$Ni(CO)_4$;[14] the structure of the proposed complex is sketched in Figure 4.[15]

Registry No.—I, 25127-62-2.

(14) R. H. B. Mais, P. G. Owston, D. T. Thompson, and A. M. Wood, *J. Chem. Soc. A*, 1744 (1967).

(15) NOTE ADDED IN PROOF.—The proposed structure of the Ni complex has been confirmed by an independent X-ray study (G. Bergerhoff, private communication).

Acknowledgment.—The author is pleased to thank Professor F. Cramer for his interest in and support of this work and Dr. P. C. Manor for critically reading the manuscript. The computations were carried out with IBM 7040 and UNIVAC 1108 computers at the Aerodynamische Versuchsanstalt and Gesellschaft für wissenschaftliche Datenverarbeitung, Göttingen, respectively.

Nucleophilic Substitution at Phosphorus[1]

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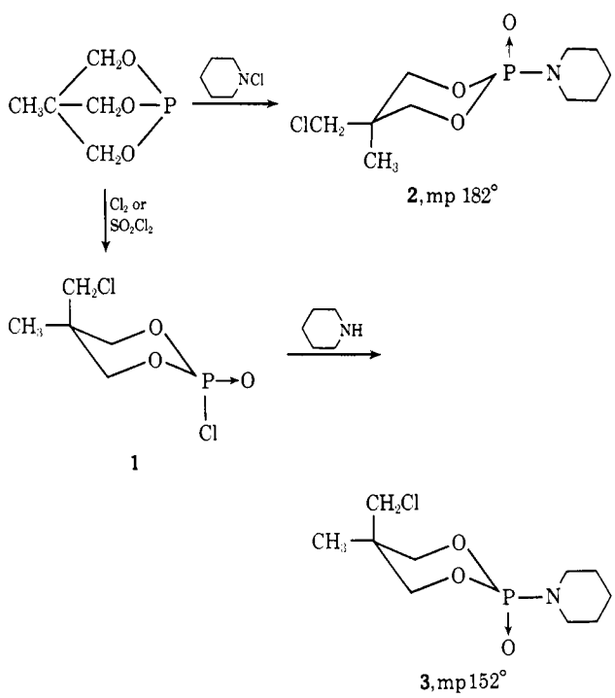
cis-5-Chloromethyl-5-methyl-2-oxo-2-chloro-1,3,2-dioxaphosphorinane was treated with a number of nucleophiles and the course of substitution at phosphorus was determined by analysis of the nmr spectra of the products. The geometry of the products with the aid of single-crystal X-ray analysis could be determined from the conformation of groups at the fifth position. In this manner the stereochemical outcome was found to be influenced by the basicity of the attacking nucleophile.

The mechanism of substitution reactions at phosphorus has been a subject of intensive study from which conflicting results have emerged. Mechanisms have been postulated on the basis of both kinetic and stereochemical results and both bimolecular, SN2(P), with and without inversion, and in a few cases monomolecular, SN1(P), pathways have been advanced.[2] In this paper we report results which we have obtained by means of a unique diagnostic tool which allows us to distinguish between possible stereochemical pathways.

In prior publications[3,4] we described the preparation of 2-substituted 5-halomethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinanes which entailed the treatment of a bicyclic phosphite with halogen or alkyl halide in the normal Arbuzov manner. Thus, *cis*-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxophosphorinane (1), which is the starting point of our study, is prepared by treating methyl bicyclic phosphite with either chlorine or sulfuryl chloride.[5] The product, a phosphorochloridate, mp 69–70°, is easily recrystallized from carbon tetrachloride. Its configuration is based upon the known configuration of 2-bromo-5-bromomethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane,[6] and is a consequence of its mode of formation.

Two isomeric phosphoramidates were obtained by treating the bicyclic phosphate with *N*-chloropiperidine and the phosphorochloridate with piperidine.[7]



Single-crystal X-ray analysis[8] of the low-melting trans isomer, **3**, has shown it to have the piperidinyl group equatorial and the chloromethyl group axial. The different chemical shifts of the methyl and chloromethyl hydrogens (Figure 1) indicate that the groups at the 5 position in the higher melting cis isomer, **2**, have a different environment. Consequently, as a result of the mechanism of the Arbuzov reaction and the caged structure of the starting phosphite it is most likely that the piperidinyl group in **2** is also equatorial and that the

(1) Taken in part from the Ph.D. Thesis of H. L. Horten, 1970, and M.S. Thesis of S. Larsen, 1971. Portions of this work were presented at the 5th Midwest Regional Meeting of the American Chemical Society, Kansas City, Mo., 1969, and the 4th Great Lakes Regional Meeting of the American Chemical Society, Fargo, N. D., 1970.

(2) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," W. A. Benjamin, New York, N. Y., 1966, Chapter 5; A. I. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, Amsterdam, 1967, Chapter 10; W. E. McEwen, "Topics in Phosphorus Chemistry," Vol. 2, M. Grayson and E. J. Griffith, Ed., Wiley, New York, N. Y., 1965; R. F. Hudson, "Structure and Mechanism in Organo-Phosphorus Chemistry," Academic Press, New York, N. Y., 1965, Chapter 8; M. J. Gallagher and I. D. Jenkins in "Topics in Stereochemistry," Vol. 3, E. L. Eliel and N. L. Allinger, Ed., Wiley, New York, N. Y., 1968, Chapter 1; P. Haake and P. S. Ossip, *Tetrahedron Lett.*, 4841 (1970).

(3) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Amer. Chem. Soc.*, **84**, 610 (1962).

(4) W. S. Wadsworth, Jr., *J. Org. Chem.*, **32**, 1603 (1967).

(5) In an earlier communication, W. S. Wadsworth, Jr., and H. L. Horten, *J. Amer. Chem. Soc.*, **92**, 3785 (1970), we stated that two different isomers of the phosphorochloridate were obtained under these conditions. We have since found the material reported to have mp 59–60° to be a mixture of isomeric phosphorochloridates produced upon distillation of the pure cis isomer.

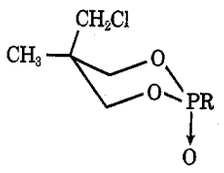
(6) T. A. Beineke, *Chem. Commun.*, 860 (1966).

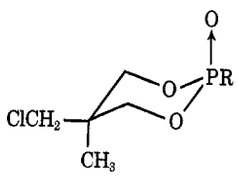
(7) A third phosphoramidate, mp 136–138°, reported in our previous paper[5] has subsequently been found to be a mixture of **2** and **3**.

(8) The X-ray analyses were carried out in this laboratory under the supervision of W. Jensen. Presented at the 163rd National Meeting of the American Chemical Society, Boston, Mass., 1972.

TABLE I

CHEMICAL SHIFTS OF 5,5-DISUBSTITUTED 2-AMINO-1,3,2-DIOXAPHOSPHORINANES[a]



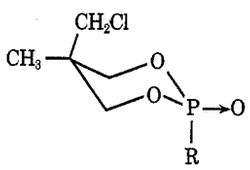


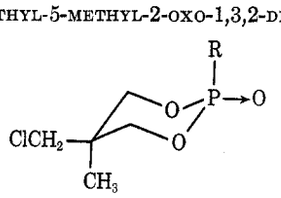
R	Registry no.	CH_3	CH_2Cl	Registry no.	CH_3	CH_2Cl
NC_5H_{11}	21071-82-9	0.98	3.83	21071-83-0	1.28	3.60
$NHC(CH_3)_3$	36912-22-8	0.95	3.70			
NHC_6H_5	36912-23-9	0.99	3.51			
p-$NHC_6H_4OCH_3$	36912-24-0	0.90	3.68			
$NHCH_2C_6H_5$	36912-25-1	0.90	3.62			

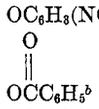
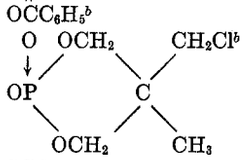
[a] Measured with a Varian A-60A instrument. In parts per million downfield from external TMS in $CDCl_3$.

TABLE II

CHEMICAL SHIFTS OF 2-SUBSTITUTED 5-CHLOROMETHYL-5-METHYL-2-OXO-1,3,2-DIOXAPHOSPHORINANES[a]





R	Registry no.	CH_3	CH_2Cl	Registry no.	CH_3	CH_2Cl
OCH_3	28097-12-3	1.01	3.89	36912-27-3	1.32	3.61
$OCH(CH_3)_2$				36912-28-4	1.36	3.60
OH	36912-29-5	1.03	3.80			
OC_6H_5	36912-30-8	0.98	3.77	36895-18-8	1.29	3.32
$OC_6H_4OCH_3$	36912-31-9	0.90	3.70	36912-32-0	1.25	3.32
$OC_6H_4CH_3$	36912-33-1	0.93	3.71	36912-34-2	1.28	3.29
OC_6H_5Br	36912-35-3	0.94	3.74	36912-36-4	1.30	3.32
$OC_6H_4NO_2$	36912-37-5	1.01	3.78	36912-38-6	1.38	3.40
$OC_6H_3(NO_2)_2$	36912-39-7	1.03	3.78	36912-40-0	1.43	3.40
						
OCC_6H_5[b]	36912-41-1	0.97	3.75	36912-42-2	1.36	3.45
	36914-95-1	1.03	3.77		1.41	3.42
SC_6H_5	36912-43-3	0.96	3.72	36912-44-4	1.19	3.11

[a] All samples run in $CDCl_3$ as solvent. In parts per million downfield from external TMS in $CDCl_3$. [b] In these cases the configuration at phosphorus is unknown.

structure drawn for **2** is correct. Interconversion between the isomers is not observed at temperatures over 200° or in solution, which is strong evidence that the two are indeed geometrical isomers.

We have used the variation in chemical shifts of hydrogens on groups at the 5 position to distinguish between isomers and in turn as a diagnostic tool in our study of substitution. The hydrogens of an axial chloromethyl group are shifted downfield from those of an equatorial chloromethyl group. Likewise the methyl hydrogens when axial are shifted downfield relative to those of an equatorial methyl group (Tables I and II).

The question of ring mobility in solution has yet to be fully clarified, although much work has been reported on analogous systems.[9] The phosphoramidates

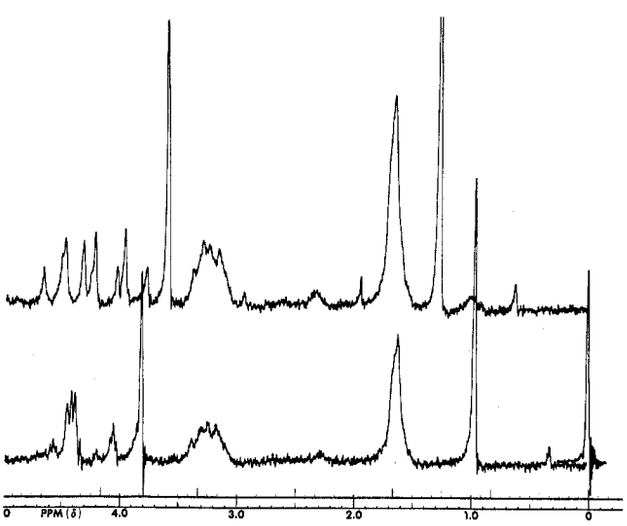


Figure 1.—Nmr spectra of phosphoromidates in $CDCl_3$: top, prepared from chloroamine and phosphite; bottom, prepared from amine and phosphorochloridate.

(9) R. S. Edmundson and E. W. Mitchell, *J. Chem. Soc. C*, 3033 (1968); R. S. Edmundson and E. W. Mitchell, *ibid.*, 752 (1970); A. R. Katritsky, M. R. Nesbit, J. Michalski, Z. Tulimowski, and A. Zwierzak, *J. Chem. Soc. B*, 140 (1970); D. W. White, G. K. McEwen, R. D. Bertrand, and J. G. Verkade, *ibid.*, 1454 (1971).

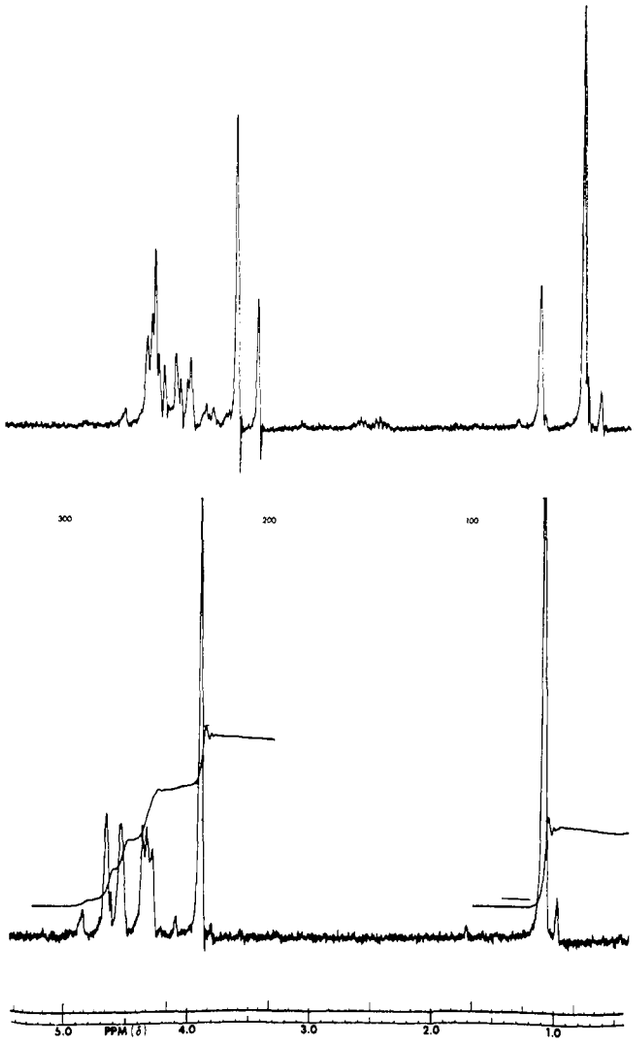


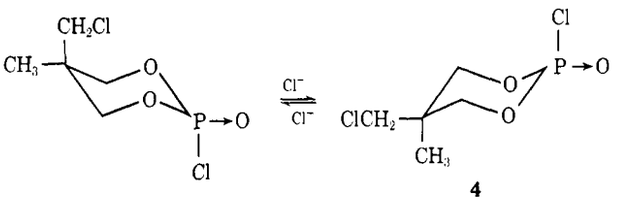
Figure 2.—Nmr spectra of phosphorochloridate (1): top, in DMF-d_7; bottom, in $CDCl_3$.

and other isomers described herein may indeed undergo conformational mobility; however, mobility in those cases where it does exist does not hinder us from distinguishing between two geometrical isomers.[10] Peaks never tend to coalesce even at elevated temperatures.

Treatment of the phosphorochloridate **1** with a number of amines, including *tert*-butylamine and aniline, gave, regardless of the solvent employed, a single isomer. Based on the similarity of the chemical shifts of groups at the fifth position (Table I) with those of the phosphoramidate **3**, the isomers are trans. It is apparent that amines attack solely by inversion of configuration at phosphorus. *p*-Nitroaniline did not react even upon refluxing the reagents in acetonitrile.

A sample of the phosphorochloridate which had been highly purified by means of repeated recrystallizations from carbon tetrachloride showed no evidence of isomerization when it was dissolved in polar solvents, *i.e.*, acetonitrile, nitrobenzene, trifluoroacetic acid, and the solutions were heated at 65° for 1 month.[10] Addition of LiCl to an acetonitrile-d_3 solution of pure phosphorochloridate did cause isomerization, as witnessed by the slow appearance of new peaks assigned to equatorial chloromethyl and axial methyl groups. Upon standing at room temperature for 1 month a final 2.5:1 ratio of isomers was observed with the original, cis, predominating. No isomerization was observed upon addition of $LiClO_4$ or $LiOSO_2C_6H_4CH_3$ to acetonitrile solutions of the pure phosphorochloridate. A 2.5:1 ratio of phosphorochloridate isomers was also obtained upon vacuum distillation of the pure starting material. The distillation is accompanied by partial decomposition. It is believed, upon the basis of these results and those reported by others with respect to reactions of phosphorochloridates,[11] that the phosphorochloridate reacts *via* an associative bimolecular mechanism and that the observed isomerization is initiated by added chloride ion or by chloride ion produced by decomposition during distillation.[12]

Addition of piperidine to an isomerized mixture of phosphorochloridate gave the two amides, **2** and **3**, in a 1:2.5 ratio and it is therefore assumed based on the preference for amines to react with inversion that the new isomer, **4**, also has the chlorine at phosphorus in an axial position.



4

Upon dissolving the phosphorochloridate in dimethylformamide (DMF), isomerization to the equilibrium mixture was complete within 15 min (Figure 2). In this instance as with acyclic dialkyl phosphorochloridates[13] there is probably solvent participation with concurrent chloride ion formation. A similar phenomenon was observed when pyridine-d_5 was employed.

The preferred conformation of each isomer appears to be regulated by the preference of groups at phosphorus to be either axial or equatorial. Whereas single-crystal analysis has shown the amino group to prefer an equatorial position, we have by similar techniques shown that in the case of the phenyl esters the phenoxy group, like chloride, assumes in the solid state an axial position. It is obvious that in order to determine the stereochemical outcome of substitutions each class of compounds must be handled separately and the configuration about phosphorus must be known with certainty. The 2.5:1 equilibrium ratio of isomers obtained upon equilibration indicates that the chloromethyl group prefers an axial position, which may be the result of a dipole interaction between the chloromethyl group and ring oxygens. The ratio appears to be independent of the solvent employed.[14]

(10) In a subsequent paper we will describe in detail solvent and temperature studies with these and other isomer pairs. The isomers with chloromethyl group axial exist within experimental error in a single conformation. Nmr analysis indicates the isomers with chloromethyl group equatorial to exist as a mixture of the two possible conformers with the conformer having the chloromethyl group equatorial predominating by approximately a 3:1 ratio. There is very little, if any, effect of solvent on conformer ratios.

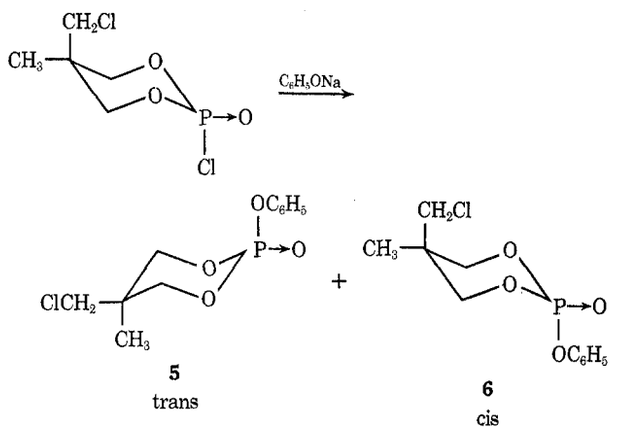
(11) P. Haake and P. S. Ossip, *J. Amer. Chem. Soc.*, **93**, 6924 (1971).

(12) Only the most favorable conformations of the isomers are shown.

(13) F. Cramer and M. Winter, *Ber.*, **94**, 989 (1961).

(14) The preference of the chloromethyl to be axial has been noted in the case of 5-chloromethyl-5-methyl-2-methoxy-1,3,2-dioxaphosphorinans: D. W. White, R. D. Bertrand, G. K. McEwen, and J. G. Verkade, *J. Amer. Chem. Soc.*, **92**, 7125 (1970).

Treatment of an acetonitrile solution of phosphorochloridate (1) with sodium phenoxide gave a mixture of isomers which could be separated by chromatography (Figure 3). Single-crystal X-ray analysis indicated that the isomers have the phenoxy groups in an axial position. Thus substitution proceeds by both inversion and retention. Each isomer showed no tendency



5
trans

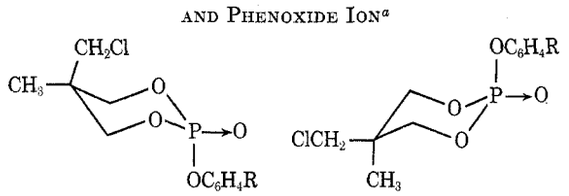
6
cis

to isomerize on dissolving in polar solvents and heating the solutions. Also, an acetonitrile-d_3 solution of each to which sodium phenoxide had been added, when heated at 70° for 4 days, gave no indication of isomerization. The product ratio is therefore kinetically controlled. The same was true for the *p*-methoxyl, *p*-methyl, and *p*-bromophenyl esters.

As in the case of the phosphoramidates the isomers can easily be identified by chemical shift differences (Table II), once the configuration at phosphorus is known.

The ratio of geometrical isomers obtained varies with the basicity of the nucleophile (Table III). The

TABLE III
PHENYL ESTERS OBTAINED FROM PHOSPHOROCHLORIDATE 1 AND PHENOXIDE ION[a]



R	%	%
OCH_3	57	43
CH_3	50	50
H	48	52
Br	36	64
NO_2[b]	6	94

[a] Isomer ratios (%) were obtained by integration of spectra obtained in $CDCl_3$ as solvent. Reactions were carried out in dried acetonitrile. [b] Care had to be taken to avoid the use of excess sodium *p*-nitrophenoxide.

stronger the basicity of the nucleophile the greater the substitution by retention. In the case of the pure trans *p*-nitrophenoxy ester, as in the case of the other phenyl esters there was no observed isomerization when an acetonitrile-d_3 or DMF-d_7 solution was heated at 70° for 1 month. Addition of a small amount of sodium *p*-nitrophenoxide in this case, however, did cause isomerization with the final 2.5:1 cis to trans ratio being obtained in acetonitrile after 3 days at room temperature and in DMF-d_7 after 2 hr (Figure 4). The results reflect the enhanced ability of *p*-nitrophenoxide ion to act as a leaving group. It is possible that the small amount of cis isomer obtained upon treatment of the phosphorochloridate with sodium *p*-nitrophenoxide might arise from subsequent isomerization of the product, and substitution in this case is entirely by inversion.

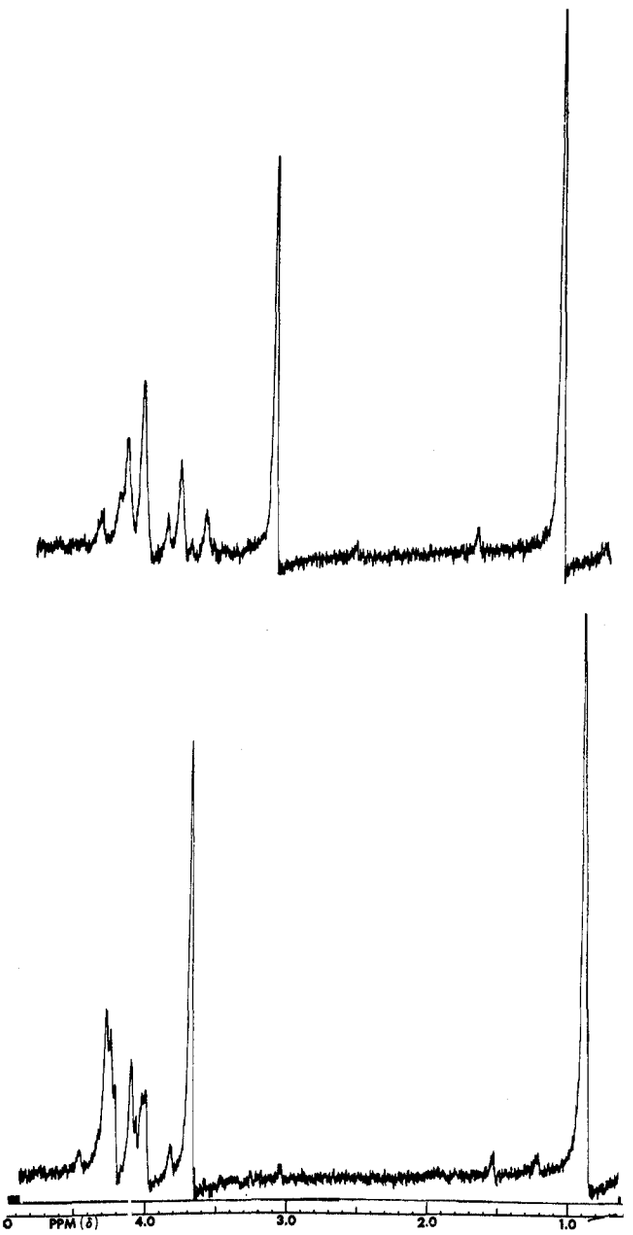


Figure 3.—Nmr spectra of phenyl esters in $CDCl_3$: top, trans; bottom, cis.

There was a noticable difference in the cis to trans ratio of isomers obtained when the substitutions were carried out in solvents in which the sodium salts were insoluble. Thus when sodium phenoxide was added to a benzene solution of the phosphorochloridate the amount of cis isomer rose to 85%. Under similar heterogeneous conditions the amount of *cis*-*p*-methoxyphenyl ester rose to 88% and the *p*-nitrophenyl ester to 40%. Under essentially homogeneous conditions, regardless of the solvent, results were similar to those obtained in acetonitrile, in which the salts were at least

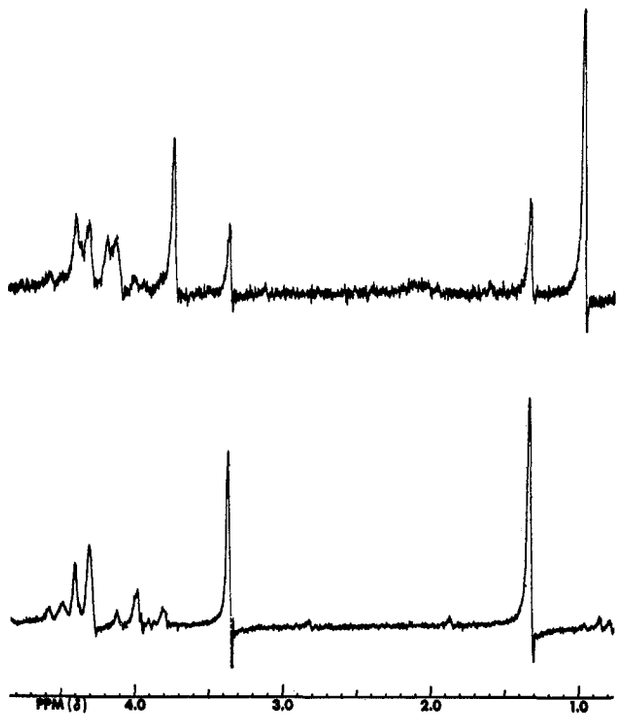
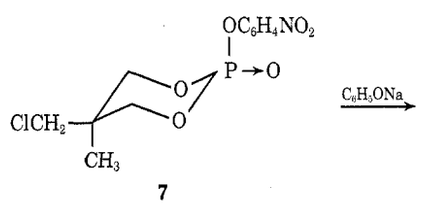


Figure 4.—Nmr spectra of *p*-nitrophenyl esters: bottom, ester **7** in DMF-d_7; top, after equilibration with sodium *p*-nitrophenoxide.

partially soluble. Thus retention is enhanced under heterogenous conditions.

Treatment of a benzene solution of the pure *trans*-*p*-nitrophenyl ester **7** with sodium phenoxide gave a mixture of phenyl esters. Again the cis isomer may arise



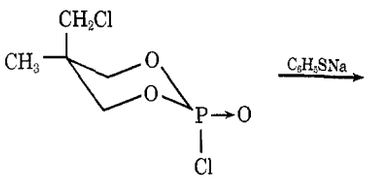
7

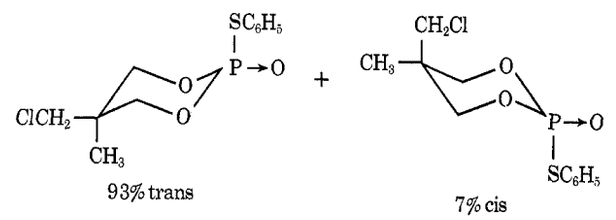
75% trans (**5**) + 25% cis (**6**)

from partial equilibration of the starting material by *p*-nitrophenoxide ion formed as a by-product. Treatment of an equilibrated, 2.5:1 cis to trans mixture of *p*-nitrophenyl ester isomers with sodium phenoxide gave a mixture of phenyl ester isomers in a 2.5:1 cis to trans ratio. Thus substitution appeared to proceed predominantly by retention, which again reflects the ability of charged nucleophiles to substitute in this fashion. *p*-Nitrophenoxide ion is an excellent leaving group, which may also be a factor.

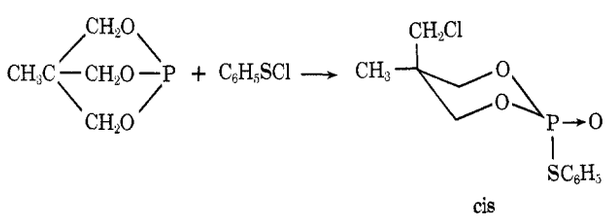
In contrast to results obtained at room temperature, under prolonged reflux in acetonitrile trans *p*-nitrophenyl ester **7** reacted with added sodium *p*-nitrophenoxide to give *p*-nitrophenyl ether. A similar C–O bond scission to give *N*-*p*-nitrophenylpiperidine took place when the ester was warmed with piperidine. In the latter case no products resulting from substitution at phosphorus could be detected.

Treatment of the phosphorochloridate dissolved in acetonitrile with sodium thiophenoxide gave a mixture of isomers with that having chloromethyl group equatorial predominating, 93%. When carried out in benzene the same isomer fell to 89% of the mixture, which would again indicate that heterogeneous conditions favor retention although substitution by inversion is the favored pathway. As in the case of the phenoxy analogs, the phosphoryl oxygen is assigned



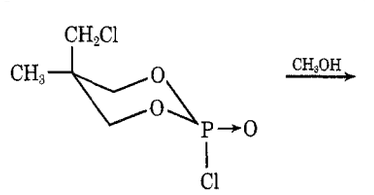


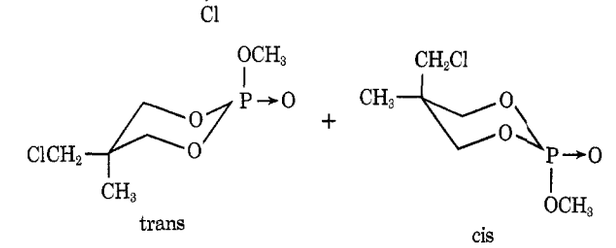
an equatorial position. Treatment of methyl bicyclic phosphate with benzene sulfenyl chloride gave a single isomer with the chloromethyl group axial. Based on the structure of the phosphite and the mechanisms



of the ring opening the product must be cis with the phosphoryl oxygen equatorial.

Upon distillation of a methanolic solution of the phosphorochloridate which had stood for 18 hr at room temperature, a mixture of isomers in which the trans predominated was obtained (Figure 5). We have





assumed based on an analogy with the phenyl esters that the methoxy groups at phosphorus which have the same magnetic environment in both isomers prefer an axial position.[15]

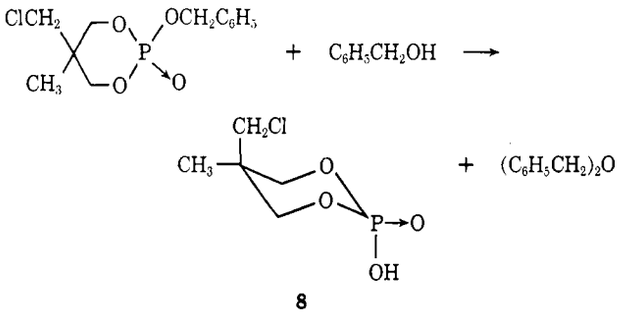
The solvolysis could be conveniently followed by employing methanol-d_4 and observing the appearance of new peaks due to the formation of equatorial chloro-

(15) There is precedent for assuming an equatorial phosphoryl oxygen in esters of this type: H. J. Geise, *Recl. Trav. Chim. Pays-Bas*, **86**, 362 (1967); D. W. White, G. K. McEwen, R. D. Bertrand, and J. G. Verkade, *J. Chem. Soc. B*, 1454 (1971); J. R. Campbell and L. D. Hall, *Chem. Ind.* (*London*), 1138 (1971).

methyl and axial methyl groups. Interestingly, upon continued standing, the peaks due to the cis isomer, chloromethyl group axial, slowly increased while those of the trans isomer decreased until after 1 month the equilibrium 2.5:1 ratio was obtained. Apparently the initially formed product is equilibrated by acid-catalyzed methanol exchange. A similar slow isomerization was observed by adding the trans methyl ester to methanol-d_4 containing *p*-toluenesulfonic acid.

Methanolysis in the presence of 1 equiv of sodium bicarbonate which removed HCl as it formed gave essentially pure trans isomer (Figure 5). In this case acid-catalyzed alcohol exchange was eliminated and no equilibrium of the initially formed product was observed. It is apparent that initially methanolysis proceeds by inversion of configuration, a not unexpected result considering the low basicity of the nucleophile. Solvolysis with isopropyl alcohol also gave, based on the chemical shifts of groups at the 5 position, pure trans isomer. In the latter case no equilibration due to alcohol exchange was observed even without removal of HCl. Alcohol exchange, if it does occur, must be extremely slow.

The solvolysis are complicated by concurrent formation of acid **8**. The acid arises from C–O bond scission, as indicated by the isolation of benzyl ether from a mixture of the phosphorochloridate and benzyl alcohol which had stood at room temperature for 6 months. The acid does not undergo esterification



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when placed in methanol to which a small amount of *p*-toluenesulfonic acid had been added. Thus it is unlikely that results obtained upon methanolysis are complicated by esterification of the acid by-product. Unfortunately, treatment of a solution of the trans methyl ester with sodium methoxide gave an exothermic reaction from which the sodium salt of the acid **8** was the only isolable product.

The nmr spectrum of the acid (Table II) indicates that the chloromethyl group prefers an axial position. Treatment of an acetonitrile solution of the acid containing 1 equiv of triethylamine with benzoyl chloride gave a mixture of 2-benzoyloxy isomers in which, again assuming the phosphoryl oxygen to be equatorial, the cis predominated over the trans by a 3:1 ratio. Our results would indicate that the hydroxyl group is predominantly in the axial position.

The mechanism leading to inversion can be readily explained by assuming a trigonal bipyramid transition state in which the entering and leaving groups occupy axial positions. The transition state leading to retention is more difficult to define. There are a number of options, *i.e.*, a trigonal bipyramid with entering

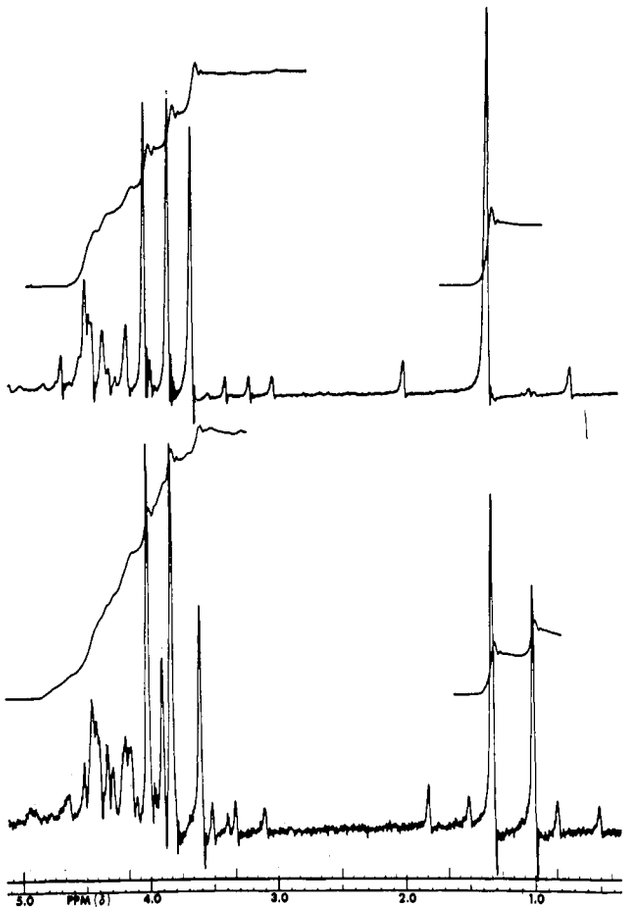
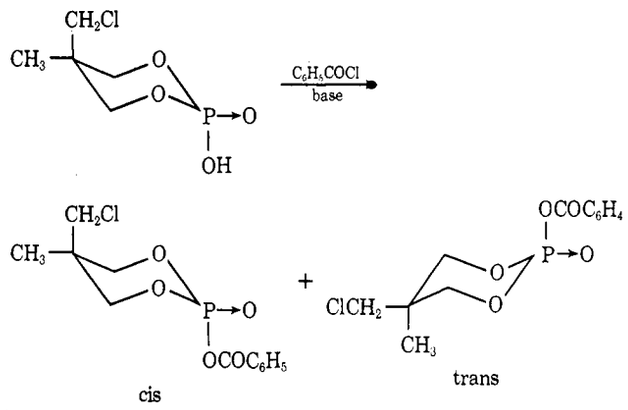


Figure 5.—Nmr spectra of methyl esters in $CDCl_3$: bottom, product resulting from methanolysis of phosphorochloridate (1); top, methanolysis in the presence of 1 equiv of solid sodium bicarbonate.



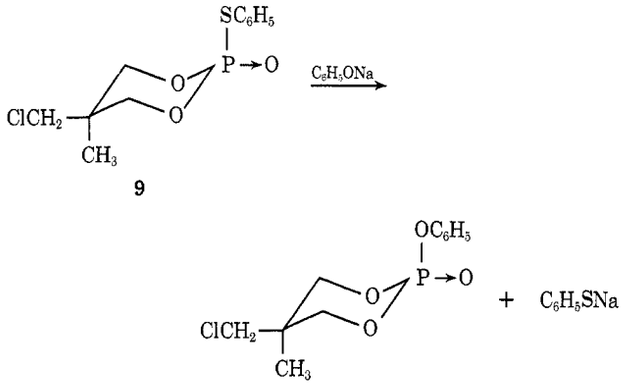
and leaving groups in different planes which may entail pseudorotation,[16] or a square pyramid with entering and leaving groups in radial positions. Pseudorotation appears to be unattractive, for the six-membered ring would be required to span both axial and equatorial positions, which might require considerable ring strain.

The stereochemical outcome appears to depend primarily upon the basicity of the attacking nucleophile, at least in those cases where a charged nucleophile is employed. Thus the thiophenoxide ion, which is a weaker base but stronger nucleophile than the phenoxide ion, displaces predominantly by inversion whereas the latter is more capable of substitution by

(16) F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968).

retention. The P–O bond is nearly twice as strong as the P–S bond, which may be a factor.

The importance of the basicity of the nucleophile and its role in the stereochemistry of the displacement is perhaps best exemplified by the observation that phenoxide ion is capable of completely displacing thiophenoxide ion from phosphorus. Treatment of an acetonitrile solution of *trans*-2-thiophenoxyphosphorinane (**9**) with 1 equiv of sodium phenoxide gave



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at room temperature the trans phenyl ester. No starting material was recovered. As in the case of the treatment of the *p*-nitrophenyl esters with sodium phenoxide, the substitution proceeds entirely by retention. Again, the fact that treatment of the phosphorochloridate **1** with sodium phenoxide results in displacement with partial inversion would indicate that the leaving group has an influence on the stereochemical results.

The possibility of a dissociative mechanism is not supported by the evidence. Isomerization does not occur when the purified phosphorochloridate or esters are dissolved in polar solvents and the solutions heated. In contrast, when a better leaving group than chloride ion, *i.e.*, benzoyloxy, is at the 2 position, isomerization occurs readily merely upon melting or allowing solutions to stand.[17] In the latter case the rate of isomerization is dependent upon solvent polarity and is believed to involve prior ionization to a phosphoryl cation. A similar dissociative mechanism has been observed for pyrophosphate and 2,4-dinitrophenyl esters.[18]

Experimental Section

2-Chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane.—A solution of methyl bicyclic phosphite, 37.0 g (0.25 mol), in 200 ml of carbon tetrachloride was added dropwise with ice-bath cooling and stirring to a solution of sulfuryl chloride, 33.75 g (0.25 mol), in 200 ml of carbon tetrachloride. After the exothermic addition, the solution was stirred for 1 hr and stripped under reduced pressure. The liquid residue which crystallized on standing was recrystallized twice from carbon tetrachloride to give 49 g (91% yield) of white crystalline product, mp 69–71°.

Anal. Calcd for $C_5H_9Cl_2O_3P$: C, 27.43; H, 4.15; P, 14.10. Found: C, 27.32; H, 4.25; P, 14.41.

The nmr spectrum of the product confirmed its structure. After heating a sample at 150° for 48 hr a dark liquid was obtained which upon distillation, bp 130–140° (0.2 mm), gave a distillate whose nmr spectrum indicated a mixture of isomers with that isomer having the chloromethyl group axial predominating in a 2.5:1 ratio, mp 59–60°. Near the end of the distillation violent decomposition took place.

(17) W. S. Wadsworth, Jr. *J. Chem. Soc., Perkin Trans. 2*, in press.
(18) To be published.

5-Chloromethyl-5-methyl-2-oxo-2-piperidino-1,3,2-dioxaphosphorinane (3).—A sample of the phosphorochloridate, mp 69–71°, was dissolved in benzene and a slight excess of piperidine was added. After the initial exotherm had subsided, the solution was stripped under reduced pressure and the residue after a water wash was recrystallized from hexane, mp 153–154°. The yield was nearly quantitative.

Anal. Calcd 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.

Using an identical procedure the distilled phosphorochloridate gave a mixture of phosphoramidates, mp 137–138°.

2-Piperidino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane (2).—A procedure identical with that reported earlier by the author[4] was followed.

Isomerization of Phosphorochloridate (1).—The phosphorochloridate, 1.0 g (0.0046 mol), was added to 5 ml of freshly distilled DMF. After standing for 2 hr, the solution was treated with an excess of piperidine, giving rise to an exotherm. The solution was stripped at reduced pressure and the crystalline residue was washed well with water. The insoluble material was dried to give 0.8 g (66% yield) of a mixture of the two phosphoramidates **2** and **3** in a 1:2.5 ratio as determined by nmr, mp 137–138°. The mixture could be separated into the pure phosphoramidates by fractional crystallization from hexane.

2-Hydroxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane.—Phosphorochloridate (1), 10.0 g (0.046 mol), was added to 25 ml of water and the mixture was heated with a low flame until it became homogeneous. The solution was chilled in an ice bath and suction filtered to give a white, crystalline product which after recrystallization from acetonitrile gave 8.5 g (92% yield), mp 144–146°.

Anal. Calcd for $C_5H_{10}O_4PCl$: C, 30.00; H, 5.00; Cl, 17.50. Found: C, 30.11; H, 5.14; Cl, 17.54.

Methanolysis of 2-Chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxphosphorinane.—The phosphorochloridate, 10 g (0.046 mol), was dissolved in 50 ml of methanol. After standing for 18 hr excess methanol was removed under reduced pressure. The viscous residue was distilled to give 6.35 g (65% yield) of viscous distillate, bp 140–142° (0.6 mm), which crystallized on standing. The nmr spectrum confirmed the structure as 2-methoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxophosphorinane. The methyl hydrogens are split into a doublet by the phosphorus atom.

Anal. Calcd 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 nonvolatile residue from the distillation was recrystallized from acetonitrile and proved to be identical with authentic acid **8**. A sample of the isomeric methyl esters when refluxed overnight in methanol and excess solvent removed under reduced pressure gave a nearly quantitative yield of the acid.

The methanolysis was repeated with the exception that the starting phosphorochloridate was added to methanol in which 1 equiv of sodium bicarbonate had been added. After standing for 18 hr the solution was filtered and the product was isolated as previously described, 60% yield. The nmr spectrum of the product in this case, however, showed the presence of only one isomer, that with the chloromethyl group equatorial.

The trans methyl ester was placed in methanol-d_4 and the solution was allowed to stand at room temperature for 2 weeks. No change in isomer ratio was noted. There was also no change upon warming a DMF-d_7 solution of the isomer. Addition of a small amount of *p*-toluenesulfonic acid to the methanol-d_4 solution gave slow equilibration to a 2.5:1 ratio of cis to trans isomers.

2-Isopropoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane.—Phosphorochloridate (1), 10.0 g (0.045 mol), was dissolved in 100 ml of isopropyl alcohol and the solution was allowed to stand for 2 weeks. Solvent was removed under reduced pressure. The residue which solidified upon cooling was recrystallized twice from hexane, 7.2 g (65% yield), mp 74–75°.

Anal. Calcd for $C_8H_{16}ClO_4P$: C, 39.66; H, 6.61; P, 12.81. Found: C, 39.39; H, 6.86; P, 12.88.

The nmr spectrum of the product showed it to contain a single isomer having the chloromethyl group equatorial.

Benzyl Ether.—Phosphorochloridate (1), 5.0 g (0.023 mol), was dissolved in 75 ml of benzyl alcohol and the solution was allowed to stand for 6 months. Excess solvent was removed under reduced pressure and the semisolid residue was extracted with chloroform. The insoluble material was recrystallized from acetonitrile to give 3.4 g (74% yield) of acid **8**, identical with

authentic material. The chloroform filtrate was distilled, giving 2.10 g (46% yield) of product at 190° (60 mm) whose ir spectrum was identical with that of authentic dibenzyl ether.

2-Phenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane.—Phosphorochloridate, 4.36 g (0.02 mol), and sodium phenoxide, 2.32 g (0.02 mol), were added to 20 ml of freshly distilled acetonitrile. The mixture was stirred at room temperature for 10 hr and stripped under reduced pressure. The residue was washed well with water and recrystallized from hexane to give 3.05 g (60.3% yield) of product which proved from its nmr spectrum to be a mixture of isomers, Table II. Recrystallization did not change the isomer ratio of the crude product.

Anal. Calcd for $C_{11}H_{14}ClO_4P$: C, 47.82; H, 5.07; P, 11.23. Found: C, 47.73; H, 5.12; P, 11.17.

A procedure similar to that described above was used to prepare other esters. The phenyl ester isomers were separated by silica gel column chromatography using chloroform elution; the isomer with the axial chloromethyl group has mp 105°; the isomer with the equatorial chloromethyl group has mp 131°. A DMF-d_7 solution of either isomer when warmed to 85° showed no sign of equilibration.

2-*p*-Nitrophenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane.—The phosphorochloridate (1), 8.72 g (0.04 mol), and sodium *p*-nitrophenoxide, 6.44 g (0.04 mol), were added to 50 ml of acetonitrile. The mixture was stirred overnight at room temperature and filtered. The filtrate was stripped of solvent under reduced pressure to give a viscous residue which crystallized on standing. The product was recrystallized from carbon tetrachloride to give 10.0 g (78% yield) of crystalline product, mp 106–107°. The nmr spectrum showed predominantly one isomer, that with the chloromethyl group equatorial.

Anal. Calcd for $C_{22}H_{23}ClNO_6P$: C, 41.12; H, 4.05; P, 9.65. Found: C, 40.96; H, 4.21; P, 9.47.

The nearly pure trans isomer was equilibrated by adding the product obtained above, 1.61 g (0.005 mol), and sodium *p*-nitrophenoxide, 0.81 g (0.005 mol), to 5 ml of DMF. The solution was stirred at room temperature for 2 hr and diluted with a large excess of water. The solution was filtered and the product was recrystallized to give 1.45 g (90% yield) of a mixture of isomers (Figure 4).

Transesterification with Sodium Phenoxide.—The trans *p*-nitrophenyl ester **7**, 1.6 g (0.005 mol), and sodium phenoxide, 0.56 g (0.005 mol), were added to 20 ml of acetonitrile. The solution after being stirred overnight at room temperature, was filtered and the filtrate was stripped at reduced pressure. The residue was washed well with water and recrystallized from hexane to give a mixture of phenyl isomers (60% yield). Recrystallization of the crude product mixtures from hexane had no noticable affect on isomer ratios.

***p*-Nitrophenyl Ether.**—The *p*-nitrophenyl ester **7**, 3.21 g (0.01 mol), and sodium *p*-nitrophenoxide, 1.61 g (0.01 mol), were added to 10 ml of acetonitrile. The solution was refluxed for 2 days, cooled, and filtered. The water-soluble precipitate, 1.2 g (55% yield), proved to be the sodium salt of the acid **8**, which was converted to the acid by treatment with HCl. The filtrate was stripped at reduced pressure to give 0.7 g (27% yield) of product, mp 141° (lit.[19] mp 142°), whose ir spectrum was identical with that of an authentic sample of *p*-nitrophenyl ether. The alcohol filtrate from the recrystallization was stripped to a viscous oil which was not characterized further.

(19) "Handbook of Chemistry and Physics," 49th ed, R. C. Weast, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1968, p C-318.

***N*-*p*-Nitrophenylpiperidine.**—*p*-Nitrophenyl ester **7**, 1.61 g (0.005 mol), was treated with 5 ml of piperidine and the solution was warmed at 40–45° for 5 hr. The solution was cooled and suction filtered to give 0.85 g (58% yield) of a water-soluble precipitate whose ir spectrum was identical after recrystallization from acetonitrile with that of the authentic piperidine salt of acid **8**. The filtrate was stripped of excess piperidine at reduced pressure and the residue was recrystallized from ethanol mp 105° (lit.[20] mp 105°), 0.55 g (55% yield).

2-Thiophenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane.—Phosphorochloridate, 8.72 g (0.04 mol), and sodium thiophenoxide, 5.28 g (0.04 mol), were added to 40 ml of freshly distilled acetonitrile. The mixture was stirred at room temperature for 3 hr and stripped under reduced pressure. The residue was washed well with water and recrystallized from carbon tetrachloride to give 9.4 g (80.3% yield) of product, mp 88–89°, which proved from its nmr spectrum to be a mixture of isomers with the trans isomer, chloromethyl group equatorial, predominating by a 15:1 ratio. Recrystallization did not change the isomer ratio of the crude product.

Anal. Calcd for $C_{11}H_{14}ClO_3PS$: C, 45.24; H, 4.79; Cl, 11.98. Found: C, 45.31; H, 4.72; Cl, 12.07.

When repeated in benzene an 8:1 ratio of isomers was obtained with the trans predominating.

The pure cis isomer, chloromethyl group axial, was obtained by adding methyl bicyclic phosphite to a chloroform solution of benzenesulfenyl chloride. A procedure previously reported[21] for trialkyl phosphites was employed. The product (42% yield) was recrystallized from hexane, mp 124–125°.

Anal. Calcd for $C_{11}H_{14}ClO_3PS$: C, 45.24; H, 4.79; Cl, 11.98. Found: C, 45.18; H, 4.82; Cl, 12.10.

Treatment of 2-Thiophenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-phosphophorinane with Sodium Phenoxide.—To a solution of *trans*-2-thiophenoxyphosphorinane, 1.55 g (0.0053 mol), in 10 ml of dry acetonitrile was added sodium phenoxide, 0.62 g (0.0053 mol). The mixture was stirred at room temperature for 48 hr and solvent was removed under reduced pressure. The residue was washed well with water and recrystallized twice from hexane. The product, 1.029 (70% yield), had an nmr spectrum identical with that of the trans-2-phenoxy phosphorinane, mp 131°, chloromethyl group equatorial.

2-Benzoyloxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane.—To the acid, 4.0 g (0.02 mol), and triethylamine, 2.02 g (0.02 mol), in 50 ml of acetonitrile was added dropwise with stirring and cooling benzoyl chloride, 2.80 g (0.02 mol). The mixture was stirred for 1 hr and suction filtered. Solvent was removed from the filtrate under reduced pressure, and the crystalline residue was washed well with water and dried, 5.4 g (90% yield). The nmr spectrum of the crude product showed a trans to cis ratio of 1:3. The pure cis form which equilibrated to a 2.5:1 cis to trans mixture of isomers on melting, 105–107°, could be obtained pure by fractional crystallization from benzene.

Anal. Calcd for $C_{12}H_{14}O_5PCl$: C, 47.36; H, 4.60; Cl, 11.51. Found: C, 47.40; H, 4.59; Cl, 11.66.

Registry No.—**1**, 28097-07-6.

Acknowledgment.—We are grateful to the National Science Foundation for support (Grant No. GP-10959).

(20) R. L. Lantz and P. M. J. Obellianne, French Patent 1,094,452 (1955); *Chem. Abstr.*, **53**, 1248*i* (1959).

(21) D. C. Morrison, *J. Amer. Chem. Soc.*, **77**, 181 (1958).