Table I. Phosphorylation by Means of Bis(*O*-thiocarbonyl) Disulfides and Triphenylphosphine

Compd	Alkyl	Yield, %, of 6	R_f value[a]
6a	Ethyl	84	0.82
6b	*n*-Propyl	82	0.84
6c	*n*-Butyl	85	0.86
6c	*n*-Butyl	83[b]	0.85
6c	*n*-Butyl	63[c]	0.86
6d	*n*-Pentyl	83	0.87
6e	Benzyl	76	0.86

[a] Paper chromatography was performed by the desending technique using Toyo Roshi No. 51 paper. Solvent system used was 2-propanol–concentrated ammonia–water, 7:1:2 (A). [b] Three equivalents each of reagents, bis(*n*-butyl) dithiobis(thioformate) and triphenylphosphine, were used. [c] One equivalent each of reagents, bis (*n*-butyl) dithioformate and triphenylphosphine.

Table II. Solvent Effects in Phosphorylation by Means of Bis(*n*-butyl)dithiobis(thioformate) and Triphenylphosphine

Solvent	Yield, %, of 6c	Solvent	Yield, %, of 6c
THF	85	Dioxane	76
Pyridine	85	CH_2Cl_2	80
DMF	67	$CHCl_3$	78
CH_3CN	70		

In a similar manner, various mixed diesters of phosphoric acid (6) were obtained in high yields (see Table I).

The effect of the solvent was examined in order to find a suitable condition for the preparation of **6c**. Of various solvents examined, it was found that the yield of **6c** decreased when dimethylformamide (DMF) is used as the solvent (see Table II).

In the above reactions, it was shown that the yields of **6** depend on the amount of **1** and **2**. As an example, when *p*-nitrophenyl phosphate was treated with 3 equiv each of **1c** and **2**, the result was almost the same as those obtained when 5 equiv each of **1c** and **2** were used. However, when 1 equiv each of **1c** and **2** were used, the yield of **6c** remarkably decreased (see Table I).

Finally, the synthesis of 3′-*O*-acetylthymidine 5′-ethyl phosphate was attempted. When 3′-O-acetylthymidine 5′-phosphate was treated with 3 equiv each of bis(ethyl) dithiobis(thioformate) (**1a**) and **2** in dry pyridine at room temperature for 8 h, the corresponding 3′-*O*-acetylthymidine 5′-ethyl phosphate was obtained in 98% yield.

In conclusion, it was noted that this type of phosphorylation was found to be effective for the preparation of pure mixed diesters of phosphoric acid in good yield under mild condition. Differing from the case of the phosphorylation with the use of dicyclohexylcarbodiimide, trichloroacetonitrile, or 2,2′-dipyridyl disulfide and triphenylphosphine, this reaction proceeds without the formation of by-product such as symmetrical pyrophosphate to afford the phosphorylated products in high yields.

Further studies on the synthesis of carboxylic esters are now in progress.

Experimental Section

Descending paper chromatography was performed on Toyo Roshi No. 51 or 51A paper using the solvent system 2-propanol–concentrated ammonia–water, 7:1:2 (solvent A), or 1-butanol–water–concentrated ammonia, 84:16:1 (solvent B). The R_f values of different compounds are given in Table I. Paper electrophoresis was performed in a high-voltage apparatus using Toyo Roshi No. 51A paper and 0.05 M phosphate buffer at pH 7 or 8. The phosphorus compounds were detected by means of a spray of Hanes–Isherwood reagent[6] on paper. Bis(ethyl) (**1a**), bis(*n*-propyl) (**1b**), bis(*n*-butyl) (**1c**), bis(*n*-pentyl) (**1d**), and bis(benzyl) dithiobis(thioformate) (**1e**) were prepared by the procedures in the literature.[7,8] *p*-Nitrophenyl phosphate was prepared by the method of Hata.[9] Triphenylphosphine was obtained from a commercial source and purified by recrystallization. 3′-O-Acetylthimidine 5′-phosphate was prepared by acetylation of thymidine 5′-phosphate with acetic anhydride in dry pyridine.

General Method. Reaction of *p*-Nitrophenyl Phosphate with Bis(*O*-thiocarbonyl) Disulfide and Triphenylphosphine. To a solution of *p*-nitrophenyl phosphate (21.9 mg, 0.1 mmol) and bis(*O*-thiocarbonyl) disulfide (**1**, 0.5 mmol) in dry tetrahydrofuran (1 ml), triphenylphosphine (**2**, 131 mg, 0.5 mmol) was added with vigorous stirring at room temperature for 2 h. To the reaction mixture, 1 ml of water was added and then the mixture was stirred at room temperature for several minutes. The mixture was then concentrated to dryness and the residue was dissolved in water (10 ml). Chromatography was performed on paper using solvent A and B for development. Yield of the compound **6** was determined spectrophotometrically using λ_{max} (H_2O) 291 nm (ϵ 10 000) (pH 7) for alkyl *p*-nitrophenyl phosphate (**6**). The results are summarized in Tables I and II.

3′-*O*-Acetylthymidine 5′-Ethyl Phosphate. To a solution of 3′-*O*-acetylthymidine 5′-phosphate (d-pTOAc, 0.5 mmol) and bis(ethyl) dithiobis(thioformate) (**1a**, 363 mg, 1.5 mmol) in dry pyridine (2.5 ml), triphenylphosphine (**2**, 393 mg, 1.5 mmol) was added and the mixture was kept standing at room temperature. After 8 h, water (5 ml) was added and then the solution was stirred at room temperature for several minutes. The mixture was then concentrated to dryness and the residue was dissolved in water (25 ml) and extracted with ether (three 20-ml portions). The aqueous layer was evaporated to dryness, and the residue was dissolved in water, converted into the sodium form, evaporated to dryness, and dissolved in dry methanol (10 ml). Addition of dry ether (200 ml) gave a precipitate which was collected and dried in vacuo to give 252 mg (98%) of 3′-*O*-acetylthymidine 5′-ethyl phosphate as a white solid: uv (pH 7) λ_{max} (H_2O) 268 nm (ϵ 9600). Paper chromatography (solvent A) R_f 0.72. Paper electrophoresis (0.05 M phosphate, pH 8) Rd-pT 0.54. Anal. Calcd for $C_{14}H_{20}PO_9N_2Na\cdot1.5H_2O$: C, 31.08; H, 4.29; N, 5.18. Found: C, 31.17; H, 4.35; N, 5.23.

Registry No.—**1a**, 502-55-6; **1b**, 3750-28-5; **1c**, 105-77-1; **1d**, 869-91-0; **1e**, 23363-97-5; **2**, 603-35-0; **6a**, 17659-67-5; **6b**, 18123-85-8; **6c**, 18123-87-0; **6d**, 29690-44-6; **6e**, 18123-91-6; d-pTOAc, 4304-30-7; *p*-nitrophenyl phosphate, 330-13-2; sodium 3′-*O*-acetylthymidine 5′-ethyl phosphate, 57821-08-6.

References and Notes

(1) H. G. Khorana and A. R. Todd, *J. Chem. Soc.*, 2257 (1953).
(2) F. Cramer and G. Weimann, *Chem. Ber.*, **91**, 996 (1961).
(3) T. Mukaiyama and M. Hashimoto, *Bull. Chem. Soc. Jpn.*, **44**, 196 (1971).
(4) (a) H. Takaku and Y. Shimada, *Chem. Pharm. Bull.*, **21**, 445 (1973); (b) H. Takaku, Y. Shimada, and K. Arai, *Bull. Chem. Soc. Jpn.*, **47**, 779 (1974); (c) H. Takaku and Y. Shimada, *Chem. Pharm. Bull.*, **22**, 1743 (1974); (d) H. Takaku and Y. Shimada, *Tetrahedron Lett.*, 1279 (1974); (e) H. Takaku, Y. Shimada, and T. Hata, *Chem. Lett.*, 873 (1975).
(5) (a) I. Iwasaki and S. R. B. Cooke, *J. Am. Chem. Soc.*, **80**, 285 (1958); *J. Phys. Chem.*, **63**, 1321 (1959); (b) E. Klein, J. K. Bosarge, and I. Norman, *ibid.*, **64**, 1666 (1960); (c) C. A. Bunton, P. Ng, and L. Sepulveda, *J. Org. Chem.*, **39**, 1130 (1974); (d) C. A. Bunton, J. E. Salame, and L. Sepulveda, *ibid.*, **39**, 3128 (1974).
(6) C. S. Hanes and F. A. Isherwood, *Nature (London)*, **164**, 1107 (1947).
(7) G. Bulmer and F. G. Mann, *J. Chem. Soc.*, 974 (1945).
(8) G. Losse and E. Wottgen, *J. Prakt. Chem.*, **13**, 260 (1961).
(9) K. J. Chong and T. Hata, *Bull. Chem. Soc. Jpn.*, **44**, 2741 (1971).

Phosphorus Tribromide Promoted Allylic Rearrangement of a Tertiary Vinyl Carbinol. Stereochemistry of the Reaction Product and Application to the Synthesis of JH-25, a Potent Juvenile Hormone Mimic

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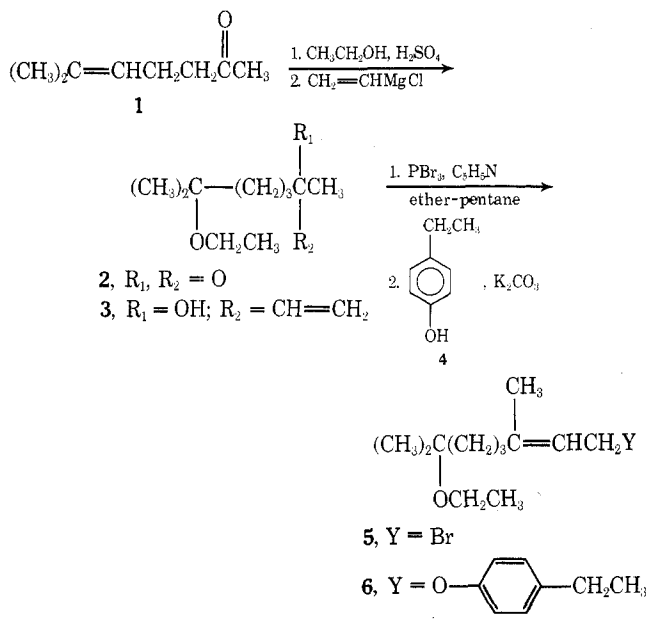
In recent years considerable attention[1] has been given to the possibility of controlling insect pests by interfering with the action of certain hormones that regulate normal

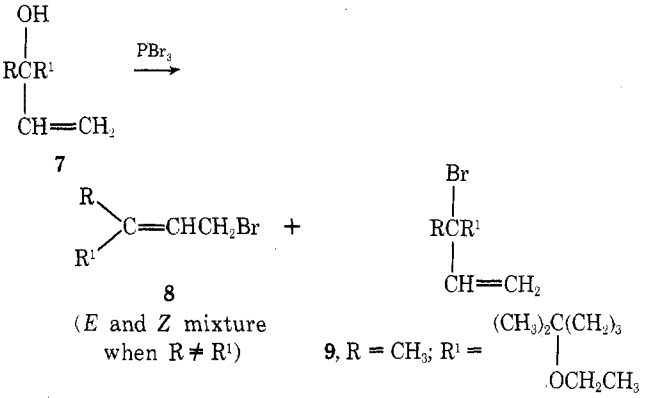
development. Interest in particular has been focused on methyl *trans,trans,cis*-10,11-epoxy-7-ethyl-3,11-dimethyltrideca-2,6-dienoate, which is one of two juvenile hormones occurring naturally in the silk moth *Hyalophora cecropia*.[2] In attempts to discover potentially more effective agents that possess activity similar to the latter chemical, a large number of organic compounds have been synthesized and evaluated as mimics of the natural product.[1] Among the more potent of the synthetic juvenile hormone mimics reported to date is 7-ethoxy-1-(*p*-ethylphenoxy)-3,7-dimethyl-2-octene (**6**) (called JH-25),[3] a facile synthesis of which is reported in this note.

In the previous synthesis[3] of JH-25 (**6**), the 7-ethoxy substituent was introduced in the last stage by a two-step process involving ethoxymercuration of 1-(*p*-ethylphenoxy)-3,7-dimethyl-2,6-octadiene, followed by demercuration using sodium borohydride. In order to expedite matters and avoid the problem of selective electrophilic addition to the latter diene, this same functionality was conveniently introduced at an early stage by acid-catalyzed addition of ethanol to the commercially available[4] 6-methyl-5-hepten-2-one (**1**). Although this reaction proceeded quite slowly in relationship to the corresponding methanolysis[5] of keto olefin **1**, 6-ethoxy-6-methyl-2-heptanone (**2**) could be obtained in approximately 60% yield after purification via fractional distillation. Subsequent addition of vinylmagnesium chloride to ketone **2**, followed by rearrangement of tertiary vinyl carbinol **3** using phosphorus tribromide, proceeded smoothly to afford the primary allylic halide **5**. The synthesis was completed by treatment of the latter (**5**) with *p*-ethylphenol (**4**) and potassium carbonate in acetone to yield, after purification by fractional distillation, JH-25 (**6**) in 54% overall yield from keto ether **2**. The NMR spectrum and physical properties of the final product were fully consistent with those previously reported[3] for this juvenile hormone mimic.

Scheme I



Since the *E* stereoisomer of JH-25 (**6**) is the one necessary for maximum biological activity, the stereochemistry of the final product was ascertained both by VPC and NMR analysis, and the *E*/*Z* ratio was found to be 75/25. Since the stereochemistry of the $\Delta^{2,3}$ double bond is determined during the allylic rearrangement of tertiary vinyl carbinol **3** to the primary allylic bromide **5**, these results indicate, not surprisingly, that such allylic transpositions



(i.e., **7** → **8**) do not necessarily proceed stereoselectively. Previous reports of this same type of rearrangement in the literature[6] fail to mention the stereochemistry of the rearranged double bond, although the implication is that it has the *E* (trans) configuration.

In an attempt to improve the yield and the stereoselectivity of the rearrangement step (**3** → **5**), the reaction was run at −70 °C and the results were compared with those obtained using a reaction temperature of −5 °C. The low-temperature reaction gave an increased material balance (92% vs. 79% when run at −5 °C), but the crude product contained approximately 30% of the unrearranged tertiary vinyl bromide **9**. Since the latter compound (**9**) affords a mixture of uncharacterized dienes in the next step of the synthesis, JH-25 (**6**) was produced in comparable yield in both cases. Furthermore, VPC and NMR[7] analysis indicated that the final product (**6**) was a 75:25 mixture of *E*:*Z* stereoisomers, irrespective of the temperature at which the rearrangement was effected.

Experimental Section[8]

6-Ethoxy-6-methyl-2-heptanone (2). Concentrated H_2SO_4 (7.0 ml) was added dropwise over a period of 10 min to an ice-cold solution of 16.94 g (134 mmol) of 6-methyl-5-hepten-2-one[4] in 51.5 ml (880 mmol) of absolute ethanol. After this mixture was stirred at room temperature for 70 h, it was poured into 400 ml of water and the product was isolated in the usual manner[8] by extraction with methylene chloride. Fractional distillation afforded 13.21 g (57%) of keto ether **2**: bp 51–55 °C (0.25 mm); 98% pure by VPC analysis,[9] oven temperature 133 °C, retention time 4.2 min; ν_{max} (film) 1715 (C=O), 1252, 1204, 1167, 1150, 1130, 1107, 1067, 945 cm^{-1}; δ_{Me_4Si} (CCl_4) 3.32 (quartet, J = 7 Hz, OCH_2CH_3), 2.06 (s, $O{=}CCH_3$), 1.11 (s, 6 H, geminal CH_3's), 1.09 ppm (t, J = 7 Hz, OCH_2CH_3). Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.71; H, 11.70. Found: C, 69.70; H, 11.70.

7-Ethoxy-3,7-dimethyl-1-octen-3-ol (3). A solution of 1.730 g (10.03 mmol) of ketone **2** in 6.0 ml of anhydrous ether was added dropwise over a period of 5 min to 6.0 ml of 2.2 M vinylmagnesium chloride–tetrahydrofuran solution, cooled to 0 °C in an ice water bath. After this mixture was stirred at 0 °C for 20 min, the reaction was quenched by dropwise addition of saturated aqueous NH_4Cl solution. Extraction[8] of the product with ether, followed by evaporative distillation, afforded 1.794 g (89%) of tertiary vinyl carbinol **3**: bp 60–73 °C (bath temperature, 0.08 mm); ν_{max} (film) 3460 (OH), 3115, 1635 (C=C), 1240, 1185, 1160, 1105, 1060, 985, 940, 905 cm^{-1}; δ_{Me_4Si} (CCl_4) 5.87 ($CH{=}CH_2$, J_{AC} = 10, J_{BC} = 18 Hz), 5.29–4.85 ($CH{=}CH_2$, rest of ABC pattern[10]), 3.31 (quartet, J = 7 Hz, OCH_2CH_3), 1.22 (s, $HOCCH_3$), 1.10 (s, 6 H, geminal CH_3's), 1.10 ppm (t, J = 7 Hz, OCH_2CH_3). Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 71.76; H, 12.06.

1-Bromo-7-ethoxy-3,7-dimethyl-2-octene (5). A solution of 0.25 ml (2.63 mmol) of PBr_3 in 5.0 ml of anhydrous ether was added dropwise slowly over a period of 10 min to a solution of 560 mg (2.79 mmol) of tertiary vinyl carbinol **3** and 0.25 ml of dry pyridine in 15 ml of pentane and 10 ml of anhydrous ether, maintained at a temperature of −70 °C using a dry ice–isopropyl alcohol bath. After this mixture was stirred at −70 °C for 70 min, it was poured into 25 ml of ice water and the product was isolated[8] by extraction with pentane. To ensure removal of the pyridine, the extracts were washed twice with 5% (v/v) aqueous H_2SO_4. The yield[11] of color-

less oily bromide (**5** and **9**), too unstable to purify and therefore used directly in the next step, was 671 mg (92%): ν_{max} (film) 1655 (C=C), 1245, 1200, 1150, 1110, 1070, 950 cm^{-1}; δ_{Me_4Si} (CCl_4), 5.49 (t, J = 8.5 Hz, C=CH), 3.93 (d, J = 8.5 Hz, CH_2Br), 3.30 (quartet, J = 7 Hz, OCH_2CH_3), 1.78 ("Z" vinyl CH_3), 1.73 ("E" vinyl CH_3), 1.11 (s, 6 H, geminal CH_3's), 1.10 ppm (t, J = 7 Hz, OCH_2CH_3). NMR analysis indicated that approximately 30% of the bromide mixture consisted of tertiary vinyl bromide **9**, characterized by peaks at 6.33, 6.17, 6.05, and 5.88 ppm ($CH=CH_2$) as well as a singlet ($W_{1/2}$ = 1.4 Hz) at 1.83 ppm ($BrCCH_3$).

7-Ethoxy-1-(*p*-ethylphenoxy)-3,7-dimethyl-2-octene (6). A mixture of 666 mg (2.53 mmol) of crude bromide **5**, 3.5 ml of acetone, 350 mg (2.86 mmol) of 4-ethylphenol, and 1.36 g of anhydrous K_2CO_3 was stirred vigorously at room temperature for 15 h. Isolation of the product by extraction[8] with pentane, followed by fractional distillation, afforded 506 mg (66%) of JH-25 (**6**): bp 120–140 °C (bath temperature, 0.05 mm); >97% pure by VPC analysis,[9] oven temperature 225 °C, E/Z ratio 75/25, retention times 8.2 (Z), 9.4 min (E); ν_{max} (film) 1665 (C=C), 1610, 1578, 1505, 1240, 1225, 1167, 1105, 1065, 1000, 950, 817 cm^{-1}; δ_{Me_4Si} (CCl_4) 6.81 (AB quartet, 4 aryl H, peaks at 7.05, 6.91, 6.74, 6.59), 5.43 (t, J = 6 Hz, C=CH), 4.43 (doublet, J = 6 Hz, CH_2OAr), 3.27 (quartet, J = 7 Hz, OCH_2CH_3), 2.56 (quartet, J = 7 Hz, $ArCH_2CH_3$), 1.77 ("Z" vinyl CH_3), 1.71 (s, "E" vinyl CH_3), 1.09 (s, 6 H, geminal CH_3's), 1.08 ppm (t, J = 7 Hz, 2 CH_3).

Registry No.—**1**, 110-93-0; **2**, 51079-72-2; **3**, 57762-04-6; **4**, 123-07-9; **5**, 51079-70-0; (*E*)-**6**, 52730-76-4; (*Z*)-**6**, 57762-05-7; **9**, 57762-06-8; PBr, 7789-60-8.

References and Notes

(1) J. J. Menn and M. Beroza, Ed., "Insect Juvenile Hormones: Chemistry and Action", Academic Press, New York, N.Y., 1972.
(2) H. Röller, K. H. Dahm, C. C. Sweeley, and B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, **6**, 179 (1967).
(3) R. Sarmiento, T. P. McGovern, M. Beroza, G. D. Mills, Jr., and R. E. Redfern, *Science*, **179**, 1342 (1973).
(4) Aldrich Chemical Co., Inc., Milwaukee, Wis.
(5) J. D. Surmatis and A. Ofner, *J. Org. Chem.*, **28**, 2735 (1963).
(6) A. Caliezi and H. Schinz, *Helv. Chim. Acta*, **35**, 1649 (1952); A. Mondon, *Chem. Ber.*, **88**, 724 (1955); O. Isler, R. Rüegg, L. Chopard-dit-Jean, H. Wagner, and K. Bernhard, *Helv. Chim. Acta*, **39**, 897 (1956); W. G. Dauben, G. H. Beasley, M. D. Broadhurst, B. Muller, D. J. Peppard, P. Pesnelle, and C. Suter, *J. Am. Chem. Soc.*, **97**, 4973 (1975).
(7) The E/Z ratio was determined by integration of the signals for the vinyl methyl group. Chemical shift data for vinyl methyls in similar functionalized trisubstituted olefins have been previously reported. See R. B. Bates and D. M. Gale, *J. Am. Chem. Soc.*, **82**, 5749 (1960); K. Ogura, T. Nishino, T. Koyama, and S. Seto, *ibid.*, **92**, 6036 (1970).
(8) Reactions were carried out under a nitrogen atmosphere. Unless indicated otherwise, the isolation of reaction products was accomplished by pouring the mixture into water or saturated brine and extracting thoroughly with the specified solvent. The combined extracts were washed with 1 M aqueous NaOH and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was removed from the dried extracts by using a rotary evaporator under reduced pressure. Evaporative distillation refers to bulb-to-bulb (Kugelrohr) short-path distillation. The NMR spectra were recorded with a Varian A-60 NMR spectrometer and infrared spectra were obtained using a Beckman Acculab 1 spectrophotometer. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill.
(9) A 6 ft × 0.125 in. SE-30 column was used for this analysis.
(10) Resolution of the signal peaks between δ 5.29 and 4.85 was not sufficient to allow a simple determination of J_{AB} and the chemical shifts for these two protons.
(11) When the reaction was run at −5 °C, the yield of crude bromide **5** was 79%, and none of the tertiary vinyl bromide **9** could be detected in the product.

Substitution at Phosphorus. The Unusual Effect of the Lithium Ion

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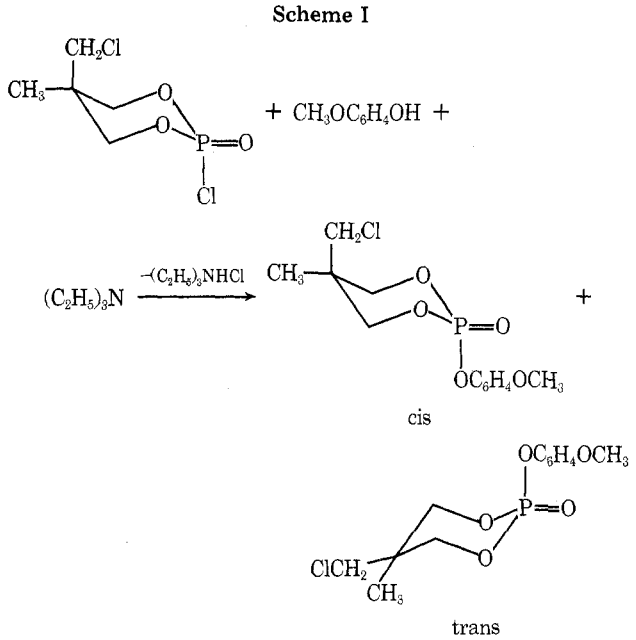
In previous papers we have shown that nucleophilic substitution at phosphorus in phosphates is strongly influenced by added cations.[1,2] We wish to report additional observations in this area and present a possible rationalization for them. As before, the conformationally immobile 2-substituted 5-chloromethyl-5-methyl-2-oxo- or 2-thio-1,3,2-dioxaphosphorinan systems were employed as substrates.[3] Inversion or retention at phosphorus upon substitution can conveniently be determined by NMR spectroscopy. Hydrogens on groups at the 5 position have different chemical shifts depending upon whether they are axial or equatorial.[4]

We have found that we can control the stereochemical pathway in at least one system (Scheme I) by the judicious selection of the cation, Table I.

Table I

	Solvent	Added salt	Retention, %	Inversion, %
a	CH_3CN	0	8.8	91.2
b	CH_3CN	$LiClO_4$ (1 equiv)	96.1	3.9
c	CH_3CN	$Mg(ClO_4)_2$ (1 equiv)	0	100
d	CH_3CN	$KClO_4$ (1 equiv)	0	100
e	Benzene	0	40.8	59.2
f	CH_3CN	$LiClO_4$ (½ equiv)	88.3	11.7
g	Tetrahydrofuran	$LiClO_4$ (1 equiv)	78.6	21.4
h	CH_3CN	$(C_2H_5)_3N^+CH_2C_6H_5Cl^-$ (1 equiv)	38.4	61.6
i	CH_3CN	$(C_2H_5)_3N^+CH_2C_6H_5Cl^-$ (1 equiv) + $LiClO_4$ (1 equiv)	94.5	5.5
j	CH_3CN	LiCl (1 equiv)	87.5	12.5

Scheme I



The combined product yields are greater than 90% with the product ratio unaffected by work-up procedures. The small yield of minor isomer in those cases where it is obtained may be due to prior isomerization of starting material by chloride ion formed as by-product. Thus, under identical reaction conditions the phosphorochloridate is slowly isomerized by slightly soluble triethylammonium chloride with 3 days required to establish equilibrium. In contrast substitutions are over in a matter of minutes. Prior isomerization would be expected in h where a soluble quaternary chloride is employed.

Strangely, the starting phosphorochloridate does not isomerize when triethylamine is added to acetonitrile or chloroform solutions. This behavior contrasts with the ac-