Anchimeric Participation of a Methoxy Group in a Reaction of a Metathiophosphate

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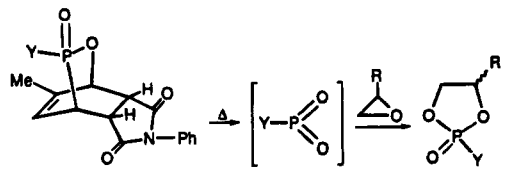
Received March 4, 1994 (Revised Manuscript Received June 28, 1994®)

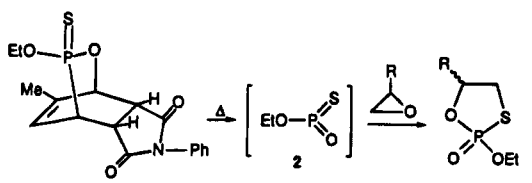
Thermolysis of derivatives of the 2,3-oxaphosphabicyclo[2.2.2]octene ring system with phosphorus in the phosphonothionoate state accomplishes the extrusion of *O*-alkyl metathiophosphates, ROP(S)O, as highly reactive intermediates. With alcohol present, the intermediate is trapped as an *O,O*-dialkyl phosphorothionoate, (RO)(R'O)P(S)OH. With R = (*RS*)-*sec*-butyl in the metathiophosphate released, the phosphorothionoate is formed as a 1:1 mixture of diastereoisomers, but when R = (*RS*)-1-methoxy-2-propyl in the metathiophosphate, a 4:1 isomer mixture is formed in $CHCl_3$, and 2:1 in toluene. This can be explained by anchimeric participation of the methoxy group, giving diastereoisomeric 1,3,2-dioxaphospholane intermediates in amounts that are unequal due to small stability differences that arise from steric effects. The structure of the bicyclic precursor was established by X-ray diffraction analysis and led to the prediction that the major isomer would have the R^*_C,S^*_P configuration. This was proved by an independent synthesis of the same 1:1 isomer mixture from thionation of (RO)PH(O)(OR'), separation by chromatography, and X-ray diffraction analysis of the dicyclohexylamine salt of one of the isomers. This isomer had the R^*_C,R^*_P configuration and was identical to the minor isomer (with the more upfield ^{31}P NMR signal) obtained from the metathiophosphate.

We have recently observed that derivatives of metaphosphoric acid, when generated thermally from fragmentation of esters or amides with the bicyclic phosphonic acid framework of **1**, react with oxiranes to cause ring



1, Y = EtO, Et_2N

opening and formation of 1,3,2-dioxaphospholane 2-oxide derivatives. Metathiophosphates **2** can also be generated by this approach and have been found to react with oxiranes.[1] Ethyl metaphosphate also caused ring opening



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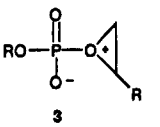
of 2-methyloxetane, although mostly polymeric products were formed. These reactions of metaphosphoric acid derivatives with oxiranes presumably are initiated by attack of the highly electrophilic phosphorus atom on a lone pair on oxygen, giving an intermediate oxonium ion represented by **3** which undergoes further chemical changes.

Since the literature also contains references to possible complexation of metaphosphates with dioxane[2] and tetrahydrofuran,[3] it appeared that ethereal oxygen in general could interact with metaphosphates. Were this true, the phenomenon of anchimeric participation might be observable in properly substituted metaphosphates. Thus, methoxy groups on γ or δ carbons are well known to participate intramolecularly in reactions with electrophilic centers,[4] influencing kinetic and steric characteristics of further reactions without being changed by these reactions. A metaphosphate involvement in anchimeric participation during the course of reaction with an alcohol can be represented as in Scheme 1.



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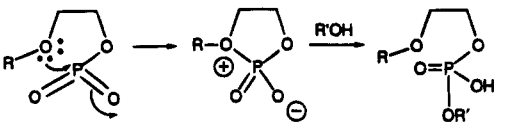
Scheme 1



It would not be expected that a kinetic effect arising from alkoxy group participation in the metaphosphate would be measurable, since the formation of the metaphosphate is the slow, rate-determining step in the thermally-induced reaction of the bicyclic phosphonate **1** in the presence of nucleophiles.[5] However, it is possible to design an experiment where steric effects from the participation could be observed. This requires two modifications of the general structures shown in Scheme

® Abstract published in *Advance ACS Abstracts,* August 1, 1994.

(1) Bodalski, R.; Quin, L. D. *J. Org. Chem.* **1991**, *56*, 2666.

(2) Westheimer, F. H. *Chem. Rev.* **1981**, *81*, 313.

(3) Quin, L. D.; Bourdieu, C.; Quin, G. S. *Tetrahedron Lett.* **1990**, *31*, 6473.

(4) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; pp 268–272.

(5) Jankowski, S.; Quin, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 7011.

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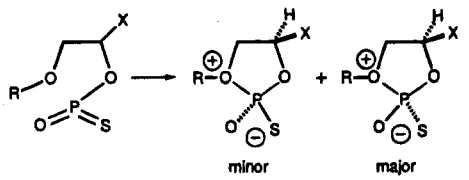
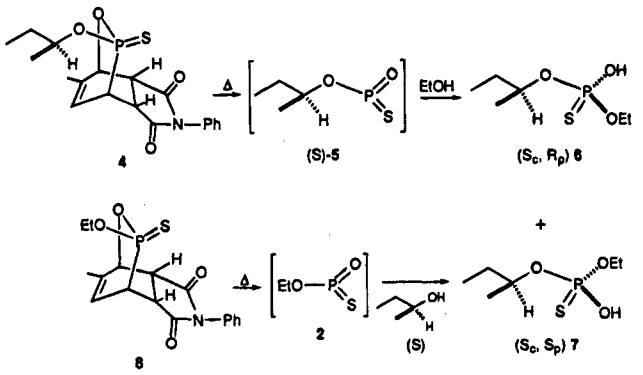
Scheme 2



Scheme 3



1: a substituent must be placed on C-1 or C-2 of the alkoxy group and one oxygen on phosphorus must be replaced by sulfur. Since phosphorus is planar[6] in the 3-coordinate condition, anchimeric participation of the alkoxy group would give rise to two different cyclic intermediates (Scheme 2), each of which would then react with an alcohol to give isomeric thionophosphates. However, the steric differences in the two cyclic intermediates that arise from interaction of X with S in one form and X with O in the other would lead to unequal amounts of the thionophosphate products.

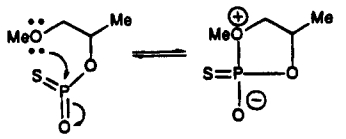
Metathiophosphates that do not have a group capable of participation with phosphorus are known[7] to react with alcohols to give a 1:1 mixture of diastereomeric thionophosphates if the alkoxy substituent bears a chiral carbon. Thus, (*S*)-*sec*-butyl metathiophosphate (**5**), on generation from the precursor **4** in the presence of ethanol, gave the diastereomeric thionophosphates **6** and **7**, in nearly equal amounts (Scheme 3). This establishes also that there is no significant influence from the chiral *sec*-butyl group on the isomer ratio. The same 1:1 isomer mixture was obtained when ethyl metathiophosphate was generated in the presence of (*S*)-*sec*-butyl alcohol.

This paper is concerned with the reduction to practice of this experimental proposal for the detection through a steric effect of anchimeric participation in a metathiophosphate and the presentation of evidence that is consistent with the operation of the participation phenomenon.

Results and Discussion

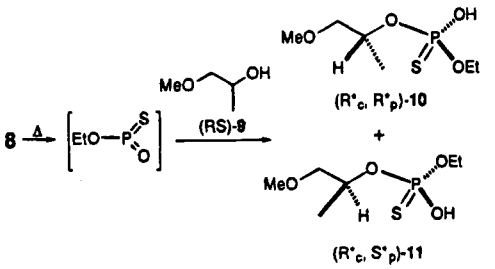
The 1-methoxy-2-propyl group was selected as a substituent that might be involved in anchimeric participation with the phosphorus center of a metathiophosphate.

It was first shown that (*RS*)-1-methoxy-2-propanol (**9**) functioned as a trapping agent for ethyl metathiophosphate to give the same stereochemical result as found for (*RS*)-*sec*-butyl alchol. Thus, from (*RS*)-**9** was obtained



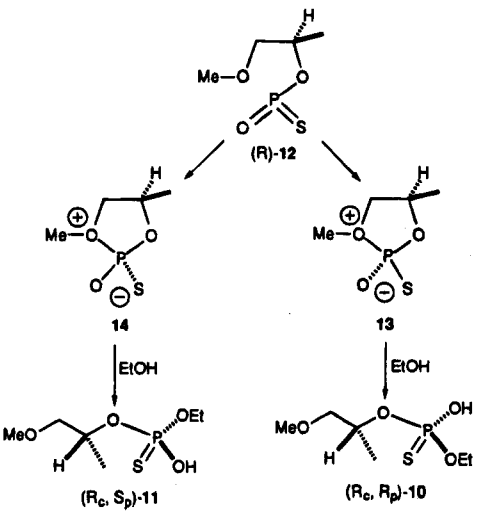
a 1:1 mixture of diastereomeric thionophosphates **10** and **11**, whose relative configurations were designated (R^*_C,R^*_P) and (R^*_C,S^*_P), respectively (Scheme 4). The

Scheme 4



structure of these isomers was confirmed by NMR and mass spectral studies. The alkyl substituents in this process were then interchanged, so that ethyl alcohol was reacted with (*R*,*S*)-1-methoxy-2-propyl metathiophosphate (**12**) (Scheme 5). A mixture of **10** and **11** would

Scheme 5



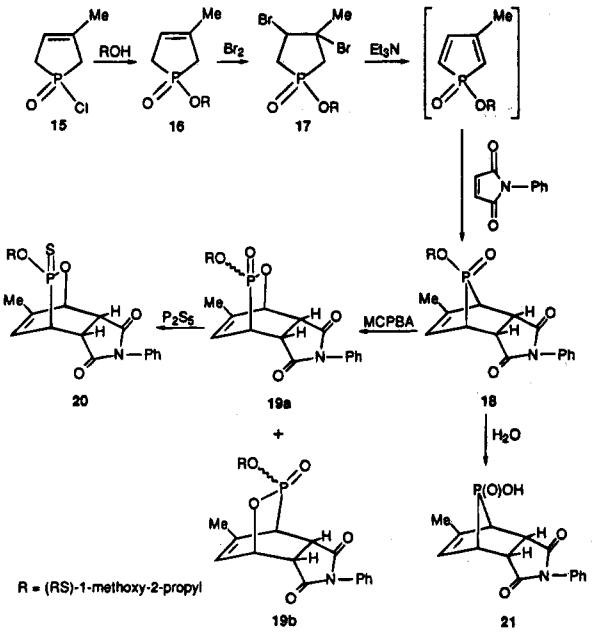
again result *but not necessarily with the 1:1 ratio* as observed in the former case. A difference would arise from the participation of the methoxy group with the electrophilic phosphorus center of **12**. As seen in Scheme 5, the two dioxaphospholane intermediates with tetrahedral phosphorus (e.g., **13** and **14** from the *R*-ester; the mirror images would also be formed from the *S*-ester) have a small energy difference arising from the interaction of the ring methyl group with a *cis* sulfur atom on the one hand (as in **13**) or a *cis* oxygen atom on the other hand (as in **14**). The latter form should have the lower energy, and this would lead to the prediction that the thionophosphate formed from it with an alcohol would predominate in the mixture. This reaction would proceed through the usual trigonal-bipyramidal intermediate or transition state, resulting in inversion at phosphorus.

The synthesis of the new precursor **20** for the thermal generation of the racemic metathiophosphate **12** was accomplished without difficulty by the same sequence of

(6) Friedman, J. M.; Knowles, J. R. *J. Am. Chem. Soc.* **1985**, *107*, 6126. Freeman, S.; Friedman, J. M.; Knowles, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 3166.

(7) Quin, L. D.; Sadanani, N. D.; Wu, X.-P. *J. Am. Chem. Soc.* **1989**, *111*, 6852.

Scheme 6

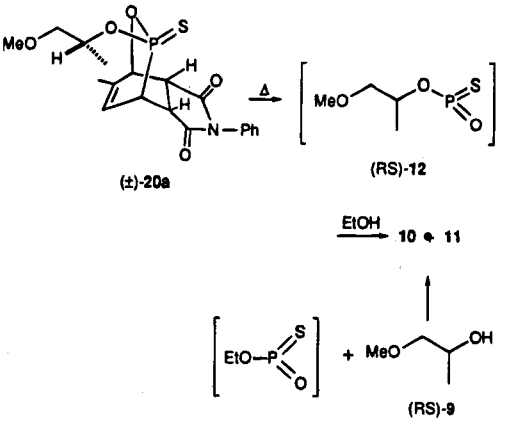


reactions that we have used previously[7,8] and is outlined in Scheme 6. We did note that the ester with the 7-phosphanonorbornene structure (**18**) was unusually sensitive to traces of water, and unless extra caution was used in its handling it was hydrolyzed to the acid **21**. The MCPBA reaction on **18** gave the diastereoisomeric position isomers **19a** and **19b**, with the former in predominance. Each position isomer was a mixture with *syn* and *anti* disposition of the alkoxy group. The formation of such isomers is frequently observed in similar reactions.[8,9] Fractional recrystallization of the thionation product **20** allowed the isolation of a single bicyclic ester (**20a**), whose relative configuration was unambiguously assigned using X-ray diffraction analysis.[10] This is the first X-ray analysis of a *P*-sulfide in the 2,3-oxaphosphabicyclo[2.2.2]octene ring system. The same location of the methyl on the double bond, and the *syn* orientation of the *P*-alkoxy group, have been observed for the major isomer of *P*-oxides.

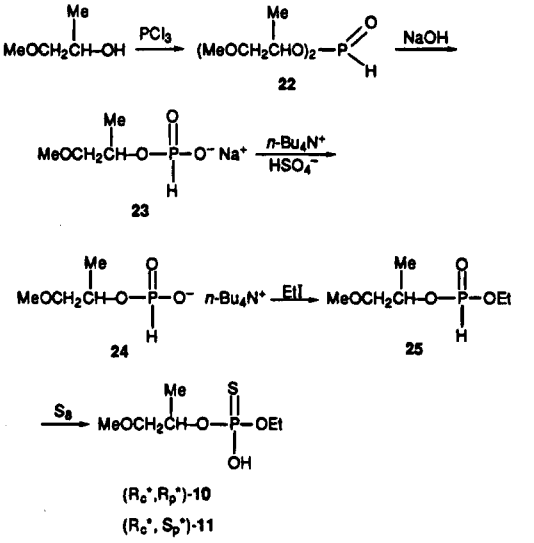
The fragmentation reaction performed with **20a** in chloroform followed first-order kinetics for more than 3 half-lives with $k = (8.85 \pm 0.21) \times 10^{-4}\ s^{-1}$. Very similar kinetics [$k = (3.91 \pm 0.52) \times 10^{-4}\ s^{-1}$] had been found[5] for the analogous reaction with the bicyclic ester **8**, indicating that the methoxy group in **20a** did not cause a significant rate enhancement in the generation of the metaphosphate **12** and that there is no significant interaction of the methoxy group with phosphorus in this step.

(*RS*)-1-Methoxy-2-propyl metathiophosphate (**12**) was then generated from **20a** on being heated in a closed tube in chloroform (100 °C) or toluene (120 °C) in the presence of ethanol. The metathiophosphate was largely trapped by the ethanol as the diastereoisomeric thionophosphates **10** and **11**, which were spectrally identical to the products obtained from the trapping of ethyl metathiophosphate

Scheme 7



Scheme 8



with (*RS*)-1-methoxy-2-propanol (Scheme 7). As expected, *the diastereoisomers, with shifts of δ 66.61 and 63.35, were not formed from* **12** *in the same amounts*; a ratio of 4:1 in chloroform and 2:1 in toluene solution was observed by integration of the ^{31}P NMR signals.

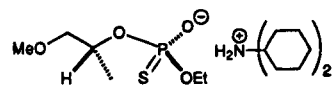
According to the interpretation of Scheme 5, the major isomer should have the (R^*_C,S^*_P) configuration (**11**); the less-crowded cyclic intermediate would be **14**, which reacts with alcohol with inversion at P. We have synthesized the isomeric thionophosphates **10** and **11** in large amounts by the reactions outlined in Scheme 8 so as to attempt a separation and produce a crystalline derivative for X-ray analysis.

The mixture of **10** and **11** formed a crystalline product with dicyclohexylamine; the mixture was separated by fractional crystallization, and there was obtained one of the salts in suitable condition for X-ray analysis. This salt was derived from the minor member of the **10**,**11** mixture and had the more upfield ^{31}P NMR shift. The X-ray diffraction analysis[10] established the acid component of the salt (**26**) as having structure **10** (R^*_C,R^*_P), thus confirming the prediction that the major product would have the (R^*_C,S^*_P) configuration, indicative of anchimeric participation in a metathiophosphate intermediate.

Conclusions

The results of this study indicate that replacing a γ-methyl by a methoxy group in the alkoxy substituent

(8) Quin, L. D.; Wu, X.-P.; Sadanani, N. D.; Lukes, I. *J. Org. Chem.*, in press.
(9) Quin, L. D. *Rev. Heteroatom Chem.* **1990**, *3*, 39.
(10) The authors have deposited atomic coordinates for **20a** and **26** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.



(R*c, R*p)-26

of a thiometaphosphate leads to a pronounced biasing of the steric outcome of the reaction with a nucleophile. Thus, with a *sec*-butyl substituent, a 1:1 mixture of diastereoisomeric thionophosphates is observed, indicating no influence of the chiral center on the outcome of the reaction. But with the 1-methoxy-2-propyl substituent, a mixture of diastereoisomers is obtained wherein one isomer accounts for 80% of the product (in $CHCl_3$). This result can be interpreted as arising from anchimeric participation of the methoxy group with the powerfully electrophilic phosphorus center, giving a cyclic species that has two nonequivalent faces for attack by the alcohol (Scheme 5). The stereostructure of one (the minor) of the isomeric thionophosphate products was determined by X-ray analysis; the structure then assigned to the major isomer was that predicted to be formed from the least crowded of the two possible cyclic intermediates. There seems to be no other logical explanation for the biasing of the stereochemical result of this reaction than anchimeric participation of the methoxy group, and this involvement of the ethereal oxygen is certainly consistent with other facts known about metaphosphates.

If the argument is accepted that the stereochemical biasing is caused by participation of the methoxy group with the phosphorus center of the metathiophosphate, the conclusion must be drawn that the metathiophosphate is present in the medium as a free species, albeit of very short lifetime. This is consistent with the conclusion drawn from kinetic studies[5] of the 2,3-oxaphosphabicyclo[2.2.2]octene ring system, which showed that fragmentation to form a metaphosphate was a first-order, concerted process whose rate was not affected by the presence of an alcohol.

Experimental Section

General. Melting points are uncorrected. NMR spectra were recorded on $CDCl_3$ solutions as in other studies.[8] For GC-MS analyses, a DB-5 30 m × 0.25 mm column was employed. 1-Chloro-3-methyl-3-phospholene 1-oxide (**15**) and *endo*-3-ethoxy-6-methyl-*N*-phenyl-2,3-oxaphosphabicyclo[2.2.2]-oct-5-ene-7,8-dicarboximide 2-sulfide (**8**) were prepared following the published procedures.[6]

1-(1-Methoxy-2-propoxy)-3-methyl-3-phospholene 1-Oxide (16). A solution of (*RS*)-1-methoxy-2-propanol (14.6 g, 0.16 mol) and triethylamine (16.9 g, 0.16 mol) in ether (150 mL) was cooled to 0 °C. Then a solution of 1-chloro-3-methyl-3-phospholene 1-oxide (**15**) (21.7 g, 0.14 mol) in ether (100 mL) was added dropwise with stirring. Stirring was continued for 4 h and then the solvent was evaporated under reduced pressure. The residue was distilled *in vacuo* to give **16** (13.0 g, 44.1%) as a colorless liquid, bp 105–108 °C (0.6 mmHg): ^{1}H NMR ($CDCl_3$) δ 1.33 (d, $^3J_{HH}$ = 6.4 Hz, 3H), 1.81 (s, 3H), 2.36–2.60 (m, 4H), 3.38 (s, 3H), 3.43 (d, $^3J_{HH}$ = 7.32 Hz, 2H), 4.66–4.79 (m, 1H), 5.54 (d, $^3J_{PH}$ = 34.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 18.70 (s) and 18.73 (s) (CH_3CH for different isomers); 20.68 and 20.72 (both J_{PC} = 13.1 Hz, CH_3C= for different isomers); 31.68 (J_{PC} = 87.2 Hz) and 31.73 (J_{PC} = 89.5 Hz, $-CH_2CH$= for different isomers); 34.2 (J_{PC} = 91.3 Hz) and 34.4 (J_{PC} = 93.5 Hz, $CH_2C(CH_3)$ for different isomers), 58.9 (CH_3O), 71.0 (J_{PC} = 6.8 Hz, $-CH_2O$), 76.4 (J_{PC} = 3.9 Hz, $CHOCH_3$), 120.0 (J_{PC} = 11.1 Hz) and 120.5 (J_{PC} = 11.5 Hz, CH_2CH= for different isomers); 135.9 (J_{PC} = 17.3 Hz) and 136.4 (J_{PC} = 17.2 Hz, $-CH_2C(CH_3)$= for different isomers); ^{31}P NMR ($CDCl_3$) δ 74.7; GC-MS with DB-5 30 m, 0.25-mm i.d. column (60 °C for 2 min and then 5°/min) showed two isomers in a ratio 1:1 with retention times 17.47 and 17.81 min with identical spectra *m/z* 204.25 (M^+ calcd for $C_9H_{17}O_3P$, 204.20. Anal. Calcd for $C_9H_{17}O_3P$: C, 52.93; H, 8.39; P, 15.16. Found: C, 52.54; H, 8.12; P, 14.77

3,4-Dibromo-1-(1-methoxy-2-propoxy)-3-methylphospholane 1-Oxide (17). To a stirred solution of ester **16** (12.9 g, 0.063 mol) in chloroform (75 mL) at 0 °C was added dropwise a solution of bromine (10.9 g, 0.068 mol) in chloroform (75 mL). The reaction mixture was left at room temperature for 6 h. The solvent was evaporated *in vacuo* to give the crude oily **17** as a mixture of diastereoisomers (23.0 g, 100%): ^{31}P NMR ($CDCl_3$) δ 66.52, 65.39, 65.02 in a ratio of 4.2:2.0:2.2, respectively. The product was used immediately in the synthesis of **18**.

***endo*-2-*syn*-1-(1-Methoxy-2-propoxy)-4-methyl-*N*-phenyl-2-phosphabicyclo[2.2.1]hept-4-ene-6,7-dicarboximide 2-Oxide (18).** To a solution of the crude mixture of the isomers of **17** (23.0 g, 0.062 mol) and *N*-phenylmaleimide (11.7 g, 0.068 mol) in dry benzene was added a solution of triethylamine (15.8 g, 0.156 mol) in 500 mL of benzene. After the reaction mixture had been stirred under argon for 7 days at room temperature, it was filtered to remove precipitated amine salt. The filtrate was concentrated by rotary evaporation to give a brown oil. Column chromatography on silica gel (Merck grade 60, 230–400 mesh) using chloroform–hexane (8:2), chloroform, chloroform–methanol (9.7:0.3), and chloroform–methanol (9.4:0.6) as eluants gave **18** as a white solid (15.8 g, 66.6%): mp 202–204 °C; ^{1}H NMR ($CDCl_3$) δ 1.18 (d, $^3J_{HH}$ = 6.0 Hz, 3H), 1.87 (s, 3H), 3.19–3.49 (m, 4H), 3.34 (s, 3H), 3.80 (d, $^3J_{HH}$ = 3.0 Hz, 2H), 4.70 (broad s, 1H), 5.85–6.10 (m, 1H), 7.05–7.41 (m, 5H); ^{31}P NMR ($CDCl_3$) δ 79.9. Anal. Calcd for $C_{19}H_{22}NO_5P$: C, 60.80; H, 5.91; P, 8.25. Found: C, 61.15; H, 6.30; P, 8.09.

Solutions of **18** deposited an insoluble solid which was characterized as the acid (**21**) from hydrolysis: mp 232–233 °C; ^{31}P NMR δ ($CHCl_3$, CF_3COOH; D_2O lock) 81.9. Anal. Calcd for $C_{15}H_{14}NO_4P$: C, 59.40; H, 4.65. Found: C, 59.87; H, 5.01.

***endo*-3-(1-Methoxy-2-propoxy)-6-methyl-*N*-phenyl-2,3-oxaphosphabicyclo[2.2.2]oct-5-ene-7,8-dicarboximide 3-Oxide (19).** A solution of **20** (15.8 g, 0.042 mol) and MCPBA (30.0 g, 0.174 mol) in 400 mL of chloroform was stirred at room temperature for 20 h. Anhydrous potassium fluoride (30.0 g, 0.51 mol) was then added to form an insoluble complex with the benzoic acids and the reaction mixture was stirred for an additional 3 h. After the white solid was filtered off, the filtrate was concentrated *in vacuo* to give the crude product as a mixture of five components; the ^{31}P NMR spectrum of this material showed all **19** to have reacted and exhibited resonances at δ 26.76, 27.52, 28.26, 29.01, and 29.39 in a ratio of 1:1.5:1:1.5:1. The mixture was separated by column chromatography on Florosil (Fisher Scientific, 100–200 mesh) with chloroform–hexane (8:2), chloroform, and chloroform–methanol (9.7:0.3) as eluants. Some decomposition occurred, but two product fractions were obtained: (a) oil, 2.3 g (13.9%), and (b) colorless plates, 1.4 g (8.5%); these contained the same two isomers of **19** in a ratio for (a) of 2:1 and for (b) of 1:3, as determined from their ^{31}P NMR spectra, which in $CDCl_3$ contained two signals attributed to the isomers at δ 25.45 and 23.83, respectively. Mixture b had the following characteristics: mp 128–130 °C, ^{1}H NMR ($CDCl_3$) δ 1.18 (d, $^3J_{HH}$ = 6.3 Hz, 3H) and 1.24 (d, $^3J_{HH}$ = 8.0 Hz, 3H) in a 1:3 ratio for different isomers, 1.82–1.84 (m, 3H), 3.23–3.49 (m, 3H), 3.29 (s, 3H) and 3.33 (s, 3H) in a 3:1 ratio for different isomers, 3.61–3.71 (m, 1H), 3.88–3.98 (m, 1H), 4.60–4.80 (m, 1H), 5.09 (dm, $^3J_{PH}$ = 23.4 Hz, 1H), 5.70 (broad s, 1H) and 6.00 (broad s, 1H) in a 1:3 ratio for different isomers, 7.04–7.41 (m, 5H); ^{31}P NMR ($CDCl_3$) δ 23.83 and 25.45 in a 3:1 ratio. Anal. Calcd for $C_{19}H_{22}NO_6P$: C, 58.30; H, 5.66. Found: C, 57.92; H, 5.13.

***endo*-3-(1-Methoxy-2-propoxy)-6-methyl-*N*-phenyl-2,3-oxaphosphabicyclo[2.2.2]oct-5-ene-7,8 dicarboximide 3-Sulfide (20a).** To a solution of **19** (2.30 g, 5.87 mmol, with ^{31}P NMR ($CDCl_3$) δ 23.83 and 25.41 in a 1:2 ratio) in methylene chloride (150 mL) was added phosphorus pentasulfide (6.52 g, 29.3 mmol). The suspension was stirred at room tempera-

ture for 48 h. The reaction mixture was then filtered through Celite, the solid was washed with methylene chloride, and the combined filtrates were evaporated to dryness *in vacuo*. Column chromatography of the residue on silica gel (Merck grade 60, 230–400 mesh) with methylene chloride–hexane (8:2), methylene chloride, and finally methylene chloride–methanol (9.8:0.2) as eluants afforded a sample which crystallized on standing at room temperature. Recrystallization (ether–chloroform) gave colorless plates of **20a**, 0.42 g (17.5%): mp 121–122 °C; ^{1}H NMR ($CDCl_3$) δ 1.24 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 1.93 (d of d, $^3J_{HH}$ = 3.0 Hz, $^4J_{HH}$ = 3.0 Hz, 3H), 3.30–3.40 (m, 3H), 3.38 (s, 3H), 3.72–3.93 (m, 2H), 4.80–5.00 (m, 1H), 5.20 (ddd, $^3J_{PH}$ = 22.2 Hz, $^3J_{HH}$ = 3.0 Hz, $^4J_{HH}$ = 3.0 Hz, 1H), 6.02–6.12 (m, 1H), 7.10–7.50 (m, 5H); ^{31}P NMR ($CDCl_3$) δ 86.4. Anal. Calcd for $C_{19}H_{22}NO_5PS$: C, 56.00; H, 5.44. Found: C, 55.53; H, 5.81.

(R^*_C,R^*_P)- and (R^*_C,S^*_P)-*O*-Ethyl *O*-(1-Methoxy-2-propyl) Phosphorothionoate (10, 11) from Thermolysis of 20a with Ethanol Present. A solution of **20a** (0.0327 g, 0.080 mmol) and ethanol (0.020 g, 0.43 mmol) in toluene (1.0 mL) was heated in a sealed tube at 120 °C for 1.5 h. Toluene was then evaporated *in vacuo* to give the crude product **10,11** as a yellow oil. The ^{31}P NMR spectrum of this material in $CHCl_3$ showed resonances at δ 66.81 and 64.39 as expected for the diastereoisomeric thiophosphoric acids **10** and **11** and also at δ −0.22 (a phosphoric acid derivative) in the ratio 1.9:1.0:0.3, respectively.

(R^*_C,R^*_P)- and (R^*_C,S^*_P)-*O*-Ethyl *O*-(1-Methoxy-2-propyl) Phosphorothionoate (10,11) from Thermolysis of 8 with 1-Methoxy-2-propanol Present. A solution of **8** (0.406 g, 1.118 mmol) and (*RS*)-1-methoxy-2-propanol (0.112 g, 1.243 mmol) in toluene (6 mL) was heated in a sealed tube at 120 °C for 2 h. The solvent was partially evaporated *in vacuo*; the ^{31}P NMR spectrum of the residue showed signals at δ 66.29 and 63.73 attributed to the isomers **10** and **11** and a signal for an unidentified phosphoric acid derivative (δ −0.6) in the ratio 1:1:0.6, respectively. Further evaporation of the reaction mixture gave a yellow oil (0.55 g) which was subsequently separated by chromatography on a silica gel column (Merck grade 60, 230–400 mesh) using chloroform, chloroform–methanol (9.7:0.3), and chloroform–methanol (9.3:0.7) as eluants. Individual isomers have the following characteristics: **10**, colorless oil, 0.031 g (13.9%); ^{1}H NMR ($CDCl_3$) δ 1.12–1.50 (m, 6H), 3.31–3.55 (m, 2H), 3.44 (s, 3H), 4.18 (dq, $^3J_{HH}$ = 6.8 Hz, $^3J_{PH}$ = 6.8 Hz, 2H), 4.40–5.10 (m, 1H); ^{31}P NMR ($CDCl_3$) δ 58.08; **11**, colorless oil, 0.0221 g (9.9%); ^{1}H NMR ($CDCl_3$) δ 1.12–1.55 (m, 6H), 3.20–3.50 (m, 2H), 3.38 (s, 3H), 4.19 (dq, $^3J_{HH}$ = 7.0 Hz, $^3J_{PH}$ = 7.0 Hz, 2H), 4.50–5.20 (m, 1H); ^{31}P NMR ($CDCl_3$) δ 57.70.

(*R,*R**)-Bis(1-methoxy-2-propyl) Hydrogen Phosphite (22a), (*r*,*r*$_P$,*s*)-bis(1-methoxy-2-propyl) Hydrogen Phosphite (22b), and (*r*,*s*$_P$,*s*)-Bis(1-methoxy-2-propyl) Hydrogen Phosphite (22c).** To a stirred solution of 1-methoxy-2-propanol (77.5 g, 0.86 mol) in benzene (100 mL) was added dropwise phosphorus trichloride (39.5 g, 0.29 mol). Stirring was continued for 0.5 h at 8–12 °C. In order to remove hydrogen chloride, dry nitrogen was bubbled through the reaction mixture under reduced pressure. After 3 h the solvent was evaporated (Rotavap) and the residue was distilled *in vacuo* to give a mixture of **22a**, **22b**, and **22c** (37.4 g, 57.4%) as a colorless liquid, bp 119.0–125.0 °C (3.0 mmHg): ^{1}H NMR ($CDCl_3$) δ 1.33 (dd, $^3J_{HH}$ = 6.5 Hz, $^4J_{HP}$ = 1.6 Hz, 6H), 3.38 (s, 6H), 3.41–3.49 (m, 4H), 4.63–4.85 (m, 2H), 7.58[a] (d, $^1J_{PH}$ = 622.0 Hz, 1H), 7.63[b] (d, $^1J_{HP}$ = 622.0 Hz, 1H), 7.68[c] (d, $^1J_{HP}$ = 622.0 Hz, 1H; the signals a, b, and c were in the ratio 7:10:5); ^{31}P NMR ($CDCl_3$) δ 5.70, 6.70, and 7.50 also in the ratio 7:10:5, respectively. Anal. Calcd for $C_8H_{19}O_5P$: C, 42.48; H, 8.47; P, 13.69. Found: C, 42.77; H, 8.69; P, 13.20.

Sodium 1-Methoxy-2-propyl Hydrogen Phosphite (23). To a stirred solution of bis(1-methyl-2-methoxyethyl) hydrogen phosphites **22a–c** (36.3 g, 0.16 mol) in 1-methyl-2-propanol (70 mL) were added sodium hydroxide pellets (6.40 g, 0.16 mol) in a few portions for 7 h at 20–30 °C. After the addition was complete, stirring was continued for a further 12 h. Evaporation of the solvent from the resultant solution under reduced pressure gave the crude **23** (28.2 g, 100%) as a viscous oil: ^{1}H NMR (D_2O) δ 1.73 (d, ^3J = 6.5 Hz, 3H), 3.87 (s, 3H), 3.95 (d, ^3J = 5.0 Hz, 2H), 4.25–4.63 (m, 1H), 7.26 (d, $^1J_{HP}$ = 637.0 Hz, 1H); ^{31}P NMR (D_2O) δ 5.10.

Tetrabutylammonium 1-Methoxy-2-propoxy Hydrogen Phosphite (24). To a solution of tetrabutylammonium hydrogen sulfate (54.2 g, 0.16 mol) in water (35 mL) was added a 20% aqueous solution of sodium hydroxide (40 mL). The reaction mixture was stirred and maintained below 25 °C while a solution of sodium 1-methyl-2-methoxyethyl hydrogen phosphite (**23**) (28.2 g, 0.16 mol) in water (25 mL) was added dropwise at 20–25 °C. Stirring was continued for 15 min and the resultant precipitate was filtered. After extraction of the filtrate with CH_2Cl_2 (4 × 60 mL) and drying the combined organic layers with $MgSO_4$, removal of the solvent *in vacuo* afforded the crude **24** (52.5 g, 82.9%) as a yellow syrup: ^{1}H NMR ($CDCl_3$) δ 1.00 (t, $^3J_{HH}$ = 6.0 Hz, 12H), 1.14 (d, $^3J_{HH}$ = 6.0 Hz, 2H), 1.24–1.86 (m, 16H), 3.16–3.34 (m, 8H), 3.36 (s, 3H), 3.43 (d, $^3J_{HH}$ = 5.0 Hz, 2H), 4.23–4.62 (m, 1H), 6.98 (d, $^1J_{PH}$ = 587.0 Hz, 1H); ^{31}P NMR ($CDCl_3$) δ 1.8.

(*R$_C$,*R**$_P$)-Ethyl 1-Methoxy-2-propyl Hydrogen phosphite (25a) and (*R**$_C$,*S**$_P$)-Ethyl 1-Methoxy-2-propyl Hydrogen Phosphite (25b).** To a solution of the crude tetrabutylammonium 1-methoxy-2-propyl hydrogen phosphite (**24**; 52.0 g, 0.13 mol) in acetonitrile (250 mL) was added ethyl iodide (24.6 g, 0.16 mol), and the reaction mixture was stirred at 50 °C for 8 h. After evaporation of acetonitrile under reduced pressure, hexane (100 mL) was added and the resulting precipitate filtered and washed with hexane (2 × 25 mL). The hexane layer was separated from the combined filtrates and concentrated *in vacuo*. Distillation of the residue gave a 1:1 mixture of **25a** and **25b** (8.34 g, 34.8%) as a colorless liquid, bp 112–115 °C (5.0 mmHg): ^{1}H NMR ($CDCl_3$) δ 1.34 (d, $^3J_{HH}$ = 6.0 Hz, 3H), 1.36 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 3.39 (s, 3H), 3.42 (d, $^3J_{HH}$ = 7.0 Hz), 4.04–4.36 (m, 2H), 4.58–4.85 (m, 1H), 6.18[a] (d, $^1J_{PH}$ = 811.0 Hz, 1H), 6.26[b] (d, $^1J_{PH}$ = 811.0 Hz, 1H) (the signals a and b were in the ratio 1:1); ^{31}P NMR ($CDCl_3$) δ 6.40 and 7.20 also in the ratio 1:1. Anal. Calcd for $C_6H_{15}O_4P$: C, 39.56; H, 8.30; P, 17.01. Found: C, 39.83; H, 8.71; P, 16.57.

(*R$_C$,*R**$_P$)-*O*-Ethyl *O*-(1-Methoxy-2-propyl) Phosphorothionoate (10) and (*R**$_C$,*S**$_P$)-*O*-Ethyl *O*-(1-methoxy-2-propyl) Phosphorothionoate (11).** A 1:1 mixture of diastereomeric 1-methoxy-2-propyl phosphites (**25a** and **25b**; 2.60 g, 0.014 mol) was dissolved in benzene (10 mL). While the solution was vigorously stirred under an argon atmosphere, dry finely-powdered sulfur (0.50 g, 0.015 mol) was added in one portion, followed by a solution of triethylamine (1.60 g, 0.016 mol) in benzene (5 mL) dropwise at 20 °C. After an additional 12 h of stirring, the reaction mixture was poured into cold (5 °C) water (40 mL). The aqueous layer was separated, acidified with a 10% HCl solution to pH 1, and extracted with $CHCl_3$ (4 × 50 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated *in vacuo* and finally at 0.05 mmHg to give a 1:1 mixture of **10** and **11** (2.20 g, 72.0%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.32 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.33 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 3.27–3.57 (m, 2H), 3.43[a] (s, 3H), 3.45[b] (s, 3H), 3.94–4.34 (m, 2H), 4.54–4.98 (m, 1H), 7.28 (s, 1H; the signals a and b were in the ratio 1:1); ^{31}P NMR ($CDCl_3$) δ 59.05 and 58.67 also with ratio 1:1. Anal. Calcd for $C_6H_{15}O_4PS$: P, 14.46. Found: P, 14.00.

(*R$_C$,*R**$_P$)-Dicyclohexylammonium *O*-Ethyl *O*-(1-methoxy-2-propyl) Phosphorothionoate (26).** Freshly distilled dicyclohexylamine (1.25 g, 6.90 mmol) was added to a solution of the 1:1 mixture of diastereomeric *O*-ethyl *O*-(1-methoxy-2-propyl) phosphorothionoates (**10** and **11**; 1.48 g, 6.90 mmol). After being stirred for 24 h at 20 °C, the reaction mixture was concentrated to 1/4 of its original volume with a rotary evaporator. Hexane was then added dropwise as long as a colorless oil precipitated. The ^{31}P NMR ($CDCl_3$) spectrum showed two resonances at δ 55.08 and 55.13 in the ratio of 1.0:0.2. After 48 h standing at 0 °C, the oil partially solidified. The solid was filtered, washed with hexane (3 × 5 mL), and recrystallized several times from a mixture of ether and hexane to give an analytical sample of **26** (0.45 g, 16.4%) as colorless plates: mp 136.5 °C; ^{1}H NMR (CD_3COCD_3) δ 1.08 (t,

$^3J_{HH}$ = 6.5 Hz, 3H), 1.12 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 1.22–2.20 (m, 20 H), 2.73–2.87 (m, 2H), 3.19 (s, 3H), 3.21 (d, $^3J_{HH}$ = 6.0 Hz, 1H), 3.33 (d, $^3J_{HH}$ = 6.0 Hz, 1H), 3.82 (dq, $^3J_{HH}$ = 7.5 Hz, $^3J_{HP}$ = 7.0 Hz, 1H), 3.83 (dq, $^3J_{HH}$ = 7.5 Hz, $^3J_{HP}$ = 7.0 Hz), 4.45 (d of sex, $^3J_{HH}$ = 7.0 Hz, $^3J_{HP}$ = 7.0 Hz, 1H), 8.90 (s, 1H); ^{31}P NMR ($CDCl_3$) δ 55.13. Anal. Calcd for $C_{18}H_{38}NO_4PS$: C, 54.66; H, 9.68; P, 7.83. Found: C, 54.51; H, 10.00; P, 7.51.

(R^*_C,R^*_P)-*O*-Ethyl O-(1-Methoxy-2-propyl) Phosphorothionoate (10). (R^*,R^*_P)-Dicyclohexylammonium *O*-ethyl *O*-(1-methoxy-2-propyl) phosphorothionoate (**27**; 0.35 g, 0.88 mmol) was dissolved in water (6 mL). The solution was acidified with 5 N hydrochloric acid to pH 1 and then extracted with ether (4 × 10 mL). The combined extracts were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was chromatographed on a short silica gel column (Merck 60, 230–400 mesh) using 8:2 chloroform: methanol as eluant to give an analytical sample of **10** (0.162 g, 86.0%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.30 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.31 (d, $^3J_{HH}$ = 6.5 Hz, 3H), 3.39 (s, 3H), 3.43 (d, $^3J_{HH}$ = 6.0 Hz, 1H), 3.50 (d, $^3J_{HH}$ = 6.0 Hz, 1H), 4.10 (dq, $^3J_{HH}$ = 7.5 Hz, $^3J_{PH}$ = 7.0 Hz, 1H), 4.12 (dq, $^3J_{HH}$ = 7.5 Hz, $^3J_{PH}$ = 7.0 Hz, 1H), 4.72 (d of sex, $^3J_{HH}$ = 7.0 Hz, $^3J_{PH}$ = 7.0 Hz, 1H), 5.36 (s, 1H); ^{31}P NMR ($CDCl_3$) δ 58.25. Anal. Calcd for $C_6H_{15}O_4PS$: C, 33.64; H, 7.06; P, 14.46. Found: C, 33.83; H, 7.41; P, 14.03.

Addition of **10** to the original mixture of **10** and **11** caused a distinct increase of the intensity of the upfield ^{31}P NMR signal.

Kinetic Experiments. The rate of disappearance of substrate was determined from the reduction of the size of its ^{31}P NMR signal. A chloroform solution (2 mL) of **20a** (0.053 mol/L) and ethanol (0.348 mol/L) was placed in a 10-mm NMR tube, and a sealed 5-mm coaxial NMR tube containing a $CDCl_3$ solution of the phosphorus standard (Ph_3PO) was installed. The external tube was flushed with dry argon and sealed. The tube was thermostated at 100 °C and at seven time intervals was cooled in an ice–water bath for NMR measurements. The ^{31}P NMR spectra were recorded on a Bruker MSL 300 spectrometer. Signals of the substrate, two reaction products, and the standard were observed. The rate constant was determined from the peak areas of the substrate and the standard. The kinetics were followed up to 35 min; then the sample was heated for an additional 75 min. No signal for the substrate was present; products at δ 66.03 and 64.49 (attributed to the isomeric thiophosphoric acids **10** and **11**) were observed in a ratio of 4.4:1.

X-ray Analysis of 20a and 26. Prismatic crystals of **20a** and thin, platelike crystals of **26** were obtained from saturated solutions of chloroform/ether and hexane/ether, respectively. Accurate unit cell determination and data collection were carried out on a KM4 diffractometer with Cu Kα radiation. Intensities were measured by $\omega/2\Theta$ scan technique up to Θ = 82° for **20a** and Θ = 65° for **26**. Of the 3877 for **20a** and 3637 for **26** independent intensities measured, 3259 with $|F_o| > 4\delta(F_o)$ (only 1645 with $|F_o| > 3\delta(F_o)$ for **26**) were considered observed and used in the refinement. The data were corrected for Lorentz and polarization factors and for absorption[11] in the case of **20a**. The structures were solved using the direct methods and refined with the full-matrix least-squares method. The weights in the final cycles were $1/\sigma^2(F_o) + 0.00112F^2$ (**20a**) and $\sigma^{-2}(F_o)$ (**26**). Extinction correction [g = 0.008(4)] was also applied for **20a**. Most hydrogen atoms were visible on a difference Fourier map but they were calculated geometrically and refined in rigid groups. The maximum and minimum electron densities on the final Fourier map were 0.49 and −0.33 for **20a** and 0.28 and −0.25 e Å^{-3} for **26**, respectively. The calculations were performed on an IBM PS2 computer using the programs from the SHELXTL PC.[12]

Crystal data for 20a: $C_{19}H_{22}NO_5PS$, M_r = 407.4, monoclinic from chloroform/ether, $P2_1/c$, a = 11.217(2), b = 19.101(4), and c = 9.823(2) Å, β = 109.22(3)°, V = 1987.3 Å^3, Z = 4, D_x = 1.36 g/cm^3, μ = 2.45 mm^{-1}, $F(000)$ = 856, T = 293 K, R = 0.046, R_w = 0.064.

Crystal data for 26: $C_6H_{14}O_3SPO^-$ $C_{12}H_{24}N^+$, M_r = 395.5, triclinic, $P\bar{1}$, a = 9.815(1), b = 10.135(1), and c = 12.090(1) Å, α = 93.12(1)°, β = 104.96(1)°, γ = 90.74(1)°, V = 1159.7 Å^3, Z = 2, D_x = 1.33 g/cm^{-3}, μ = 2.03 mm^{-1}, $F(000)$ = 432, T = 293 K, R = 0.068, R_w = 0.060.

Acknowledgment. The U.S. Army Research Office is thanked for a grant that supported this research and the Polish State Committee for Scientific Research for supporting the crystallographic experiments (Project 3.0302.91.01).

Supplementary Material Available: Results of X-ray analysis of **20a** and **26** (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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