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I. LOW TEMPERATURE DEOXYGENATION REACTIONS
INVOLVING DIHALOPHOSPHITES

II. THE MECHANISM OF NUCLEOPHILIC SUBSTITUTION AT
PHOSPHORUS: EVIDENCE FOR AN $S_N1(P)$ MECHANISM

BY

HENRY LILAND HORTEN, JR.

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

1970

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I. LOW TEMPERATURE DEOXYGENATION REACTIONS

INVOLVING DIHALOPHOSPHITES

II. THE MECHANISM OF NUCLEOPHILIC SUBSTITUTION AT
PHOSPHORUS: EVIDENCE FOR AN $S_N1(P)$ MECHANISM

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

Thesis Adviser

Date

Head, Chemistry Dept.

Date

ACKNOWLEDGEMENTS

To Prof. William S. Wadsworth Jr., my boss, whose bark is far worse than his bite (although he'll never admit it). Students indicate that the most respected teacher is the man who is also active in the pursuit of independent research. The man who can excel in both areas is rare. This university is fortunate to have such a man as Dr. Wadsworth, and this author is grateful to have had the opportunity to be associated with him.

To Prof. V. S. Webster, Head, Department of Chemistry, in acknowledgement of his too often overlooked and too seldom rewarded efforts to maintain a progressive department in an environment which sometimes dictates this direction to be against the grain.

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To my friends, without whom this work would never have been completed.

And to the memory of Richard Corey, a brother in spirit, in acknowledgement of his goals and ideals.

HLH

ABSTRACT

PART I

An intermediate species in the Arbuzov ring opening of bicyclic phosphites was discovered. Addition of chlorine or bromine to 1-alkyl-4-phospha-3,5,8-trioxabicyclo(2.2.2) octane at low temperatures produced a solid P,P-dihalo phosphonium intermediate which ring-opened at room temperature to form the 5-alkyl-5-halomethyl-2-halo-2-oxo-1,3,2-dioxaphosphorinan. The intermediate was found to deoxygenate alcohols, ethers, aldehydes and ketones to produce the bicyclic phosphate and the various alkyl halides. The intermediate also cleaved acids and esters to form the acyl halides. The mechanism of the deoxygenation reaction was proposed to involve a type of S_Ni pathway that included the collapse of a pentacovalent phosphorus intermediate.

PART II

A system which may shed new light on the chemistry of nucleophilic substitution at phosphorus was investigated. Three isomeric 5-methyl-5-chloromethyl-2-oxo-2-alkylamino-1,3,2-dioxaphosphorinans were synthesized from 1-methyl-4-phospha-3,5,8-trioxabicyclo(2.2.2)-octane. Methanolysis of the trans-5-methyl-5-chloromethyl-2-oxo-2-chloro-1,3,2-dioxaphosphorinan produced two isomeric esters, and is proposed to have proceeded via an $S_N1(P)$ mechanism involving a

phosphoryl cation intermediate. The kinetics of the methanolysis reaction of the chlorophosphorinan and also the bromophosphorinan were investigated. The aminolysis of the methyl ester was found to produce an amine salt of the acid together with the N-methyl amine. The reactions which were investigated should increase our understanding of the chemistry of phosphorus esters and their derivatives. These types of compounds are important in biological systems such as ATP and ADP.

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AND

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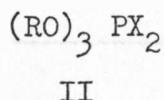
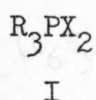
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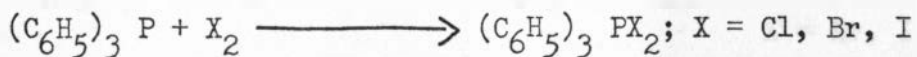
I. LOW TEMPERATURE DEOXYGENATION REACTIONS
INVOLVING DIHALOPHOSPHITES

The existence of pentavalent dihalo derivatives of trisubstituted phosphines and phosphites has been known since before the turn of the century (1). Their separation from solution as isolable solids, however, has only recently been accomplished (2,3,4). The purpose of this section is to discuss these compounds (I,II) and to bring into light a new and useful compound of this type.

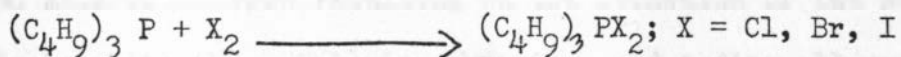


R = alkyl, aryl
X = halogen

Pentavalent dihalo aromatic phosphines have usually been studied in solution using triphenyl phosphine as the original substrate to which the halide was added (5,6,7,8,9). The procedure involved the addition of elemental halogen to a solution of the phosphine in a suitable solvent. Aliphatic phosphines have also been used, but



were not as reactive as the aromatic species, and only tributyl phosphine has been reported as a reagent (5,7,9).

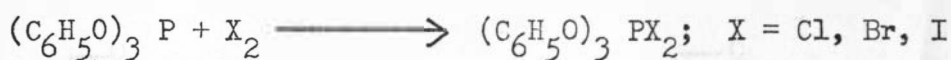


Only two dihalo aromatic phosphines have been isolated as solids. Of these, only the triphenyl phosphine dichloride has been characterized (2). The dichloride precipitated from a suitable

solvent as yellow needle-like crystals.

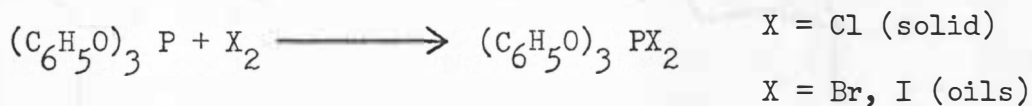


Dihalo derivatives of aromatic phosphites have also been studied in solution. They have been synthesized by direct halogenation of the phosphite (3), or by reacting phosphorus pentachloride with phenol to produce the dichloride and hydrochloric acid (10). Pentavalent dihalo aromatic phosphites have been isolated as solids. Coe and

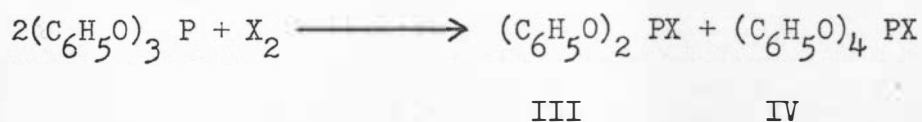


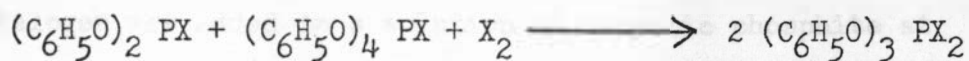
Ar = various substituted aromatics

co-workers have prepared these compounds by reacting equivalent amounts of reagents in a one-step synthesis (3). Rydon began his



synthesis by adding one equivalent of halogen to two equivalents of phosphite to produce III and IV. To these compounds was added the second mole of halogen resulting in the formation of two moles of dihalophosphite (V). Chlorine, bromine, and iodine all produced solid derivatives.

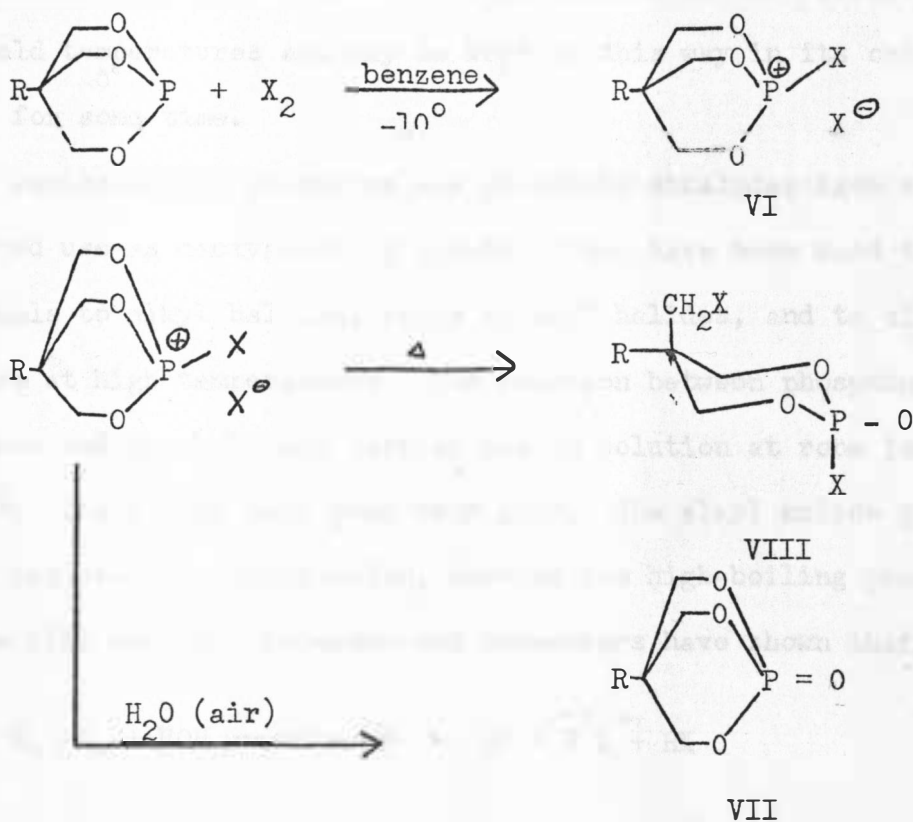




V

X = Cl, Br, I

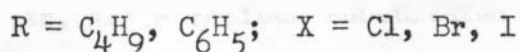
Previously, no trialkyl phosphite dihalide has been isolated either in solution or as a solid. There has been evidence supporting their existence as intermediates in the Arbuzov reaction (11), and in the triphenylphosphine dihalide deoxygenation of alcohols (9). We have prepared a semistable dihalophosphite by direct addition of halogen to a bicyclic phosphite in solution at low temperatures.



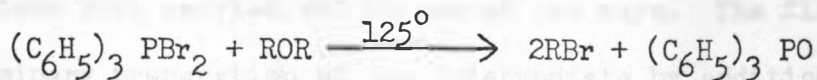
R = CH₃, C₂H₅; X = Br, Cl

The halogen was added to a solution of bicyclic phosphite at temperatures ranging from -15° to $+5^{\circ}$. The intermediate phosphonium dihalide (VI) precipitates as a solid and can be filtered off. It is unstable when isolated from solution or exposed to heat. It reacts with moisture in air to form the halo acid and the bicyclic phosphate (VII). The dichloride ring-opens to form the chloridate at approximately 0° , and the dibromide opens to form the bromidate (VIII) at about 30° . The intermediate can be filtered off and stored in a vacuum desiccator, but will eventually decompose. The intermediate is quite stable as a suspension in the reaction solvent at cold temperatures and may be kept in this way in its original form for some time.

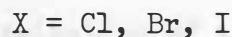
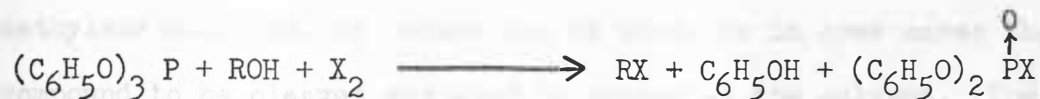
Pentacovalent phosphine and phosphite dihalides have seen limited use as deoxygenating agents. They have been used to convert alcohols to alkyl halides, acids to acyl halides, and to cleave ethers at high temperatures. The reaction between phosphine dihalides and alcohols was carried out in solution at room temperature (7,9). The yields have been very good. The alkyl halide products were isolated by distillation, leaving the high-boiling phosphine oxide (IX) behind. Anderson and co-workers have shown that



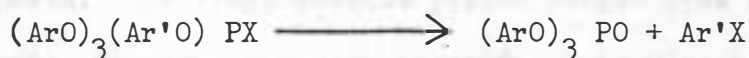
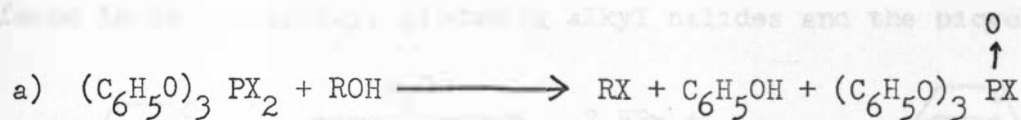
triphenylphosphine dibromide cleaves ethers at elevated temperatures (12).



Pentavalent phosphite dihalides also react with alcohols to yield alkyl halides. These reactions can be carried out by directly combining the phosphite, alcohol, and halogen in solution to produce the alkyl halide, phenol and a phosphonate (8,12). The deoxygenation of alcohols can also be effected by combining the alcohol in situ



with a previously prepared phosphite dihalide (3,10). Aromatic halides can be prepared from substituted phenols at high temperatures using this method.

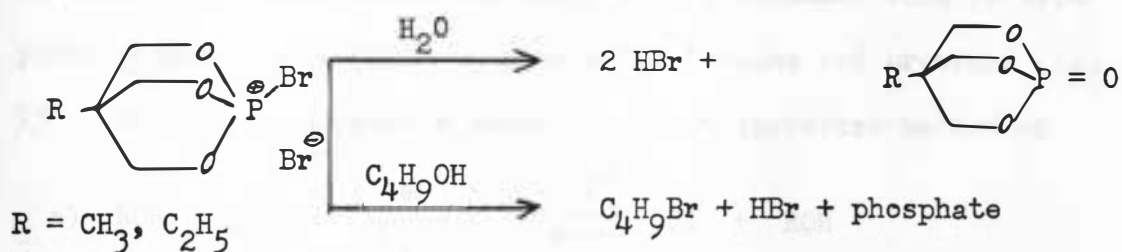


Ar, Ar' = various substituted aromatics

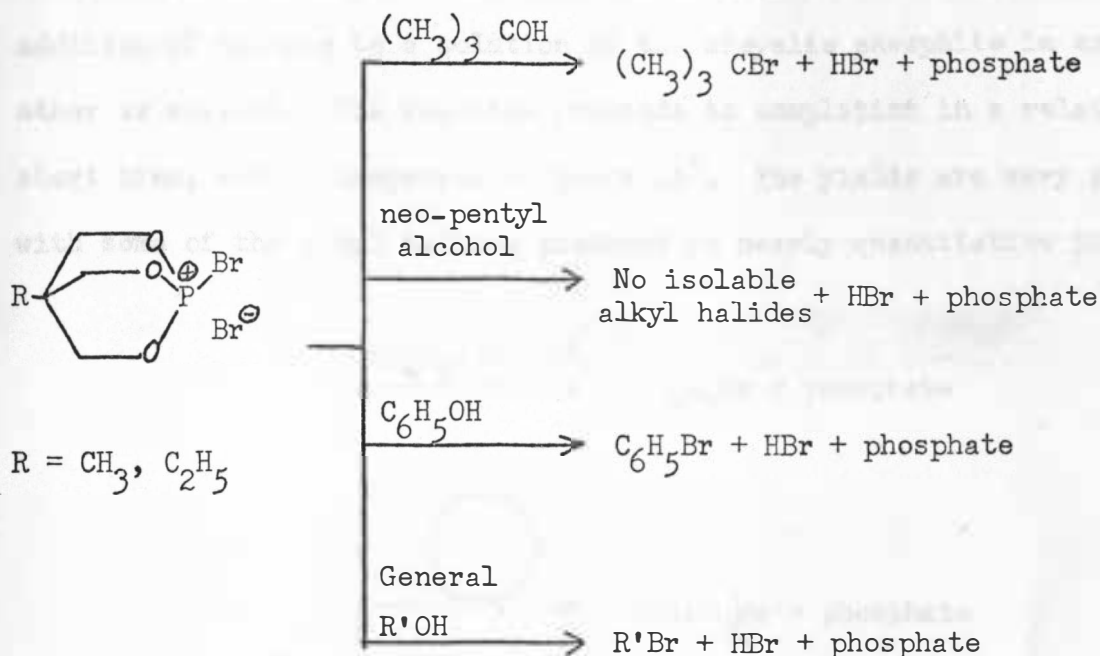
The alkyl phosphonium dihalide which has been prepared in our work has proven to be a useful reagent for effecting several types

of deoxygenation reactions at temperatures of less than 15° . The reactions were carried out in one of two ways. The first involved preliminary preparation of the intermediate by addition of elemental halogen to a cold solution of bicyclic phosphite in an inert solvent. The compound to be deoxygenated was then added to the suspension of the intermediate in the solvent. The second method involved addition of elemental halogen to a cold solution of the phosphite and the compound to be deoxygenated. An inert solvent such as benzene, methylene chlorine, or hexane can be used, or in some cases the compound to be cleaved was used in excess as the solvent. The progress of the reaction is followed by the dissipation of the intermediate into solution.

Since the intermediate was found to hydrolyze violently with water, the reaction with alcohols was investigated first. They were found to react rapidly, producing alkyl halides and the bicyclic

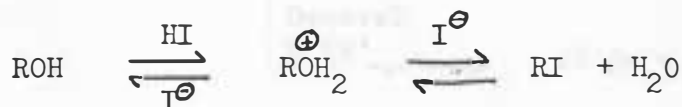
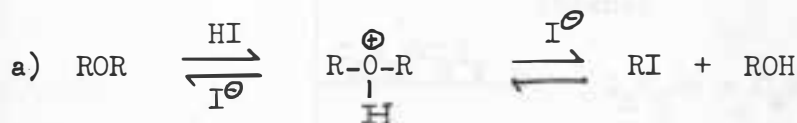


phosphate. The alkyl bromide yields ranged from fifty to ninety percent. The products were identified via gas chromatography and isolated by distillation. An interesting case to be discussed later involves the reaction with neo-pentyl alcohol. No isolable alkyl halides were identified in the benzene solution, even though

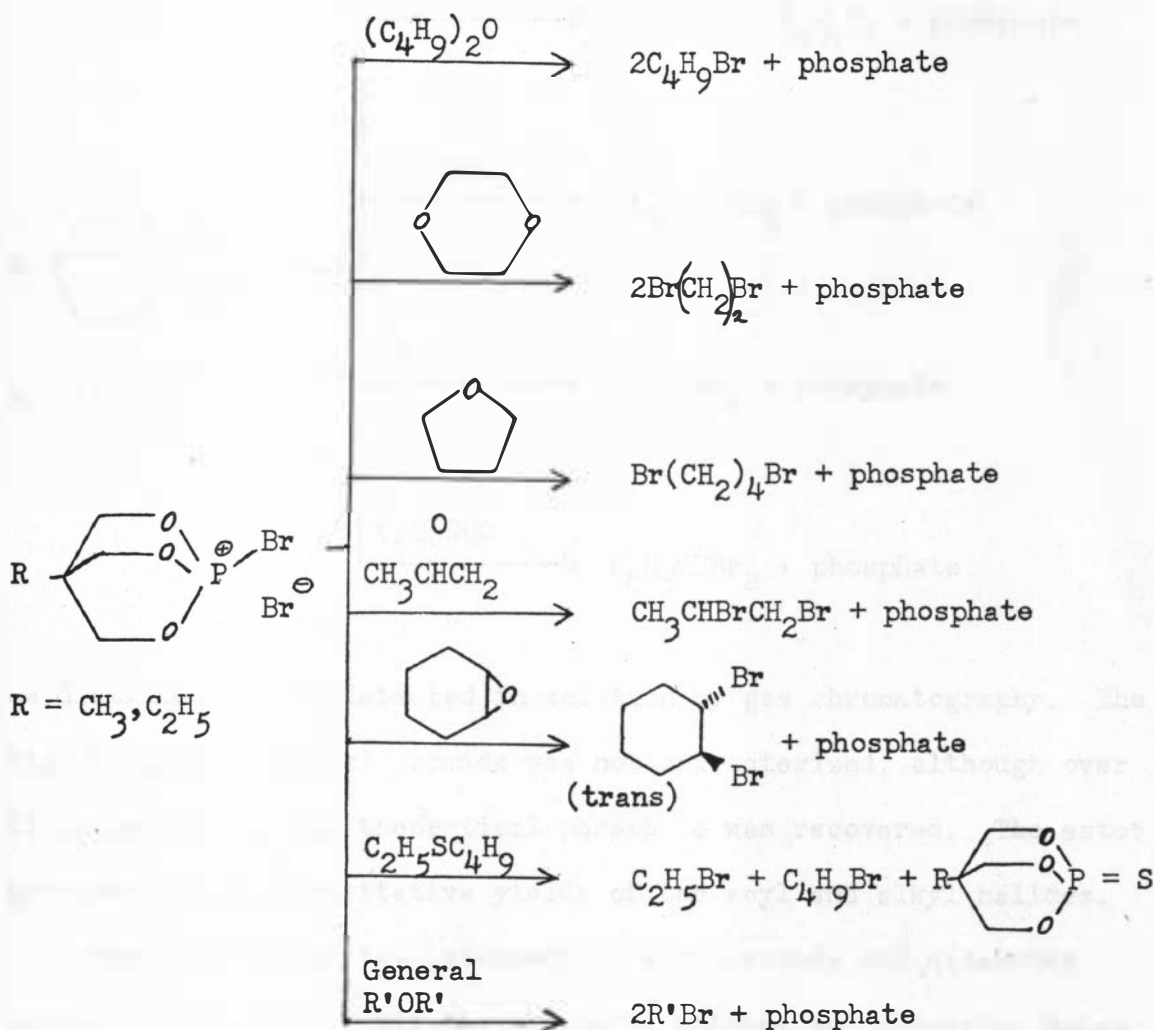


the alcohol did react with the intermediate giving a good yield of phosphate by-product.

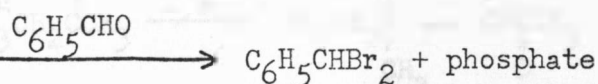
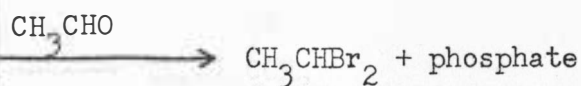
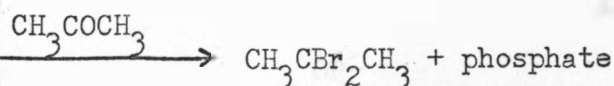
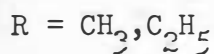
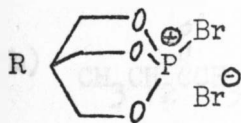
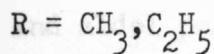
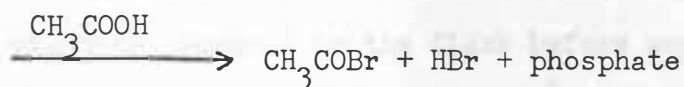
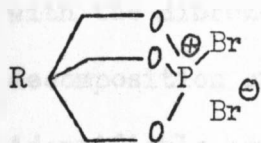
Previous to our work, the only methods of ether cleavage involved high temperature refluxing with hydroiodic acid or triphenylphosphine dibromide to give alkyl iodides and bromides (12, 13). We have discovered a versatile low-temperature method of



ether cleavage using the intermediate. The reaction involves direct addition of halogen to a solution of the bicyclic phosphite in excess ether as solvent. The reaction proceeds to completion in a relatively short time, and at temperatures below 15° . The yields are very good, with some of the alkyl halides produced in nearly quantitative yields.



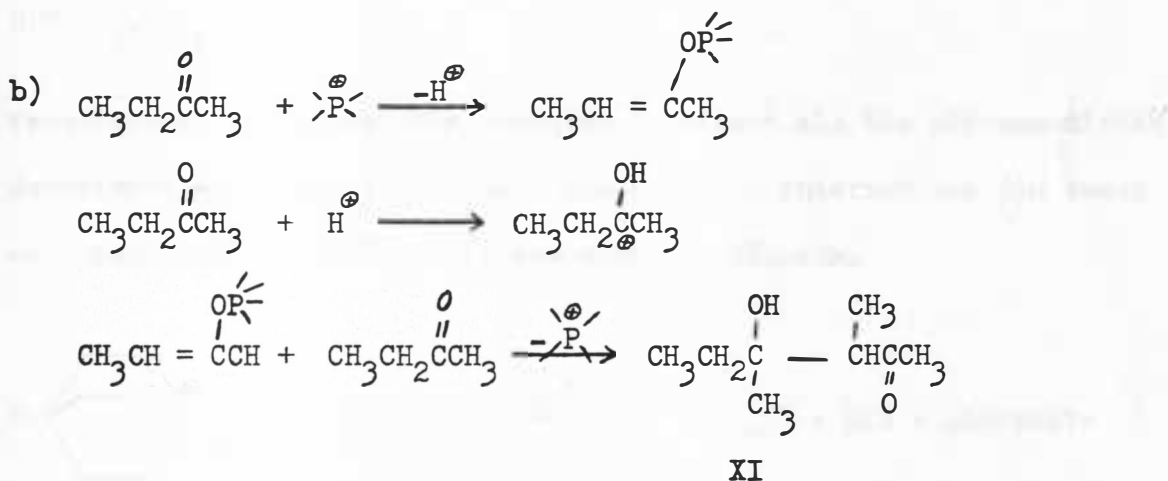
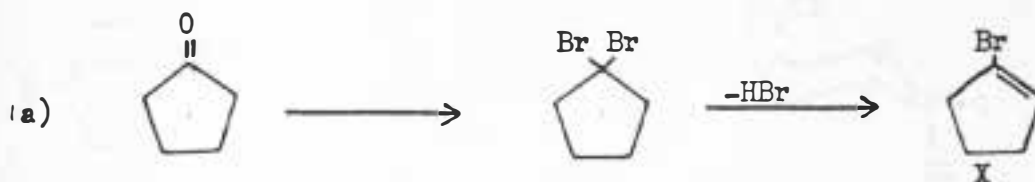
The intermediate has also been found to react with other oxygen-containing compounds such as acids, esters, aldehydes and ketones to yield acyl and alkyl halides. The acyl and alkyl halide products can



be distilled off or detected in solution by gas chromatography. The high-boiling propionyl bromide was not characterized, although over fifty percent of the theoretical phosphate was recovered. The ester produced almost quantitative yields of the acyl and alkyl halides.

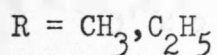
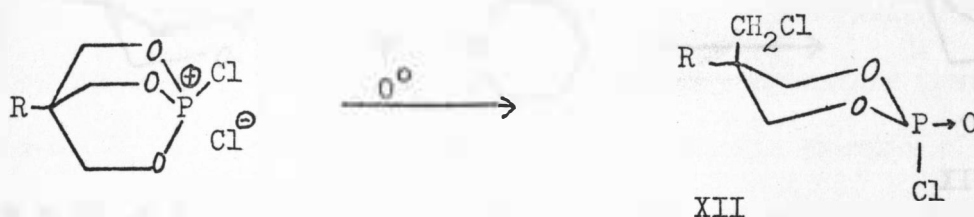
The reaction of the intermediate with ketones and aldehydes proved to be unique. All the aliphatic ketones and aldehydes which were investigated did react with the intermediate, but only acetone and acetaldehyde reacted to give stable alkyl dihalides which could be isolated as pure compounds. All other carbonyl compounds reacted

with the dibromo intermediate to give good yields of phosphate, but decomposition of the products occurred in the flask before any other identifiable compounds were detected. We suspect that eliminations and aldol polymerizations may have occurred. Evidence for the presence of vinyl hydrogens did appear in the nmr spectrum of the

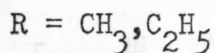
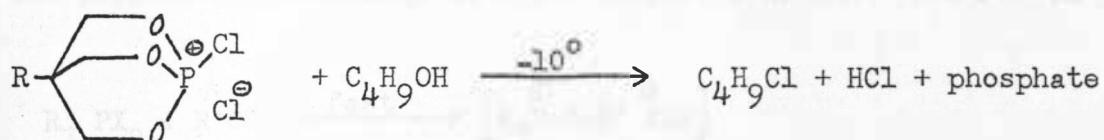


reaction mixture of the cyclopentanone reaction. This offers evidence that olefinic species (X) may have existed for a brief period of time. The presence of the positive phosphonium ion in the intermediate provides a suitable Lewis acid which can act as a catalyst for the aldol reaction producing addition compounds such as (XI). The fact that acetaldehyde normally undergoes rapid aldol condensations with itself, but in this instance reacts with the intermediate to give the stable dibromoethane, is unexplainable.

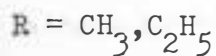
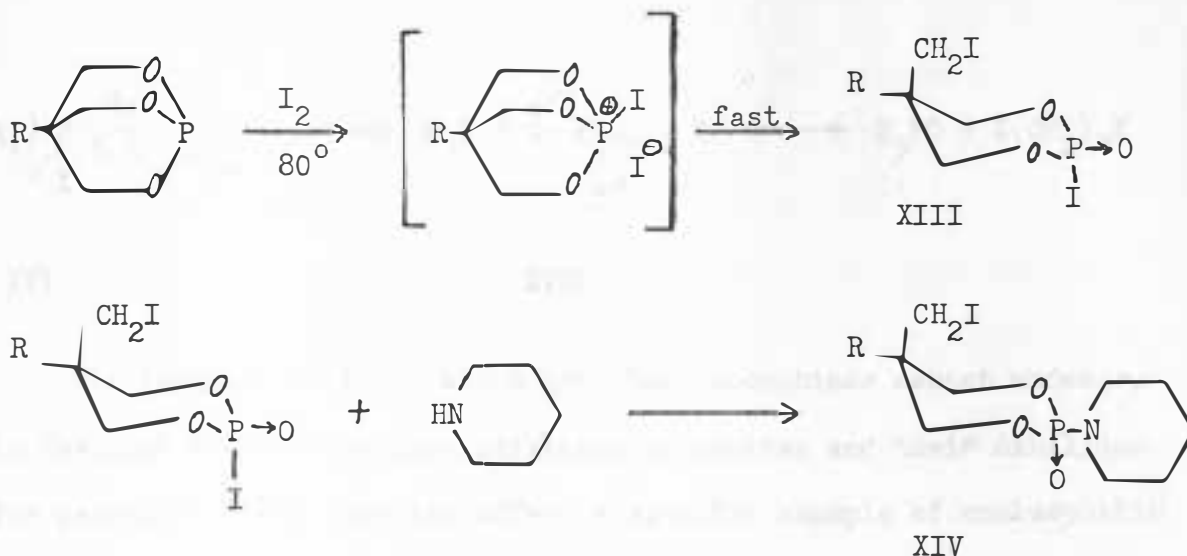
The reactions involving the dihalo intermediate proceed very nicely using chlorine as halogen. The dichloro intermediate was not investigated to the extent of the dibromide due to the fact that the dichloride undergoes a ring opening reaction to form the phosphorochloridate (XII) at approximately 0° . Hence keeping the exothermic



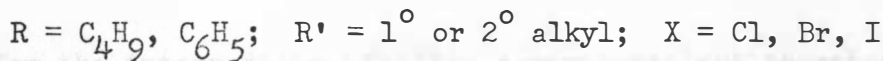
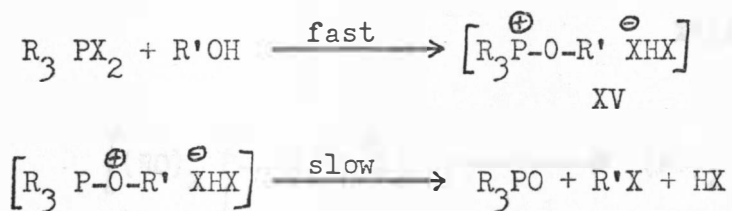
reactions at low enough temperatures to affect all the aforementioned deoxygenations was not pursued. The dichloro intermediate did react with *n*-butanol at -10° to produce *n*-butyl chloride.



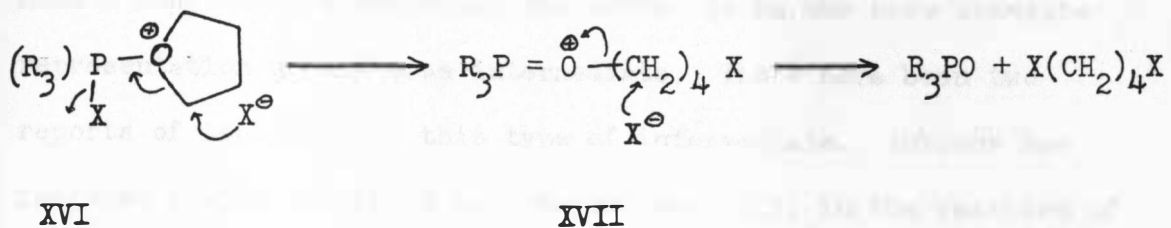
Iodine was added to a refluxing solution of bicyclic phosphite in benzene, and addition of piperidine to the resulting solution affected the formation of small amounts of the phosphoroamidate derivative (XIV). This indicated that the ring-opened phosphoriodate (XIII) is present. Hence the phosphonium diiodide intermediate may form, but probably ring opens immediately to produce the phosphoriodate molecule.



The mechanisms of some of these deoxygenation reactions have been studied. Wiley and co-workers have suggested a rather concerted path for their phosphine dihalide deoxygenations (9). Evidence for the proposed intermediate (XV) was supported by NMR. Wiley suggested



other possible mechanisms, and eliminated them on the basis of his experimental observations. He proposed one mechanism similar to that which we will later propose. The collapse from (XVI) to (XVII) seemed logical. Tetrahydrofuran, however, was not cleaved by Eiley's reagents.



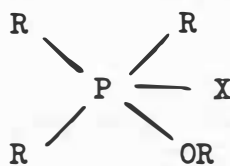
The Arbuzov reaction, which trivalent phosphines cannot undergo, is involved in the reactions utilizing phosphites and their dihalides. The general Arbuzov reaction offers a specific example of nucleophilic attack by trivalent phosphorus (11). The generally accepted mechanism proceeds in two stages. The first stage involves bimolecular attack by phosphorus at the alkyl halide to form the alkoxyphosphonium ion (XVIII). The second step involves dealkylation of the alkoxyphosphonium ion by an S_N2 mechanism. Two structures have been suggested



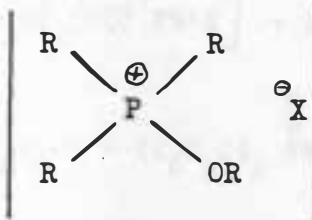
XVIII



for the intermediate (XVIII)--a pentacovalent phosphorus (V) compound (XIX), and an ionic pair phosphonium compound (XX) (14). Dipole

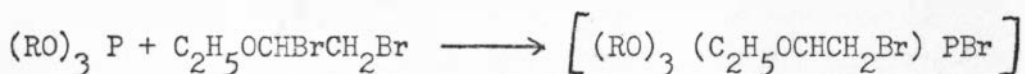


XIX

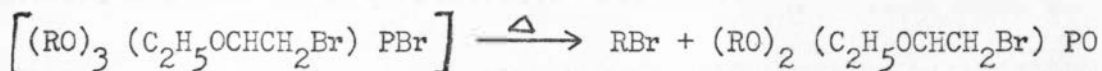


XX

moment studies have suggested the latter to be the more accurate representation of the true intermediate. There have been two reports of isolation of this type of intermediate. Abramov has isolated a viscous oil as an intermediate (XXI) in the reaction of a dihalo ether with trimethoxy phosphite (15). Landauer has reported



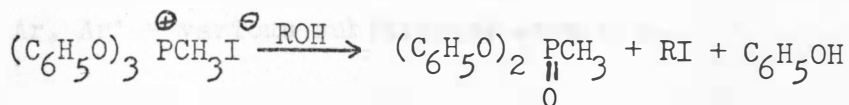
XXI



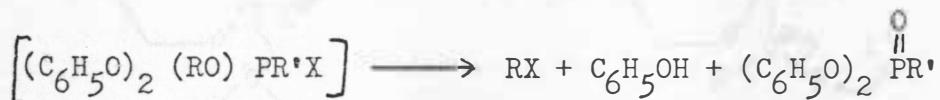
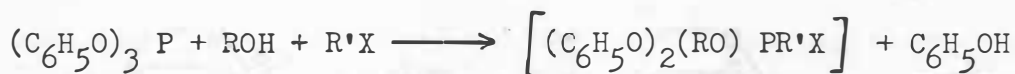
the preparation of triphenylphosphine methiodide (XXII) and isolated the product as needle-like crystals (16). The product is stable when kept in a vacuum desiccator. Landauer further suggests that



XXII



the Arbuzov reaction involving aryl phosphites may proceed via an "S₂" mechanism involving ester interchange (16). The possibility of



that particular component in the sample injected, and therefore in the reaction solution. The total volume of a component was then obtained by multiplying the percent volume of the component times the total volume of the reaction solution. The weight of the component was then calculated as the product of the volume times the density of the compound. The percent yield was then obtained as the quotient of the weight of the compound divided by the calculated theoretical yield.

4-Methyl-2,6,7-trioxa-1-phosphabicyclo(2.2.2)octane (Methyl bicyclic phosphite)

Into a 500 ml three-necked 19/22 standard taper flask was placed 2-hydroxyethyl-2-methyl-1,3-propanediol (120 g, 1.0 mole), triethyl phosphite (166 g, 1.0 mole), and triethyl amine catalyst (1 ml). The flask was set up for distillation and heating was begun via a Glas-Col heating mantle and variac set at 45 volts. The contents were stirred by a magnetic stirrer and stirring bar. As the pot temperature rose, the diol dissolved in the phosphite, and ethanol began to distill off when the temperature reached 100°C. The distillation continued for about seven hours, at which time the pot temperature had reached 140° and 94 percent (170 ml) of the theoretical quantity of alcohol had been collected. Upon cooling, the contents of the reaction flask turned to a white solid. The flask was then set up for vacuum distillation, using either a short air condenser, or a direct take-off from the distillation head to the vacuum adapter, and using a 250 ml 19/22 standard taper flask as the receiving flask, which was

kept cool throughout the distillation via an ice water bath. The solid sublimed over at 75° - 90° C. and 0.15-0.20 mm Hg. The sublimed bicyclic phosphite was recovered in 86.5 percent yield (128 g), and melted at 91° - 93° . It was stored in a desiccator over CaCl_2 to prevent hydrolysis of the phosphite to form the bicyclic phosphate.

4-Ethyl-2,6,7-trioxa-1-phosphabicyclo(2.2.2)octane (Ethyl Bicyclic Phosphite)

Into a 500 ml three-necked 19/22 standard taper flask was placed 2-hydroxymethyl-2-ethyl-1,3-propanediol (134 g, 1.0 mole), triethyl phosphite (166 g, 1.0 mole), and triethyl amine catalyst (1 ml). The flask was set up for distillation and heating was begun via a Glas-Col mantle and variac set at 45 volts. The contents were stirred by a magnetic stirrer and bar. As the pot temperature rose, the diol dissolved in the phosphite, and ethanol began to distill off when the temperature reached 100° . The distillation continued for about seven hours, at which time the pot temperature had reached 140° and 98 percent (175 ml) of the theoretical amount of alcohol had been collected. Upon cooling, the contents of the reaction flask turned to a pale white solid. The flask was set up for vacuum distillation, using either a short air condenser, or a jacketed condenser fitted to a steam line to keep the column hot. A 250 ml 19/22 standard taper flask was used as the receiving flask, and it was kept cool by means of a cold water bath. The solid distilled over at 69° - 74° and 0.1-0.3 mm Hg. The distilled phosphite was recovered in

94 percent yield (152 g), and melted at 51-52°. It was stored in a desiccator over CaCl_2 to prevent hydrolysis to the bicyclic phosphate.

1-Ethyl-4-phosphonia-3,5,8-trioxabicyclo (2.2.2) octane dibromide

Ethyl bicyclic phosphite (5.6 g, 0.04 mole) was dissolved in 100 ml methylene chloride in a three-necked 22/40 standard taper flask, and the solution was cooled to -5° by means of a salt-ice bath. To this was added, with stirring, bromine (6 g, 0.04 mole). A pale yellow precipitate formed in the flask as the bromine was added at the cold temperature, and it was filtered via suction filtration after completion of bromine addition. The isolated solid decomposed while standing in air, however, giving off HBr gas and also some elemental bromine. Storage in a vacuum desiccator enabled the solid to be kept longer, but it still seemed to slowly decompose upon standing at room temperature for a couple days. No yield or melting point were determined.

Ethyl bicyclic phosphate

To a solution of ethyl bicyclic phosphite (7.0 g, 0.05 mole) in 50 ml benzene in 100 ml a single-neck 19/22 standard taper flask was added bromine (8.0 g, 0.05 mole) from a dropping funnel while the temperature was kept below 10° by an ice bath, and the reaction solution was stirred via a magnetic stirrer and bar. A yellow precipitate formed, and after completion of the bromine addition

ten ml water was added to the flask. The yellow solid immediately dispersed, and there remained after the reaction a white precipitate in the benzene solution. It was filtered off via suction, and recrystallized from isopropyl alcohol. Yield: 5.3 g, 75 percent; m.p. 205° - 207° .

1-Methyl-4-phosphonia-3,5,8-trioxabicyclo-(2.2.2)octane dibromide

Methyl bicyclic phosphite (10 g, 0.07 mole) was dissolved in 200 ml benzene in a three-necked 22/40 standard taper flask, and the contents cooled to 5° by means of an ice bath. The solution was stirred with a magnetic stirrer and bar, and bromine (11.2 g, 0.07 mole) was added to it dropwise from a dropping funnel. A pale yellow precipitate appeared immediately as the bromine entered the solution, and after completion of bromine addition, the precipitate was filtered via suction filtration. The isolated solid decomposed upon standing in air, giving off HBr gas and some elemental bromine. Storage in a vacuum desiccator preserved the product for a couple days, but decomposition eventually occurred. No yield or melting point were determined.

Methyl bicyclic phosphate

To a solution of methyl bicyclic phosphite (5 g, 0.04 mole) in 50 ml methylene chloride in a 250 ml single-neck 19/22 standard taper flask was added bromine (6 g, 0.04 mole) from a dropping funnel while the temperature was kept below 0° by means of a salt-

ice bath. A yellow precipitate formed, and while it was stirred by a magnetic stirrer and bar, ten ml water was added. A very exothermic reaction ensued during which the flask temperature rose from -10° to 40° in a matter of seconds, and the yellow compound dispersed. A small amount of white precipitate remained and was filtered via suction filtration. The solvent was stripped via Rinco evaporator, leaving a white solid. Both solids were recrystallized from isopropyl alcohol, and they both proved to be the bicyclic phosphate. Yield: 5.1 g, 91 percent; m.p. 251° - 253° .

2-Bromomethyl-2-methyl-1,3-propanediol-N-cyclopentylene phosphoramidate

Methyl bicyclic phosphite (10.0 g, 0.07 mole) was dissolved into 150 ml dry ether in a three-necked 22/40 standard taper flask, and the solution was cooled to -10° by means of a salt-ice bath. To this solution bromine (11.2 g, 0.07 mole) was added dropwise from a dropping funnel while the contents of the reaction flask were stirred continuously via a magnetic stirrer and bar, and kept below 0° . The solution was then brought to room temperature, and to it was added a solution of piperidine (12 g, 0.14 mole) in fifty ml ether. The resulting solution was stripped of solvent via Rinco evaporator. The residue was washed with fifty ml water to dissolve the amine salt, and the solid separated via suction filtration. This solid phosphoramidate was recrystallized twice from heptane. Yield: 0.9 g, 4 percent; m.p. 138° - 141° .

2-Bromomethyl-2-ethyl-1,3-propanediol-N-cyclopentylene phosphoramidate

Ethyl bicyclic phosphite (22 g, 0.14 mole) was dissolved into 300 ml ether in a three-necked 19/22 standard taper flask, and the solution was cooled to -10° by means of a salt-ice bath. To this solution bromine (22 g, 0.14 mole) was added dropwise from a dropping funnel while the contents of the reaction flask were stirred continuously via a magnetic stirrer and bar, and kept below 0° . The solution was then brought to room temperature, and to it was added a solution of piperidine (23.5 g, 0.28 mole) in fifty ml ether. The resulting solution was stripped of solvent via Rinco evaporator, and the residue washed with fifty ml of water to dissolve the amine salt. The insoluble solid was filtered from the water solution by suction filtration, and was recrystallized three times from heptane. Yield: 3.0 g, 16 percent; m.p. 155.5° - 156.5° .

2-Iodomethyl-2-ethyl-1,3-propanediol-N-cyclopentylene phosphoramidate

Ethyl bicyclic phosphite (7.1 g, 0.05 mole) was dissolved in 350 ml benzene in a three-necked 500 ml 19/22 standard taper flask, and the contents were heated to x reflux. Iodine (13 g, 0.05 mole) was added to the refluxing solution in small portions over a period of one hour, and the resulting purple solution was allowed to continue refluxing for an additional five hours. Piperidine (20 g, 0.21 mole) was then added to the hot solution. The solution was cooled, and the amine salt was filtered via suction. The benzene

solvent was stripped via Rinco evaporator, and the residue recrystallized twice from heptane. Yield: 1.55 g, 8.4 percent; m.p. 98-102°. Calculated for $C_{11}H_{21}IO_3NP$: C, 35.6; H, 5.12; N, 3.78. Found: C, 35.34; H, 6.56; N, 3.77.

2-Iodomethyl-2-methyl-1,3-propanediol-N-cyclopentylene phosphoramidate

Methyl bicyclic phosphite (7.0 g, 0.05 mole) was dissolved in 350 ml benzene in a three-necked 500 ml 19/22 standard taper flask, and the contents were heated to reflux. Iodine (13 g, 0.05 mole) was added to the refluxing solution in small portions over a period of one hour, and the resulting purple solution was allowed to continue refluxing for an additional five hours. Piperidine (20 g, 0.21 mole) was then added to the hot solution. The solution was cooled, and the amine salt was filtered via suction. The benzene solvent was stripped via Rinco evaporator, and the residue recrystallized twice from heptane. Yield: 1.2 g, 6.7 percent; m.p. 116-118°. Calculated for $C_{10}H_{19}IO_3NP$: C, 37.4; H, 5.46; N, 3.64. Found: C, 33.88; H, 5.56; N, 3.95.

n-Butyl bromide from n-butanol

Ethyl bicyclic phosphite (16.8 g, 0.12 mole) was dissolved in 150 ml methylene chloride in a 250 ml three-necked 22/40 standard taper flask and cooled to -10° via a salt-ice bath. The solution was stirred with a magnetic stirrer and bar, and bromine (18 g, 0.12 mole) was added dropwise from a dropping funnel. The solution

was kept below 5°C . during addition, and the yellow solid phosphonium dibromide product formed in the solution. After the halogen addition, n-butanol (11.1 ml, 9.0 g, 0.12 mole) was added in small portions. As the alcohol was added the yellow dibromide began to dissipate and a gentle exothermic reaction took place, with the temperature rising from 0° to 20° during the addition. After the alcohol addition was completed, about 120 ml of the solvent was distilled off. As the residue solution was cooled a white precipitate came out and was filtered off via suction. It proved to be bicyclic phosphate. Yield: 14 g, 67 percent; m.p. 199° - 202° . The filtrate was then analyzed for the presence of n-butyl bromide via gas chromatography on the Beckman GC-2A Gas Chromatograph. Standard reference solvents were used to compare peaks, and it was found that the desired alkyl halide was indeed present. The yield was calculated as previously described. Yield: 10.81 g, 67 percent.

Reaction of the phosphonium dibromide with t-butanol

Ethyl bicyclic phosphite (3.5 g, 0.025 mole) was dissolved in sixty ml benzene in a one-neck 100 ml 19/22 standard taper flask. The solution was stirred by a magnetic stirrer and bar, and was cooled to 0° by an ice bath. Bromine (4 g, 0.025 mole) was added dropwise from a dropping funnel, and the yellow solid phosphonium dibromide immediately formed in the solution. To the suspension of dibromide in benzene was added at 5° t-butanol (7.4 g, 0.1 mole), and the yellow dibromide dispersed in about one minute, leaving a

clear solution with the white phosphate precipitate. The closeness of the boiling points of the alcohol and alkyl halide prevented their separation by gas chromatography, and so the solvents were stripped via Rinco evaporator, and the yield of the phosphate by-product was determined after it was recrystallized from propanol. Yield: 2.15 g, 55 percent; m.p. 202° - 205° .

Reaction of the phosphonium dibromide with neo-pentyl alcohol

Ethyl bicyclic phosphite (3.5 g, 0.025 mole) was dissolved in fifty ml benzene in a one-neck 100 ml 19/22 standard taper flask, and cooled to 5° by an ice bath. The solution was stirred by a magnetic stirrer and bar, and to it was added bromine (4 g, 0.025 mole) from a dropping funnel. The yellow phosphonium dibromide formed in the solution upon halogen addition, and after completion of addition, neo-pentyl alcohol (6.6 g, 0.075 mole) was added to the yellow suspension. The dibromide immediately dissipated, leaving a clear solution with some of the white phosphate precipitate. The solution was analyzed for components by gas chromatography, but no identifiable peaks were evident. It was suspected that the alcohol cleavage by the dibromide had also resulted in further rearrangements and/or eliminations characteristic of a neo-pentyl system. The solution was then stripped of solvent via Rinco evaporator, and the phosphate residue recrystallized from propanol. Yield: 1.75 g, 45 percent; m.p. 199° - 201° .

t-Butyl chloride from t-butanol

Ethyl bicyclic phosphite (3.5 g, 0.025 mole) was dissolved in 100 ml hexane in a three-necked 22/40 standard taper flask. The solution was stirred via magnetic stirrer and bar, and cooled to -10° by a salt-ice bath. Dry chlorine gas was passed through the cold solution very slowly until the solution turned a characteristic green color indicating excess halogen. The chlorine was passed through concentrated sulfuric acid and CaCl_2 before entering the reaction flask to insure dryness. The addition of chlorine to the flask resulted in the formation of a white solid, which seemed to disperse into solution as excess halogen was added. To this solution was added t-butyl alcohol (3.5 g, 0.05 mole) at 7° . Any white solid left in the solution disappeared immediately upon alcohol addition, and the contents were then allowed to come to room temperature. Analysis for t-butyl chloride by the Beckman GC-2A Gas Chromatograph proved positive. All solvents were then stripped via Rinco evaporator, and the extent of the reaction was determined by the yield of solid phosphate residue remaining. Recrystallization of this residue from propanol gave the following: Yield: 0.8 g, 20.5 percent; m.p. 200° - 202° .

n-Butyl bromide from n-butyl ether

To sixty ml of n-butyl ether in a one-neck 100 ml 19/22 standard taper flask was added ethyl bicyclic phosphite (7 g, 0.05 mole). The

solution was cooled to 10° via an ice bath, and stirred by means of a magnetic stirrer and bar. To this solution bromine (8 g, 0.05 mole) was added dropwise from a dropping funnel. As the bromine was added, the yellow phosphonium dibromide formed, but then began to dissipate in a short time as it reacted with the ether solvent. After the completion of bromine addition, the contents of the flask were stirred for an hour at 0° , and then allowed to come to room temperature. Any white phosphate precipitate that had formed was filtered out via suction, and the filtrate was then distilled and a fraction of 13 ml was collected from 85° - 110° . This distillate was analyzed for alkyl halide using the Beckman GC-2A Gas Chromatograph. Reference solvents were used, and the presence of the desired alkyl halide was confirmed. The yield was calculated as previously described. Yield: 5.0 g, 37 percent.

1,4-Dibromobutane from tetrahydrofuran

To sixty-five ml tetrahydrofuran in a one-neck 100 ml 19/22 standard flask was dissolved ethyl bicyclic phosphite (7 g, 0.05 mole), and the solution was stirred by a magnetic stirrer and bar and cooled to 5° by an ice bath. Bromine (8 g, 0.05 mole) was then added dropwise from a dropping funnel, with the temperature being kept below 10° during addition. The yellow phosphonium dibromide formed immediately upon halogen addition, but slowly dispersed as the ether cleavage took place. After about two hours of stirring at 0° the solution was clear, and it was then allowed

to come to room temperature, and the flask set up for distillation. About fifty ml of the solvent was taken off by distillation, and upon cooling the residue, a small amount of white phosphate came out of solution, and was filtered off via suction. The filtrate was analyzed on the Beckman GC-2A Gas Chromatograph, and comparison of the chromatograph with that of reference solvents confirmed the presence of the alkyl dibromide. The yield was calculated as previously described. Yield: 7.9 g, 73 percent.

n-Butyl bromide from ethylbutyl thioether

Ethyl bicyclic phosphite (7 g, 0.05 mole) was added to a solution of ethylbutyl thioether (8.8 g, 0.075 mole) in fifty ml benzene in a 100 ml 19/22 standard taper flask. The solution was cooled below 10° by means of an ice bath, and was stirred by a magnetic stirrer and bar. Bromine (8 g, 0.05 mole) was added dropwise from a dropping funnel to this cold solution, and the yellow solid phosphonium dibromide formed immediately upon addition. This solid slowly began to react, and after the solution had been stirred in the cold for two hours it was allowed to come to room temperature. Any solid thiophosphate that had precipitated out of the benzene was filtered off via suction, and the resulting solution was analyzed for butyl bromide via the Beckman GC-2A Gas Chromatograph. Analysis proved positive, and the yield of alkyl bromide was calculated as previously described. Yield: 6.8 g, 100 percent.

1,2-Dibromoethane from dioxane

Ethyl bicyclic phosphite (7 g, 0.05 mole) was dissolved in sixty ml of dioxane in 100 ml 19/22 standard taper flask and cooled to 5° by an ice bath. The solution was stirred by a magnetic stirrer and bar, and bromine (8 g, 0.05 mole) was added dropwise from a dropping funnel. The yellow phosphonium dibromide intermediate appeared and slowly disappeared over a period of two hours of stirring in the cold. The flask was then set up for distillation, and about forty ml of dioxane were taken off. The solid phosphate that had precipitated from the remaining residue was filtered off via suction, and the filtrate was analyzed for the dibromo alkane by the Beckman GC-2A Gas Chromatograph. The alkyl dibromide presence was confirmed by comparison with a standard. Yield was calculated as previously described. Yield: 7.94 g, 84.6 percent.

1,2-Dibromo propane from propylene oxide

Ethyl bicyclic phosphite (3.4 g, 0.025 mole) was dissolved in fifty ml propylene oxide in a one-neck 100 ml 19/22 standard taper flask, and the solution was cooled to 0° by an ice bath. The solution was stirred by a magnetic stirrer and bar, and to the cold solution was added bromine (4 g, 0.025 mole) slowly from a dropping funnel. The yellow phosphonium dibromide formed upon halogen addition, and slowly dispersed as reaction with the solvent occurred. No more precipitate was evident after five minutes, but the solution

was stirred for an hour at 0° . The flask was then set up for distillation, and about forty ml of solvent were distilled. The residue was cooled to room temperature, and the solid white phosphate, which had precipitated out, was filtered by suction. The filtrate was analyzed by gas chromatography on the Beckman GC-2A Gas Chromatograph, and comparison of its chromatograph with that of reference propane dibromide indicated the presence of the alkyl dibromide as one of the reaction products. The yield of dibromide was calculated as previously described. Yield: 5.00 g, 98 percent. The solid phosphate residue was also weighed. Yield: 3.6 g, 93 percent.

1,2-Dibromocyclohexane from cyclohexene oxide

Ethyl bicyclic phosphite (7.0 g, 0.05 mole) and cyclohexene oxide (5.0 g, 0.05 mole) were dissolved in thirty ml benzene in a one-neck 100 ml 19/22 standard taper flask, and the solution was cooled to 5° by an ice bath. The solution was stirred by a magnetic stirrer and bar, and to it was added bromine (8.0 g, 0.05 mole) dropwise from a dropping funnel. The yellow phosphonium dibromide formed and slowly dissipated as it reacted with the oxide solvent. The contents were stirred for four hours in the cold, after which the solid phosphate was filtered off by suction, and the filtrate was analyzed for dibromocyclohexane. Chromatographic analysis on the Beckman GC-2A Gas Chromatograph indicated the presence of the dihaloalkane, and the yield was calculated as previously described.

Yield: 6.5 g, 54 percent. The solvent was then stripped off via Rinco evaporator, and the phosphate residue weighed. Yield: 6.0 g, 77 percent.

n-Butyl bromide and acetyl bromide from n-butyl acetate

To sixty ml of n-butyl acetate in a 100 ml one-neck 19/22 standard taper flask was added ethyl bicyclic phosphite (7 g, 0.05 mole), and the solution was stirred via magnetic stirrer and bar and cooled to 5° via an ice bath. Bromine (8 g, 0.05 mole) was then added dropwise from a dropping funnel to the solution, which was stirred continuously and kept below 10°. The yellow phosphonium dibromide formed upon the bromine addition, but slowly began to dissipate as the ester cleaved. The solution was kept cool and stirred for an hour after the solution had become clear of dibromide intermediate. The flask was then set up for distillation and 16 ml were distilled off, but little fractionation was evident as the head temperature varied. Both the distillate and residue were analyzed for presence of the alkyl halide and acid halide by gas chromatography on the Beckman GC-2A Gas Chromatograph, and comparison with the chromatograph of reference solvents confirmed their presence. The yields of the n-butyl bromide and acetyl bromide were calculated as previously described. The butyl halide and acetyl halide should have been formed in equal molar quantities, but some of the acid halide was lost in the distillation due to a faulty connection in the distillation apparatus. Yield: n-butyl

bromide: 6.53 g, 96 percent; acetyl bromide: 1.72 g, 41.5 percent.

1,1-Dibromoethane from acetaldehyde

Ethyl bicyclic phosphite (3.5 g, 0.025 mole) and acetaldehyde (1.5 g, 0.03 mole) were dissolved in fifty ml benzene in a one-neck 100 ml 19/22 standard taper flask, and the solution was cooled to 5° by an ice bath. The solution was stirred by a magnetic stirrer and bar, and to it was added bromine (4 g, 0.025 mole) dropwise from a dropping funnel. The reaction occurred over a period of thirty minutes, after which no more yellow phosphonium dibromide was apparent. The reaction mixture was then analyzed for the presence of dihaloalkane. Gas chromatographic analysis proved positive, and the yield was calculated as previously described. Yield: 1.77 g, 38 percent.

2,2-Dibromopropane from acetone

Ethyl bicyclic phosphite (3.5 g, 0.025 mole) and acetone (1.5 g, 1.9 ml, 0.025 mole) were dissolved in thirty ml benzene in a one-neck 100 ml 19/22 standard taper flask and the solution was cooled to 5° by an ice bath. The solution was stirred by a magnetic stirrer and bar, and to it was added bromine (4 g, 0.025 mole) dropwise from a dropping funnel. The reaction proceeded immediately as no dibromide intermediate appeared, and after completion of halogen addition the solution was stirred for half an hour in the cold, and then analyzed for dihaloalkane. Analysis

on the Beckman GC-2A Gas Chromatograph indicated the presence of 2,2-dibromopropane, and the yield was calculated as previously described. Yield: 1.56 g, 31 percent.

Styrene dibromide

Styrene (10.4 g, 0.10 mole) was dissolved in 100 ml methylene chloride in a 100 ml 19/22 standard taper flask. The solution was stirred by a magnetic stirrer and bar, and was cooled to 5° by an ice bath. To this cold solution bromine (16 g, 0.10 mole) was added dropwise from a dropping funnel, and after addition the solution was stripped of solvent by Rinco evaporator. There remained a solid residue which was recrystallized from propanol. Yield: 22 g, 85 percent; m.p. 70°-72°.

Styrene from styrene dibromide

Ethyl bicyclic phosphite (3.5 g, 0.025 mole) and styrene dibromide (7.5 g, 0.025 mole) were dissolved in sixty ml benzene in a 100 ml 19/22 standard taper flask, and the solution was stirred by a magnetic stirrer and bar for three days at room temperature. The contents were then analyzed for styrene by gas chromatography on the Beckman GC-2A Gas Chromatograph. Analysis and comparison with the chromatograph of pure styrene indicated that styrene was present in the reaction flask in very small amounts, proving that debromination had occurred to some extent by the phosphite acting as a Lewis base. The reaction solution was then refluxed for a

day, and the contents again analyzed. This time no styrene peak was evident. The solvent was stripped via Rinco evaporator, leaving a polymeric gummy solid which did not melt up to 255°C.

Cyclohexene from 1,2-dibromocyclohexane

Into a 100 ml one-necked 19/22 standard taper flask was placed ethyl bicyclic phosphite (3.5 g, 0.025 mole) and 1,2-dibromocyclohexane (6.05 g, 0.025 mole). The flask was set up for distillation, and heat was applied with a microburner. After about three minutes the two reagents coalesced into one miscible solution. Heating continued, and after about five minutes the contents of the flask began to reflux, and a slow takeoff was affected. A steady takeoff came over at a head temperature of 170-174°. Approximately ten ml of distillate was collected before the head temperature began to drop. The heat was then removed, and the distillate analyzed by gas chromatography for the presence of cyclohexene. Three major peaks were present, one of which was proved to be cyclohexene when compared to the chromatograph of a standard. The yield was calculated as previously described. Yield: 6.27 g, 76.5 percent.

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II. THE MECHANISM OF NUCLEOPHILIC SUBSTITUTION AT
 PHOSPHORUS: EVIDENCE FOR AN $S_N1(P)$ MECHANISM

The purpose of this section will be to summarize the chemistry of nucleophilic substitutions at phosphorus in phosphorus (V) compounds. There are three structural types of phosphorus (V) compounds: those of form (Ia) having trigonal bipyramidal geometry about the phosphorus atom; those having a square pyramidal geometry about the phosphorus atom (Ib); and the tetrahedral phosphorus compounds of forms (IIa) and (IIb). The latter include pentavalent



Ia



Ib



IIa

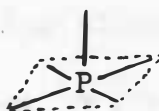


IIb

phosphorus compounds and phosphonium salts, respectively. These general forms will be discussed separately with respect to their electronic structure and the mechanism of nucleophilic substitution at the phosphorus atom. Westheimer's concept of pseudorotation in pentacovalent phosphate ester hydrolysis will also be fully discussed.

PENTACOVALENT PHOSPHORUS (V) COMPOUNDS OF TYPES Ia AND Ib

There are two possible structures for pentacovalent phosphorus (V) compounds. The square pyramid geometry (III) results from $d_{2-2P_xP_yP_z}^s$ hybridization. Compounds with this type of geometry



III

include $\text{Sb}(\text{C}_6\text{H}_5)_5$, $\text{P}(\text{C}_6\text{H}_5)_5$, and $\text{As}(\text{C}_6\text{H}_5)_5$ (1).

The trigonal bipyramid structure (IV) is formed by hybridizing a p_z orbital with a d_{z^2} orbital, and the resulting pd bonds interact with three sp^2 orbitals to form a trigonal bipyramid. The bonding in this structure is not equivalent. The axial (vertical) pd bonds

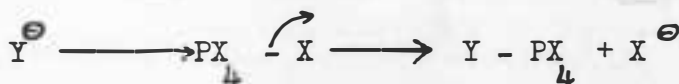


IV

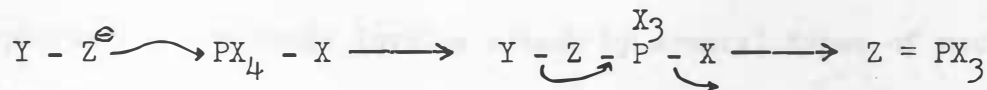
are longer and weaker than the equatorial (horizontal) sp^2 bonds. This has an important role in the mechanisms of nucleophilic substitution. Most pentacovalent phosphorus compounds are in this geometrical form.

There are three basic mechanisms suggested for nucleophilic substitution at pentacovalent phosphorus (2).

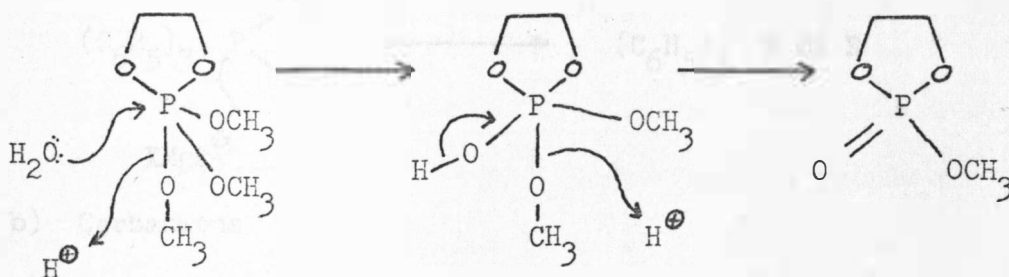
1. Direct displacement - $\text{S}_\text{N}2(\text{PX}_5)$ This involves a concerted displacement similar to the general $\text{S}_\text{N}2$ reaction in organic chemistry.



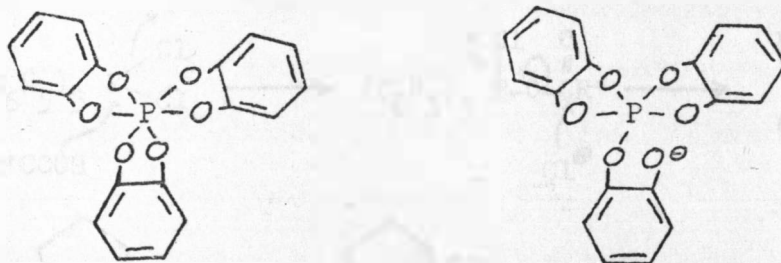
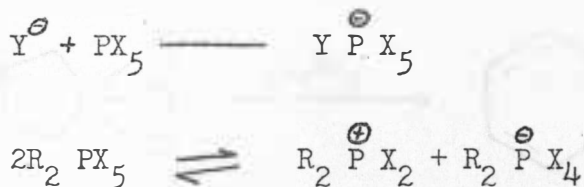
2. Displacement followed by elimination:



This reaction resembles a fast ester hydrolysis leading to an increase in pi-bond order at the phosphorus.

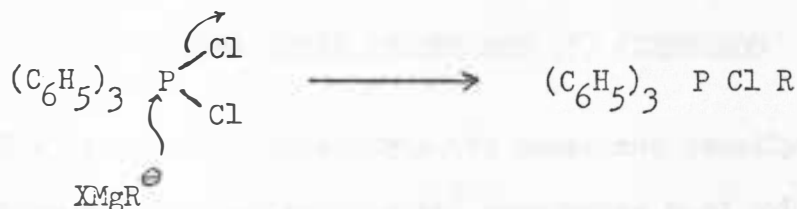


3. Addition. This mechanism has the phosphorus (V) compound acting as a Lewis acid reacting with anions to give the six-coordinate species.

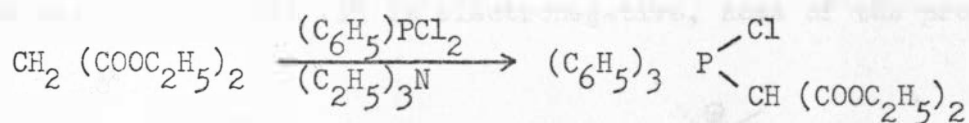


Specific examples of nucleophilic displacements at pentavalent phosphorus (V) compounds involve attack by several types of nucleophiles (2).

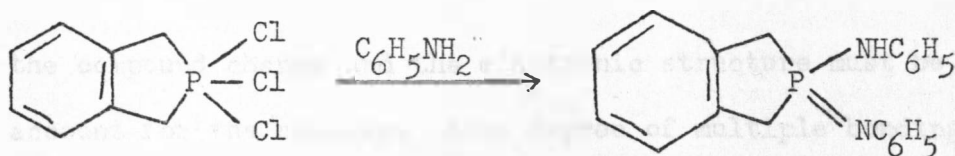
a) Grignard



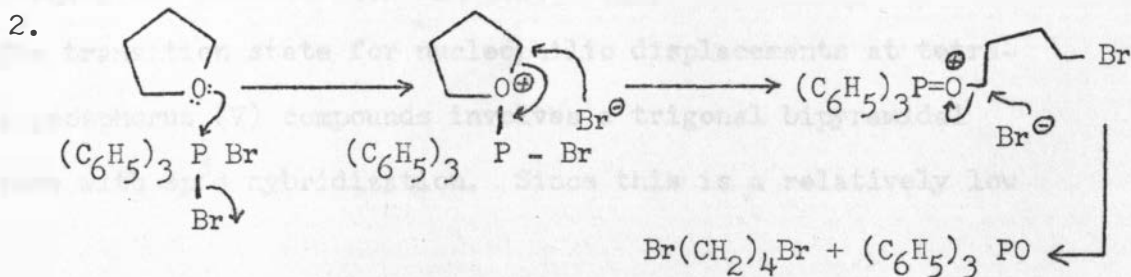
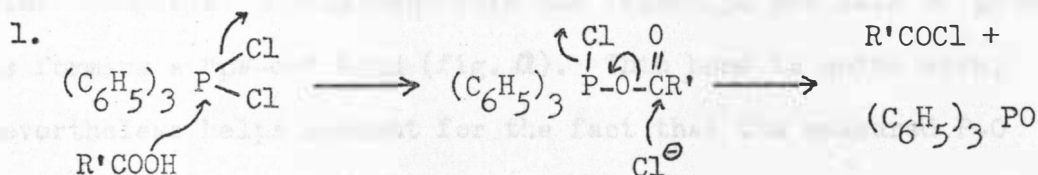
b) Carbanions



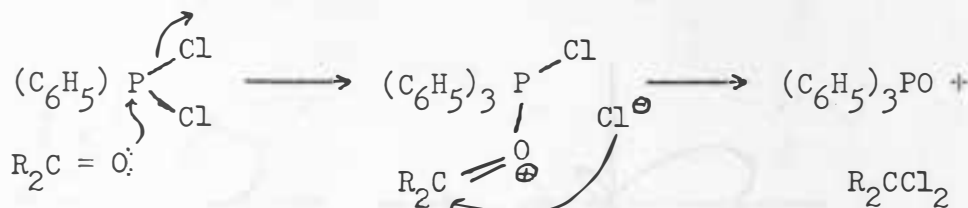
c) Nitrogen nucleophiles



d) Lewis Acids



3.



TETRAHEDRAL PHOSPHORUS (V) COMPOUNDS

The tetrahedral phosphorus (V) compounds usually provide four substituents arranged about a sp^3 phosphorus bond hybrid as a neutral molecule (V) or a phosphonium salt (VI). If one of the substituents in the neutral molecule (V) is electronegative, some of the properties



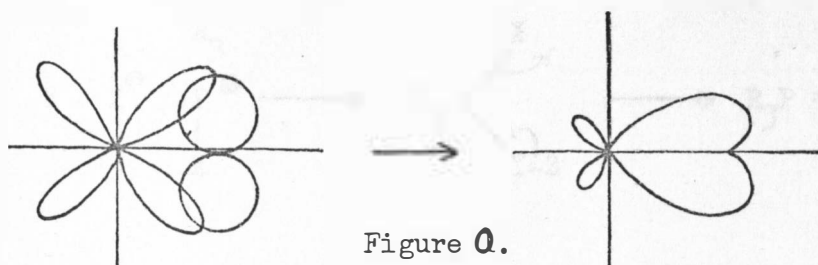
V



VI

of the compound change and the electronic structure must be modified to account for the changes. Some degree of multiple bonding is present, arising from the donation of non-bonding 2p electrons of the electronegative substituent into the vacant 3d orbitals of phosphorus forming a " $p\pi-d\pi$ " bond (fig. 2). This bond is quite weak, but nevertheless helps account for the fact that the measured P-O bond lengths are shorter than calculated (3).

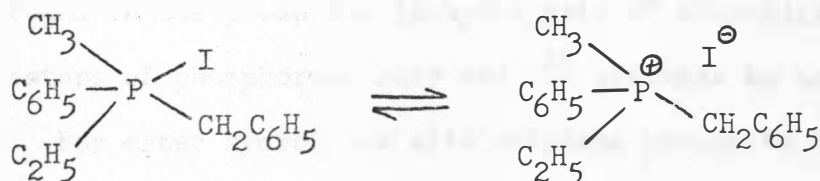
The transition state for nucleophilic displacements at tetrahedral phosphorus (V) compounds involves a trigonal bipyramidal structure with sp^3d hybridization. Since this is a relatively low



energy form of phosphorus (V), higher energy species will take advantage of any stabilization possible to form sp^3d electronic hybrids. Nucleophilic attack at the phosphoryl group is more dependant upon the bond to the leaving group. This is due to the fact that the bonds in the pentacovalent state involve d-orbitals and are weak (4).

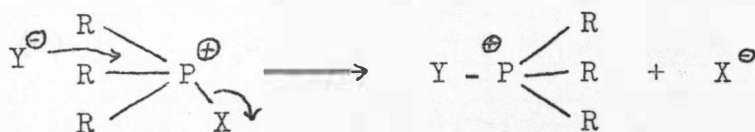
There are four mechanisms which have been noted in the study of nucleophilic attack at phosphorus in tetrahedral phosphorus compounds.

1. $S_N1(PX_5)$. These reactions are interpreted as nucleophilic attack on a positive phosphorus atom (5).

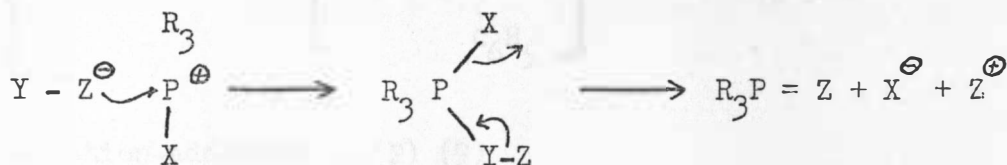


There are three paths of attack (6).

a) Direct displacement $S_N2(P^+)$



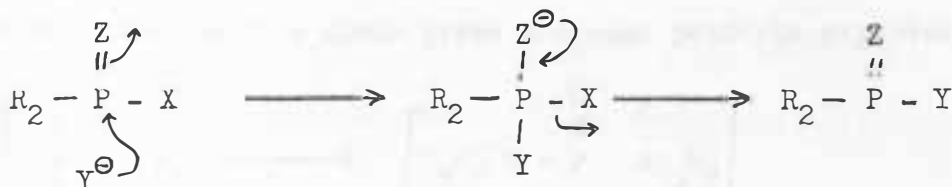
b) Addition-elimination



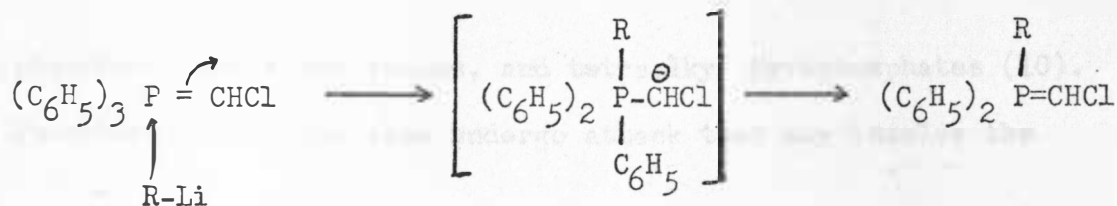
c) Addition



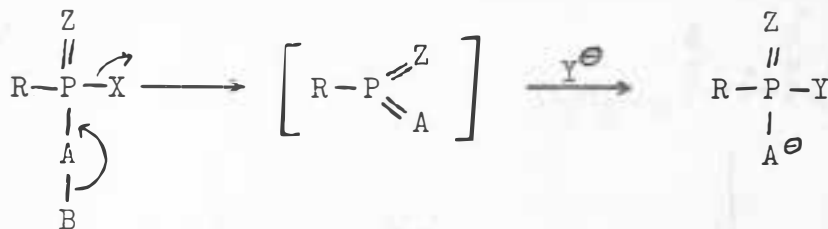
2. Addition-elimination (7)



In most cases this mechanism can be readily disproved by O^{18} exchange data. During the hydrolysis of carbonyl groups, oxygen atoms attached to the central carbon atom are equivalent and hence two atoms of O^{18} are found in the product. In hydrolysis of chlorides, fluorides, and esters of phosphorus, only one O^{18} attaches to the eventual product. For ester hydrolysis with ethylene phosphate the water leaving group must occupy equivalent positions due to parallel rate increases for O^{18} exchange with solvent and for ester hydrolysis. Alkyl-lithium addition has been known to proceed by the addition-elimination mechanism (8).

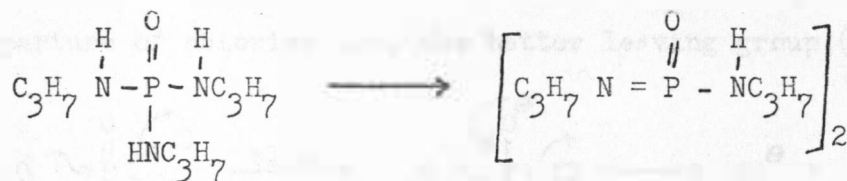


3. Elimination-addition $S_N1(P)$ (9)

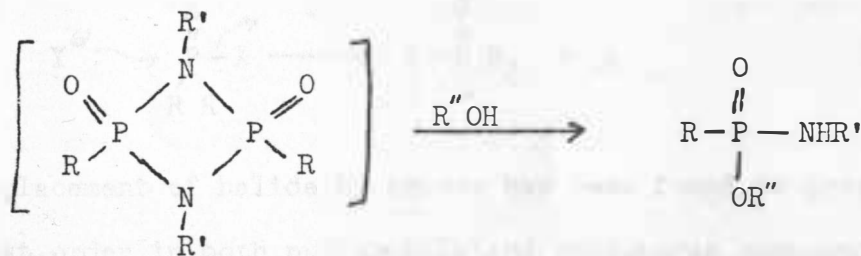


There is not much evidence for this pathway. The intermediate has not been isolated as a monomer, but rather as a dimer.

Nucleophilic attack on the dimer gives the same products expected

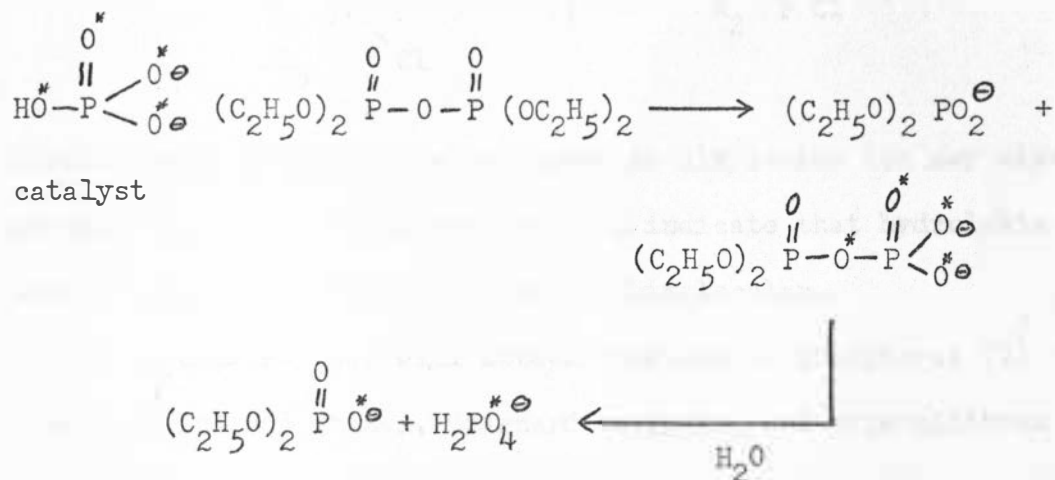


from the monomer. Nevertheless, it has been shown that the reaction does not proceed in a manner whereby the dimer first opens to form the monomer. Possible examples of $S_N1(P)$ mechanistic reactions involve reactions with phosphoramidates,

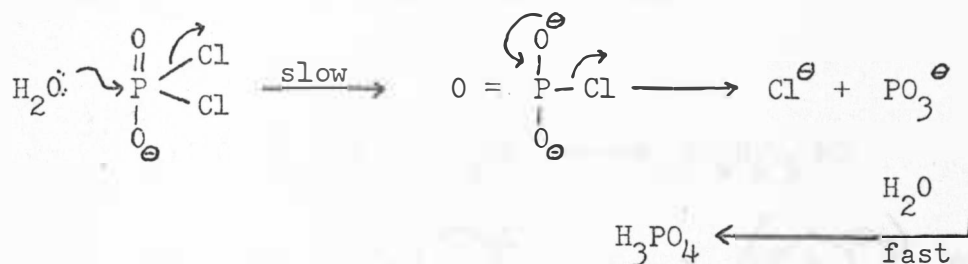


phosphonic monoester anions, and tetraalkyl pyrophosphates (10).

Phosphorochloridates also undergo attack that may involve the



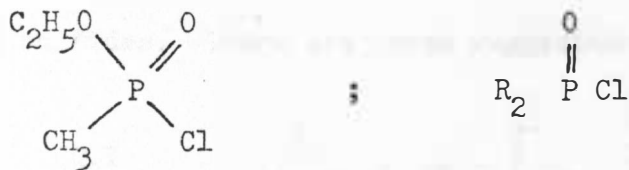
phosphonium ion. Since the chloro compound reacts faster than the fluoro, there must result in the mechanism a unimolecular departure of chloride ion, the better leaving group (11).



4. Direct displacement (11)

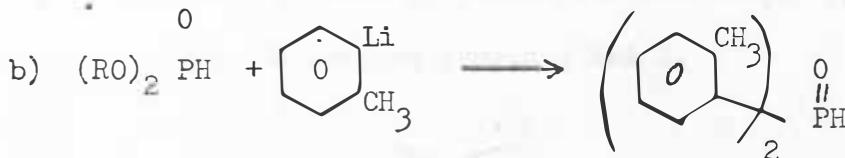
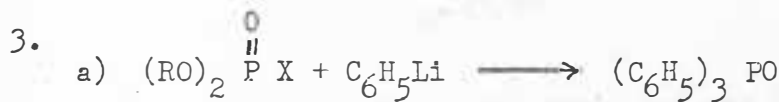
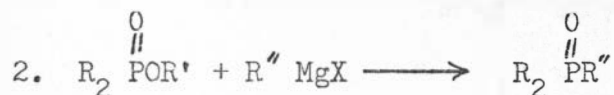
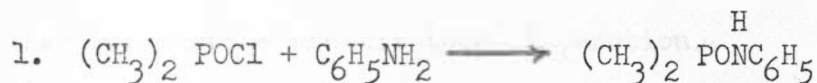


Displacement of halide by amines has been found to proceed as first order in both nucleophile and phosphorus compound. These include displacement in two kinds of phosphorus compounds.



Displacement of halides by hydroxide or alkoxide ion may also proceed directly, and solvent effects indicate that hydrolysis of the phosphorochloridate is closer to bimolecular.

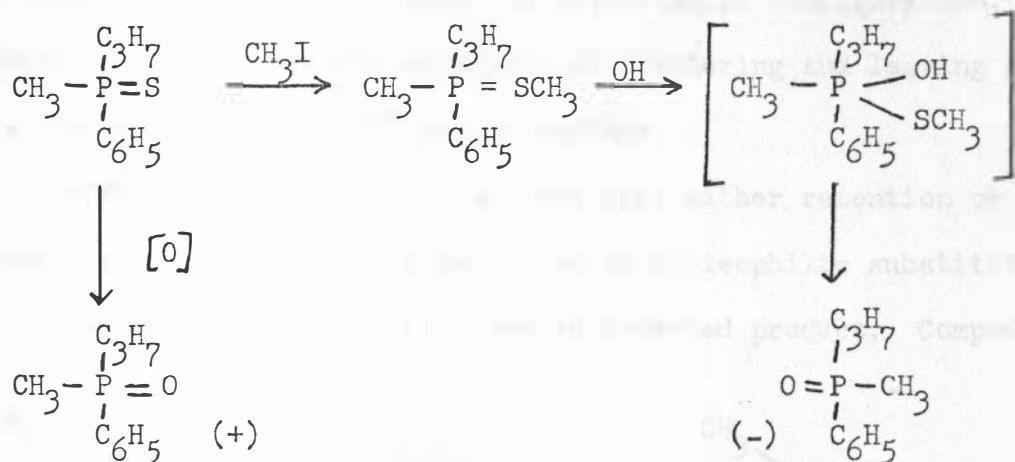
Nucleophiles that will attack tetrahedral phosphorus (V) compounds include amines, Grignard reagents, and organolithium compounds (12).



The stereochemistry of nucleophilic displacement at tetrahedral phosphorus compounds has been quite widely investigated. Examples of inversion, retention, and racemization have been discovered, although inversion dominates in most stereospecific reactions.

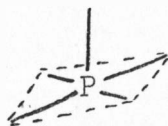
The nature of the transition state of the nucleophilic displacement has been determined by Horner and Winkler (13). They

discovered that alkylation and hydrolysis brought about inversion of phosphine sulfides. There are three suggested possibilities for



the transition state of this type of reaction.

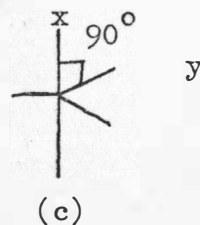
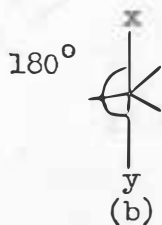
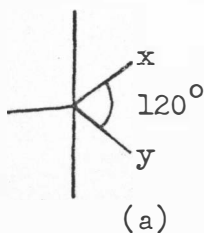
1. Square pyramid with $d_{x^2-y^2}, p_x, p_y, p_z$ hybrid.



2. Structure having three sp^2 bonds and two longer ($\frac{1}{4}sp^2-d_{xy}$) bonds to the entering and leaving groups A and B.

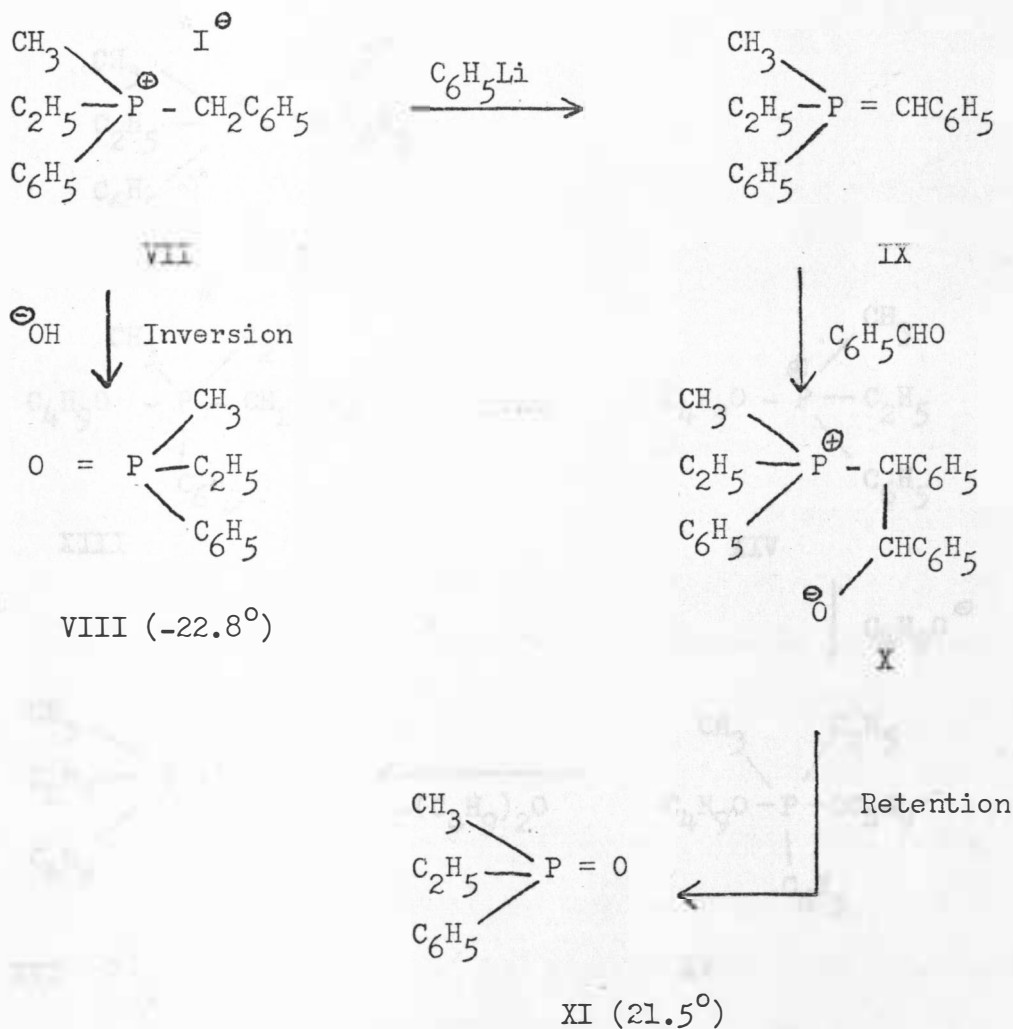


3. Trigonal bipyramid with entering and leaving groups in three possible orientations. This hybrid is made up of three sp^2

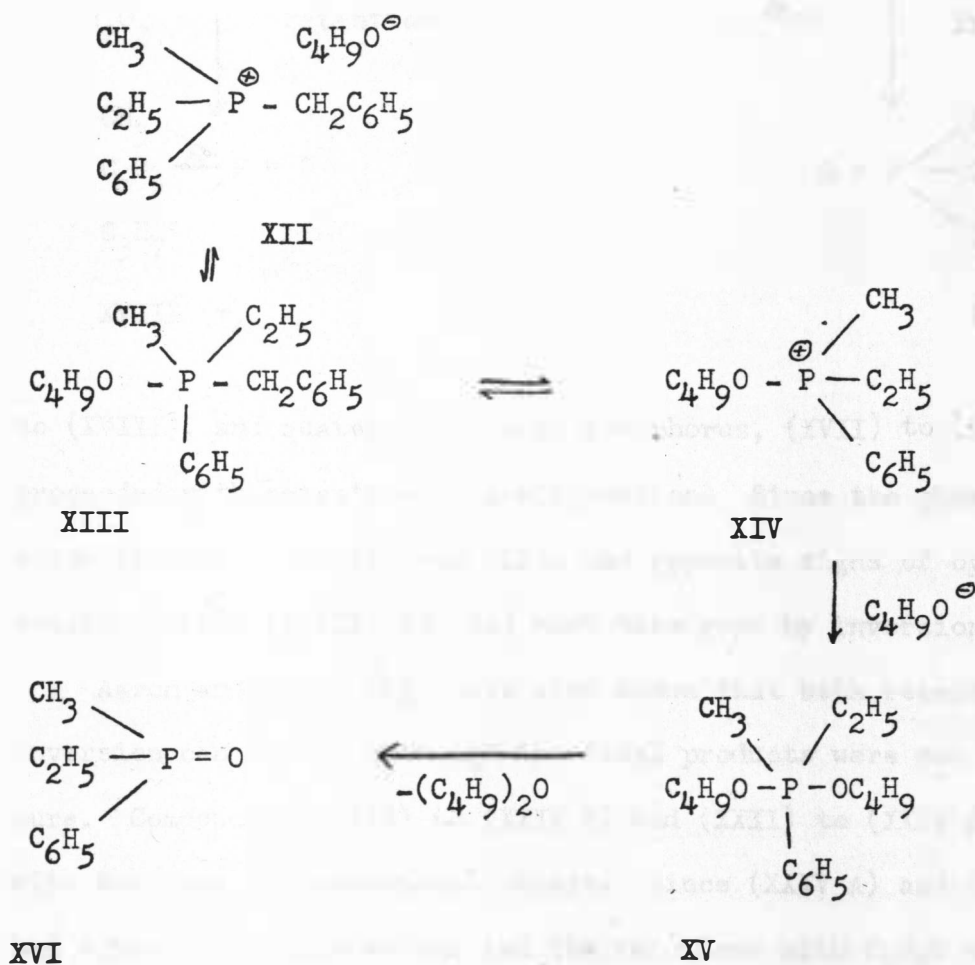


and two pd bonds. Horner rationalized that the transition state of the reaction could not involve structures of types 1. or 2. or 3c. because they should all result in retention of configuration. The state must be a trigonal bipyramid with entering and leaving groups at angles of 120° or 180° to one another.

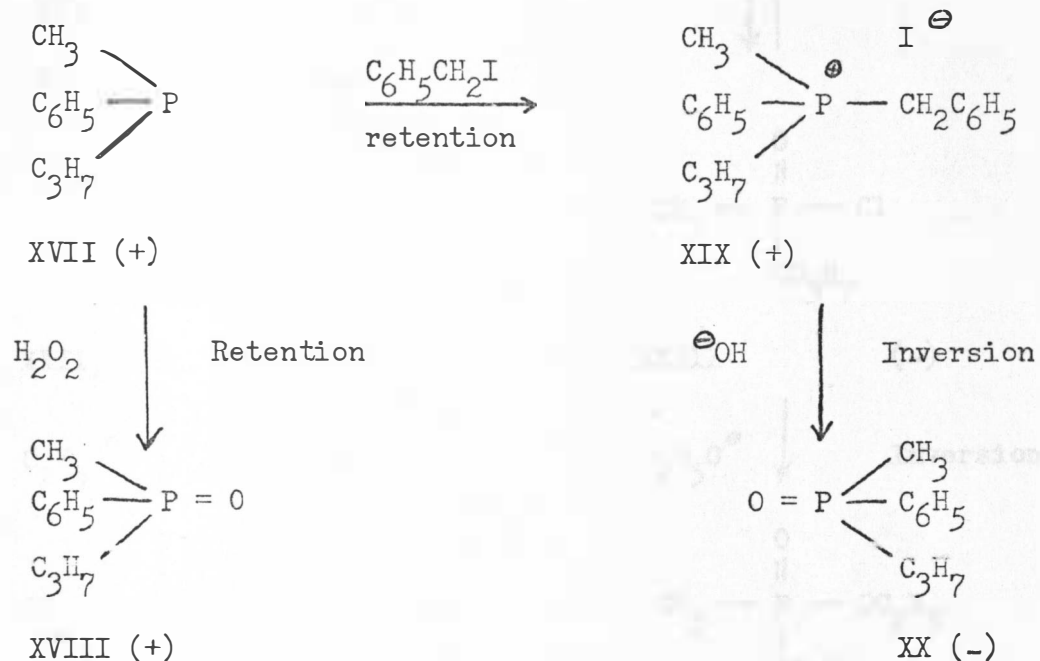
Hudson and Green (1) have shown that either retention or inversion can occur in the mechanism of nucleophilic substitution. As expected, (VII) to (VIII) gave an inverted product. Compound (XI)



was opposite in sign of optical rotation to (VIII). This change of sign showed that a positively charged phosphorus atom may undergo retention and inversion. The difficulty that arises due to racemization has been illustrated by Parisek (14). By using the logic of Hudson's work, product (XVI) was expected to have a configuration opposite that of (XII). It was found, however, to be 90 percent racemic, and was concluded that the racemization occurred in the alternate pathway (XIII) to (XIV) to (XV) to (XVI).

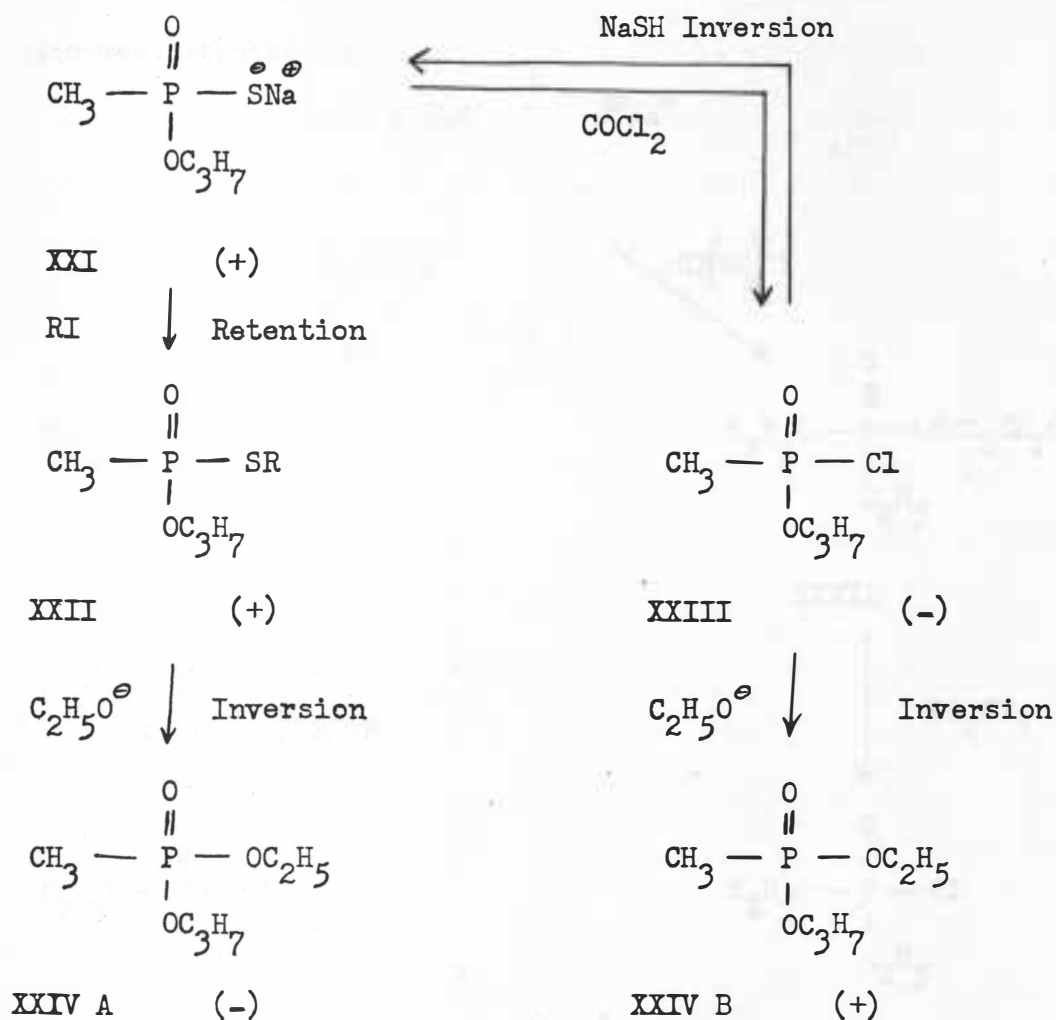


Hudson and Green (1) have found that reactions can be run to affect both retention and inversion. The nucleophilic substitution reaction goes by inversion. Reactions involving oxidation, (XVIII)



to (XVIII), and quaternization at phosphorus, (XVII) to (XIX), proceeded with retention of configuration. Since the phosphine oxide products, (XVIII) and (XX), had opposite signs of optical rotation, then (XVIII) to (XX) must have gone by inversion.

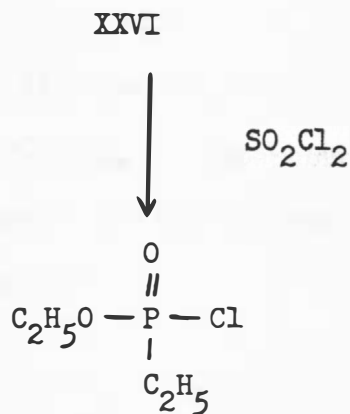
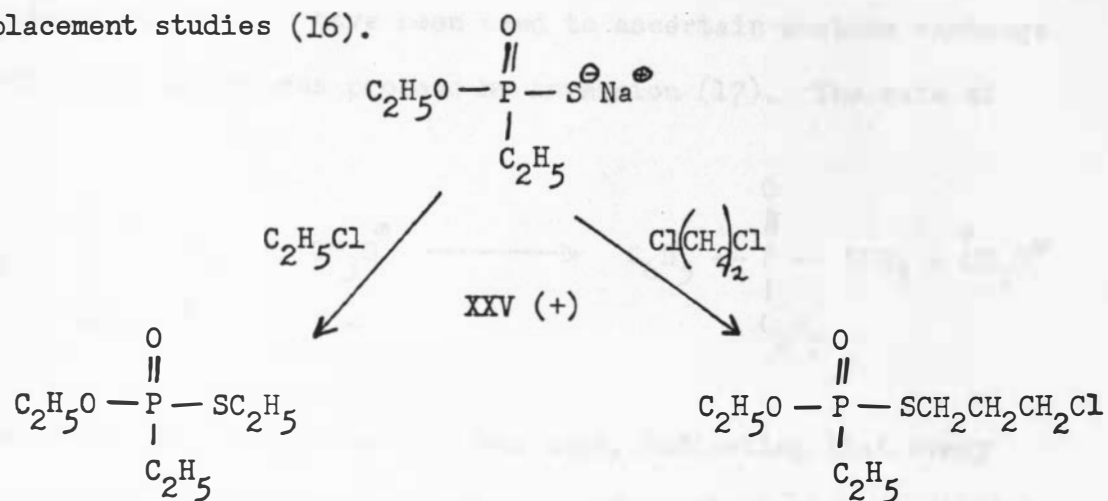
Aaron and Uyeda (15) have also shown that both retention and inversion can occur, although the final products were not optically pure. Compounds (XXIII) to (XXIV B) and (XXII) to (XXIV A) proceed with the same stereochemical change. Since (XXIV A) and (XXIV B) had opposite configurations and the reactions with $\text{C}_2\text{H}_5\text{O}$ should have given the same stereochemical changes, then (XXII) and (XXIII)



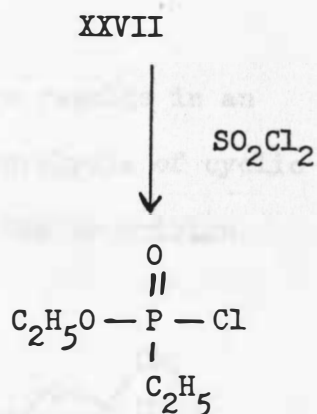
must have had opposite configurations. It was assumed that the conversion of (XXI) to (XXII) should have given retention since no phosphorus bonds were broken, and that (XXI) to (XXIII) proceeded by inversion since they had opposite configurations.

Michalski (16) has found that similar reactions do not always proceed with the same stereochemical changes. Both (+) and (-) isomers were obtained from two different thioates, (XXVI) and (XXVII), of the same configuration. This result is also evident in other

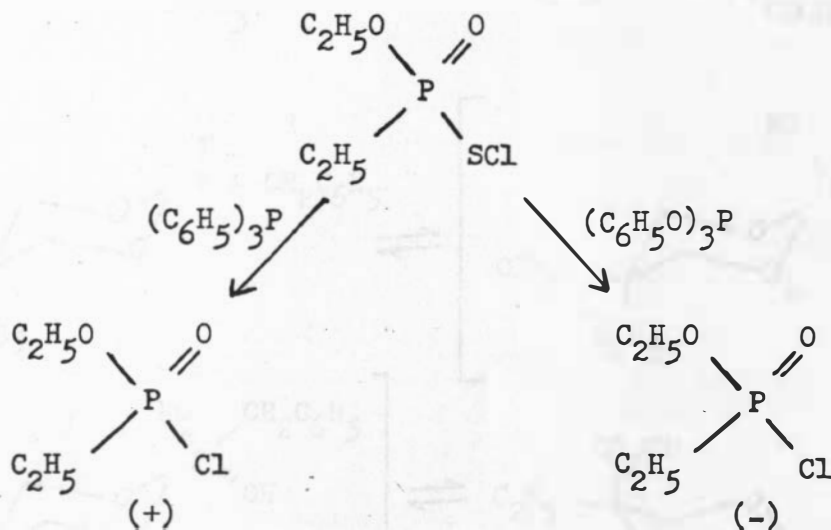
displacement studies (16).



XXVIII (-)



XXVIII (+)

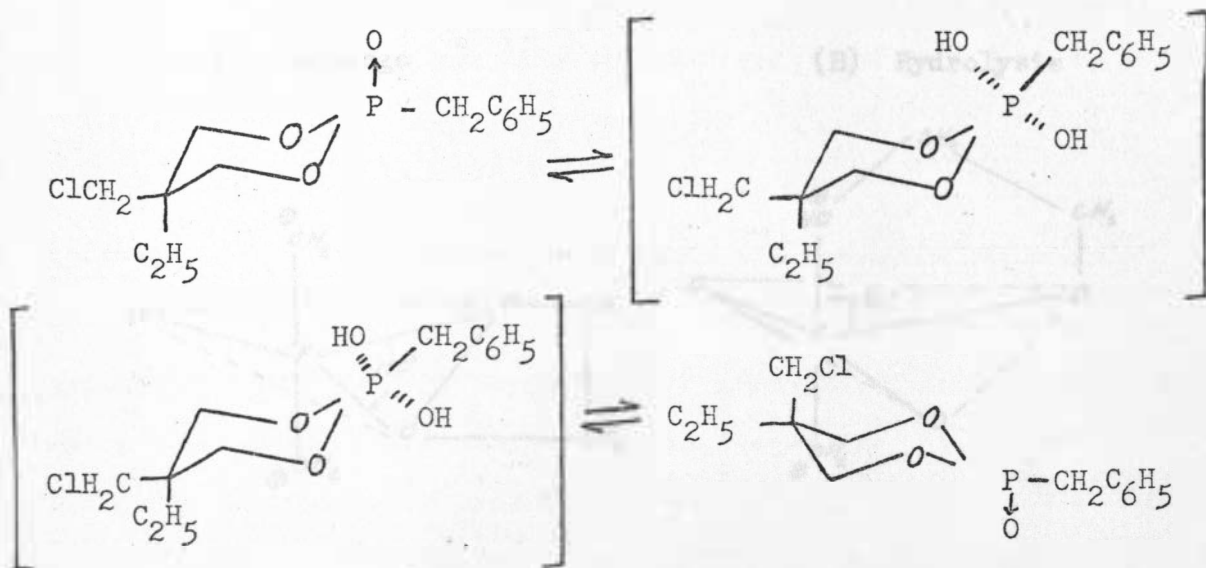
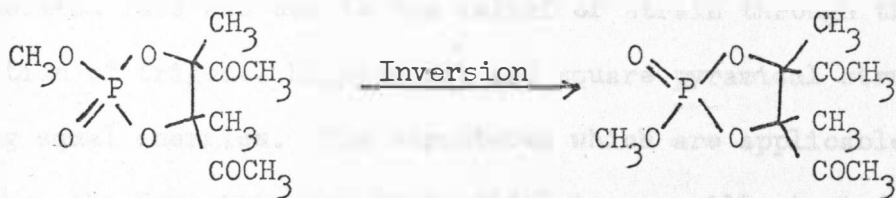


Labeling studies have been used to ascertain whether exchange reactions at phosphorus proceed by inversion (17). The rate of

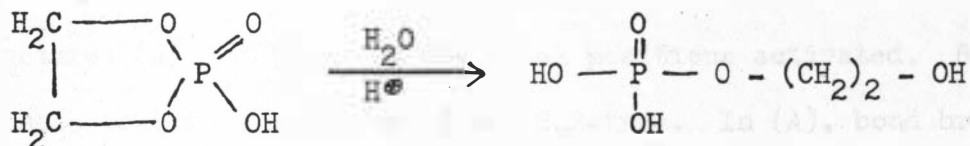


racemization was double that of exchange, indicating that every displacement reaction caused inversion of configuration about the phosphorus atom.

Stereomutation of cyclic phosphate esters results in an inversion about phosphorus (18). The acid hydrolysis of cyclic phosphate esters results in a mixture due to the transition state (19).

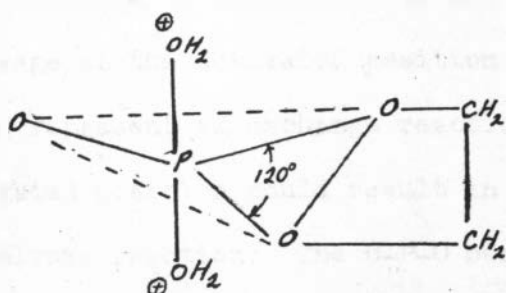


The work done by Westheimer and co-workers has proved interesting, and their postulation of the concept of pseudorotation is worthy of discussion. All the possible combinations of trigonal bipyramid and square planar structures result in six possible isomers. These structures were postulated by Haake and Westheimer as a result of experiments run on the acid catalyzed hydrolysis of phosphate esters (20). It was found that although O^{18} exchange occurred at almost the same rate in both phosphates,

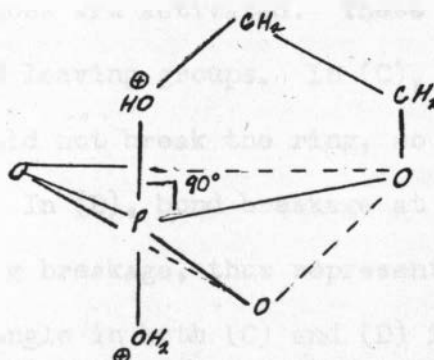


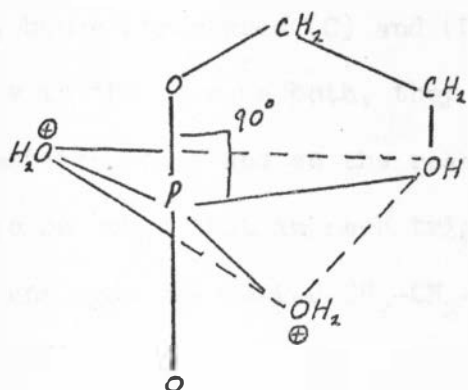
the cyclic phosphate underwent hydrolysis 10^8 times faster than the open chain analogue. The conclusion reached was that the accelerated rate was due to the relief of strain through the formation of trigonal bipyramidal and square pyramidal structures having equal energies. The structures which are applicable to our work are the four trigonal bipyramidal isomers illustrated below (21):

(A) Exchange

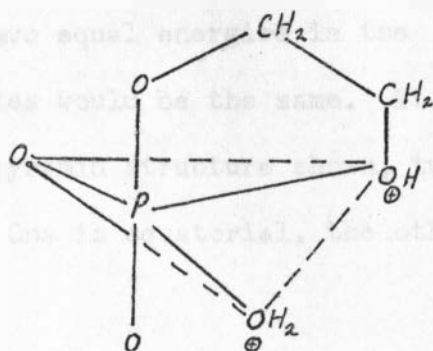


(B) Hydrolysis





(C) Exchange



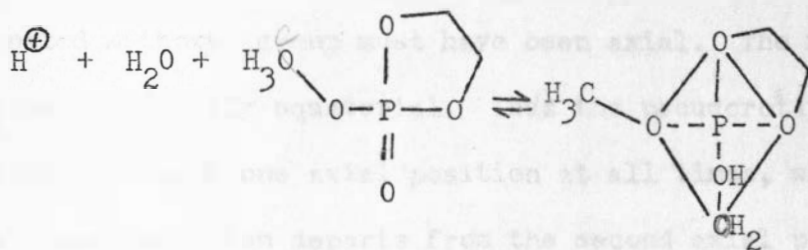
(D) Hydrolysis

Structures (A) and (B) have the axial positions activated. Reactions at these positions would be of the S_N2 -type. In (A), bond breaking at the activated positions would not break the ring. Thus (A) represents an exchange reaction. In (B), bond breakage at the activated positions could result in ring cleavage, thus representing a hydrolysis reaction. In (A) the O-P-O bond angle is 120° ; in (B) it is 90° . Hence both (A) and (B) are discounted since the O-P-O bond angle would have to be the same to have equal energy in the transition state. If the reaction rates are to be the same, it is necessary that the transition states have equal energy.

In (C) and (D), equatorial positions are activated. These positions are occupied by entering and leaving groups. In (C), bond breakage at the activated position would not break the ring, so (C) would represent an exchange reaction. In (D), bond breakage at the activated position could result in ring breakage, thus representing a hydrolysis reaction. The O-P-O bond angle in both (C) and (D) is

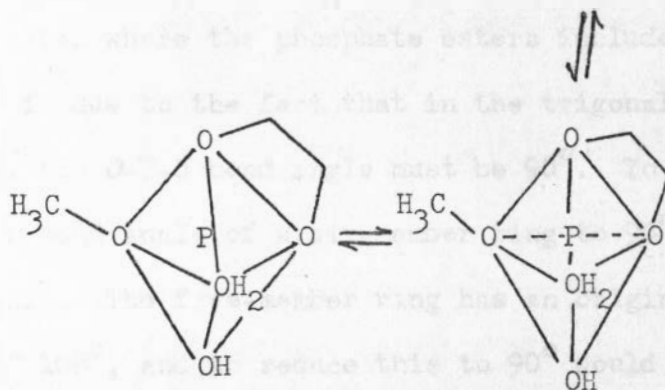
90° , hence structures (C) and (D) are acceptable. Since the bond angle is the same in both, they would have equal energies in the transition state and so the reaction rates would be the same. It is to be noted that in each trigonal bipyramid structure shown, two oxygens span the $-O-P-O-CH_2-CH_2-$ ring. One is equatorial, the other axial.

Dennis and Westheimer have reported an inversion mechanism involving a trigonal bipyramid where the attacking group was axial and the departing group, which had been equatorial, left in an axial position. This was explained by the concept of pseudorotation (22). The reaction involved the hydrolysis of methyl ethylene phosphate. In (XXIX), phosphorus exists in a tetrahedral structure. Water then adds in an axial manner to give (XXX) in a trigonal bipyramid structure. Structure (XXX) satisfies the constraints of Westheimer's hypothesis for pseudorotation to occur: (a) more polar groups, as oxygen atoms, preferentially occupy axial positions and the less polar groups, as alkyl groups, occupy equatorial positions and (b) five-member rings span one equatorial and one axial position in trigonal bipyramids (23). A proton shift transforms (XXX) to (XXXI). This isomer, containing axial and equatorial bonds, progresses to the diequatorial (XXXII). The strained (XXXII) relaxes back to a new axial-equatorial structure (XXXIII) in which the methoxyl group is axial. In (XXXI), this group had been equatorial. Proton migration produces (XXXIV), which then eliminates the protonated methoxyl group to give the final compound (XXXV). Since the configuration is



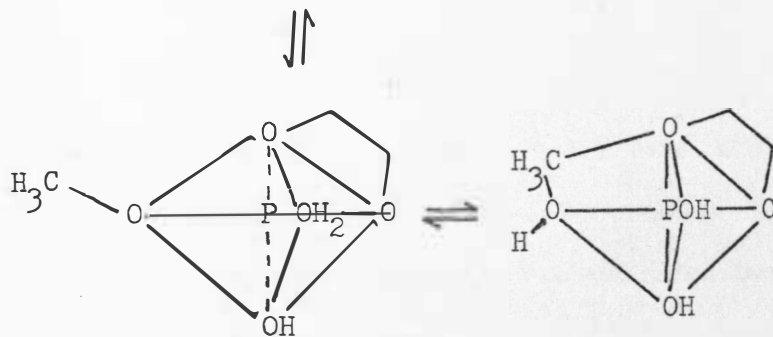
XXIX

XXX



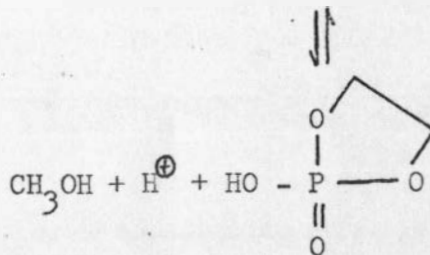
XXXII

XXXI



XXXIII

XXXIV



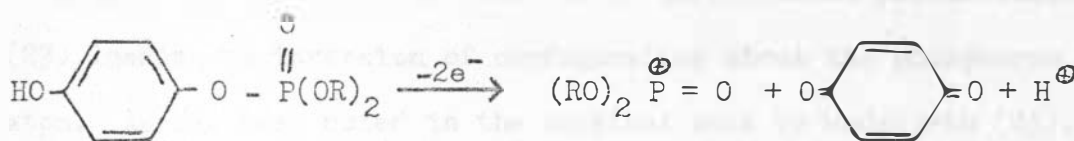
XXXV

inverted and the attacking group, H_2O , adds axially, the leaving protonated methoxyl group must have been axial. The methoxyl group was originally equatorial. Thus the pseudorotation allows the ring to occupy one axial position at all times, while one group first enters and then departs from the second axial position.

It must be noted that this mechanism of pseudorotation will not hold in cases where the phosphate esters include six-member rings. This is due to the fact that in the trigonal bipyramid intermediate, the O-P-O bond angle must be 90° . To reduce the 120° interior bond angle of a six-member ring to 90° would require too much strain. The five-member ring has an original interior bond angle of 108° , and to reduce this to 90° would require less energy.

DISCUSSION OF RESULTS

Although the $S_N2(P)$ mechanism is familiar in phosphorus chemistry, evidence for an $S_N1(P)$ mechanism has been slow to appear. Various data which can be interpreted to support the $S_N1(P)$ pathway has been presented and discussed in the previous section of this thesis. The most prominent reference to the existence of this mechanism has been presented by Hudson (24). He proposes the presence of a phosphoryl cation (XXXVI) in an oxidative phosphorylation reaction. It must be noted, however, that Hudson himself asserts that the mechanism is merely a proposal, and that it has not been concretely established.



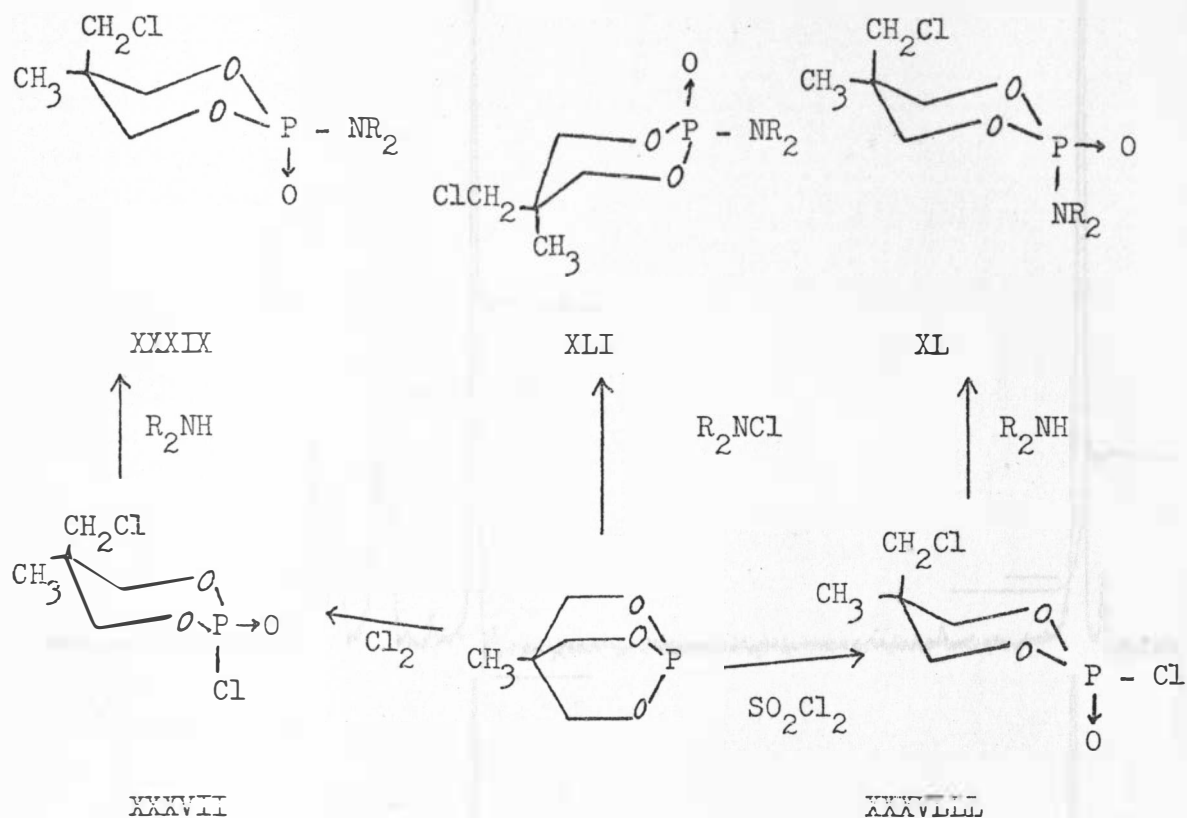
XXXVI.

We have discovered a system which may shed new light on the chemistry of nucleophilic substitutions at phosphorus (V) esters and their derivatives. Wadsworth has shown that two different phosphoramidates can be obtained from a bicyclic phosphite, depending upon their mode of preparation (25). We have continued on this original work in an attempt to elucidate the structure of the products and transition states which result upon substitution at phosphorus.

Treatment of methyl bicyclic phosphite with chlorine gas at low temperatures gives a cyclic phosphorochloridate (XXXVII), m.p. 59-

60°, which lacked stability, as witnessed by its slow decomposition to resinous material upon standing. A more stable phosphorochloridate (XXXVIII), m.p. 69-70°, is obtained by adding the phosphite to a solution of sulfuryl chloride. We assume that the phosphorochloridate (XXXVII) is stereochemically analogous to 2-bromo-5-bromo-methyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, which is prepared by adding bromine to the phosphite. The structure of the latter has been confirmed by X-ray analysis (26). The two phosphorochloridates, when treated with piperidine, gave phosphoramidates having different physical properties. Due to the steric requirements of the six-membered rings, the substitutions probably proceed normally via trigonal bipyramidal transition states (27) without pseudorotation (23) leading to inversion of configuration about the phosphorus atom. As has been noted in the original work by Wadsworth (25), a third phosphoramidate (XLI) was obtained by treating the methyl bicyclic phosphite with N-chloropiperidine.

The conformation of the cyclic phosphoramides is based on nmr analysis (fig. 2) using a method described by Edmundson (28). The hydrogens in the chloromethyl group in (XLI) are upfield with respect to those in (XXXIX) and (XL), whereas the methyl hydrogens in (XLI) are downfield with respect to the methyl hydrogens in the other two (Table 1). Conversion of the phosphorochloridates (XXXVII) and (XXXVIII) to the amidates did not cause a change in the conformation of the five position. Compounds (XXXVII) and (XLI) must have a cis configuration (the terms cis and trans refer to the



configurational relationship between the phosphoryl and halomethyl groups (29) due to their mode of formation. Although the exact conformations of phosphorus in (XXXIX) and (XL) are not known with absolute certainty, the phosphoramidates must have the interrelationships shown, for they have different physical properties, including X-ray powder patterns.

The three phosphoramidates are thermodynamically stable, for there are no signs of interconversion, even at temperatures up to 250° . The energy barrier between (XL) and (XLI) can be rationalized on steric grounds, for in the transition state for conversion to (XL), 1-3 steric repulsions must be large if similarities with

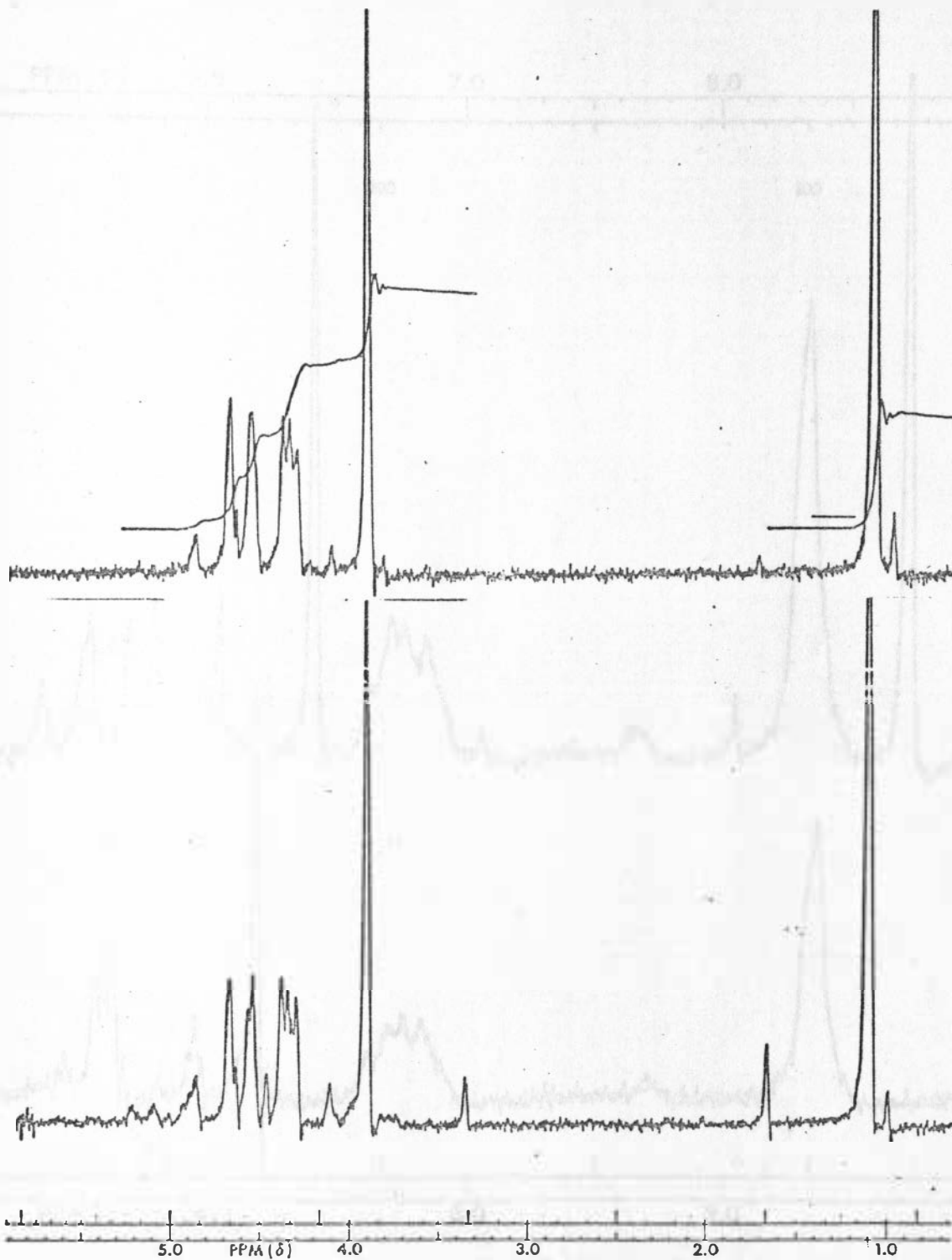


Figure 1. Bottom: Spectrum of XXXVII. Top: Spectrum of XXXVIII.
Spectra were run in deuteriochloroform, TMS external.

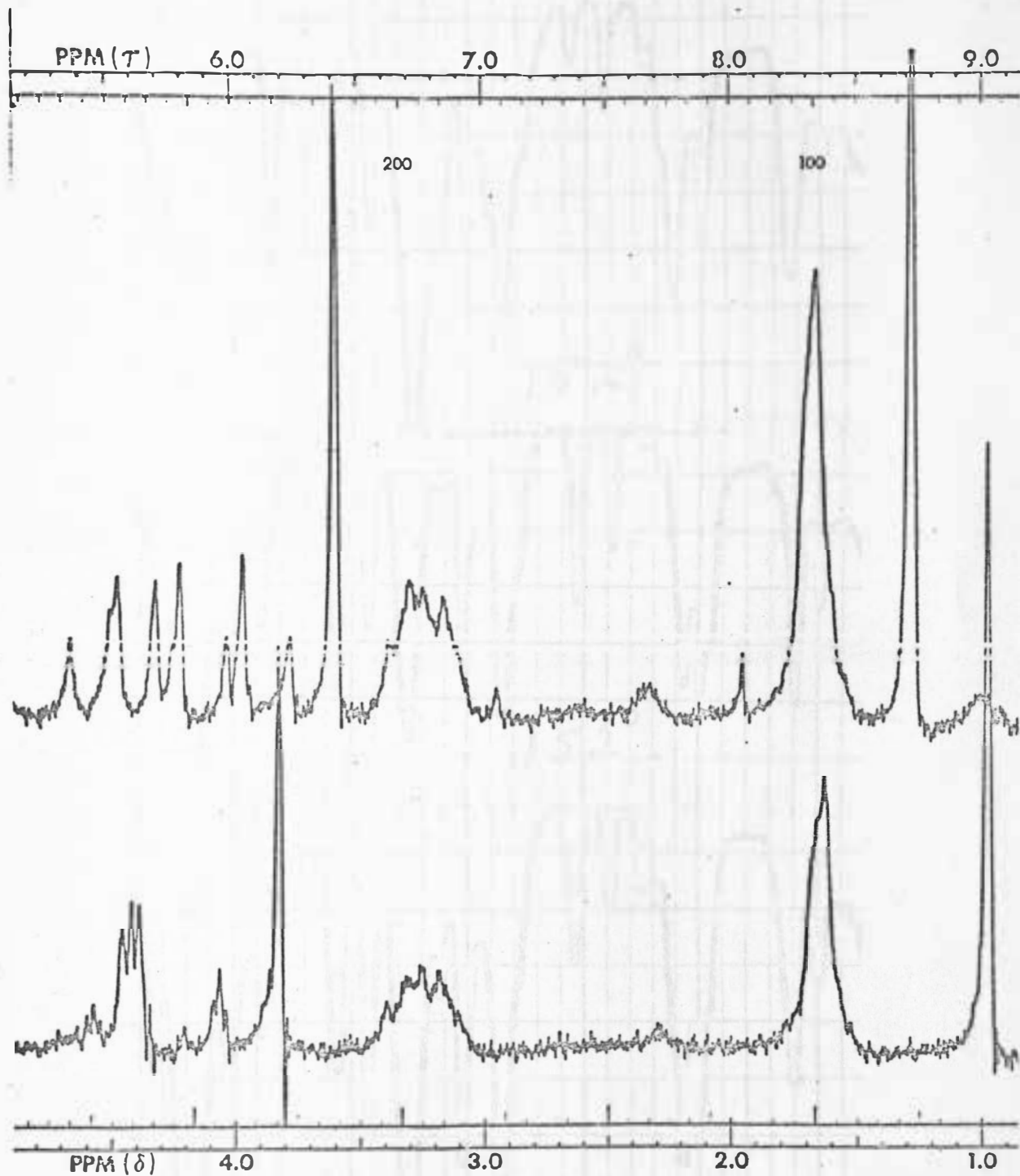


Figure 2. Spectrum of phosphoramidates XL (bottom) and XLI (top). Deuteriochloroform was used as solvent.

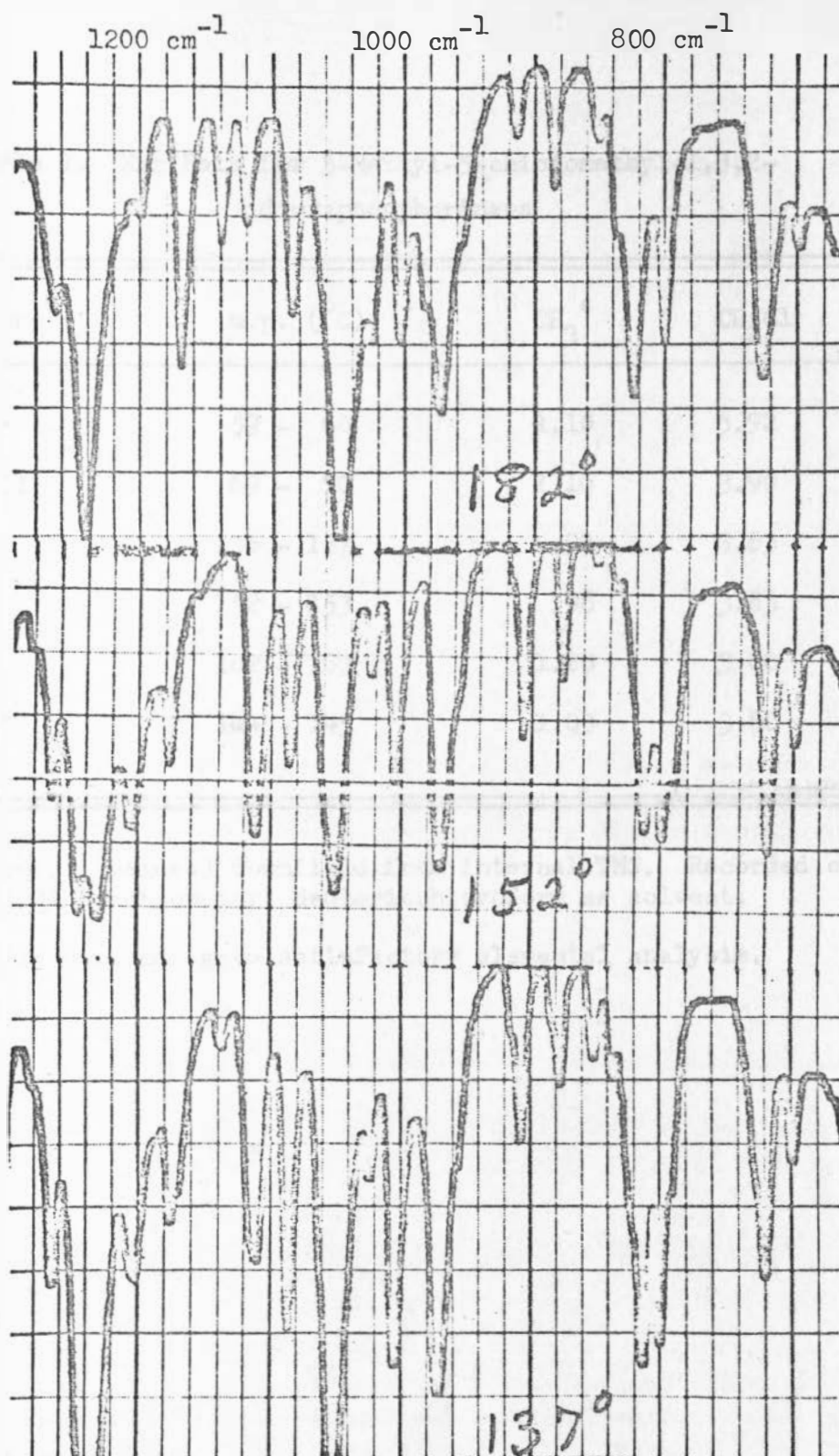


Figure 3. Partial infrared spectrum of the phosphoramides XXXIX (bottom), XL (center), and XLI (top).

Table 1. Nmr Data for 5-Methyl-5-chloromethyl-1,3,2-dioxaphosphorinans

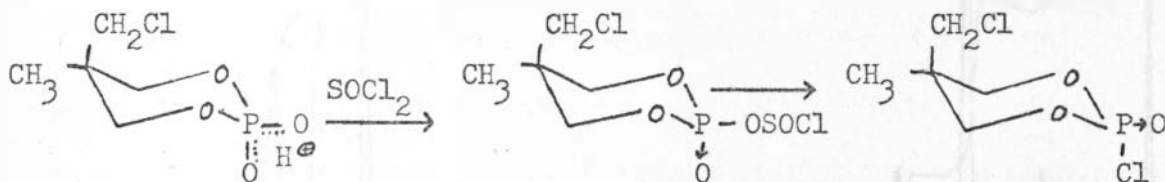
Compound ^b	m.p. (°C)	CH ₃ ^a	CH ₂ Cl
XXXVII	59 - 60	1.10	3.92
XXXVIII	69 - 70	1.10	3.90
XXXIX	136 - 137	.98	3.83
XL	152 - 153	.98	3.83
XLI	182 - 183	1.28	3.60
XLII	144 - 145	1.03	3.80

^aPpm (values) downfield from internal TMS. Recorded on a Varian A60A spectrometer, deuteriochloroform as solvent.

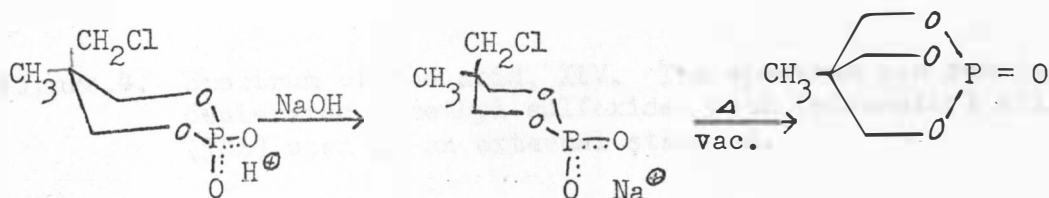
^bAll compounds gave satisfactory elemental analysis.

cyclohexane can be inferred. The stability of (XL) may be due to intramolecular dipole interactions between the chloromethyl group and the ring oxygens.

Both cyclic phosphorochloridates gave the identical acid upon hydrolysis. The acid, upon treatment with thionyl chloride in refluxing chloroform gave the least stable phosphorochloridate (XXXVII), as evidenced by its physical properties and conversion to the phosphoramidate (XXXIV). The nmr spectrum of the acid (fig. 4) indicated its chloromethyl group to be axial. The thionyl chloride may attack the oxygen at the least hindered equatorial position giving an adduct which, as indicated in the literature (15), decomposes with inversion of configuration. Treatment of the



acid with hydroxide produces a sodium salt which, when sublimed under high vacuum, recycles to form the bicyclic phosphate.



In contrast to the lack of conformational change upon treatment of the phosphorochloridate with an amine, methanolysis does produce a change. A pair of non-interconvertible isomeric esters is obtained

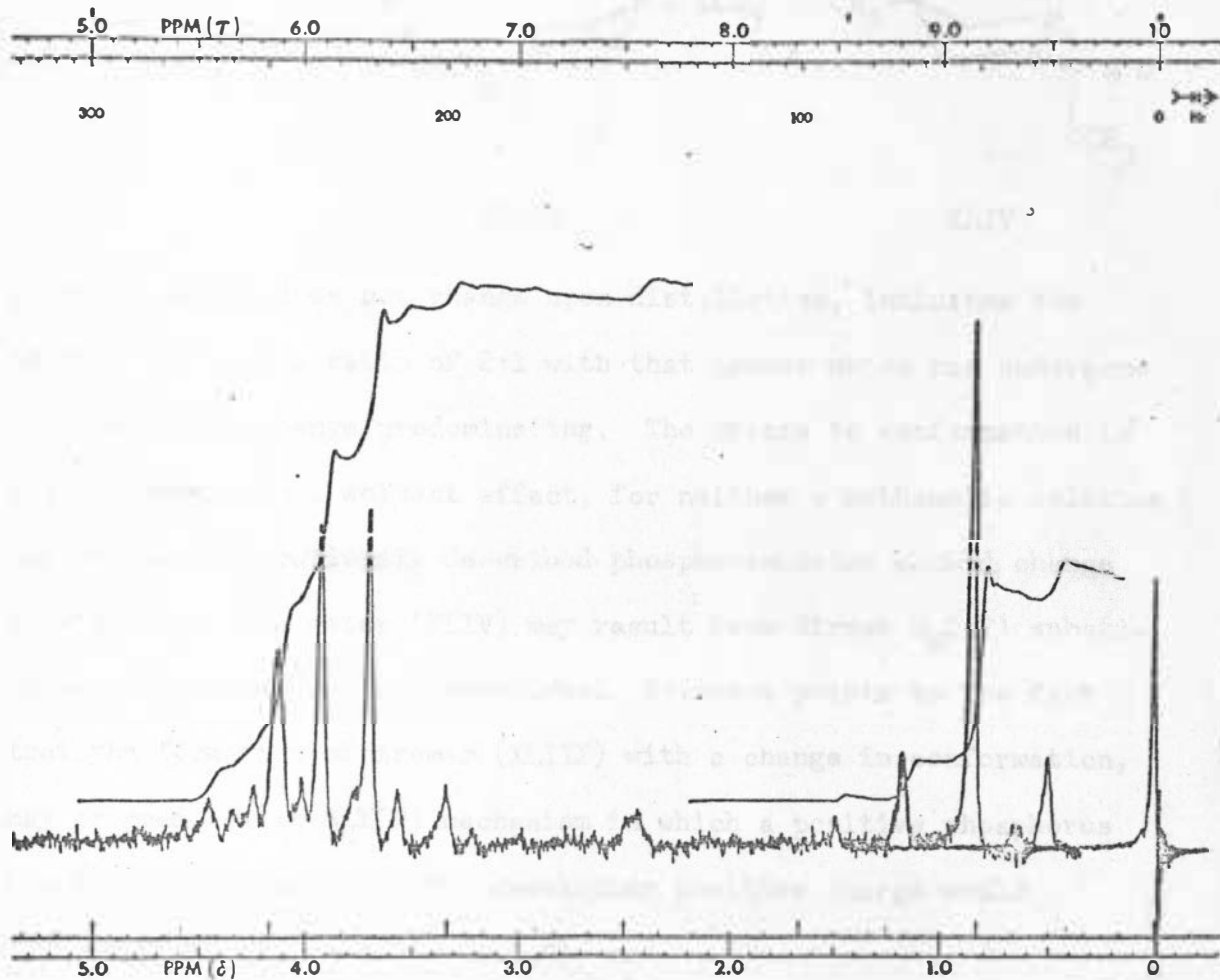
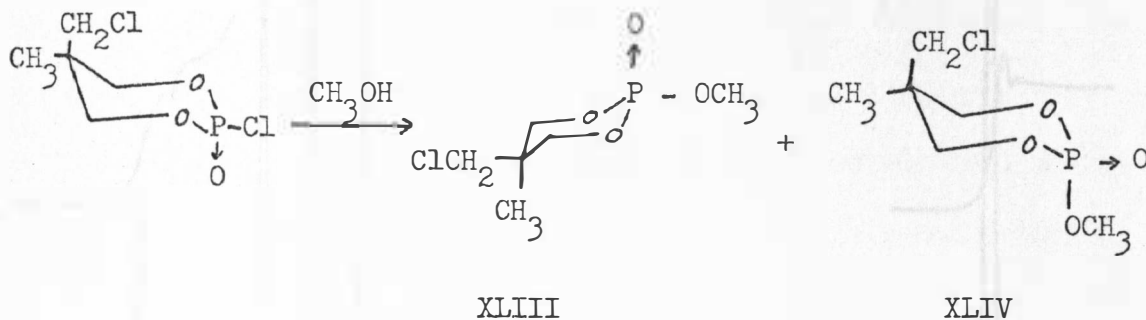
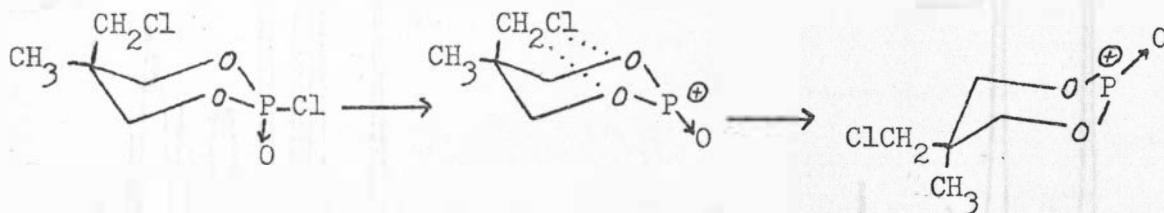


Figure 4. Spectrum of the acid, XLV. The spectrum was run in deuterated dimethyl sulfoxide, with tetramethyl silane (TMS) used as an external standard.

upon removal of excess solvent from a methanolic solution which has stood for twenty-four hours. The nmr spectrum of the product



(fig. 5), which does not change upon distillation, indicates the isomers to be in a ratio of 2:1 with that isomer which has undergone conformational change predominating. The change in conformation is not due merely to a solvent effect, for neither a methanolic solution nor any of the previously described phosphoramidates showed change on standing. The ester (XLIV) may result from direct $S_N2(P)$ substitution with inversion at phosphorus. Evidence points to the fact that the formation of isomer (XLIII) with a change in conformation, may proceed via an $S_N1(P)$ mechanism in which a positive phosphorus ion is an intermediate. The developing positive charge would



decrease the dipole interaction, thus allowing conformational mobility at the five position. Our evidence for an $S_N1(P)$ mechanism and indeed for assuming that (XLIV) occurs by $S_N2(P)$ substitution

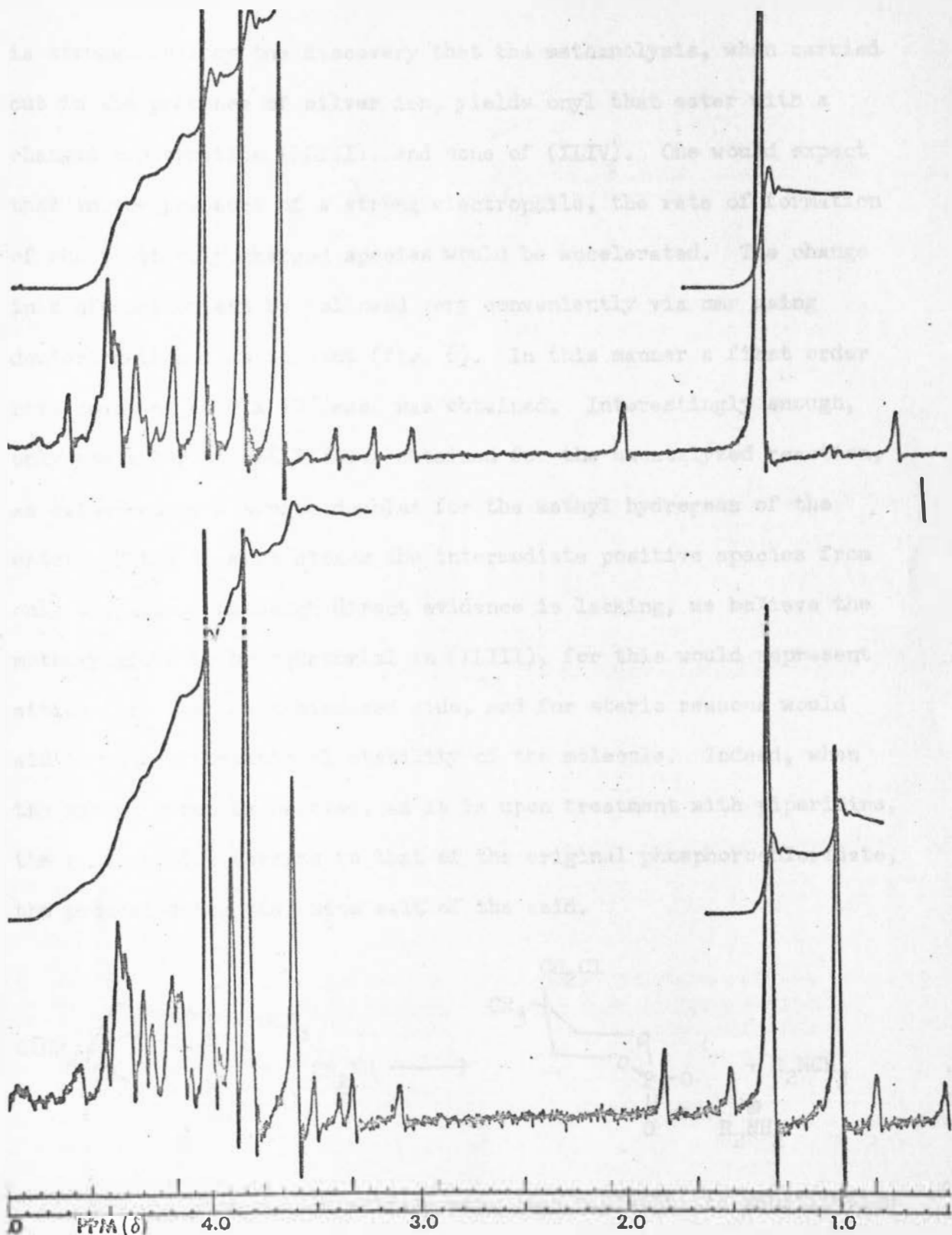
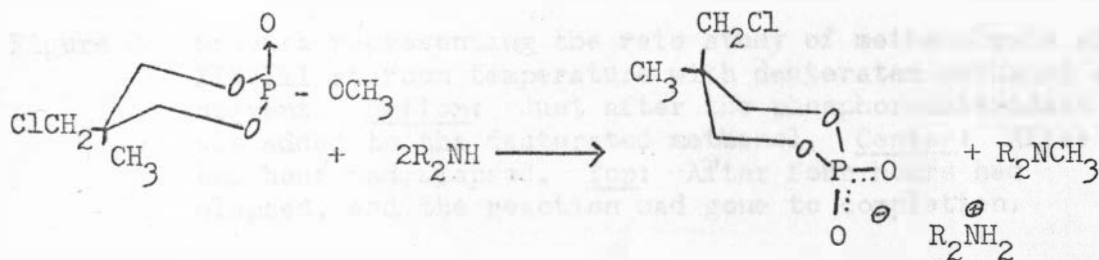


Figure 5. Bottom: Product given by methanolysis of XXXVIII. Top: Product given by methanolysis of XXXVIII in the presence of silver nitrate. Spectra run in deuteriochloroform.

is strengthened by the discovery that the methanolysis, when carried out in the presence of silver ion, yields only that ester with a changed conformation (XLIII), and none of (XLIV). One would expect that in the presence of a strong electrophile, the rate of formation of the positively charged species would be accelerated. The change in conformation can be followed very conveniently via nmr using deuteriomethanol as solvent (fig. 6). In this manner a first order rate constant of 4×10^4 /sec. was obtained. Interestingly enough, only one ester of (XLIII) was obtained for the uncatalyzed reaction, as evidenced by a single doublet for the methyl hydrogens of the ester. Methanol must attack the intermediate positive species from only one side. Although direct evidence is lacking, we believe the methoxy group to be equatorial in (XLIII), for this would represent attack from the least hindered side, and for steric reasons would aid in the conformational stability of the molecule. Indeed, when the methyl group is removed, as it is upon treatment with piperidine, the conformation reverts to that of the original phosphorochloridate, the product being the amine salt of the acid.



The cis phosphorochloridate undergoes nucleophilic substitution by pyridine, but only approximately one-third of the substitution

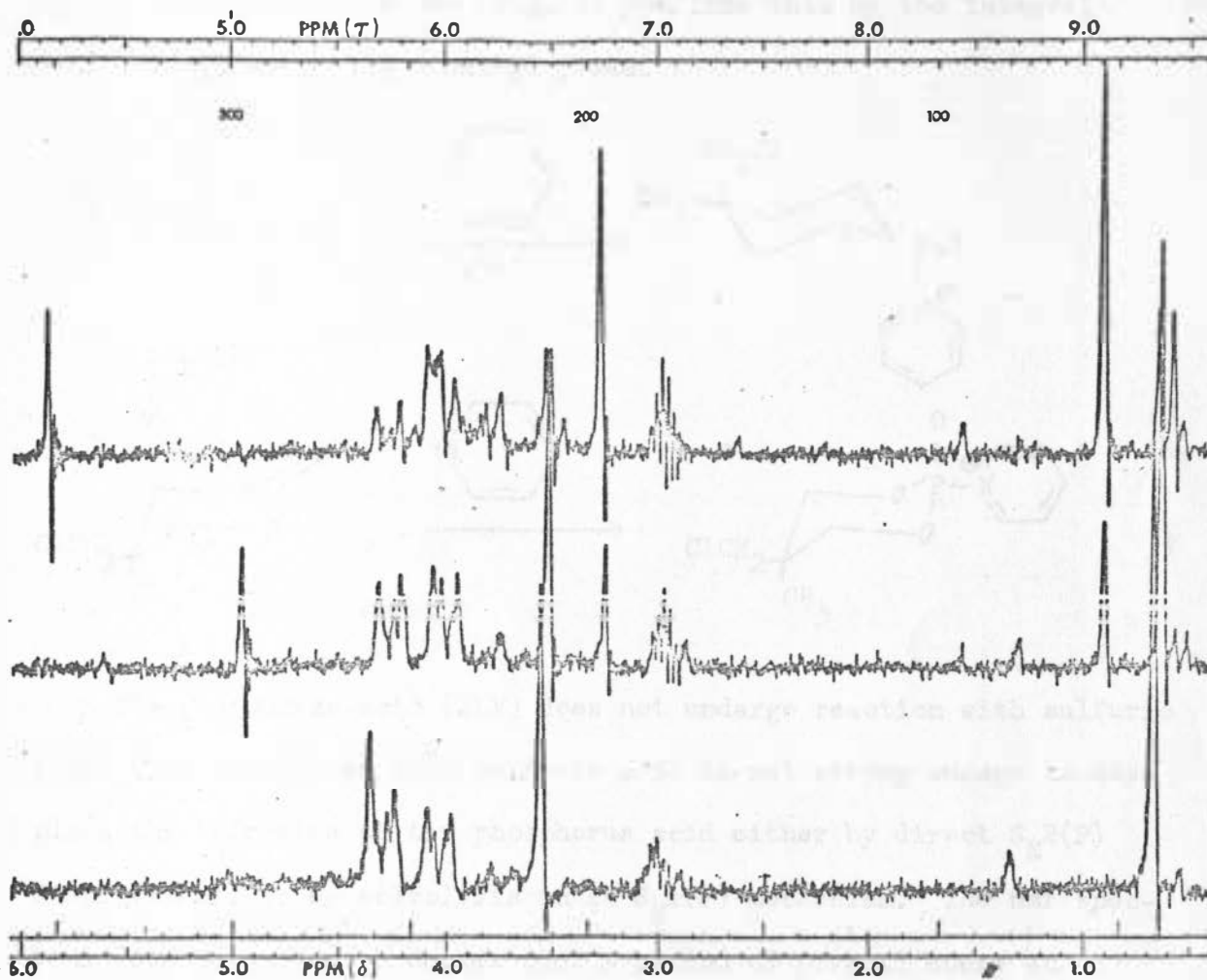
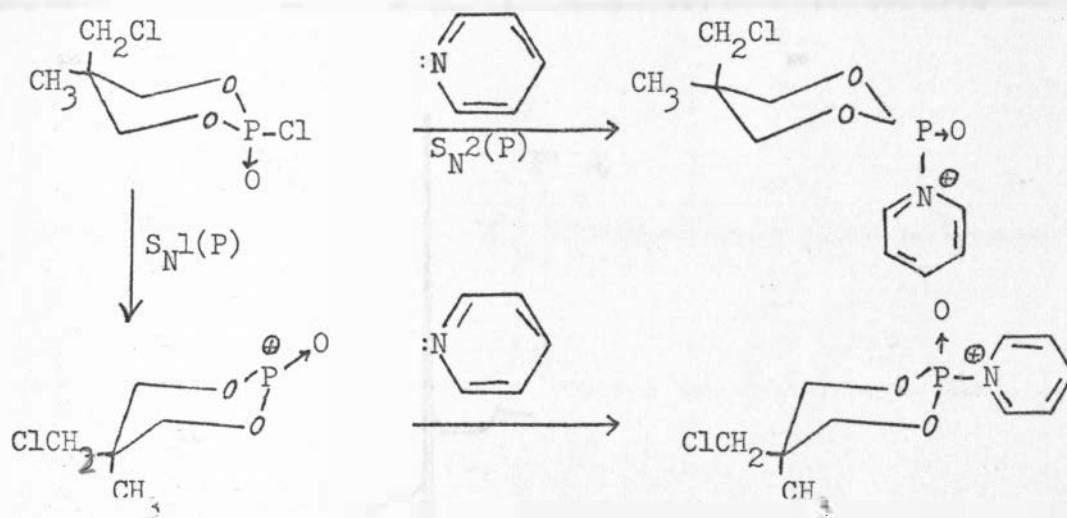
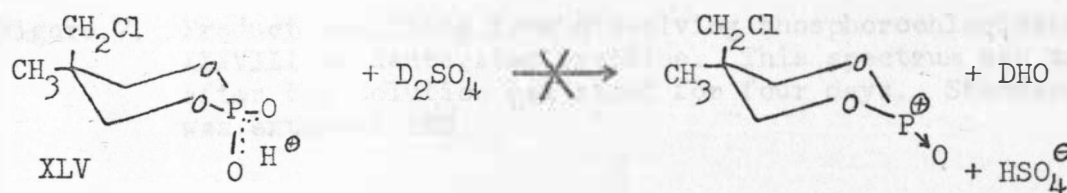


Figure 6. Spectra representing the rate study of methanolysis of XXXVIII at room temperature with deuterated methanol as solvent. Bottom: Just after the phosphorochloridate was added to the deuterated methanol. Center: After one hour had elapsed. Top: After four hours had elapsed, and the reaction had gone to completion.

proceeds through the phosphonium ion to produce the ring-flipped isomer. The major part of the reaction apparently proceeds via the $S_N2(P)$ mechanism. The nmr (fig. 7) confirms this by the integral ratio of cis and trans 5-methyl peaks.



The phosphorus acid (XLV) does not undergo reaction with sulfuric acid. This indicates that sulfuric acid is not strong enough to displace the hydroxide of the phosphorus acid either by direct $S_N2(P)$ displacement, or by solvolysis in an $S_N1(P)$ mechanism. The nmr spectrum (fig. 8) shows no change over a period of several hours at temperatures of approximately 50°.



In contrast to the methanolysis of the phosphorochloridate (XXXVIII), the phosphorobromidate (XLVI), under identical conditions,

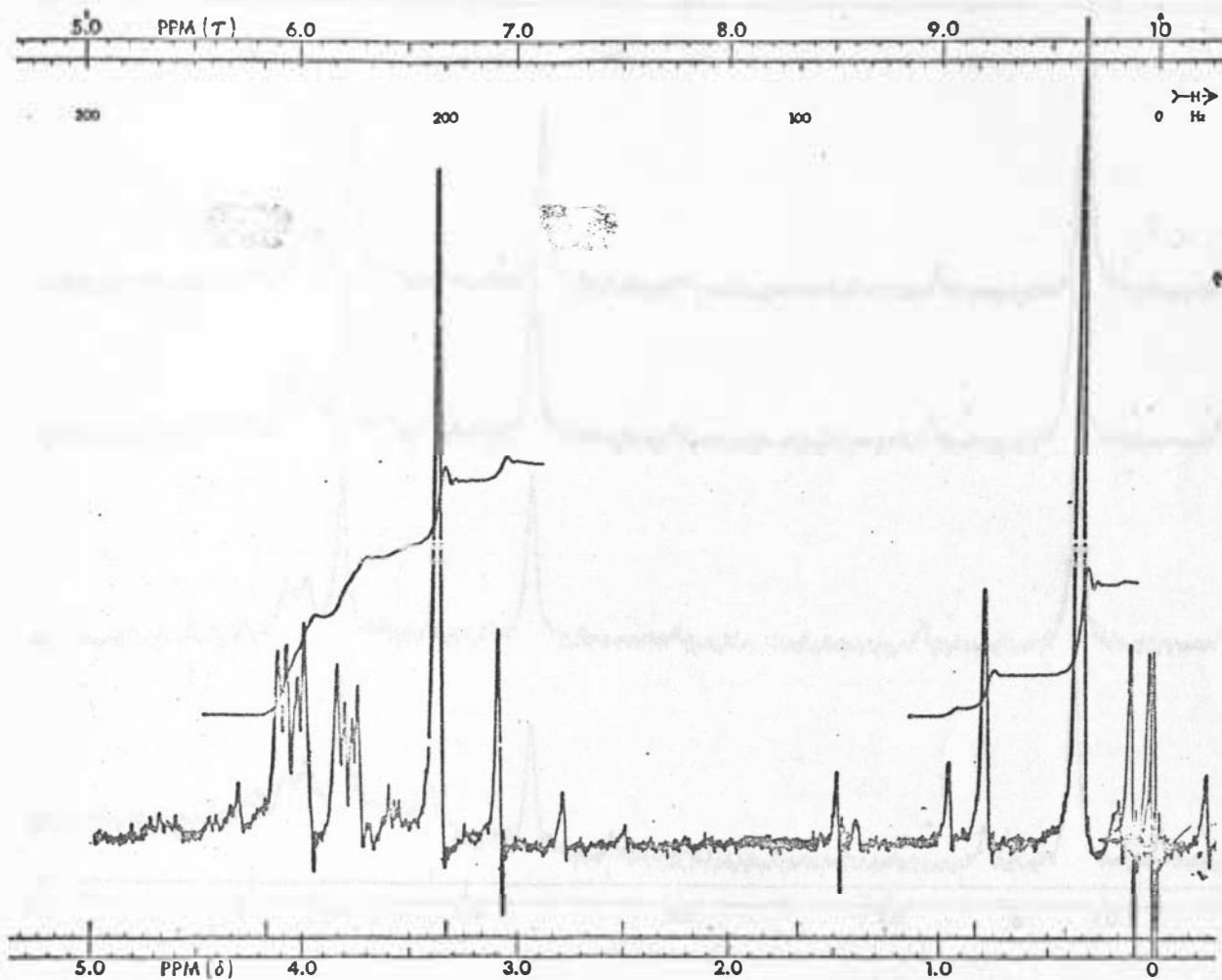


Figure 7. Product resulting from dissolving phosphorochloridate XXXVIII in deuterated pyridine. This spectrum was taken after the solution had stood for four days. Standard was external TMS.

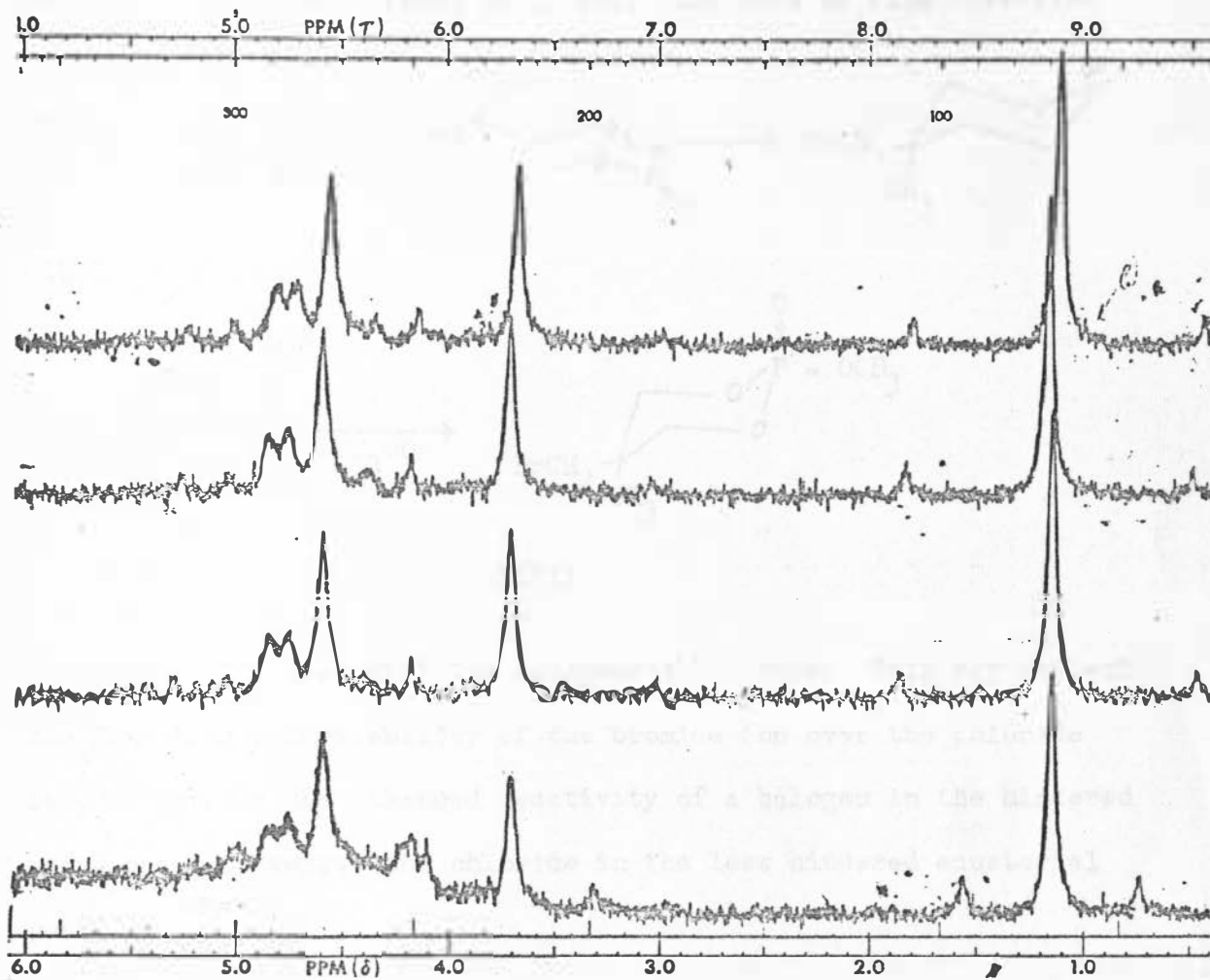
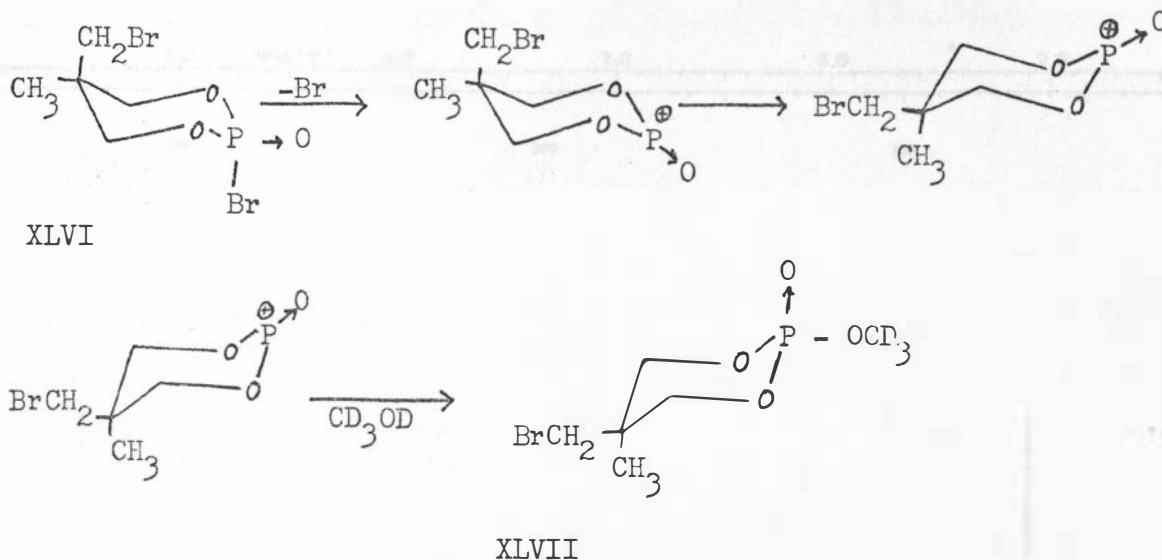


Figure 8. Spectrum of the acid, XLV, dissolved in deuterated sulfuric acid. Note that no change has occurred from the bottom spectrum which represents the initial solution of XLV in acid at 0° , and the top spectrum which was taken after the solution had been kept at 50° for two hours.

gave only that isomer with a changed conformation (XLVII). The reaction could also be conveniently followed via nmr using deuteriomethanol as solvent (fig. 10). The rate of ring inversion



was much faster than with the phosphorochloridate. This may reflect the increased polarizability of the bromide ion over the chloride ion, or perhaps the enhanced reactivity of a halogen in the hindered axial position versus the chloride in the less hindered equatorial position.

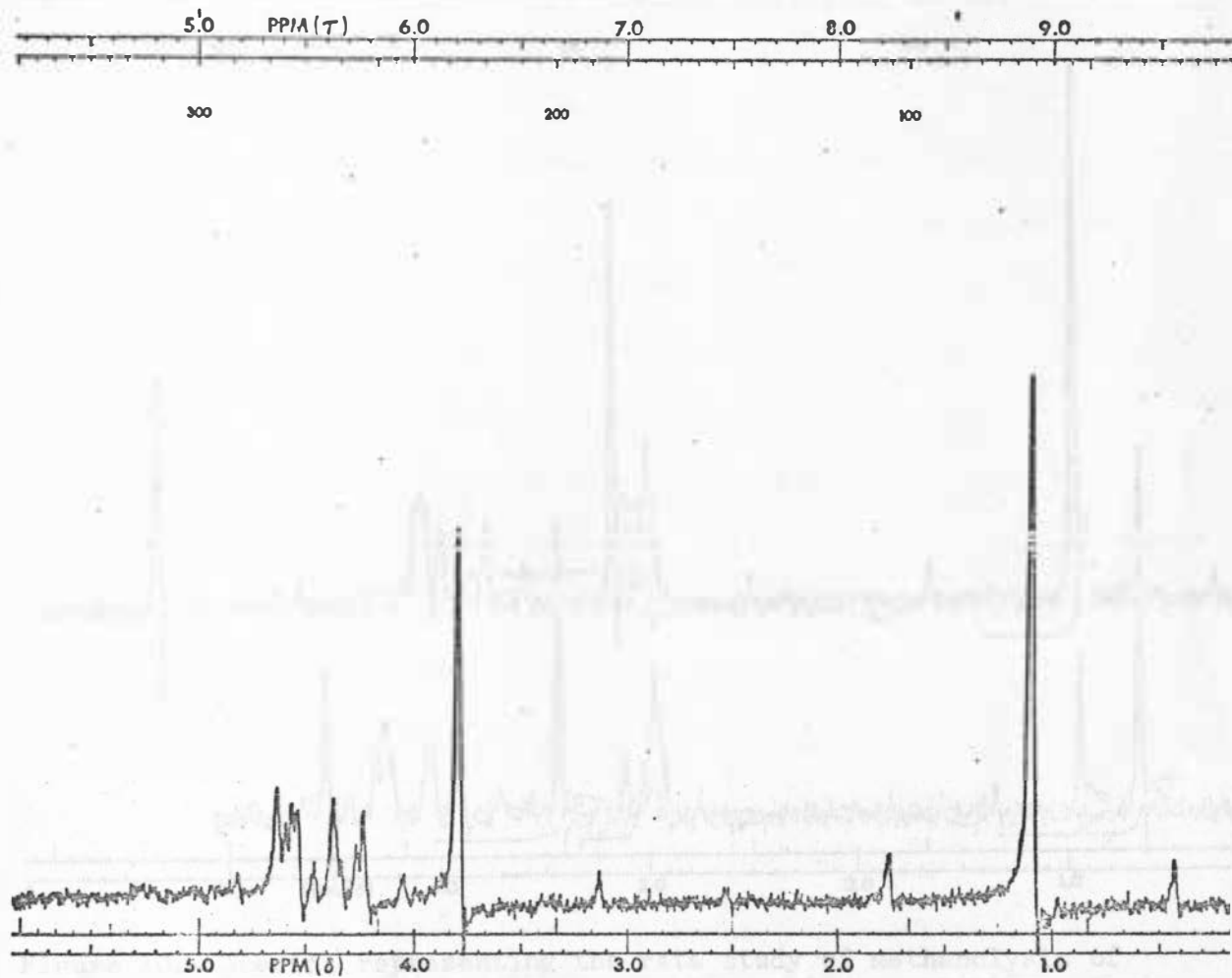


Figure 9. Spectrum of the phosphorobromidate, XLVI. Solvent used was deuteriochloroform. External TMS standard.

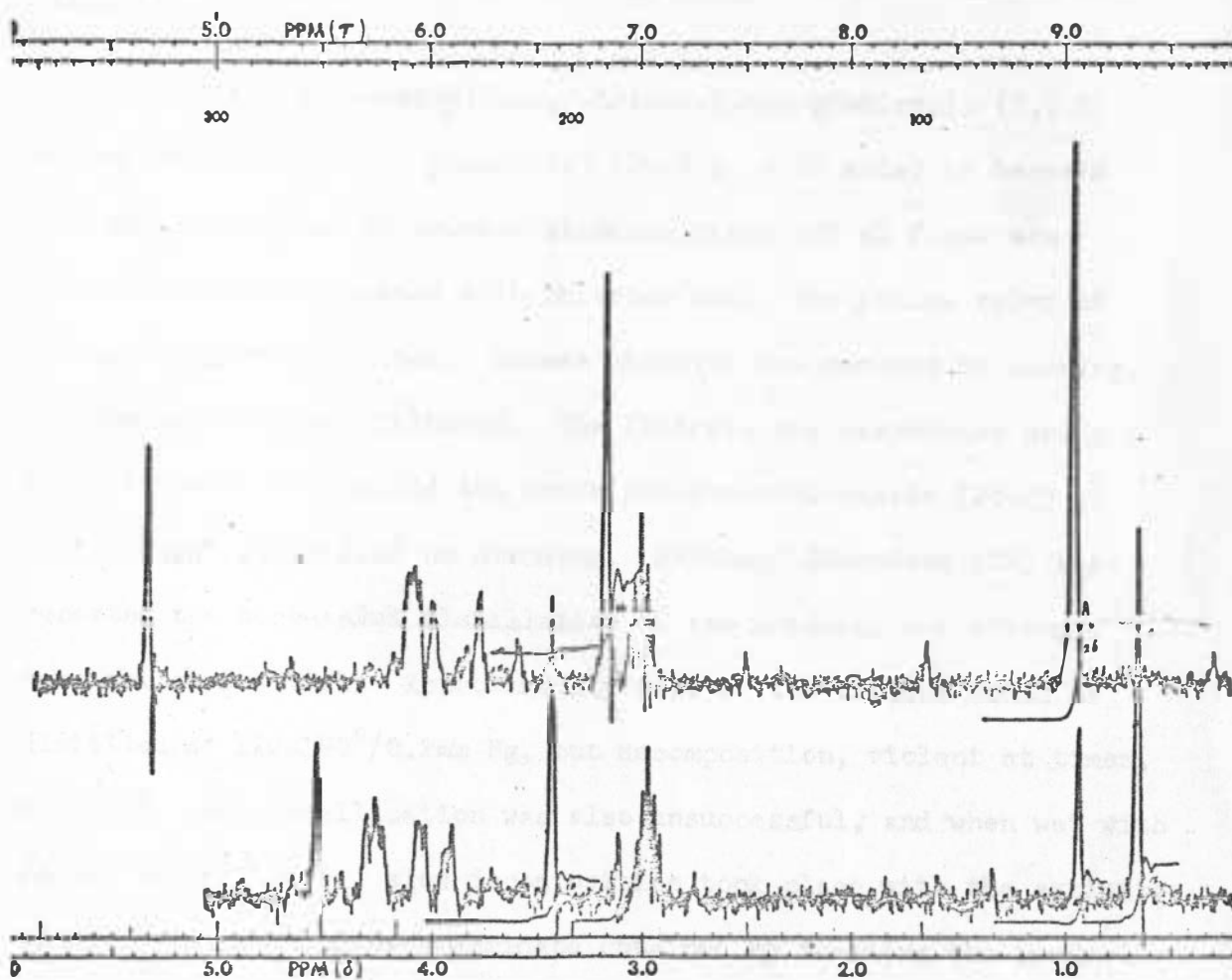


Figure 10. Spectra representing the rate study of methanolysis of XLVI with deuterated methanol as solvent. Bottom: Just after the phosphorobromidate was dissolved in the deuterated at 0° . Top: After the solution had stood at room temperature for twenty minutes, and the reaction had gone to completion.

EXPERIMENTAL

Cis-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan
(XXXVII)

A solution of 4-methyl-2,6,7-trioxa-1-phosphabicyclo (2.2.2) octane (methyl bicyclic phosphite) (14.8 g, 0.10 mole) in benzene (200 ml) in a 19/22 three-neck standard taper 500 ml flask was cooled in ice and treated with chlorine until the yellow color of excess chlorine persisted. Excess chlorine was removed by warming, and the solution was filtered. The filtrate was evaporated using a Rinco evaporator to yield the crude phosphorochloridate (20-25 g) which slowly solidified on standing. Although Edmundson (28) has reported the successful distillation of the product, our attempts were not so fruitful. Approximately half of the product could be distilled at 120-140°/0.2mm Hg, but decomposition, violent at times, occurred. Recrystallization was also unsuccessful, and when wet with carbon tetrachloride, slow decomposition took place with the evolution of HCl. Since the phosphoramidate obtained by treating the product with piperidine was identical to that obtained by Edmundson, the structure of the impure product was verified. The preparation of the cis phosphorochloridate by the above procedure at times produced the more stable isomer. The isomerization requires further investigation.

Cis-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,4-dioxaphosphorinan
(XXXVII)

2-Hydroxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (2.0 g, 0.01 mole) was added to fifty ml chloroform in a 19/22 standard taper 100 ml flask. Thionyl chloride (5.0 g, 0.042 mole) was added and the mixture refluxed for five days. The solution was stripped of solvent under reduced pressure via Rinco evaporator and taken up in ether to separate out the pyrophosphate. The mixture was filtered, and the ether removed via Rinco evaporator to give a viscous, semicrystalline residue. The residue was proved to be the cis-phosphochloridate by treating it with excess piperidine and isolating the trans phosphoramidate, as described previously, m.p. 136-138°, identical with an authentic sample.

Trans-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan
(XXXVIII)

A solution of methyl bicyclic phosphite (37.0 g, 0.25 mole) in 200 ml of carbon tetrachloride, was added dropwise with cooling and stirring to a solution of sulfuryl chloride (33.75 g, 0.25 mole) in 200 ml of carbon tetrachloride in a 19/22 standard taper 500 ml flask. After the exothermic addition, the solution was stirred for one hour and stripped of solvent under reduced pressure by a Rinco evaporator. The liquid residue which crystallized on standing was recrystallized twice from carbon tetrachloride to give 49 grams (91 percent) of white crystalline product, m.p. 69-71°. Calculated

for $C_5H_9Cl_2O_3P$: C, 27.4; H, 4.15; P, 14.1. Found: C, 27.32; H, 4.25; P, 14.41. The nmr spectrum of the product confirmed its structure.

Trans 5-chloromethyl-5-methyl-2-oxo-2-piperidino-1,3,2-dioxaphosphorinan (XXXIX)

A sample of the phosphorochloridate was dissolved in benzene and a slight excess of piperidine added. After the initial exotherm had subsided, the solution was stripped under reduced pressure by Rinco evaporator. The residue was water washed, and then recrystallized from hexane, m.p. 136-137°. The product was identical to that reported by Edmundson.

Cis 5-chloromethyl-5-methyl-2-oxo-2-piperidino-1,3,2-dioxaphosphorinan (XL)

A sample of the trans phosphorochloridate (XXXVIII) m.p. 69-71°, was dissolved in benzene, after which a slight excess of piperidine was added. After the initial exotherm had subsided, the solution was stripped under reduced pressure by Rinco evaporator. The residue was water-washed and then recrystallized from hexane, m.p. 153-154°. Calculated for $C_{10}H_{19}ClNO_3P$: C, 44.85; H, 7.14; N, 5.17; P, 11.61. Found: C, 44.53; H, 7.12; N, 5.29; P, 11.68.

Reaction between Methyl Bicyclic Phosphite and N-Chloropiperidine

N-Chloropiperidine (4.0 g, 0.034 mole) in fifteen ml of carbon tetrachloride was added dropwise to methyl bicyclic phosphite (3.8 g,

0.026 mole) dissolved in fifteen ml of carbon tetrachloride in a 19/22 one-neck standard taper flask. After standing overnight, the solvent was removed under reduced pressure by Rinco evaporator, and the residue was recrystallized from hexane, m.p. 182° . The product was identical to that reported by Edmundson.

2-Hydroxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (XLV)

Trans phosphorochloridate (10.0 g, 0.046 mole) was added to 25 ml water in a 19/22 standard taper 100 ml flask, and the mixture heated with a low flame until it became homogeneous. The solution yielded a solid precipitate upon cooling in ice, and filtration gave a white crystalline product, m.p. $144-146^{\circ}$ (8.5 g, 92 percent yield). Calculated for $C_5H_{10}O_4PCl$: C, 30.0; H, 5.0; Cl, 17.5. Found: C, 30.11; H, 5.14; Cl, 17.54.

Sodium 5-methyl-5-chloromethyl-2-dioxo-1,3,2-dioxaphosphorinanate

Cis-2-chloro-5-methyl-5-chloromethyl-2-oxo-1,3,2-dioxaphosphorinan (18 g, 0.08 mole) was placed in a 100 ml one-necked 19/22 standard taper flask, and the contents were cooled to 5° by an ice bath and stirred by magnetic stirrer and bar. The flask was fitted with an addition funnel, and to the solution was added 8 N (20 ml, 0.16 mole) dropwise. A white solid precipitated out of the solution and was filtered off by suction filtration and recrystallized from water. Yield: 17.3 g, 94 percent, m.p. $260-265^{\circ}$ C.

Sodium 5-ethyl-5-chloromethyl-2-dioxo-1,3,2-dioxaphosphorinane

Cis-2-oxo-5-ethyl-5-chloromethyl-2-oxo-1,3,2-dioxaphosphorinan (19 g, 0.08 mole) was placed in a 100 ml one-necked 19/22 standard taper flask, and the contents were cooled to 5° by an ice bath and stirred by magnetic stirrer and bar. The flask was fitted with an addition funnel, and to the solution was added 8 N NaOH (20 ml, 0.16 mole) dropwise. A white solid precipitated out of the solution and was filtered off by suction filtration and recrystallized from water. Yield: 20 g, 100 percent; m.p., above 270°.

Methyl bicyclic phosphate from the sodium phosphorinane

Methyl sodium salt (3.0 g, 0.015 mole) was placed in a vacuum sublimator, and the pressure was reduced to 0.2 mm Hg by means of a vacuum pump. The contents were heated to 225° by an oil bath, but no reaction occurred. A flame was applied to the sublimator tube, and the compound began to sublime, eventually leaving a white solid sublimed on the cold finger tube of the apparatus, and some black residue in the sublimator tube itself. The white solid was recrystallized from isopropyl alcohol. Yield: 1.16 g, 45 percent; m.p. 250-253°.

Ethyl bicyclic phosphate from the sodium phosphorinane

Ethyl sodium salt (3.1 g, 0.015 mole) was placed in a vacuum sublimator, and the pressure reduced to 0.15 mm Hg by a vacuum pump.

The sublimer tube was heated with a flame until the compound began to sublime and a white solid began to collect on the cold finger tube. The white solid was recrystallized from isopropyl alcohol. Yield: 1.05 g, 41 percent; m.p. 202-205°.

Cis-2-bromo-5-methyl-5-bromomethyl-2-oxo-1,3,2-dioxaphosphorinan
(XLVI)

Methyl bicyclic phosphite (3.0 g, 0.025 mole) was dissolved in fifty ml benzene in a one-necked 100 ml 19/22 standard taper flask. The flask and contents were cooled by an ice bath to 5°, and the flask was fitted with an addition funnel. To the cold solution bromine (4.0 g, 0.025 mole) was added dropwise while the reactants in the flask were stirred via magnetic stirrer and bar. The yellow dibromophosphonium intermediate precipitated out of the benzene, and, upon completion of the halogen addition, was filtered via suction filtration. This precipitate was then added immediately to 300 ml hexane, which was then brought to a boil. The solid appeared to dissolve in the hot hexane, and after boiling 150 ml of the hexane off and cooling the remaining solution, a white solid precipitated out. This solid was again recrystallized from hexane, filtered via suction filtration and dried. Yield: 2.2 g, 34 percent; m.p. 76-78°.

Methanolysis of trans-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan

The phosphorochloridate (10 g, 0.046 mole) was dissolved in fifty ml of methanol in a 100 ml flask. After standing for two days, excess methanol was removed under reduced pressure by Rinco evaporator. The viscous residue was distilled to give 6.35 g (65 percent yield) of viscous distillate, b.p. 140-142°/0.6 mm Hg, which crystallized upon standing. Calculated for $C_6H_{12}ClO_4P$: C, 33.64; H, 5.60; Cl, 16.35. Found: C, 33.97; H, 5.95; Cl, 16.41. The nmr spectrum confirmed the structure as 2-methoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan. The methyl hydrogens are split into a doublet by the phosphorus atom.

The non-volatile residue which resulted from the distillation was recrystallized from acetonitrile and proved to be identical to the authentic acid, 2-hydroxy-5-chloro-methyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan. This undoubtedly resulted from the hydrolysis of the chloridate for no attempt was made to dry the methanol before use.

The above procedure was then repeated with the exception that the starting phosphorochloridate was added to the methanol in which an equivalent of silver nitrate had been added. After standing, the precipitated silver chloride was removed by filtration and the product isolated as previously described. The nmr spectrum of the product in this case, however, showed the presence of only one isomer.

A sample of the methyl ester was treated with two equivalents of piperidine. After the mild exotherm, the mixture was cooled and suction filtered. The solid product was recrystallized from acetonitrile and proved to be identical in all respects to the amine salt obtained by adding piperidine to 2-hydroxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan.

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