46,47} which leads to substitution by retention.

As a result of complex formation, the positive charge on phosphorus is increased due to the reduction in backbonding by sulfur lone pair electrons with vacant 3d orbitals of phosphorus. Nucleophiles may attack the complex with direct displacement in an $S_N2(P)$ fashion without the formation of an intermediate. Complex formation by increasing the positive charge on phosphorus and by reducing charge repulsion by the negative sulfur atom leads to a lowering of the energy of activation for direct attack, a situation which would lead to inversion.

With this mechanistic scheme, it is obvious, that the added salt would shift the substitution to the inversion pathway, Table 6.

Table 6: Effects of Added Salt^a on Substitution Reactions of Various Cis-thiophosphates with Sodium p-Methylphenoxide in Acetonitrile.

R	% inversion	
	without salt	with salt
$-\text{OC}_6\text{H}_5$	1.5 ^b	25.0
$-\text{OC}_6\text{H}_4\text{Br}$	2.6	22.2
$-\text{OC}_6\text{H}_4\text{NO}_2$	4.8	20.0
$-\text{Cl}^c$	60.0	93.8

^a Salt added was tetramethylammonium chloride. ^b Ratios were obtained by integration of nmr spectra obtained in CDCl_3 as solvent. ^c The trans-thiophosphorochloridate was used.

By means of these mechanisms the influence of the basicity of the nucleophile on the retention-inversion ratios can be explained.

Retention is favored by an increase in the basicity of the nucleophile which is in accordance with the "Polarity rule". The more negative the attacking atom, the greater would be its preference for attack at a maximum distance from the electronegative sulfur atom thereby leading to retention.

As shown by our results, the mode of substitution is also dependent upon the leaving group. It would be expected that the percentage of inversion should vary with the leaving group if the inversion mechanism proceeded via direct S_N2 displacement, especially if the third step in the retention pathway was not rate determining.

It has been shown⁴⁸ that in the decomposition of suspected pentacovalent intermediates, the departure of the leaving group is rate determining in those cases involving a poor leaving group whereas formation of the intermediate becomes the slow step in cases which involve good leaving groups such as chloride or phenoxide ions. These leaving groups were employed in our study. Under identical conditions the percentage of inversion is increased with the efficiency of the leaving group, Table 3. We believe this to be evidence that inversion of configuration at phosphorus proceeds by a one step mechanism without the formation of an intermediate.

When piperidine is treated with trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan, substitution by inversion predominates even without the influence of added salt. To account for

this, one has to consider the transition state, 15, (Scheme 6). The

Scheme 6

charge on the thiophosphoryl sulfur is partially neutralized as is the charge on nitrogen which results in a lowering of the energy of activation. Since inversion is predominant, it appears that the leaving group must depart as the entering group approaches from the back side and that no intermediate is involved.

COMPARISONS OF THIOPHOSPHATES AND PHOSPHATES

In making a comparison between thiophosphates and phosphates, it is necessary to understand the bonding characteristics of both the P→S and P→O groups. It is generally accepted that the phosphorus oxygen bond in phosphoryl compounds has at least partial $d_{\pi}-p_{\pi}$ multiple-bond character.⁴⁹ The oxygen lone pair electrons can backbond with the vacant 3d orbitals on the phosphorus by multiple-bond formation. Thus, since both pairs of oxygen 2p orbitals are equally capable of overlay, the P→O bond has the characteristics of a triple bond, rather than those of a double bond. Charge transfer to the phosphorus atom is probably far from complete, and the oxygen retains a net negative charge. In resonance language, the P→O bond is best represented as a hybrid of the canonical forms (16) and (17). Form (18) makes little, if any, contribution.¹⁰

Since the atomic size of sulfur is greater than that of oxygen the 3d orbitals of phosphorus can more easily form multiple bond with the 2p orbitals of oxygen than with the 3p orbitals of sulfur.

Therefore the P→S bond is weaker than the P→O bond. Infrared spectra of phosphates⁵⁰ indicate a strong P→O stretching frequency at 1250-1300 cm⁻¹, Figure 10, whereas bands of variable intensity have been reported at 713-835 cm⁻¹ and 568-675 cm⁻¹ for P→S stretching frequencies, Figure 11. The lower stretching frequencies for the P→S bond are indicative of a smaller bond strength.

It is expected that the replacement of oxygen by sulfur would result in a system with similar properties but one which is less reactive toward nucleophilic reagents. When sulfur is substituted for oxygen in the P⁺—O⁻ position, the atom of smaller electronegativity, sulfur, will produce a smaller amount of positive character on phosphorus. This interpretation is strengthened by the fact that phosphates possess larger dipole moments than the corresponding thiophosphates.⁵¹ The fact that the rate of hydrolysis of phosphate esters^{52,53} is greater than the rate of hydrolysis of corresponding thiophosphates, Table 7, is also a result of the lower positive charge on

Table 7: Rates of hydrolysis for (RO)₂P(S or O)OR^{52,53}

R	R''	k ₂ (25°)	
		→ O	→ S
p-C ₆ H ₄ NO ₂	CH ₃	34	1.4
C ₂ H ₅	p-C ₆ H ₄ NO ₂	0.52	5.7 x 10 ⁻²
p-C ₆ H ₄ NO ₂	C ₂ H ₅	4.3	0.4

phosphorus in the case of the sulfur analogues. Likewise, in our isomerization studies of geometrical isomers, we found that phosphates isomerized much faster than thiophosphates under identical conditions. A fact that is further indicative of the relatively lower electrophilicity of the phosphorus atom in the latter.

Trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan was dissolved in deuterated dimethylformamide at room temperature. Isomerization of the pure trans isomer was followed by observing the changes in nmr peak ratios, Figure 9. Isomerization of the corresponding phosphorochloridate, cis-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, was compared under identical conditions. It was found that within 15 minutes, the isomerization of cis-phosphorochloridate reached an equilibrium mixture with a cis/trans ratio of 2.5 to 1, whereas the isomerization of trans-thiophosphorochloridate took 14 days to reach an equilibrium mixture with a cis/trans ratio of 2.8 to 1. Interesting enough, pyrophosphate formation was observed during the isomerization of trans-thiophosphorochloridate but not in the case of cis-phosphorochloridate.⁵⁴ In both cases dimethylformamide acts as a nucleophile, the carbonyl oxygen displacing the chloride ion.

Cis-2-(p-nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan was dissolved at room temperature in deuterated acetonitrile which was saturated with sodium p-nitrophenoxide. The retention-inversion ratio (cis/trans) was 20 to 3 after sixteen days. It had not reached the approximate 2.8 to 1 equilibrium ratio. In

contrast, trans-2-(p-nitrophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan reached an equilibrium ratio of cis : trans :: 2.9 : 1 under identical conditions after 30 hours.⁵⁴

Since 2,4-dinitrophenoxide ion is a good leaving group, isomerization of both 2,4-dinitrophenyl thiophosphate and 2,4-dinitrophenyl phosphate was also compared. Cis-2-(2,4-dinitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan in dimethylformamide showed no isomerization after standing for twenty days at room temperature. Under identical conditions, trans-2-(2,4-dinitrophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan reached an equilibrium ratio of cis : trans :: 3 : 1 after ten days. Dimethylformamide is a strong enough nucleophile to displace 2,4-dinitrophenoxide ion from the phosphate but not, due to its lower electrophilicity, from the thiophosphate.

The final equilibrium mixture of isomers reflects the preference of the chloromethyl group for an axial position possibly due to dipole interaction between the group and ring oxygens.⁵⁵

R = S or O

X = -Cl, -OC₆H₄NO₂, -OC₆H₃(NO₂)₂

In our studies of nucleophilic substitution reactions at phosphorus, we have discovered some similarities and differences between cyclic thiophosphates and cyclic phosphates. As for the dependence of substitution product ratios upon the basicity of nucleophiles, both phosphates and thiophosphates show that the weaker basic nucleophiles tend to yield more inversion product, Table 8.

With the exception of the corresponding chloridates where removal of the chloride ion may be aided directly by the electrophilic cation via complex formation with the leaving group, thiophosphates undergo substitution with a greater degree of retention than do phosphates. This can be seen by comparison of the retention-inversion ratios obtained by substitution of p-nitrophenyl thiophosphate and p-nitrophenyl phosphate with sodium p-methylphenoxide in acetonitrile, Table 10. Other thiophosphates also gave a high proportion of the retention product.

The greater retention obtained with thiophosphates is not surprising. In the case of the phosphates with their higher positive charge on the phosphorus atom one would expect the energy of activation for direct substitution to be less than in the case of the thiophosphates. The faster rate of direct substitution by attack of a charged nucleophile on the more positive phosphorus atom in phosphates would thus lead to a greater yield of the inversion product in the latter.

Solvent effects upon substitution was also compared, Table 9.

Table 8: Phenyl Ester Obtained from Trans (Cis-)-2-thio (oxo-)-phosphorochloridate and Various Nucleophiles in Acetonitrile.

Nucleophiles	% retention		% inversion	
	→ 0	→ S	→ 0	→ S
$\text{NaOC}_6\text{H}_4\text{OCH}_3$	57	50	43	50
$\text{NaOC}_6\text{H}_4\text{CH}_3$	50	40	50	60
$\text{NaOC}_6\text{H}_4\text{Br}$	36	24	64	76
$\text{NaOC}_6\text{H}_4\text{NO}_2$	6	5	94	95

Table 9: Treatment of Cis (Trans)-2-(p-nitrophenoxy)-5-chloro-methyl-5-methyl-2-thio (oxo)-1,3,2-dioxaphosphorinan with Sodium p-Methylphenoxide in Various Solvents.^a

Solvents	% retention		% inversion	
	→ 0	→ S	→ 0	→ S
CH_3CN	55.5	95.2	44.5	4.8
$\text{HCN}(\text{CH}_3)_2$	25.5	87.1	74.5	12.9
$\text{HCN}(\text{CH}_3)_2 + 1 \text{ eq. } (\text{CH}_3)_4\text{N}^+\text{Cl}^-$	14.0	76.2	86.0	23.8

^a Solvents were purified with standard procedure.

For both *cis*-*p*-nitrophenyl thio ester and *trans*-*p*-nitrophenyl ester, it was found that the amount of inversion was favored by an increase in the solubility of the salt produced as byproduct and by added salts. *Trans*-*p*-nitrophenyl ester can complex easier with a cation than can the thiophosphate and in the former case a cation should be more effective in shifting the initial equilibrium to the right. As expected, *trans*-*p*-nitrophenyl ester gave more inversion product in all cases.

It was reported,⁵⁶ that the reaction of *trans*-2-(*p*-nitrophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan with sodium *p*-methylphenoxide in acetonitrile at room temperature gave an isomer mixture with an inversion-retention ratio of 44.5 to 55.5

Similar treatment of *cis*-phosphorochloridate under identical conditions gave an inversion-retention ratio of 55.8 to 44.2.

thiophosphate ester gave a much lower yield of inversion product (4.8%). In our studies, we found that *cis*-2-(*p*-nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan under identical conditions gave an inversion-retention ratio of 4.8 to 95.2.

Similarly *trans*-thiophosphorochloridate gave a ratio (*cis*/*trans*) of 60 to 40.

As was described, both thiophosphates and phosphates give an increase of substitution by inversion when chloridate was used as substrate in place of *p*-nitrophenoxy ester. The results are not surprising for chloride ion is a better leaving group than the *p*-nitrophenoxy ion. Thus direct displacement would have a lower energy of activation in the case of the chloridate and the amount of inversion should increase.

The thiochloridate is an anomaly, for it turned out that *trans*-thiophosphorochloridate gave a greater percentage yield of inversion product (60%) than does *cis*-phosphorochloridate (55.8%), whereas the

thiophosphate ester gave a much lower yield of inversion product (4.8%) than the corresponding phosphate (44.5%). In the case of the thiophosphorochloridate with its lower positive charge on phosphorus, chloride ion is more easily removed. Thus complex formation between a cation and chlorine in the transition state leading to inversion would be more keenly felt in the case of the thio analogues. The other leaving groups would not be expected to complex with the cation and thus inversion would not be expected to be catalyzed in a similar manner.

The fact that cations can complex with chloride ion and divert substitution to inversion especially in the case of the thiophosphorochloridate was indicated by the effect of added salt, tetramethylammonium chloride. Added salt has a greater effect on trans-thio-

phosphorochloridate than it does on cis-phosphorochloridate.

The effect of added salt on phenyl esters was also compared, Table 10. Since oxygen due to its greater electronegativity can

Table 10: Effects of Added Salt^a upon Substitution Reactions of Phosphates^b and Thiophosphates^c in Acetonitrile.

R	R*	% inversion	
		without salt	with salt
-H		1.5	25.0
-Br		2.6	22.2
-NO ₂		4.8	20.0
	-NO ₂	44.5	86.0

^a Salt added was tetramethylammonium chloride. ^b Only trans-p-nitro-phenyl ester was studied. ^c All thiophosphates are pure cis isomers.

complex with cations easier than sulfur, added salt has a greater effect on p-nitrophenyl ester than it does on the thiophosphate ester. Thus added salts due to more efficient complex formation have a greater ability to shift the equilibrium between uncomplexed and complexed forms further to the right in the case of the phosphates than thiophosphates. A much higher yield of the inversion product produced from the complex is obtained with the former.

The reaction of piperidine with thiophosphates and/or phosphates was of further interest. It was found that treatment of excess piperidine with cis-phosphorochloridate gave almost exclusively trans-phosphoramidate with inversion of configuration at phosphorus.

Reaction of piperidine with trans-thiophosphorochloridate on the other hand gave more retention although inversion was still the predominate pathway.

To account for the predominant inversion product, we have postulated that 19 may be the transition state for the reaction of amine with chloridates. Neutralization of the positive charge by oxygen would be greater than by sulfur for the former is more electro-negative. Thus the energy of activation would be relatively lower for the phosphate than the thiophosphate and inversion would be a more favored pathway, Figure 12.

X = O or S

Figure 12

CONCLUSIONS

- a.) The stereochemical pathway for substitutions at thiophosphoryl centers is dependent upon the basicity of the charged nucleophile. Retention is favored as the basicity of the nucleophile is increased.
- b.) Added cations tend to direct the substitution toward the inversion pathway.
- c.) Inversion becomes more favorable as the stability of the leaving group is increased.
- d.) Substitutions by retention are more favorable at thiophosphoryl centers than at phosphoryl centers.
- e.) Substitution of chlorine in thiophosphoryl chloridate is an anomaly due perhaps to electrophilic catalysis by cations.
- f.) Substitution at thiophosphoryl centers has a higher energy of activation than at phosphoryl centers and proceeds at a slower rate.
- g.) Results are explained by assuming a duality of mechanisms. An equilibrium between complexed and uncomplexed phosphates precedes attack by the nucleophile.

EXPERIMENTAL

Proton Nuclear Magnetic Resonance (H-NMR) spectra were obtained on a Varian A-60A spectrophotometer at 60 MHz with TMS as an external standard. All melting points were reported in degree centigrade and are uncorrected. Values were determined on a Thomas Hoover capillary melting point apparatus. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Infrared spectra were obtained on Perkin-Elmer 700 and 521 spectrophotometers with KBr disks. All reactions were studied at room temperature unless otherwise stated.

1-chloromethyl-1,1-dihydroxymethylethane:⁵⁷

Thionyl chloride (119 g, 1 mol) was added dropwise to 1,1,1-trihydroxymethylethane (120 g, 1 mol) and pyridine (80 g, 1 mol) and the mixture heated at 140-160° (oil bath) for 20 hr. The cooled mixture was diluted with water (1 vol.) and extracted with ethyl acetate (total 500 ml). The extract was washed with 2N-hydrochloric acid, then with water, and dried over anhydrous magnesium sulfate. Vacuum distillation of the solution gave pale yellow crystals (103-107°, 0.3 mm Hg). The solid was recrystallized from toluene to give a white solid product, (40 g, 30% yield) m.p. 79-80°.

Cis- and Trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan:

Thiophosphoryl chloride, PSCl_3 , (22 ml, 0.22 mol) was added

dropwise with stirring and cooling to a stirred mixture of 1-chloromethyl-1,1-dihydroxymethylethane, (30.14 g, 0.22 mol) ether (150 ml) and pyridine (34.5 ml, 0.44 mol). The solution was stirred for 1 hr and white pyridine hydrochloride was removed by filtration. The filtrate was washed well with 5% hydrochloric acid followed by water, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give a mixture of isomers, (36 g, 70% yield) cis : trans :: 1 : 2 (by NMR).

Trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan:

The thiophosphoryl chloridate mixture was recrystallized four times from a mixture of hexane and chloroform (10/1, v/v) to give pure trans isomer, m.p. 64-65^o; IR 675 cm⁻¹ (P=S), Figure 13.

Analysis: Calculated for C₅H₉ClO₂PS: C, 25.53; H, 3.83; Cl, 30.21; S, 13.62. Found: C, 25.77; H, 3.94; Cl, 30.43; S, 13.77.

Cis- and Trans-2-(2,4-dinitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan:

The sodium salt of 2,4-dinitrophenol (3.9 g, 0.02 mol) was added to a mixture of 2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan, (5 g, 0.02 mol) cis : trans :: 1 : 2, and acetonitrile (100 ml). The solution was stirred for two days. Water was added to precipitate the product and the precipitate washed thoroughly with water and dried under reduced pressure. A pale yellow solid (7.2 g, 88% yield) was obtained, cis : trans :: 3 : 1 (by NMR).

Cis-2-(2,4-dinitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan:

The isomer mixture was recrystallized twice with a mixed solvent, carbon tetrachloride : acetonitrile (10/1, v/v), to give pure cis isomer, m.p. 134-135°; IR 675 cm^{-1} (P=S), Figure 14.

Analysis: Calculated for $\text{C}_{11}\text{H}_{12}\text{ClN}_2\text{O}_7\text{PS}$: C, 34.56; H, 3.14; Cl, 9.16; S, 8.38. Found: C, 34.71; H, 3.20; Cl, 9.36; S, 8.44.

Cis- and Trans-2-(p-nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan:

Sodium p-nitrophenoxide (8 g, 0.05 mol) was added to a mixture of 2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (12 g, 0.05 mol) and acetonitrile (100 ml). The solution was stirred for three days and water added to precipitate the product. The precipitate was washed thoroughly with water and dried under reduced pressure. A pale yellow solid (16.2 g, 95% yield) was obtained, cis : trans :: 2 : 1 (by NMR).

Cis-2-(p-nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan:

The mixture of isomers was boiled with 20 ml ether and liquid removed by filtration. The residue was boiled again with another 20 ml ether and liquid removed by filtration. The residue was recrystallized twice from carbon tetrachloride to give the pure cis isomer, m.p. 122-123°; IR 675 cm^{-1} , Figure 11.

Analysis: Calculated for $\text{C}_{11}\text{H}_{13}\text{ClNO}_5\text{PS}$: C, 39.17; H, 3.86;

Cl, 10.39; S, 9.50. Found: c, 38.96; H, 3.71; Cl, 10.62; S, 9.62.

Cis- and Trans-2-(p-bromophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan:

The crude product was recrystallized twice from a mixture of carbon tetrachloride and hexane (5/10, v/v) to give the pure cis isomer, m.p. 140-141°; IR 675 cm⁻¹ (P=S), Figure 10. Sodium p-bromophenoxide (5 g, 0.03 mol) was added to a mixture of 2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (6 g, 0.03 mol) and acetonitrile (200 ml). The solution was stirred for two days and water added to precipitate the product. The precipitate was washed well with water and dried under reduced pressure. A white product (8.78 g, 92% yield) was obtained, cis : trans :: 7 : 4 (by NMR).

Cis-2-(p-bromophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan:

The crude product which contained both isomers was recrystallized three times from carbon tetrachloride to give the pure cis isomer, m.p. 145-146°; IR 675 cm⁻¹ (P=S), Figure 15.

Analysis: Calculated for C₁₁H₁₃ClBrO₃PS: C, 35.58; H, 3.50; Cl, 9.43; S, 8.62. Found: C, 35.34; H, 3.56; Cl, 9.65; S, 8.74.

Cis- and Trans-2-phenoxy-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan:

Sodium phenoxide (16 g, 0.14 mol) was added to a mixture of 2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (32 g, 0.14 mol) and acetonitrile (100 ml). The solution was stirred for three days and water added to precipitate the product. The precipitate was washed thoroughly with water and dried under reduced pressure. A

solid product (28 g, 70% yield) was obtained.

Cis-2-phenoxy-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan:

The crude product was recrystallized twice from a mixture of carbon tetrachloride and hexane (1/10, v/v) to give the pure cis isomer, m.p. 110-111^o; IR 675 cm⁻¹ (P=S), Figure 16.

Cis- and Trans-2-piperidino-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan:

2-Chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (2.25 g, 0.01 mol) was added to a mixture of piperidine (2.5 ml, 0.02 mol) and acetonitrile (20 ml). The solution was stirred overnight and water added to precipitate the product. The precipitate was washed well with water and dried under reduced pressure. A pale brown solid (2.5 g, 93% yield) was obtained, cis : trans :: 9 : 8 (by NMR).

Cis-2-piperidino-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan:

The product mixture was recrystallized twice from a mixture of hexane and carbon tetrachloride (10/1, v/v) to give the pure cis isomer, m.p. 89-90^o; IR 650 cm⁻¹ (P=S), Figure 17.

Attempted oxidation of cis-2-phenoxy-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan:

A 10% excess of 0.1 M m-chloroperoxybenzoic acid in methylene chloride was added to a 0.5% solution of cis-2-phenoxy-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan in methylene chloride at 0^o.

The mixture was stirred and refluxed for one week. The solution was washed with 5% sodium hydroxide solution followed by water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. A white solid was obtained. Its NMR spectrum showed no significant difference from the starting material. It had not reached the approximately 2.8 to 1 ratio.

Thermal isomerization of cis-2-(2,4-dinitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan and cis-2-(p-bromophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan:

Compounds were sealed under vacuum in separate tubes and heated in an oil bath at 190° for three days. After heating the extent of isomerization was determined. From the NMR spectra of the samples in deuterated chloroform, it appeared that there was no isomerization in either case at elevated temperature.

Isomerization of trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan:

A sample of the pure isomer was dissolved in deuterated dimethylformamide at room temperature. Isomerization of the pure trans isomer was followed by observing the changes in NMR peak ratios. The solution started to become enriched in the cis isomer after three days and reached to an equilibrium with a cis-trans ratio of 2.8 to 1 after 13 days. Pyrophosphate formation was also observed during isomerization.

Isomerization of cis-2-(p-nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan:

A sample of pure cis isomer was dissolved at room temperature in deuterated acetonitrile which was saturated with sodium p-nitrophenoxide. Isomerization of the pure cis isomer was followed by observing the changes in NMR peak ratios at room temperature. The sample gave a cis-trans ratio of 40 to 60 after sixteen days. It had not reached the approximately 2.8 to 1 ratio.

Isomerization of cis-2-(2,4-dinitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan:

A sample of pure cis isomer was dissolved in deuterated dimethylformamide at room temperature. Isomerization of this pure cis isomer was followed by observing the change in peak ratios. It showed no isomerization after standing for twenty days.

A solution of this cis isomer in deuterated acetonitrile was saturated with sodium 2,4-dinitrophenoxide and sealed in an nmr tube. The isomerization of the pure cis isomer in this case was followed by observing the change in NMR peak ratios at 65°. Pyrophosphate formation was observed during the isomerization. The solution gave a cis-trans ratio of 2.6 to 1 after 80 hr.

The isomerization of the pure cis isomer in deuterated acetonitrile was also studied in the absence of sodium 2,4-dinitrophenoxide at 65°. It was found that the mixture of the pure isomer gave a cis-trans ratio of only 50 to 1 after standing for five months.

Reaction of trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with sodium p-methylphenoxide in benzene:

The trans isomer (0.3 g, 0.001 mol) was added to a mixture of sodium p-methylphenoxide (0.2 g, 0.0015 mol) and benzene (15 ml). The solution was stirred at room temperature for two days and solvent removed under reduced pressure. The residue was washed with water and water removed by decantation. The sticky residue was set in the hood for three days. The NMR spectrum of the residue showed a retention-inversion ratio of 89.2 to 10.8 (percentage).

Reaction of trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with sodium p-methylphenoxide in acetonitrile saturated with lithium perchlorate:

To a solution of acetonitrile (15 ml) and sodium p-methylphenoxide (0.25 g, 0.02 mol) was added lithium perchlorate (0.18 g, 0.0017 mol). Trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.4 g, 0.0017 mol) was added to the stirred mixture. The solution was stirred at room temperature for two days and water added to precipitate the product. The sticky residue was separated from the water and set in the hood for three days. The NMR spectrum of the residue showed a retention-inversion ratio of 87.5 to 12.5 (percentage).

Reaction of trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with sodium p-methylphenoxide in acetonitrile:

Sodium p-methylphenoxide (0.14 g, 0.001 mol) was dissolved in acetonitrile (15 ml) and the trans isomer (0.2 g, 0.00085 mol) added to this mixture. The solution was stirred at room temperature for

two days and water added to precipitate the product. The precipitate was washed well with water and dried under reduced pressure. A mixture of cis- and trans-2-(p-methylphenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.25 g, 94% yield) with a retention-inversion ratio of 40 to 60 (percentage) was obtained.

Reaction of trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with sodium p-methylphenoxide in acetonitrile saturated with tetramethylammonium chloride:

Sodium p-methylphenoxide (0.2 g, 0.0015 mol) and tetramethylammonium chloride (0.16 g, 0.0015 mol) was dissolved in acetonitrile (15 ml). To the solution was added trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.35 g, 0.0015 mol). The mixture was stirred at room temperature for two days and water added to precipitate the product. The precipitate was washed thoroughly with water and dried under reduced pressure. The product (0.42 g, 91% yield) gave an NMR spectrum which showed a retention-inversion ratio of 6.2 to 93.8 (percentage).

Reaction of trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with sodium p-methylphenoxide in dimethylformamide:

To a solution of sodium p-methylphenoxide (0.2 g, 0.0015 mol) and dimethylformamide (15 ml) was added the trans isomer (0.3 g, 0.0013 mol). The mixture was stirred at room temperature for two days and water added to precipitate the product. The precipitate was washed well with water and dried under reduced pressure. The product (0.36 g, 92% yield) had an NMR spectrum which showed a retention-

inversion ratio of 5.7 to 94.3 (percentage).

Reaction of trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with sodium p-methylphenoxide in dimethylformamide saturated with tetramethylammonium chloride:

To the mixture of sodium p-methylphenoxide (0.2 g, 0.0015 mol) and tetramethylammonium chloride (0.14 g, 0.0013 mol) in dimethylformamide (15 ml) was added trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.3 g, 0.0013 mol). The solution was stirred at room temperature for two days and water added to precipitate the product. The precipitate was washed well with water and dried under reduced pressure. The NMR spectrum of the product (0.33 g, 85% yield) showed a retention-inversion ratio of 5.1 to 94.9 (percentage).

Reaction of trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with sodium p-methoxyphenoxide in acetonitrile:

To a solution of sodium p-methoxyphenoxide (0.2 g, 0.0015 mol) and acetonitrile (15 ml) was added trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.3 g, 0.0013 mol). The mixture was stirred at room temperature for two days and water added to precipitate the product. The precipitate was washed thoroughly with water and dried under reduced pressure. The product (0.22 g, 54% yield) had an NMR spectrum which showed a retention-inversion ratio of 50 to 50 (percentage).

Reaction of trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with sodium p-bromophenoxide in acetonitrile:

To the solution of sodium p-bromophenoxide (0.25 g, 0.0013 mol) and acetonitrile (15 ml) was added trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.3 g, 0.0013 mol). The mixture was stirred at room temperature for two days and water added to precipitate the product. The precipitate was washed thoroughly with water and dried under reduced pressure. The solid product (0.44 g, 93% yield) had an NMR spectrum which showed a retention-inversion ratio of 23.7 to 76.3 (percentage).

Reaction of trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with sodium p-nitrophenoxide in acetonitrile:

To a solution of sodium p-nitrophenoxide (0.2 g, 0.0012 mol) and acetonitrile (15 ml) was added trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.27 g, 0.0011 mol). The mixture was stirred at room temperature for two days and water added to precipitate the product. The precipitate was washed well with water and dried under reduced pressure. The solid product (0.36 g, 92% yield) had an NMR spectrum which showed a retention-inversion ratio of 5.1 to 94.9 (percentage).

Reaction of trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with piperidine in acetonitrile:

An excess of piperidine (1.0 ml, 0.011 mol) was dissolved in acetonitrile (15 ml). To the solution was added trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.2 g, 0.00085 mol). The mixture was stirred at room temperature for two days and

water added to precipitate the product. The precipitate was washed thoroughly with water and dried under reduced pressure. The solid product (0.22 g, 92% yield) had an NMR spectrum which showed a retention-inversion ratio of 82.8 to 17.2 (percentage).

Reaction of cis-2-(p-nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with sodium p-methylphenoxide in benzene:

To the solution of sodium p-methylphenoxide (0.2 g, 0.0015 mol) and benzene (15 ml) was added cis-2-(p-nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.39 g, 0.0012 mol). The mixture was stirred at room temperature for two days and the solvent removed under reduced pressure. The residue was washed thoroughly with water and dried under reduced pressure. The NMR spectrum of the solid product was identical to that of the reactant which indicated that substitution had not occurred.

Reaction of cis-2-(p-nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with sodium p-methylphenoxide in acetonitrile:

To a solution of sodium p-methylphenoxide (0.1 g, 0.0008 mol) and acetonitrile (15 ml) was added cis-2-(p-nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.26 g, 0.0008 mol). The mixture was stirred at room temperature for two days and water added to precipitate the product. The precipitate was washed thoroughly with water and dried under reduced pressure. The solid product (0.17 g, 70% yield) had an NMR spectrum which showed a retention-inversion ratio of 95.2 to 4.8 (percentage).

Reaction of cis-2-(p-nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with sodium p-methylphenoxide in acetonitrile saturated with tetramethylammonium chloride:

To the solution of sodium p-methylphenoxide (0.14 g, 0.0011 mol) and tetramethylammonium chloride (0.1 g, 0.001 mol) in acetonitrile (15 ml) was added cis-2-(p-nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.26 g, 0.001 mol). The mixture was stirred at room temperature for two days and water added to precipitate the product. The precipitate was washed well with water and dried under reduced pressure. The product (0.22 g, 94% yield) had an NMR spectrum which showed a retention-inversion ratio of 80 to 20 (percentage).

Reaction of cis-2-(p-nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with sodium p-methylphenoxide in dimethylformamide:

To a solution of sodium p-methylphenoxide (0.2 g, 0.0015 mol) and dimethylformamide (15 ml) was added cis-2-(p-nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.4 g, 0.0012 mol). The mixture was stirred at room temperature for two days and water added to precipitate the product. The precipitate was washed well with water and dried under reduced pressure. The NMR spectrum of the product (0.33 g, 92% yield) showed a retention-inversion ratio of 87.1 to 12.9 (percentage).

Reaction of cis-2-(p-nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with sodium p-methylphenoxide in dimethylformamide saturated with tetramethylammonium chloride:

Sodium p-methylphenoxide (0.2 g, 0.0015 mol) and tetramethylammonium chloride (0.14 g, 0.0013 mol) was dissolved in dimethylformamide (15 ml). A sample of cis-2-(p-nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.4 g, 0.0012 mol) was added and stirred at room temperature for two days. An excess amount of water was added to precipitate the product. The precipitate was washed well with water and dried under reduced pressure. The NMR peak ratio of the product (0.3 g, 83% yield) showed a retention-inversion ratio of 76.2 to 23.8 (percentage).

Reaction of cis-2-(p-bromophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with sodium p-methylphenoxide in acetonitrile:

To the solution of sodium p-methylphenoxide (0.16 g, 0.0012 mol) and acetonitrile (15 ml) was added cis-2-(p-bromophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.4 g, 0.0011 mol). The mixture was stirred at room temperature for two days and water added to precipitate the product. The precipitate was washed well with water and dried under reduced pressure. The product (0.27 g, 82% yield) had an NMR spectrum which showed a retention-inversion ratio of 97.4 to 2.6 (percentage).

Reaction of cis-2-(p-bromophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with sodium p-methylphenoxide in acetonitrile saturated with tetramethylammonium chloride:

Sodium p-methylphenoxide (0.2 g, 0.0015 mol) and tetramethylammonium chloride (0.15 g, 0.0013 mol) was dissolved in acetonitrile (15 ml). A sample of cis-2-(p-bromophenoxy)-5-chloromethyl-5-methyl-

2-thio-1,3,2-dioxaphosphorinan (0.4 g, 0.0011 mol) was added to the solution and the mixture stirred at room temperature for two days. Water was added to precipitate the product. The precipitate was washed thoroughly with water and dried under reduced pressure. The white product (0.23 g, 70% yield) had an NMR spectrum which showed a retention-inversion ratio of 77.8 to 22.2 (percentage).

Reaction of cis-2-phenoxy-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with sodium p-methylphenoxide in acetonitrile:

To a solution of sodium p-methylphenoxide (0.2 g, 0.0015 mol) and acetonitrile (15 ml) was added cis-2-phenoxy-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.4 g, 0.0014 mol). The mixture was stirred at room temperature for two days and water added to precipitate the product. The precipitate was washed thoroughly with water and dried under reduced pressure. The NMR spectrum of this solid product (0.31 g) showed a mixture of starting material and p-methylphenoxy ester. The calculation based on the integration ratio showed only 0.21 g (50% yield) of substitution product. The retention-inversion ratio of the product was 98.5 to 1.5 (percentage).

Reaction of cis-2-phenoxy-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with sodium p-methylphenoxide in acetonitrile saturated with tetramethylammonium chloride:

Sodium p-methylphenoxide (0.16 g, 0.0012 mol) and tetramethylammonium chloride (0.13 g, 0.0012 mol) was dissolved in acetonitrile (15 ml). A sample of cis-2-phenoxy-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.35 g, 0.0012 mol) was added to the solution

and the mixture stirred at room temperature for two days. An excess amount of water was added to precipitate the product. The precipitate was washed well with water and dried under reduced pressure. The NMR spectrum of the precipitate (0.3 g) showed that the product is a mixture of the reactant and p-methylphenoxy ester. The calculation based on NMR integration ratio indicated only 0.2 g (54% yield) was the substitution product. The retention-inversion ratio of the product was 75 to 25 (percentage).

Cis-2-(p-methylphenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan:

The substitution products of all the esters with sodium p-methylphenoxide were combined and recrystallized twice from a mixture of hexane and carbon tetrachloride (10/1, v/v) to give the pure cis isomer, m.p. 135-136°; IR 675 cm^{-1} (P=S), Figure 18.

Analysis: Calculated for $\text{C}_{12}\text{H}_{16}\text{ClO}_3\text{PS}$: C, 47.06; H, 5.23; Cl, 11.44; S, 10.46. Found: C, 47.20; H, 5.34; Cl, 11.60; S, 10.43.

Reaction of cis-2-(2,4-dinitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with sodium p-methylphenoxide in acetonitrile:

To a solution of sodium p-methylphenoxide (0.2 g, 0.0015 mol) and acetonitrile (15 ml) was added cis-2-(2,4-dinitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.54 g, 0.0014 mol). The mixture was stirred at room temperature for two days and water added to precipitate the product. The precipitate was washed well with water and dried under reduced pressure. The solid product had an

NMR spectrum which showed that substitution at phosphorus had not occurred. The reaction proceeded entirely by C-O bond cleavage to produce an aromatic ether, (p-methylphenyl-2,4-dinitrophenyl ether), based on its NMR spectrum, Figure 7.

When the acetonitrile was saturated with one equivalent weight of tetramethylammonium chloride, the reaction still proceeded via C-O bond cleavage to give the ether as the only product.

Isomerization of cis-2-(p-methylphenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan:

A sample of cis-2-(p-methylphenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan was dissolved in deuterated acetonitrile which was saturated with sodium p-methylphenoxide. The isomerization of the pure cis isomer was followed by observing the change in NMR peak ratios at room temperature. It was found that no isomerization had occurred after the solution had stood for seven days. This is indicative that the reaction product ratio obtained by substitution of esters with sodium p-methylphenoxide is a kinetic ratio not an equilibrium ratio.

APPENDIX

Figure 1: NMR spectra of 2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinane in CDCl_3 : top, mixture of cis and trans isomers; bottom, pure trans isomer.

Figure 2: NMR spectra of 2-(p-nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan in CDCl₃: top, mixture of cis and trans isomers; bottom, pure cis isomer.

Figure 3: NMR spectra of 2-(p-bromophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan in CDCl₃: top, mixture of cis and trans isomers; bottom, pure cis isomer.

Figure 4: NMR spectra of 2-(2,4-dinitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan in CDCl_3 : top, mixture of cis and trans isomers; bottom, pure cis isomer.

Figure 5: NMR spectra of 2-phenoxy-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan in CDCl_3 : top, mixture of cis and trans isomers; bottom, pure cis isomer.

Figure 6: NMR spectra of 2-(p-methylphenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan in CDCl_3 : top, mixture of cis and trans isomers; bottom, pure cis isomer.

Figure 7: NMR spectrum of the reaction product obtained by treating sodium p-methylphenoxide with cis-2-(2,4-dinitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan. The spectrum was run in CDCl_3 , with TMS as an external standard.

Figure 8: NMR spectrum of the substitution product obtained by treating piperidine with trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan. The spectrum was run in CDCl_3 , with TMS as an external standard.

Figure 9: Isomerization of trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan in DMF-d₇: top, pure trans-chloridate; center, after 18 days had elapsed; bottom, after 40 days had elapsed.

NO. 007-1061-modified

REMARKS

ORIGIN _____

PURITY _____

PHASE KBr Pellet

CONCENTRATION _____

THICKNESS _____

DATE February 21, 1973OPERATOR Yuh-Geng TsayPERKIN-ELMER
MODEL 700

SPECTRUM NO. _____

SAMPLE 1 _____

SAMPLE 2 _____

Figure 10: Infrared spectrum of trans-2-(p-nitrophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane.

NO. 007-1061-modified

REMARKS

ORIGIN

PURITY

PHASE KBr Pellet

CONCENTRATION

THICKNESS

DATE February 21, 1973OPERATOR Yuh-Geng TsayPERKIN-ELMER
MODEL 700SPECTRUM NO. MODEL 700

SAMPLE 1

SAMPLE 2

Figure 11: Infrared spectrum of cis-2-(p-nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan.

SAMPLE T-35-A

SPECTRUM NO.
ABSORBANCE

NO. 007-1061-modified

REMARKS

ORIGIN _____

PURITY _____

PHASE KBr Pellet

CONCENTRATION _____

THICKNESS _____

DATE February 21, 1973OPERATOR Yuh-Geng Tsay**PERKIN-ELMER**
MODEL 700

SPECTRUM NO. _____

SAMPLE 1 _____

SAMPLE 2 _____

Figure 13: Infrared spectrum of trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan.
phosphorinan.

SAMPLE I-7-B

SPECTRUM NO. ABSORBANCE

NO. 007-1061-modified

REMARKS

ORIGIN _____

PURITY _____

PHASE KBr Pellet

CONCENTRATION _____

THICKNESS _____

DATE February 21, 1973

OPERATOR Yuh-Geng Tsay

PERKIN-ELMER
MODEL 700

SPECTRUM NO. _____

SAMPLE 1 _____

SAMPLE 2 _____

Figure 14: Infrared spectrum of cis-2-(2,4-dinitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan.

SAMPLE T-10-A

SPECTRUM NO. ABSORBANCE

NO. 007-1061-modified

REMARKS

ORIGIN _____

PURITY _____

PHASE KBr Pellet

CONCENTRATION _____

THICKNESS _____

DATE February 21, 1973OPERATOR Yuh-Geng TsayPERKIN-ELMER
MODEL 700

SPECTRUM NO. _____

SAMPLE 1 _____

SAMPLE 2 _____

Figure 15: Infrared spectrum of cis-2-(p-bromophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan.

SAMPLE T-20-A

SPECTRUM NO.
ABSORBANCE

NO. 007-1061-modified

REMARKS

ORIGIN _____

PURITY _____

PHASE KBr pellet

CONCENTRATION _____

THICKNESS _____

DATE March 17, 1973OPERATOR Yuh-geng TsayPERKIN-ELMER
MODEL 700

SPECTRUM NO. _____

SAMPLE 1 _____

SAMPLE 2 _____

Figure 16: Infrared spectrum of cis-2-phenoxy-5-chloro-methyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan.

SAMPLE T-30-A

SPECTRUM NO.
ABSORBANCE

NO. 007-1061-modified

REMARKS

ORIGIN

PURITY

PHASE KBr pellet

CONCENTRATION

THICKNESS

DATE March 17, 1973

OPERATOR Yuh-geng Tsay

PERKIN-ELMER
MODEL 700

SPECTRUM NO.

SAMPLE 1

SAMPLE 2

Figure 17: Infrared spectrum of cis-2-piperidino-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan.

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NO. 007-1061-modified

REMARKS

ORIGIN

PERKIN-ELMER
MODEL 700

SPECTRUM NO.

PURITY

SAMPLE 1

PHASE KBr pellet

CONCENTRATION

THICKNESS

SAMPLE 2

DATE March 17, 1973OPERATOR Yuh-geng Tsay

Figure 18: Infrared spectrum of cis-2-(p-methylphenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinane.

SAMPLE T-49

SPECTRUM NO. ABSORBANCE

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