*cis*-**2,5-Di-*p*-bromobenzyl-2,5-dicarbethoxycyclohexane-1,4-dione (VIa)** was obtained as colorless crystals, very soluble in hot toluene and sparingly soluble in the cold. Single crystals for X-ray diffraction were obtainable by crystallization from chloroform: mp 151–152°; ir (KBr) 1710 $cm^{-1}$ (ketonic and ester C=O); nmr ($CDCl_3$) 7.42 (d, 4, $J$ = 9.0 Hz, $C_6H_4Br$), 6.93 (d, 4, $J$ = 9.0 Hz, $C_6H_4Br$), 4.17 (q, 4, $J$ = 7.0 Hz, $CH_2CH_3$), 3.23 (d, 2, $J$ = 14.0 Hz, $CH_2C_6H_4$), 3.11 (d, 2, $J$ = 14.0 Hz, $CH_2C_6H_4Br$), 2.90 (d, 2, $J$ = 16 Hz, $C_6$ ring methylene H), 2.26 (d, 2, $J$ = 16.0 Hz, $C_6$ ring methylene H), 1.28 ppm (t, 6, $J$ = 7.0 Hz, $CH_2CH_3$) ppm.

*Anal.* Calcd for $C_{26}H_{26}O_6Br_2$: C, 52.53; H, 4.37; Br, 26.90. Found: C, 52.78, 52.78; H, 5.63, 4.60; Br, 26.92.

*trans*-**2,5-Di-*p*-bromobenzyl-2,5-dicarbethoxycyclohexane-1,4-dione (VIb)** was obtained as colorless crystals slightly soluble in chloroform and acetone and very sparingly soluble in cold benzene and toluene. Single crystals were obtainable by crystallization from 1:1 acetone–benzene: mp 216–217°; ir (KBr) 1710 $cm^{-1}$ (ketonic and ester C=O); nmr ($CDCl_3$) 7.45 (d, 4, $J$ = 9.0 Hz, $C_6H_4Br$), 7.03 (d, 4, $J$ = 9.0 Hz, $C_6H_4Br$), 4.07 (q, 4, $J$ = 7.0 Hz, $CH_2CH_3$), 3.20 (s, 4, $CH_2C_6H_4Br$), 2.83 (d, 2, $J$ = 16.0 Hz, $C_6$ ring methylene H), 2.66 (d, 2, $J$ = 16.0 Hz, $C_6$ ring methylene H), 1.13 ppm (t, 6, $J$ = 7.0 Hz, $CH_2CH_3$).

*Anal.* Calcd for $C_{26}H_{26}O_6Br_2$: C, 52.53; H, 4.37; B, 26.92. Found: C, 52.66, 52.55; H, 4.62, 4.64; Br, 26.74.

**Reaction between Disodiosuccinosuccinic Ester and Benzhydryl Bromide.** A mixture of 30 g (0.1 mol) of carefully dried disodiosuccinosuccinic ester and 54.3 g (0.22 mol) of freshly distilled benzhydryl bromide free from HBr was placed in a round-bottom flask fitted with a reflux condenser. Dry toluene was added into the flask in an amount just sufficient to wet the solid mixture. The flask was heated in an oil bath under reflux for 3 hr. The color of the mixture changed from magenta to dirty green. More dry toluene was added into the flask, and the mixture was boiled for a few minutes and then filtered by suction. The filtrate partially crystallized on standing. On filtration, it gave the first crop of crystals, amounting to 23 g. By cooling the mother liquor, a second crop of crystals (10 g) was obtained which was slightly yellow owing to contamination of succinosuccinic ester. This latter can be removed from the main constituent by recrystallization from ligroin (bp 80–100°). The combined crude product free from succinosuccinic ester was crystallized from benzene. The crystals that separated were recrystallized several times from benzene. The purified product melted at 213–215° and was characterized as 2,5-dibenzhydryl-2,5-dicarbethoxycyclohexane-1,4-dione, probably having the cis configuration (VIIa). The trans isomer, which should have a higher melting point, did not seem to have been formed.

*cis*-**2,5-Dibenzhydryl-2,5-dicarbethoxycyclohexane-1,4-dione (VIIa)** was obtained as crystals: mp 213–215°; soluble in benzene, sparingly soluble in cold ethanol; ir (KBr) 1730 (ketonic C=O) and 1750 $cm^{-1}$ (ester C=O), and absorption maximum characteristic of phenyl group; nmr ($CDCl_3$) 7.20 (m, 20, $C_6H_5$), 5.55 (s, 2, CH), 3.85 (q, r, $J$ = 7.0 Hz, $CH_2CH_3$), 3.43 (d, 2, $J$ = 16.0 Hz, $C_6$ ring methylene H), 1.97 (d, 2, $J$ = 16.0 Hz, $C_6$ ring methylene H), 0.83 ppm (t, 6, $J$ = 7.0 Hz, $CH_2CH_3$).

*Anal.* Calcd for $C_{38}H_{36}O_6$: C, 77.72; H, 6.11. Found: C, 77.53, 77.81; H, 6.31, 6.15.

**Registry No.**—Ia, 50378-31-9; Ia dioxime, 50378-32-0; Ib, 50378-33-1; Ib dioxime, 50378-34-2; IIa, 50378-35-3; IIa dioxime, 50378-36-4; IIa′, 50378-37-5; IIb, 50378-38-6; IIb dioxime, 50378-39-7; IIb′, 50378-40-0; IIIa, 50378-41-1; IIIb, 50378-42-2; IVa, 50378-43-3; IVb, 50378-44-4; VIa, 50378-45-5; VIb, 50378-46-6; VIIa, 50378-47-7.

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# Nucleophilic Substitution at Phosphorus. Phosphorothioates[1]

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Cis and trans isomers of 2-substituted 5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinans were used as substrates to determine the stereochemical course of substitution at a thiophosphoryl center. Retention was found to increase with the basicity of the nucleophile while inversion increased with added salts. A mechanism is suggested.

The preparation of an optically active triester of phosphoric acid has not until very recently[2] been accomplished. Thus a definitive study of the stereochemical consequences of nucleophilic substitution at phosphorus in trialkylphosphates has been hindered by the lack of a suitable substrate. This deficiency has, at least to some extent, been overcome by the discovery[3,4] that 2-substituted 5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinans can be prepared in separable cis and trans forms. Fortunately, the geometrical isomers, owing to constraints put on the system by the large preference of groups at phosphorus to be either axial or equatorial, are for all practical purposes conformationally immobile. We have now extended the system to the 2-thio analogs and have studied, as was done previously with their 2-oxo counterparts, the influence of nucleophiles, leaving groups, and salts upon the stereochemistry of nucleophilic substitution at phosphorus.

The stereochemistry of nucleophilic substitutions at thiophosphoryl centers has been the subject of systematic investigations. Most studies which have employed optically active pyrophosphonothioates, phosphonothioic acids, and phosphonochloridothioates have concluded that substitution at thiophosphoryl centers occurs almost exclusively by inversion.[5] Optically active thiophosphates, owing to difficulties in their preparation, have not been investigated.

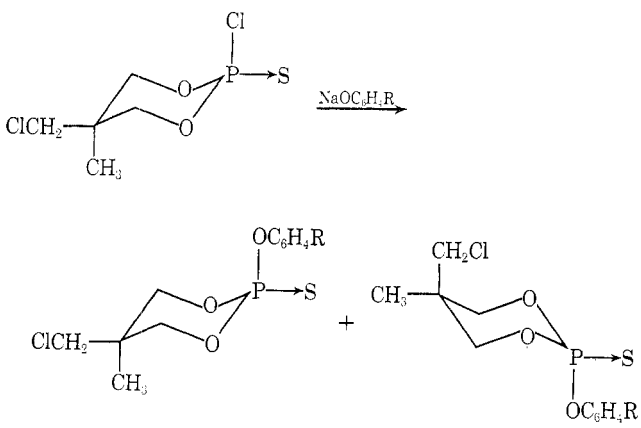
We have been successful in preparing, and in some cases purifying, a number of 2-substituted 5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinans. In all cases only a single conformer of each isomer was detected, which is in accordance with that reported for similar sys-

**Table I**
**Chemical Shifts of 2-Substituted 5-Chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinans[a]**

| R | Cis, 1 | | Trans, 2 | |
|---|---|---|---|---|
| | $CH_3$ | $CH_2Cl$ | $CH_3$ | $CH_2Cl$ |
| Cl | 1.01 | 3.74 | 1.43 | 3.37 |
| $OC_5H_4OCH_3$ | 0.96 | 3.76 | 1.17 | 3.39 |
| $OC_6H_4CH_3$ | 0.96 | 3.77 | 1.18 | 3.39 |
| $OC_6H_5$ | 0.97 | 3.89 | 1.20 | 3.39 |
| $OC_6H_4Br$ | 0.98 | 3.76 | 1.20 | 3.40 |
| $OC_6H_4NO_2$ | 1.01 | 3.81 | 1.29 | 3.47 |
| $OC_6H_3(NO_2)_2$ | 1.02 | 3.79 | 1.38 | 3.42 |

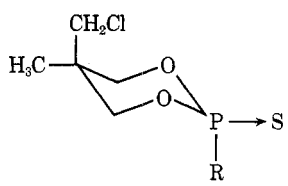
[a] Measured with a Varian A-60A spectrometer at room temperature using $CDCl_3$ as solvent. In parts per million downfield from TMS as an external standard.

**Table II**
**Treatment of *trans*-2-Chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with Various Nucleophiles in Acetonitrile**

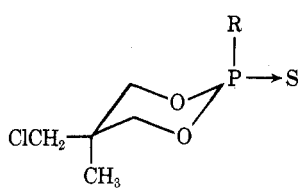



| R | % trans (retention) | % cis (inversion) |
|---|---|---|
| $OCH_3$ | 50.0 | 50.0 |
| $CH_3$ | 40.0 | 60.0 |
| Br | 23.7 | 76.3 |
| $NO_2$ | 5.1 | 94.9 |

tems based on ir studies.[6] The lack of conformational mobility persists upon heating samples to over 190°. If indeed mobility does exist to some degree in solution, it has not proved to be a hindrance in the determination of isomer ratios. As with the 2-oxo system, isomer ratios based upon the nmr spectra of isomer mixtures for groups at the 5 position have different chemical shifts dependent upon their being equatorial or axial (Table I). We have previously shown by X-ray analysis that in analogous 2-oxo esters phosphoryl oxygen occupies an equatorial position. We have assumed a similar configuration for the 2-thio esters, phosphoryl sulfur equatorial. Our assumption was validity based on the change in isomer ratios owing to effects discussed in this paper. If effects are to parallel those found in the oxo case, which they do, sulfur must be equatorial. The large preference for sulfur to be equatorial may be a major factor in limiting conformation mobility.



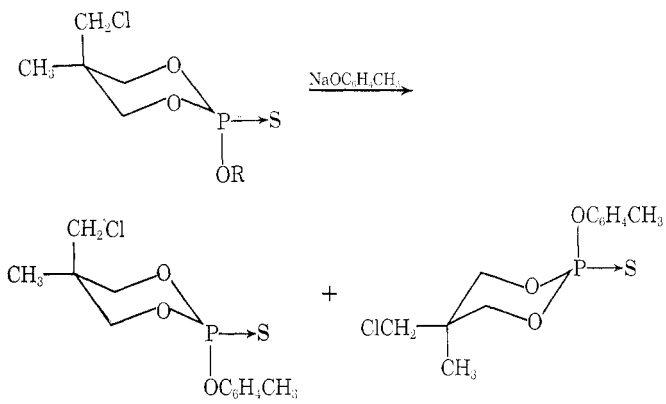

cis, 1




trans, 2

A mixture of the cis and trans isomers, 1 and 2 (R = Cl), of 2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan was prepared from thiophosphoryl chloride and 1-chloromethyl-1,1-dihydroxymethylethane. The pure trans isomer (Figure 1)[7] could be isolated by simple recrystallization and proved to be much more hydrolytically stable than the 2-oxo chloridates. It was added under standard conditions to various sodium para-substituted phenoxides, the products were isolated, and isomer ratios were determined by integration of peak heights (Figure 2).[7] In the case of the newly formed esters the pure cis isomers could be purified by fractional crystallization and these were used in further experiments. No attempt was made to isolate pure trans isomers.

**Table III**
**Treatment of Various Cis-2-Substituted 5-Chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinans with Sodium *p*-Methylphenoxide in Acetonitrile**

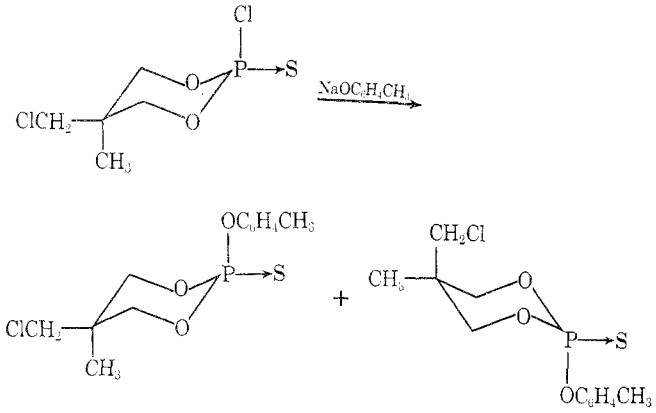



| R | % *cis* (retention) | % *trans* (inversion) |
|---|---|---|
| $C_6H_5$ | 98.5 | 1.5 |
| $C_6H_4Br$ | 97.4 | 2.6 |
| $C_6H_4NO_2$ | 95.2 | 4.8 |
| $C_6H_3(NO_2)_2$ | | |

The stereochemical outcome of substitution depended upon the structure of the attacking nucleophile (Table II). Retention increased with the basicity of the nucleophile, whereas inversion was highly favored by nucleophiles of low basicity.[8] The isomer ratios reflect the mode of substitution and are not the result of prior isomerization of the reactant or isomerization of products following their formation. Thus *trans*-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan gave no indication of isomerization after an acetonitrile solution had stood at room temperature for over 10 days. Also the pure cis isomers, separated from the initially formed products, did not undergo any detectable isomerization when dissolved in acetonitrile and the solutions allowed to stand for a period of weeks. Finally, no change in the product isomer ratios was detected under the reaction conditions and the ratios did not vary during work-up. Yields from the substitutions were consistently above 90%. Thus evidence is provided that substitutions are kinetically controlled.

We have found that the mode of substitution is also dependent upon the stability of the leaving group. Cis 2-substituted 5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinans were added to sodium *p*-methylphenoxide dissolved in acetonitrile and products were isolated. Analysis of nmr spectra indicated that inversion was aided by an increase in stability of leaving groups (Table III). Comparison of Table II with Table III indicates that the trans thio chloridate, 2 (R = Cl), substitutes with a much higher percentage of inversion than do any of the cis esters listed in Table III. Although chloride ion is a better leaving group than the phenoxide ions, which may partially

**Table IV**
**Percentage of Cis and Trans Isomers Obtained by Treating *trans*-2-Chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with Sodium *p*-Methylphenoxide in Various Solvents**



| Solvent | % *trans* (retention) | % *cis* (inversion) |
|---|---|---|
| $CH_3CN$ + 1 equiv $LiClO_4$ | 87.5[a] | 12.5 |
| $CH_3CN$ | 40.0 | 60.0 |
| $CH_3CN$ + 1 equiv $(CH_3)_4N^+Cl^-$ | 6.2 | 93.8 |
| $HCN(CH_3)_2$ | 5.7 | 94.3 |
| $HCN(CH_3)_2$ + 1 equiv $(CH_3)_4N^+Cl^-$ | 5.1 | 94.9 |

[a] Isomer ratios (per cent) were obtained by integration of nmr spectra obtained in $CDCl_3$ by means of a Varian A-60A spectrometer using TMS as an external standard.

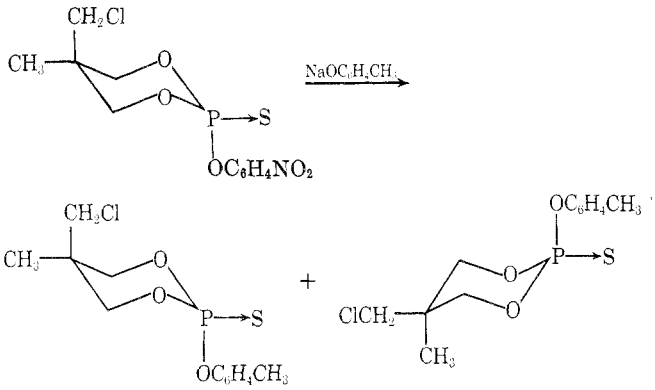
explain the results, the different ratios are also influenced by the fact that different isomers were used. Dipole interactions differ within the two ring conformations and have an effect upon the final isomer ratios. Regardless, the influence of the leaving group upon the final isomer ratio is established.

When the *cis* 2,4-dinitrophenyl ester **1** [R = $OC_6H_3(NO_2)_2$] was the substrate, substitution at phosphorus did not take place. The water-insoluble product, which was not a phosphate, appeared from its spectra to be an ether which would result from C–O bond cleavage, a situation similar to that found with phosphates.[3]

We have also, as with the 2-oxo system,[4] noted an effect of solvent upon the ratio of isomers obtained upon substitution at a thiophosphoryl center. Thus in the case of the trans 2-thiochloridate, **2** (R = Cl), the amount of inversion increased dramatically upon changing the solvent from acetonitrile to dimethylformamide (Table IV). The result is not due to a simple solvent effect, but is due to the much greater solubility of the by-product, sodium chloride, in dimethylformamide. Indeed, in a single solvent an added cation has a marked effect upon the product ratio by shifting the substitution pathway toward inversion. Sodium chloride, when added to acetonitrile solutions of the nucleophile prior to the addition of the reactant, caused a shift in the ratio, although, owing to its greater solubility, tetramethylammonium chloride had an even more dramatic effect. Owing to its lack of ionic character in organic solvents and ability to reduce the solubility of sodium chloride, lithium perchlorate had an opposite effect.

A similar solvent and salt effect was noted when *cis*-2-*p*-nitrophenyl ester was used as the substrate (Table V).

**Table V**
**Treatment of *cis*-2-(*p*-Nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan with Sodium *p*-Methylphenoxide in Various Solvents**



| Solvent | % *cis* (retention) | % *trans* (inversion) |
|---|---|---|
| $CH_3CN$ | 95.2 | 4.8 |
| $CH_3CN$ + 1 equiv $(CH_3)_4N^+Cl^-$ | 80.0 | 20.0 |
| $HCN(CH_3)_2$ | 87.1 | 12.9 |
| $HCN(CH_3)_2$ + 1 equiv $(CH_3)_4N^+Cl^-$ | 76.2 | 23.8 |

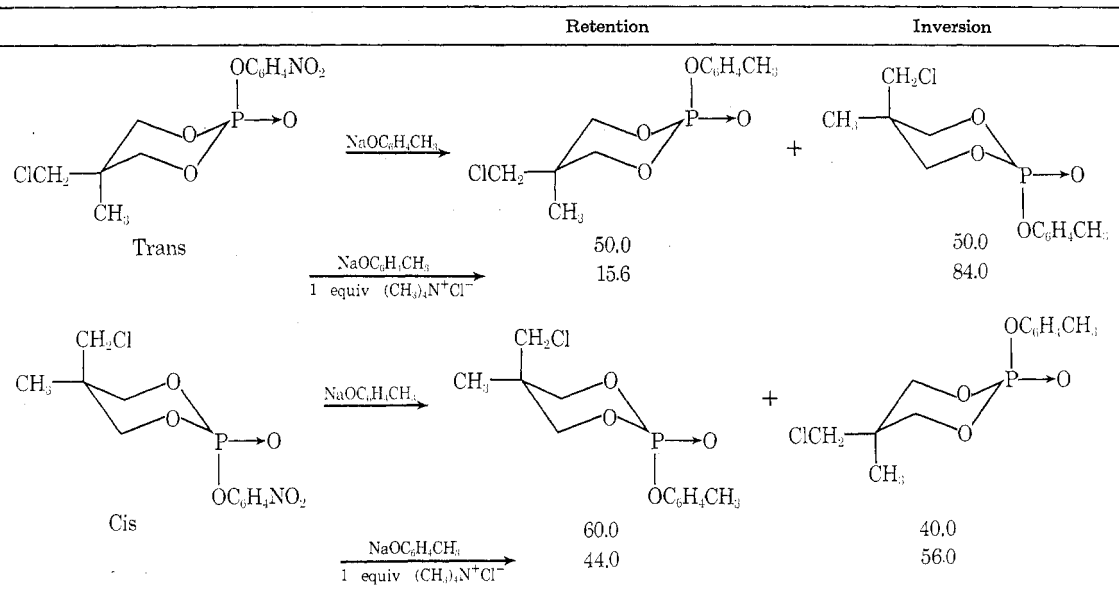
Owing to a difference in ring conformation the results were not as dramatic as in the case of the chloridate. Likewise, when *cis*-2-*p*-bromophenyl ester was added to acetonitrile containing sodium *p*-methylphenoxide, the percentage of inversion rose from 2.6 without added tetramethylammonium chloride to 22.2 in the case where salt was added to the solution prior to addition of the substrate. Thus added cations have a distinct effect.

## Discussion

We believe that our results, which correlate with those obtained previously with the 2-oxo system,[4] strengthen our assumption that nucleophilic substitution at phosphoryl centers occurs by two separate mechanisms, one for inversion and one for retention. We assume an equilibrium to be established between thiophosphate and complexed thiophosphate. A charged nucleophile would attack the uncomplexed phosphate from a side opposite the thiophosphoryl center, a position of minimum electron density. The more basic the nucleophile the greater would be its desire to attack from a position as far removed from the electron-rich phosphoryl sulfur as possible. This stereochemical pathway would lead to a pentacovalent intermediate. Since nucleophiles are assumed to enter and leaving groups depart from apical positions,[9] the intermediate would be expected to pseudorotate which would lead to overall retention. On the other hand, complex formation by increasing the positive charge on phosphorus *via* a reduction in backbonding and by reducing charge repulsion by the phosphoryl sulfur leads to a lowering of the energy of activation for direct attack, a situation which would lead to inversion. We believe that inversion does not involve an intermediate but is a direct $S_N2$ type displacement. Our evidence, although not conclusive, is based primarily upon our experiments with different leaving groups in which we find the percentage of inversion to increase with leaving group stability.

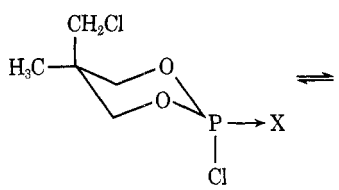
The suggested mechanism is admittedly tentative but does explain our observations, particularly the ability of

**Table VI**
**Effect of Ring Conformation on Isomer Ratios**

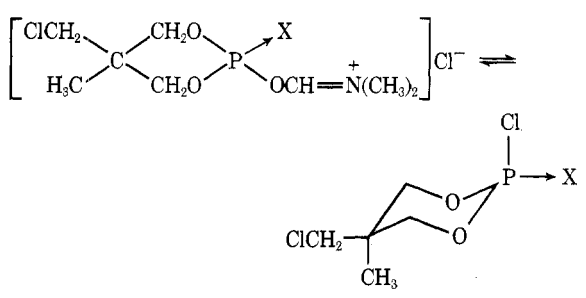



added salts to shift substitutions to the inversion pathway. Complex formation by cations *via* phosphoryl oxygen is well known[10] and it is not unlikely that a similar situation might arise with sulfur.

Although some conclusions can be drawn, with our system it is difficult to make quantitative comparisons between the phosphoryl and thiophosphoryl moieties. It is known from rates of hydrolysis[11] that due to the greater electronegativity of oxygen over sulfur, phosphorus has greater positive character in phosphates than in thiophosphates. In accordance with this conclusion we have observed a variation in the rate of isomerization of comparative compounds. Thus cis phosphorochloridate, **3** (X = O), isomerizes in dimethylformamide to give a final equilibrium ratio (2.5:1) of isomers within 15 min.[3] In contrast trans thiophosphorochloridate, **4** (X = S), under identical



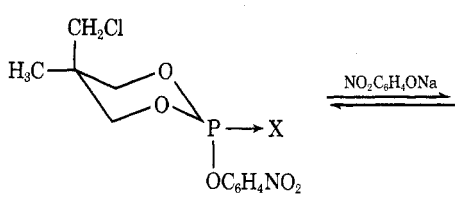
cis, **3**



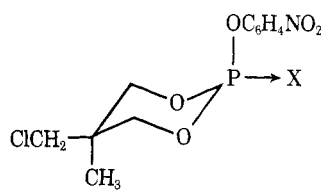
trans, **4**

conditions required 14 days to reach equilibrium (Figure 3).[7] The isomerization in the latter case was complicated by the concurrent formation of what appears from the nmr spectra to be an isomeric mixture of phosphorochloridates,[3] **3** + **4** (X = O). Thus, there is evidence for a transfer between oxygen and sulfur in the Vilsmeier-type intermediate. This phenomenon is being investigated further.

In the case of *p*-nitrophenyl esters added to deuterated acetonitrile saturated with sodium *p*-nitrophenoxide, approximately 5 days was required for the cis thiophosphate ester, **5** (X = S), to reach equilibrium whereas the cis phosphate ester, **5** (X = O), reached equilibrium under



cis, **5**



trans, **6**

identical conditions after 30 hr. From the nmr spectra no side reactions in the case of the thio ester were apparent. Substitution is clearly more facile in the case of the phosphates, where the positive charge on phosphorus is greater. In the absence of added common ion isomerization does not take place with either *p*-nitrophenyl ester regardless of the solvent employed. The *p*-methyl, *p*-methoxy, *p*-bromophenyl, and phenyl esters do not isomerize even in the presence of a common ion.

At equilibrium the ratio of isomers varied. In the case of the *p*-nitrophenyl phosphate the cis/trans isomer ratio at equilibrium was 2.5:1 whereas in the case of the sulfur analog it was 6.0:1. a dipole interaction between axial chloromethyl groups and ring oxygens has been held responsible for the excess of cis over trans at equilibrium.[12] To account for the difference in ratios, the interaction must be greater in the case of the thiophosphate. This is not unreasonable, since the positive charge on phosphorus and thus inductive effect on the ring oxygens would be less than in the phosphate case. Thus a dipole interaction would be greater in the thiophosphate ring system, which would account for the relatively greater amount of cis isomer at equilibrium. The change in dipole interactions in going from the phosphate to thiophosphate system makes a quantitative comparison between the two as regards to salt effects, etc., difficult.

Indeed, by carrying out substitutions on separate isomers of a single phosphate, the effect of a change in ring

dipole interactions upon isomer ratios can be seen. Pure *trans*-*p*-nitrophenyl phosphate when added to an acetonitrile solution of sodium *p*-methylphenoxide underwent substitution with 50.0% retention. The pure cis isomer with the chloromethyl group axial under the same conditions underwent substitution with 60% retention. Thus the position of the chloromethyl group in the starting material and substitution product does influence the retention/inversion ratio. Dipole interactions probably influence the energy of activation for each substitution mechanism. Also, the effect of added cation is more pronounced (Table VI) in the case of the trans *p*-nitrophenyl ester than with the cis. In the case of the trans isomer, the mechanism leading to inversion might be expected to have a lower energy of activation, for the ring undergoes a conformational change during substitution such that dipole interactions would be an asset. Dipole interactions, on the other hand, would be expected to hinder inversion with a cis substrate.

## Experimental Section

Analysis were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. 37921.

**2-Chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan.** Thiophosphoryl chloride, 37 g (0.22 mol), was added dropwise with stirring and cooling to 1-chloromethyl-1,1-dihydroxymethylethane,[13] 30.14 g (0.22 mol), ether (150 ml), and pyridine (34.7 g, 0.44 mol). The solution was stirred for 1 hr and filtered. The filtrate was washed with 5% HCl and $H_2O$ and dried over anhydrous magnesium sulfate. The solvent was removed to give a white solid (36 g, 70% yield) which consisted of cis and trans isomers in a 1:2 ratio. The product was recrystallized four times from a 10:1 hexane–chloroform mixture to give pure trans isomer 2 (R = Cl), mp 64–65°.

*Anal.* Calcd. for $C_5H_9ClO_2PS$: C, 25.53; H, 3.83; Cl, 30.21; S, 13.62. Found: C, 25.77; H, 3.94; Cl, 30.43; S, 13.77.

***cis*-2-(*p*-Nitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan.** To a solution of sodium *p*-nitrophenoxide (8 g, 0.05 mol) and acetonitrile (100 ml) was added the isomeric mixture of 2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan, 12.0 g (0.05 mol). The solution was stirred for 2 days, 500 ml of water was added, the solution was filtered, and the precipitate was washed well with water before drying. A pale yellow solid (16.2 g, 95% yield) was obtained. The pure cis isomer was extracted from the isomer mixture by refluxing the product in ether, filtering, and removal of solvent from the filtrate. The residue was recrystallized from carbon tetrachloride to give the pure cis isomer, mp 122–123°.

*Anal.* Calcd for $C_{11}H_{13}ClNO_3PS$: C, 39.17; H, 3.86; Cl, 10.39; S, 9.50. Found: C, 38.96; H, 3.71; Cl, 10.62; S, 9.62.

The other pure cis esters were obtained in a similar manner.

***cis*-2-(2,4-Dinitrophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan.** The isomer mixture (96.5% yield) was recrystallized twice from carbon tetrachloride–acetonitrile (10:1) to give pure cis isomer, mp 134–135°.

*Anal.* Calcd for $C_{11}H_{12}ClN_2O_7PS$: C, 34.56; H, 3.14; Cl, 9.16; S, 8.38. Found: C, 34.71; H, 3.20; Cl, 9.36; S, 8.44.

***cis*-2-(*p*-Bromophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan.** The final isomer mixture (97% yield) was recrystallized three times from carbon tetrachloride to give pure cis isomer, mp 145–146°.

*Anal.* Calcd for $C_{11}H_{13}ClBrO_3PS$: C, 35.58; H, 3.50; Cl, 9.43; S, 8.62. Found: C, 35.34; H, 3.56; Cl, 9.65; S, 8.74.

***cis*-2-(*p*-Methylphenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan.** The final isomer mixture (98% yield) was recrystallized twice from hexane–carbon tetrachloride (10:1) to give pure cis isomer, mp 135–136°.

*Anal.* Calcd for $C_{12}H_{16}ClO_3PS$: C, 47.06; H, 5.32; Cl, 11.44; S, 10.46. Found: C, 47.20; H, 5.34; Cl, 11.60; S, 10.43.

***cis*-2-Phenoxy-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan.** The final isomer mixutre (93% yield) was recrystallized twice from hexane–carbon tetrachloride (10:1) to give pure cis isomer, mp 110–111°.

*Anal.* Calcd for $C_{11}H_{14}ClO_3PS$: C, 45.20; H, 4.80; Cl, 11.98; S, 10.96. Found: C, 45.16; H, 4.91; Cl, 12.01; S, 10.97.

To determine the effect of the basicity of the nucleophile (Table II), the above were repeated using the pure trans chloridate, 2 (R = Cl).

***cis*- and *trans*-2-(*p*-Methoxyphenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan.** To a solution of sodium *p*-methoxyphenoxide (0.29 g, 0.0015 mol) and acetonitrile (15 ml) was added *trans*-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.3 g, 0.0013 mol). The mixture was stirred at room temperature for 1 hr. Substitution was actually instantaneous as indicated by a mild exotherm upon addition of the chloridate. Water (50 ml) was added, and the precipitate was washed thoroughly with water and dried, 0.39 g (96% yield). The product by nmr consisted of both cis and trans isomers in a 1:1 ratio. The above was repeated under identical conditions with sodium salts of other substituted phenoxides.

To determine the effect of leaving groups (Table III), the following standard procedure was followed. To a solution of sodium *p*-methylphenoxide (0.16 g, 0.0012 mol) and acetonitrile (15 ml) was added *cis*-2-(*p*-bromophenoxy)-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.4 g, 0.0011 mol). The mixture was stirred for 2 days and water (50 ml) was added to precipitate the product. The white solid was washed with water and dried (0.3 g, 92% yield). Integration of the nmr spectrum of the product was used to determine isomer ratios.

The following is a typical procedure which was used to determine the effect of salts on isomer ratios (Tables IV–VI). Sodium *p*-methylphenoxide (0.29 g, 0.0015 mol) and tetramethylammonium chloride (0.16 g, 0.0015 mol) were dissolved in acetonitrile (15 ml). To the solution was added *trans*-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan (0.35 g, 0.0015 mol). The mixture was stirred for 1 hr and water (50 ml) was added to precipitate the product. The precipitate was washed with water and dried (0.429 g, 91% yield). Integration of its nmr spectrum provided the isomer ratio (Table IV). The ratios reported in Table V were obtained in a similar manner. *cis*-2-*p*-Nitrophenyl ester 1, (R = $OC_6H_4NO_2$) was added in place of the trans chloridate. Data for Table VI were obtained similarly using the appropriate substrate.

***cis*-2-(*p*-Nitrophenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan.** The pure trans isomer, mp 106–107°, was prepared and equilibrated to a mixture of cis and trans isomers as previously described.[3] To separate the cis isomer from the 2.5:1 cis–trans mixture, the product obtained upon equilibration was extracted with boiling chloroform and filtered. The filtrate upon standing slowly deposited crystals of pure cis isomer which could be recrystallized from a small quantity of chloroform, mp 160–161°.

*Anal.* Calcd for $C_{22}H_{23}ClNO_6P$: C, 41.12; H, 4.05; P, 9.65. Found: C, 41.27; H, 4.14; P, 9.51. Nmr spectra[3] of both isomers confirmed their structures.

**Registry No.**—1 (R = Cl), 50378-48-8; 1 (R = $OC_6H_4OMe$), 50378-49-9; 1 (R = $OC_6H_4Me$), 50378-50-2; 1 (R = $OC_6H_5$), 50378-51-3; 1 (R = $OC_6H_4Br$), 50378-52-4; 1 (R = $OC_6H_4NO_2$), 50378-53-5; 1 [R = $OC_6H_3(NO_2)_2$], 50378-54-6; 2 (R = Cl), 50600-54-9; 2 (R = $OC_6H_4OMe$), 50378-56-8; 2 (R = $OC_6H_4Me$), 50378-57-9; 2 (R = $OC_6H_5$), 50378-58-0; 2 (R = $OC_6H_4Br$), 50378-59-1; 2 (R = $OC_6H_4NO_2$), 50378-60-4; 2 [R = $OC_6H_3(NO_2)_2$], 50378-61-5; 1-chloromethyl-1,1-dihydroxymethylethane, 21139-44-6; *cis*-2-(*p*-nitrophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-diooxaphosphorinan, 36912-38-6; *trans*-2-(*p*-nitrophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, 36912-37-5.

**Supplementary Material Available.** Nmr spectra of a mixture of cis and trans isomers, and 2 (R = Cl), the pure cis isomer, 1 (R = Cl), para-substituted phenyl esters, 1 and 2 (R = $OC_6H_7CH_3$), and equilibration of 4 (X = S) will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-984.

## References and Notes

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# The Synthesis and Properties of Heterofulvenes, Derivatives of 2,6-Dimethyl-γ-pyrone and -γ-thiapyrone and *N*-Butyl-2,6-dimethyl-γ-pyridone

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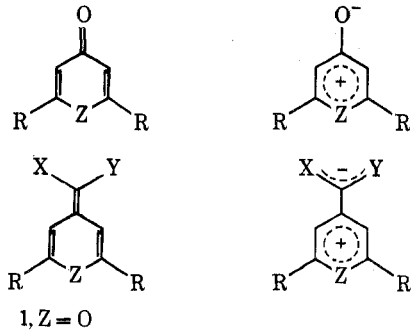
Oxygen-, sulfur-, and nitrogen-containing heterofulvenes, derivatives of 2,6-dimethyl-γ-pyrone (1) and -γ-thiapyrone (2) and *N*-butyl-2,6-dimethyl-γ-pyridone (3), have been prepared, and their properties are reported. The O and S heterocycles were prepared by condensation of 1 and 2, respectively, with active methylene compounds in acetic anhydride. The N heterocycles were obtained from the O heterocycles by reaction with butylamine. Side reactions were observed when butylamine reacted with methyl 2,6-dimethyl-4*H*-pyran-4-ylidenenitroacetate (6) and 2,6-dimethyl-4*H*-pyran-4-ylidenenitroacetone (5). A new convenient route to heterofulvenes which bear a single substituent at the exocyclic double bond was developed. Thus, heterofulvenes substituted by an acetyl group at the exocyclic double bond were found to undergo acetyl cleavage, under very mild acidic conditions, resulting in the formation of monosubstituted heterofulvenes. Deuterium exchange reactions in the systems under consideration were studied. The nmr, uv, and ir data of the disubstituted and monosubstituted heterofulvenes are discussed in terms of the heteroatom and the substituents at the exocyclic double bond.

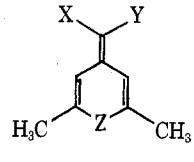
Compounds derived from the formal condensation of γ-pyrones (1), γ-thiapyrones (2), and γ-pyridones (3) with active methylene compounds, having the general structure 4, may be considered as heteroanalogs of heptafulvenes. The literature contains a number of reports on the synthesis and properties of some heterofulvenes and heterofulvalenes derived from γ-pyrones and γ-pyridones.[1] Very little, however, has been published about heterofulvenes derived from γ-thiapyrones (4, Z = S). In this paper we report the synthesis and chemistry of heterofulvenes of type 4; dynamic nmr studies on these compounds will be presented in a later paper.



1, Z = O
2, Z = S
3, Z = N-Bu
4, X, Y = electron-withdrawing groups

## Synthesis

The compounds of interest which have been prepared are listed below.



Z = O
5, X = $NO_2$; Y = $COCH_3$
6, X = $NO_2$; Y = $COOCH_3$
7, X = $NO_2$; Y = CN
8, X = $COCH_3$; Y = $COOCH_3$
9, X = $COCH_3$; Y = CN
10, X = $COOCH_3$; Y = CN
11, X = CN; Y = $CONH_2$
12, X = Y = $COCH_3$

Z = S
13, X = $NO_2$; Y = $COCH_3$
14, X = $NO_2$; Y = $COOCH_3$
15, X = $NO_2$; Y = CN
16, X = $COCH_3$; Y = $COOCH_3$
17, X = $COCH_3$; Y = CN
18, X = $COOCH_3$; Y = CN

Z = *N*-Bu
19, X = $NO_2$; Y = $COCH_3$
20, X = $NO_2$; Y = $COOCH_3$
21, X = $NO_2$; Y = CN
22, X = $COCH_3$; Y = CN
23, X = $COOCH_3$; Y = CN
24, X = CN; Y = $CONH_2$

The oxygen (Z = O) and the sulfur (Z = S) heterocycles were prepared by the condensation of 2,6-dimethyl-γ-pyrone and 2,6-dimethyl-γ-thiapyrone,[3] respectively, with the appropriate active methylene compounds in acetic anhydride (Scheme I). It has previously been reported that the acetic anhydride method is applicable only to those active methylene compounds bearing a nitrile group, but fails with compounds such as acetylacetone and methyl acetoacetate.[4] We have found, however, that this method can be considered to be a general one, inasmuch as, except for 11, all the oxygen and the sulfur analogs could be obtained in this way, although the yields with acetylacetone and methyl acetoacetate were, indeed, very poor. Compound 11 was prepared, as previously reported,[5] by