and were determined as described previously[12] with the following exceptions. Spectral solutions were 3×10^{-5} *M* and buffered solutions were prepared using citric acid–Na_2HPO_4. The maximum deviation from the mean of replicate pK_a values did not exceed 2.5% for any of the compounds studied.

The substituent chemical shifts (SCS) in hertz for the amide group methyl protons of 4′-substituted 4-biphenylacetanilides were measured on a Varian T-60 spectrometer vs. TMS at 37° in a 10% DMSO-d_6 solution. These values are reported in Table II and represent the average of at least three determinations. The maximum deviation from the mean of replicate SCS values did not exceed 0.5% for any of the compounds studied.

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An Investigation of the Scope and Limitations of the Cornforth Rearrangement

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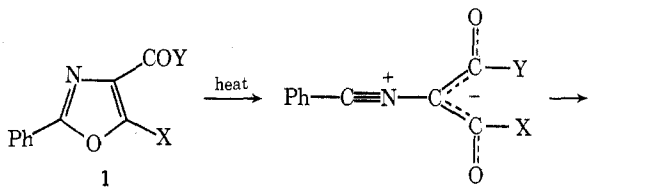
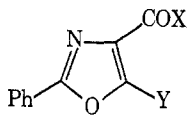
The thermal rearrangement of 4-carbonyl substituted oxazoles was first observed by Cornforth.[1] We have investigated the mechanism of this reaction by experimental[2a,b] and theoretical techniques.[3] The results of these studies suggest the intermediacy of the nitrile ylide **3** in the reaction of **1** → **2**.



1 3



2

a, X = OEt; Y = —N△

b, X = OEt; Y = —N⬭O

c, X = OEt; Y = —N⬭N

d, X = OEt; Y = —N⬭N (Me)

e, X = OEt; Y = N⬭N

f, X = OMe; Y = SPh-*p*-Me

g, X = OEt; Y = F

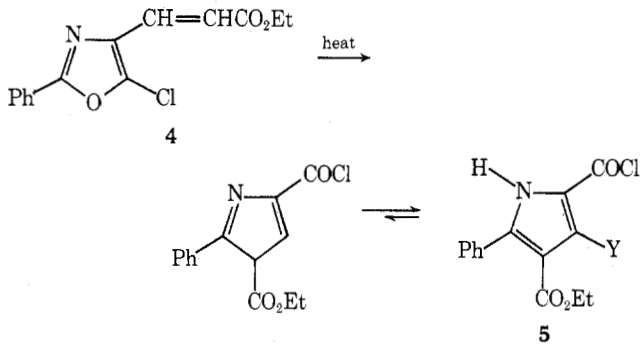
Cornforth found that 2-phenyl-5-ethoxyoxazole-4-carboxamide (**1**, X = OEt; Y = NH_2) rearranged on heating to ethyl 2-phenyl-5-aminooxazole-4-carboxylate (**2**, X = OEt; Y = NH_2).[1] We have now carried out similar rearrangements of several secondary and tertiary alkyl and aryl oxazole-4-carboxamides to the corresponding secondary and tertiary 5-aminooxazoles.[2b] We have also found that this rearrangement occurs in yields of >90% when the amide nitrogen is part of a heterocyclic ring system (**1a–e** → **2a–e**).

Trideuteriomethyl 2-phenyl-5-methoxyoxazole-4-carboxylate (**1**, X = OMe; Y = OCD_3) rearranged on heating to give a 1:1 equilibrium mixture of **1** and the corresponding rearranged ester **2** (X = OMe; Y = OCD_3).[2b] The thiol ester **1f** underwent thermal isomerization to the corresponding 5-thiooxazole **2f** in good yield under similar conditions. Prior to this investigation there was, to our knowledge, only one other method for preparing 5-thiooxazole-4-carboxylates, i.e., the reaction of 4-benzamido-1,2-dithiol-3-thione with KOH and methyl iodide to give 2-phenyl-5-methylthiooxazole-4-carbodithioate.[4] Thus the Cornforth rearrangement of 5-alkoxyoxazole-4-thiocarboxylates is a potentially general method for the synthesis of 5-thiooxazole-4-carboxylic esters.

While **1** (X = OEt; Y = Cl) rearranges to **2** (X = OEt; Y = Cl),[1] the corresponding fluoro derivative **1g** failed to rearrange.

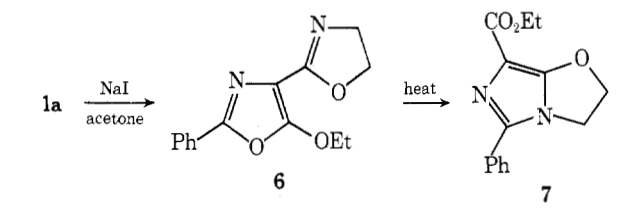
These reactions all involve compounds where a heteroatom is attached to the 5 position. One rearrangement has been reported[5] where the group X in **1** is alkyl or aryl, i.e., the interconversion of 2,5-diphenyl-4-acetyloxazole and 2-phenyl-4-benzoyl-5-methyloxazole; the reactions were, however, very slow even at 220°.

When the 4-carbonyl group of **1** was replaced by an α,β-unsaturated ester functionality, the resulting compound (**4**) failed to rearrange to the corresponding pyrrole derivative **5**, even after boiling under reflux for 17 hr in toluene.



Attempts to prepare 2-phenyl-5-ethoxyoxazole-4-carboxylic acid thioamide by the reaction of the corresponding oxazole-4-cyanide with H_2S–NaOEt failed to yield any identifiable products. Rearrangement of this thioamide should lead to ethyl 2-phenyl-5-aminothiazole-4-carboxylate.

The reaction of the aziridinyl amide **1a** with sodium iodide in acetone gave 2-(2-phenyl-5-ethoxyoxazolyl)-Δ^2-oxazoline (**6**) in 60% yield. Thermolysis of **6** in boiling toluene gave 5-phenyl-7-carboethoxyimidazo[5,1-*b*]-2,3-dihydrooxazole (**7**) in 97% yield.



Whether or not rearrangement of **1** occurs in any given case seems to depend solely on the equilibrium between reactant and product. For example, oxazole-4-carboxamides rearrange irreversibly to 5-aminooxazoles at temperatures above 90°. 5-Methoxyoxazole-4-carboxamide is calculated (by the MINDO/3 MO method[6]) to be some 6 kcal/mol less stable than the rearranged methyl 5-aminooxazole-4-carboxylate.[3]

The 5-aminooxazoles prepared via the Cornforth rearrangement could possess interesting and useful biological properties. Tests of the biological activity of several of these new compounds are now in progress.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded on a Varian A-60 instrument using solutions approximately 15% w/v in deuteriochloroform. Ir spectra were determined with a Beckman IR-8 spectrophotometer (KBr disk). Mass spectra were measured with 70-eV electrons. Elemental analyses were carried out by Galbraith Laboratories, Knoxville, Tenn., and Heterocyclic Chemical Corp., Harrisonville, Mo.

General Procedure for the Preparation of 2-Phenyl-5-ethoxyoxazole-4-carboxamides (1a–e). A solution of 2-phenyl-5-ethoxyoxazole-4-carboxylic acid chloride[1] (0.005 mol) in benzene (20 ml) was added to a solution of the corresponding amine (0.005 mol) and triethylamine (0.5 g, 0.005 mol) in benzene (40 ml) at 0°. The mixture was then stirred for 3 hr at room temperature, filtered, washed with water, and dried ($MgSO_4$) and the benzene was evaporated. The resulting amides were recrystallized several times from petroleum ether (bp 60–70°).

1a: yield 80%; mp 82–83°; ir 2970–3000 (w), 1660 (s, C=O), 1600 cm^{-1} (s, C=N); NMR δ 8.0 (m, 2 H, phenyl), 7.6 (m, 3 H, phenyl), 4.6 (q, 2 H, ethoxymethylene), 2.4 (s, 4 H, aziridine), 1.5 (t, 3H, methyl); mass spectrum *m/e* (rel intensity) 258 (21), 212 (6), 188 (12), 131 (15), 105 (100).

Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.29; H, 5.67; N, 11.05.

1b: yield 93%; mp 83–84°; ir 2720–2920 (m), 1645 (s, C=O), 1605 cm^{-1} (s, C=N); NMR δ 7.9 (m, 2 H, phenyl), 7.4 (m, 3 H, phenyl), 4.55 (q, 2 H, ethoxymethylene), 3.9 (broad m, 8 H, morpholine protons), 1.5 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 303 (21), 302 (100), 216 (11), 188 (39), 172 (15), 105 (66). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.79; H, 6.00; N, 9.20.

1c: yield 78%; mp 105–107°; ir 3160 (w), 2960 (w), 1700 (s, C=O), 1600 cm^{-1} (s, C=N); NMR δ 8.75 (d, 1 H, J = 3 Hz, 3-pyrazole proton), 7.9 (m, 3 H, phenyl and 5-pyrazole protons), 7.45 (m, 3 H, phenyl), 6.45 (dd, 1 H, 4-pyrazole proton), 4.65 (q, 2 H, methylene), 1.5 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 283 (76), 256 (19), 255 (100), 238 (19), 188 (46). Anal. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.85; H, 4.75; N, 14.64.

1d: yield 92%; mp 98–100° dec; ir 3180 and 2990 (m), 1685 (s, C=O), 1600 cm^{-1} (s, C=N); NMR δ 8.3 (d, 1 H, J = 1.5 Hz, 4-imidazole proton), 7.9 (m, 2 H, phenyl), 7.4 (m, 3 H, phenyl), 6.9 (d, 1 H, J = 1.5 Hz, 5-imidazole proton), 4.65 (q, 2 H, methylene), 2.75 (s, 3 H, imidazole methyl), 1.55 (t, 3 H, ethoxymethyl); mass spectrum *m/e* (rel intensity) 297 (35), 216 (60), 188 (45), 110 (100), 95 (53). Anal. Calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; 5.09; N, 14.13. Found: C, 64.78; H, 5.16; N, 14.06.

1e: yield 88%; mp 156° dec; ir 3150 (m), 2950 (w), 1685 (s, C=O), 1590 cm^{-1} (s, C=N); NMR δ 8.4 (m, 1 H, 2-benzimidazole proton), 7.9 (m, 3 H, phenyls), 7.4 (m, 6 H, phenyls), 4.7 (q, 2 H, methylene), 1.6 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 333 (100), 216 (63), 188 (73), 146 (77), 131 (95). Anal. Calcd for $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.54; N, 12.61. Found: C, 68.68; H, 4.69; N, 12.50.

General Procedure for the Preparation of Ethyl 2-Phenyl-5-aminooxazole-4-carboxylates (2a–e). The corresponding amides **1a–e** were heated under reflux for 17 hr in dry toluene. The solvent was then removed and the residue recrystallized from petroleum ether. Yields of >90% of pure materials were obtained.

2a: mp 118–119°, ir 3170 (w), 2950 (m), 1710 (s, C=O), 1580 cm^{-1} (s, C=N); NMR δ 7.9 (m, 2 H, phenyl), 7.4 (m, 3 H, phenyl), 4.4 (q, 2 H ethoxymethylene), 2.6 (s, 4 H, aziridine), 1.4 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 258 (100), 216 (33), 188 (73), 160 (32). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.88; H, 5.32; N, 10.74.

2b: mp 85–86°; ir 2700–2920 (m), 1685 (s, C=O), 1610 cm^{-1} (s, C=N); NMR δ 7.9 (m, 2 H, phenyl), 7.4 (m, 3 H, phenyl), 4.4 (q, 2 H, ethoxymethylene), 3.8 (m, 8 H, morpholine), 1.4 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 302 (100), 216 (11), 188 (42), 160 (25). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.62; H, 6.13; N, 9.37.

2c: mp 99–101°; ir 3150 and 2950 (w), 1710 (s, C=O), 1630 cm^{-1} (s, C=N); NMR δ 8.55 (d, 1 H, J = 3 Hz, 3-pyrazole proton), 8.15 (m, 2 H, phenyl), 7.9 (d, 1 H, J = 2 Hz, 5-pyrazole proton), 7.45 (m, 3 H, phenyl) 6.55 (dd, 1 H, 4-pyrazole proton), 4.45 (q, 2 H, methylene), 1.3 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 283 (100), 255 (99), 226 (17), 188 (37). Anal. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.49; H, 4.53; N, 14.70.

2d: mp 149–150°; ir 3130 and 2950 (w), 1740 (s, C=O), 1645 cm^{-1} (m, C=N); NMR δ 8.1 (m, 2 H, phenyl), 7.5 (m, 3 H, phenyl), 7.2 (d, 1 H, J = 1 Hz, 4-imidazole proton), 7.05 (d, 1 H, J = 1 Hz, 5-imidazole proton), 4.35 (q, 2 H, methylene), 2.45 (s, 3 H, imidazole methyl), 1.3 (t, 3 H, ethoxymethyl); mass spectrum *m/e* (rel intensity) 297 (14), 216 (76), 188 (100), 160 (52). Anal. Calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.47; H, 5.01; N, 13.96.

2e: mp 189–190°; ir 3170 and 2950 (w), 1710 (s, C=O), 1610 cm^{-1} (s, C=N); NMR δ 8.65 (broad s, 1 H, 2-benzimidazole proton), 7.8 (m, 9 H, phenyls), 4.4 (q, 2 H, methylene), 1.3 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 333 (13), 216 (3), 188 (2), 176 (15), 161 (100). Anal. Calcd for $C_{19}H_{15}N_3O_3$: C, 68.46, H, 4.54; N, 12.61. Found: C, 68.64; H, 4.60; N, 12.45.

***p*-Tolyl 2-Phenyl-5-methoxyoxazole-4-thiocarboxylate (1f).** A solution of 2-phenyl-5-methoxyoxazole-4-carboxylic acid chloride[2b] (0.005 mol, 1.19 g) in benzene (40 ml) was added to a solution of *p*-thiocresol (0.005 mol, 0.62 g) and triethylamine (0.005 mol, 0.5 g) in benzene (40 ml) at 0°. The mixture was then stirred at room temperature for 15 hr and worked up as in the preparation of **1a–e** (1.5 g, 95%): mp 104–105°; ir 2930 (w), 1670 (s, C=O), 1605 cm^{-1} (s, C=N); NMR δ 8.0 (m, 2 H, phenyl), 7.4 (m, 7 H, phenyls), 4.25 (s, 3 H, methoxymethyl), 2.4 (s, 3H, Ph-*p*-**Me**); mass spectrum *m/e* (rel intensity) 326 (12), 325 (52), 220 (100), 174 (27), 146 (12). Anal. Calcd for $C_{18}H_{15}NO_3S$: C, 66.44; H, 4.65; N, 4.30. Found: C, 66.64; H, 4.80; N, 4.31.

Methyl 2-phenyl-5-*p*-tolylthiooxazole-4-carboxylate (2f) was prepared in the same manner as **2a–e:** yield 94%; mp 94–95°; ir 3040, 2850–2950 (w), 1735 (s, C=O), 1550 cm^{-1} (m, C=N); NMR δ 7.9 (m, 2 H, phenyl), 7.35 (m, 7 H, phenyls), 4.0 (s, 3 H, methoxy-

methyl), 2.45 (s, 3 H, Ph-*p*-**Me**); mass spectrum *m/e* (rel intensity) 326 (20), 325 (81), 203 (15), 202 (100), 174 (24). Anal. Calcd for $C_{18}H_{15}NO_3S$: C, 66.44; H, 4.65; N, 4.30. Found: C, 66.36; H, 4.49; N, 4.18.

2-Phenyl-5-ethoxyoxazole-4-carboxylic Acid Fluoride (1g) (Prepared by a Modification of the Method of Olah et Al.[7]). A solution of cyanuric fluoride (0.004 mol, 0.54 g) in acetonitrile (20 ml) was added dropwise to a stirred solution of 2-phenyl-5-ethoxyoxazole-4-carboxylic acid[1] (0.01 mol, 2.33 g) and pyridine (0.01 mol, 0.79 g) in acetonitile (50 ml). (Before the addition of the cyanuric fluoride, the acid–pyridine–acetonitrile mixture was warmed on a water bath to dissolve the acid.) The reaction mixture was allowed to stand at room temperature for 3 hr. After the completion of the reaction the mixture was poured onto ice water, extracted with ether, and dried (Na_2SO_4) and the solvent was removed. The residue was recrystallized several times from petroleum ether to remove traces of the starting acid: 1.1 g (48%); mp 88–90°; ir 2990 (w), 1805 (s, C=O), 1630 cm^{-1} (s, C=N); NMR δ 7.9 (m, 2 H, phenyl), 7.4 (m, 3 H, phenyl), 4.6 (q, 2 H, methylene), 1.5 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 236 (5), 235 (27), 188 (36), 187 (100), 105 (42). Anal. Calcd for $C_{12}H_{10}NO_3F$: C, 61.28; H, 4.28; N, 5.95. Found: C, 61.13; H, 4.24; N, 5.80.

Ethyl β-(2-Phenyl-5-chlorooxazole-4)acrylate (4). A solution of 2-phenyl-5-chlorooxazole-4-carboxaldehyde[1] (0.0048 mol, 1.0 g) and (carboethoxymethylene)triphenylphosphorane (0.0072 mol, 2.55 g) in ethanol (50 ml) was allowed to stand for 3 days at room temperature. The mixture was then filtered and the solvent removed. The residue was recrystallized several times from petroleum ether to remove triphenylphosphine oxide and starting material (1.2 g, 90%): mp 90–91°; ir 3060 (w), 2900–2950 (m), 1710 (s, C=O), 1640 (s, C=N), 1600 cm^{-1} (m, C=C–C=O); NMR δ 8.0 (m, 2 H, phenyl), 7.5 (m, 4 H, phenyl and part of AB quartet of vinyl protons), 6.85 and 6.6 (1 H, part of AB quartet of vinyl protons, $J_{AB} \cong 16$ Hz), 4.3 (q, 2 H, methylene), 1.35 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 279 (17), 278 (18), 277 (64), 249 (28), 242 (37), 232 (22), 220 (100). Anal. Calcd for $C_{14}H_{12}NO_3Cl$: C, 60.55; H, 4.36; N, 5.04. Found: C, 60.46; H, 4.28; N, 5.07.

2-(2-Phenyl-5-ethoxyoxazolyl)-Δ²-oxazoline (6). A solution of **1a** (0.012 mol, 3.0 g) and NaI (22.5 g) in acetone (300 ml) was stirred at room temperature for 24 hr. The solvent was removed; the residue was extracted with hot benzene, filtered, and dried ($MgSO_4$) and the benzene was removed, leaving an oil which crystallized on standing. Recrystallization from pentane gave 1.8 g (60%) of **6**: mp 66–67°; ir 2720–2980 (m), 1665 and 1635 cm^{-1} (s, C=N); NMR δ 8.0 (m, 2 H, phenyl), 7.4 (m, 3 H, phenyl), 4.4 (m, 6 H, oxazoline and ethoxymethylenes), 1.5 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 258 (100), 213 (39), 186 (50), 156 (44), 130 (54). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.88; H, 5.51; N, 11.04.

5-Phenyl-7-carboethoxyimidazo[5,1-*b*-]-2,3-dihydrooxazole (7). A solution of **6** (0.0077 mol, 2.0 g) in dry toluene was heated under reflux for 17 hr. The solvent was removed and the solid residue was recrystallized from benzene (1.94 g, 97%): mp 166–167°; ir 3160 (w), 2900–2975 (m), 1695 (s, C=O), 1590 cm^{-1} (s, C=N); NMR δ 7.7 (m, 2 H, phenyl), 7.3 (m, 3 H, phenyl), 5.2 broad t, 2 H, NCH_2), 4.3 (m, 4 H, OCH_2 of oxazoline ring and ethoxymethylene protons), 1.35 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 259 (18), 258 (100), 213 (24), 186 (26), 156 (25), 130 (74). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.23; H, 5.63; N, 11.09.

Acknowledgments. This work was supported by the Air Force Office of Scientific Research (Contract No. F44620-71-C-0119) and the Robert A. Welch Foundation (Grant F-126). The calculations were carried out using the CDC 6400/6600 computer at the University of Texas Computation Center.

Registry No.—**1a,** 54643-95-7; **1b,** 54643-96-8; **1c,** 54643-97-9; **1d,** 54643-98-0; **1e,** 54643-99-1; **1f,** 54644-00-7; **1g,** 54644-01-8; **2a,** 54644-02-9; **2b,** 54644-03-0; **2c,** 54644-04-1; **2d,** 54644-05-2; **2e,** 54644-06-3; **2f,** 54644-07-4; **4,** 54644-08-5; **6,** 54644-09-6; **7,** 54644-10-9; aziridine, 151-56-4; morpholine, 110-91-8; 1*H*-pyrazole, 288-13-1; 2-methyl-1*H*-imidazole, 693-98-1; 1*H*-benzimidazole, 51-17-2; 2-phenyl-5-methoxyoxazole-4-carboxylic acid chloride, 54644-11-0; *p*-thiocresol, 106-45-6; cyanuric fluoride, 675-14-9; 2-phenyl-5-ethoxyoxazole-4-carboxylic acid, 54644-12-1; 2-phenyl-5-chlorooxazole-4-carboxaldehyde, 54644-13-2; 2-phenyl-5-ethoxyoxazole-4-carboxylic acid chloride, 54644-14-3.

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A Convenient Preparation of Simple Optically Active Phosphinate Esters and Derivatives from the Corresponding Menthyl Esters. Solvolysis of Menthoxyphosphonium Salts in Trifluoroacetic Acid

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Optically active phosphinate esters with chirality at phosphorus are important intermediates in the synthesis of other classes of chiral phosphorus compounds such as phosphine oxides[1,2] and phosphines,[3] phosphinamidates,[4] and phosphinothioates.[5] At present, preparation of the menthyl esters and separation of diastereomers provides the easiest route to these phosphinate esters. The use of the menthyl esters, however, suffers from certain limitations. Often, as is the case for the widely used $(S)_P$ menthyl methylphenylphosphinate, only one diastereomer is easily obtained in high optical purity. The chiral menthyl ligand, however, requires access to both epimers at phosphorus before the stereospecificity of a reaction can be established. In addition, the steric bulk of the menthyl ligand hinders transformations which involve a nucleophilic displacement at phosphorus.[2]

We would like to report a convenient stereospecific conversion of menthyl phosphinates to the more simply substituted methyl or ethyl phosphinates, which have their sole center of chirality at phosphorus and have the opposite stereochemical configuration at phosphorus than the starting menthyl esters. Thus, the limitations of the menthyl esters can be circumvented and the procedure broadens their usefulness. In addition, an extension of the method for the conversion of menthyl phosphinothionates to alkyl phosphonothiolates was found.

The general method for the above conversions is indicated in Scheme I. A general procedure applied to the examples in Table I is given in the Experimental Section. Invariably, the yields for the overall conversions of **1** to **3** were greater than 90%. The use of the trialkyloxonium *hexafluorophosphate* alkylating agents was found to be far superior to using either the tetrafluoroborate or hexachloroantimonate salts. The oxonium tetrafluoroborates are hygroscopic and usually result in phosphonium salts (**2**, $ML_n = BF_4$) which are oils and difficult to handle. While the phosphonium salts (**2**, $ML_n = SbCl_6$) resulting from alkylation with the less hygroscopic oxonium hexachloroantimonates are usually solids, the solvolysis of these phosphonium salts to the desired products (**3**) results in the formation of an insoluble mass and greatly complicates work-up. When the alkylating agent is the oxonium hexafluorophosphate, all of the above advantages and none of the disadvantages occur