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DESIGN AND SYNTHESIS OF CANDIDATE PROPHYLACTIC AND  
THERAPEUTIC COMPOUNDS F (U) ASH STEVENS INC DETROIT MI  
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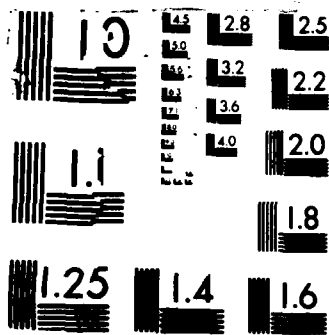
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DESIGN AND SYNTHESIS OF CANDIDATE PROPHYLACTIC AND THERAPEUTIC COMPOUNDS  
FOR USE IN THE MANAGEMENT OF ORGANOPHOSPHORUS POISONING

ANNUAL PROGRESS REPORT

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January 1985

(For the Period 1 September 1983 to 30 September 1984)

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U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND  
Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DAMD17-81-C-1140

ASH STEVENS INC.  
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) The program is directed at the design and synthesis of new compounds for use in the management of organophosphorus poisoning. In the past year 24 compounds were submitted: 12 organophosphinates, one organophosphinic acid, one organophosphinothioate, one organophosphonate, 3 organophosphates, 2 ferrocene carbamates, one each 2-aminoethylseleninic and selenonic acids, phenyl valerate and 2,2-dimethyl-3-hydroxybutylamine.		

FOREWORD

The work described herein was performed under Contract No. DAMD17-81-C-1140 for the U.S. Medical Research and Development Command, Fort Detrick, Frederick, Maryland. This Third Annual Report covers the period 1 September 1983 to 30 September 1984. Dr. C.L. Stevens served as Principal Investigator, Dr. P. Blumbergs as Associate Investigator and Dr. A.B. Ash as Program Manager, phone (313) 872-6400.

cont'd

→ The purpose of the contract is to maintain and operate a synthesis laboratory to provide chemical compounds needed in the development programs of the U.S. Army Medical Research Institute of Chemical Defense (ICD) ←  
Edgewood Area, Aberdeen Proving Ground, Maryland.

Acknowledgment

The timely advice and assistance of Dr. Brennie Hackley, Jr., the Contracting Officers Technical Representative (COTR) and Mr. Claire Lieske of the ICD is gratefully acknowledged.

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1. SUMMARY OF COMPOUNDS PREPARED AND SUBMITTED

Compounds prepared and submitted from September 1, 1983 through September 30, 1984 are listed below and form the subject matter of this report. The synthesis of the compounds is discussed in Section 2 and work in progress is listed in Section 3. Experimental details are provided in Section 4 and references cited are listed in Section 5.

Work completed in the two prior years, September 1, 1981 to August 31, 1983 inclusive, was reported in the First and Second Annual Progress Reports (ref. 1, 2).

The following 24 compounds were prepared and submitted in the past year.

1. Phenyl(trichloromethyl)phosphinic Acid

A 0.50 g sample of the title compound was shipped to Edgewood on 21 September 1983.

2.  $\gamma$ -Methyladenosine 5'-Triphosphate

A 1.0 g sample of the title compound was shipped to Edgewood on 3 October 1983.

3. 4-Nitrophenyl Ethyl(phenyl)phosphinate

A 10 g sample of the title compound was shipped to Edgewood on 14 November 1983.

4. 4-Nitrophenyl Di-1-butylphosphinothioate

A 10 g sample of the title compound was shipped to Edgewood on 14 November 1983.

5. 4-Nitrophenyl 4-Chlorophenyl(methyl)phosphinate

A 10 g sample of the title compound was shipped to Edgewood on 14 November 1983.

6. 4-Nitrophenyl Dimethylphosphinate

Two samples of the title compound were shipped to Edgewood, 10 g on 14 November 1983 and 7.0 g on 22 November 1983.

7. 4-Nitrophenyl 2-Furyl(methyl)phosphinate

A 10 g sample of the title compound was shipped to Edgewood on 14 November 1983.



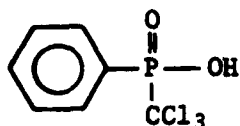
8. 4-Nitrophenyl Dichloromethyl(phenyl)phosphinate  
A 10 g sample of the title compound was shipped to Edgewood on 22 November 1983.
9. [1-[[[(Methylamino)carbonyl]oxy]imino]ethyl]ferrocene  
A 20 g sample of the title compound was shipped to Edgewood on 30 November 1983.
10. [[[4-[[[(Methylamino)carbonyl]oxy]phenyl]imino]methyl]ferrocene  
A 20 g sample of the title compound was shipped to Edgewood on 30 November 1983, followed by another 20 g sample on 8 December 1983.
11. 3,3-Dimethyl-2-butyl Dimethylphosphinate  
A 10 g sample of the title compound was shipped to Edgewood on 3 April 1984.
12. Phenyl Valerate  
A 200 g sample of the title compound was shipped to the School of Public Health, University of Michigan on 25 May 1984.
13. Di-1-butyl 2,2-Dichlorovinyl Phosphate  
A 20 g sample of the title compound was shipped to the School of Public Health, University of Michigan on 25 May 1984.
14. 4-Nitrophenyl Chloromethyl(phenyl)phosphinate  
A 20 g sample of the title compound was shipped to Edgewood on 25 May 1984.
15. 4-Nitrophenyl Phenyl(trichloromethyl)phosphinate  
A 10 g sample of the title compound was shipped to Edgewood on 25 May 1984.
16. 2,2-Dimethyl-3-hydroxybutylamine  
A 35 g sample of the title compound was shipped to Edgewood on 7 August 1984.

17. 2,2-Dichlorovinyl Di(1-butyl)phosphinate  
A 10 g sample of the title compound was shipped to the School of Public Health, University of Michigan on 10 August 1984.
18. 1-Butyl 2,2-Dichlorovinyl 1-Butylphosphonate  
A 10 g sample of the title compound was shipped to the school of Public Health, University of Michigan on 10 August 1984.
19. 4-Trimethylammoniohenyl Chloromethyl(phenyl)phosphinate Trifluoromethylsulfonate  
A 0.75 g sample of the title compound was shipped to Edgewood on 13 August 1984.
20. 2-Aminoethylseleninic Acid  
A 5.0 g sample of the title compound was shipped to Edgewood on 29 August 1984.
21. 2-Aminoethylselenonic Acid  
A 3.5 g sample of the title compound was shipped to Edgewood on 29 August 1984.
22. Monomethyl Phosphate  
A 12 g sample of the title compound was shipped to Edgewood on 29 August 1984.
23. 4-Nitrophenyl Methyl(2-trifluoromethylphenyl)phosphinate  
A 10 g sample of the title compound was shipped to Edgewood on 31 August 1984.
24. 4-Chlorophenyl Methyl(4-trimethylammoniohenyl)phosphinate  
A 10 g sample of the title compound was shipped to Edgewood on 31 August 1984.

## 2. DISCUSSION OF WORK COMPLETED

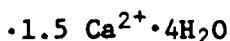
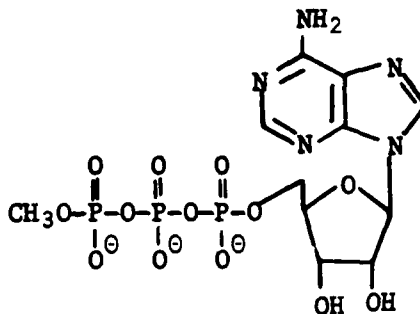
The 24 assignments completed in the past year are discussed below.

### 2.1 Phenyl(trichloromethyl)phosphinic Acid



The title compound was prepared by the three-step sequence outlined in Chart No. 1. Following literature procedures (ref. 3,4), dimethyl phenylphosphinite was treated with carbon tetrachloride under Michaelis-Arbuzov conditions to give methyl phosphinate ester 1 in 23% yield. Ester 1 was converted to phosphinic chloride 2 with phosphorus pentachloride in 87% yield. The title compound 3 was obtained as a monohydrate by the acid mediated hydrolysis of intermediate 2 (ref. 4,5). Subsequent recrystallization and drying under high vacuum gave anhydrous title compound 3 in 52% yield.

### 2.2 $\gamma$ -Methyladenosine 5'-Triphosphate



The title compound was prepared by the procedure of Moffat, et.al. (ref. 6) as shown in Chart No. 2. A solution of adenosine 5'-triphosphate disodium salt was converted to the free acid by elution of a Dowex 50W-X2 (pyridinium form) column. Treatment of the tetrahydrogen triphosphate with methanol and dicyclohexylcarbodiimide gave the desired  $\gamma$ -monomethyl ester which was isolated as a 1.5 calcium salt tetrahydrate in 61% yield.

CHART NO. 1

PHENYL (TRICHLOROMETHYL) PHOSPHINIC ACID

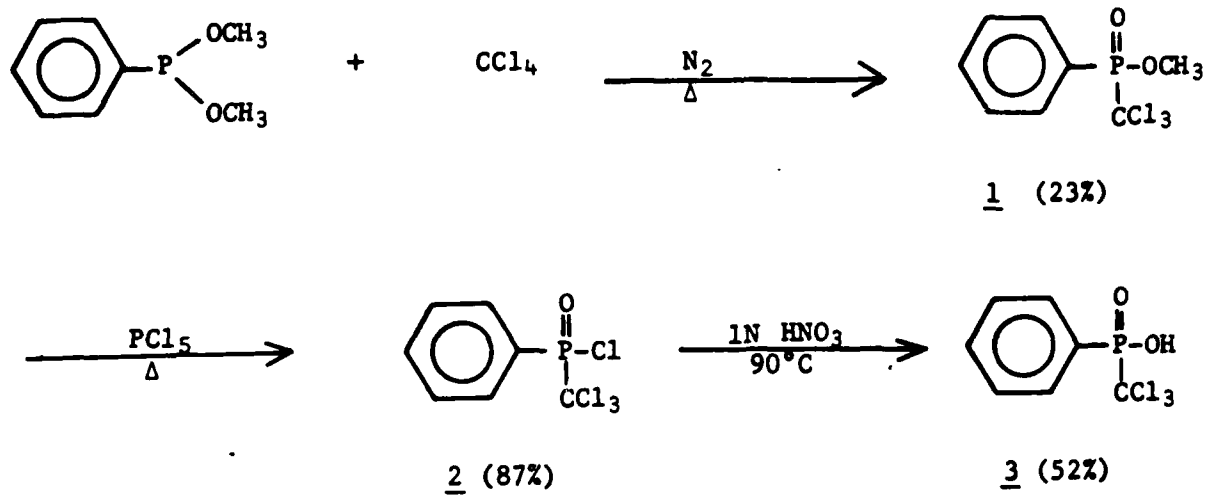
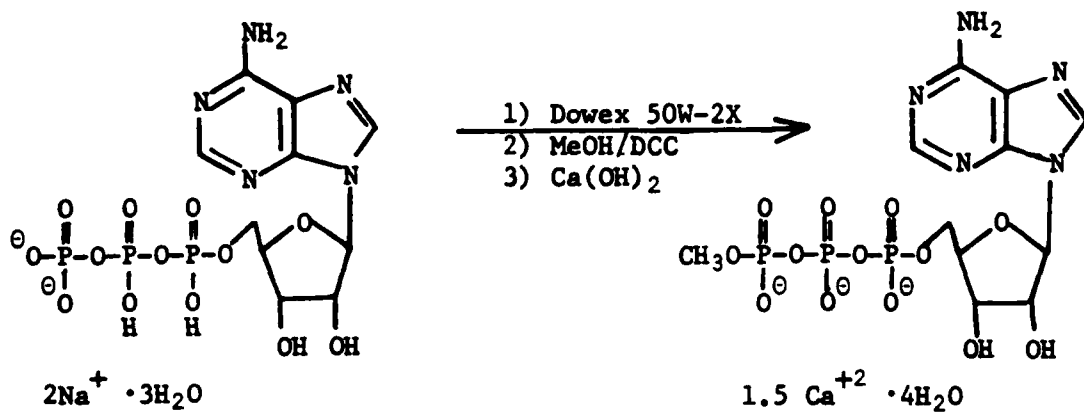
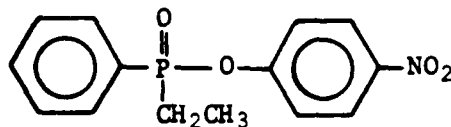


CHART NO. 2

$\gamma$ -METHYLADENOSINE 5'-TRIPHOSPHATE



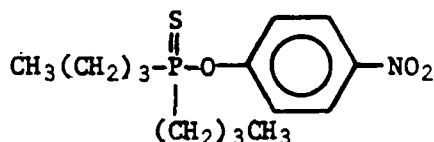
### 2.3 4-Nitrophenyl Ethyl(phenyl)phosphinate



A 10 g sample of the title compound was prepared earlier by ASI during the first year of the current contract (ref. 1, p. 14). For the resynthesis, the original procedure was employed as shown in Chart No. 3.

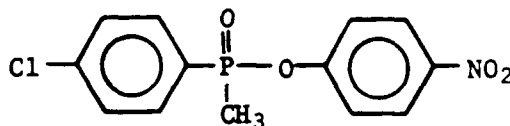
Diphenyl(ethyl)phosphine oxide was treated with powdered sodium hydroxide at 250°C to give phosphinic acid 1 in 69% yield (ref. 7). The phosphinic acid was treated with phosphorus pentachloride to afford the phosphinic chloride 2 which was coupled with 4-nitrophenol to give the title ester 3 in 70% yield (ref. 8).

### 2.4 4-Nitrophenyl Di-*n*-butylphosphinothioate



The title compound was prepared by a three-step synthetic sequence following a literature procedure (ref. 9, 10) as shown in Chart No. 4. Diethylphosphite was treated with *n*-butylmagnesium bromide followed by elemental sulfur to give crude dibutylphosphinothioic acid (1) in 73% yield. The crude acid was converted to the corresponding acid chloride 2 by treatment with phosphorus pentachloride. Treatment of compound 2 with 4-nitrophenol in the presence of triethylamine as acid acceptor gave the title ester.

### 2.5 4-Nitrophenyl 4-Chlorophenyl(methyl)phosphinate



A sample of the title compound was prepared by Ash Stevens Inc. under a prior contract (ref. 11) by a four-step synthetic sequence. A much improved two-step sequence, outlined in Chart No. 5 was developed

CHART NO. 3

4-NITROPHENYL ETHYL(PHENYL)PHOSPHINATE

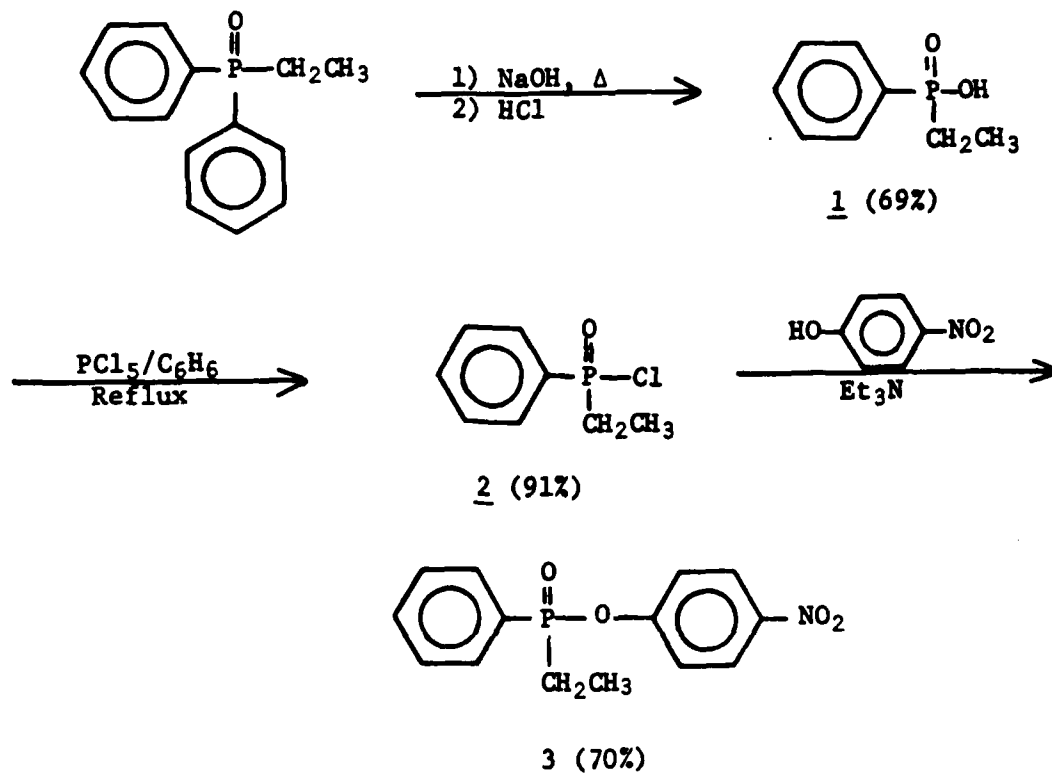


CHART NO. 4

4-NITROPHENYL DI-1-BUTYLPHOSPHINOTHIOATE

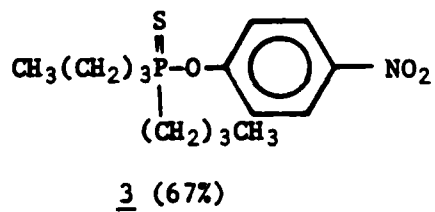
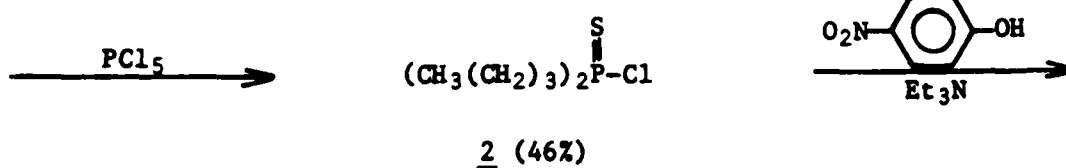
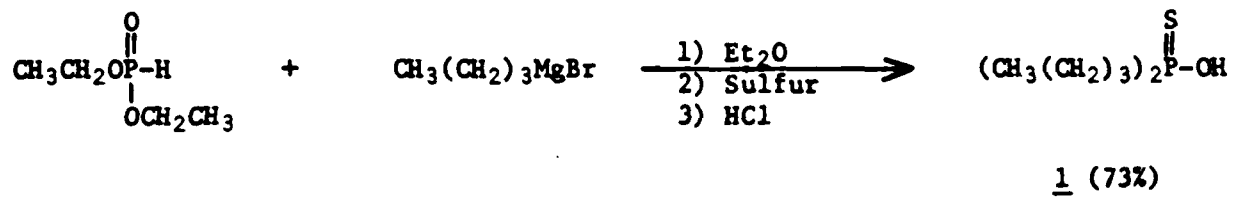
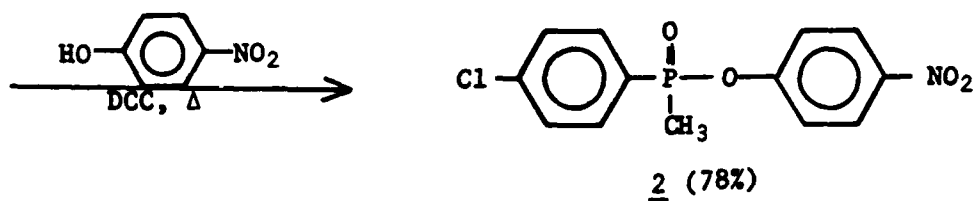
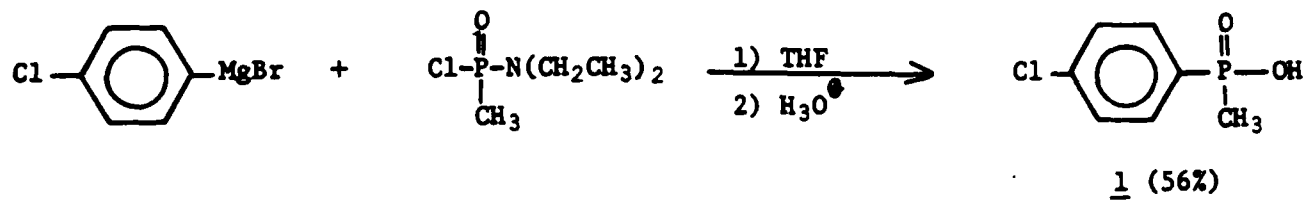




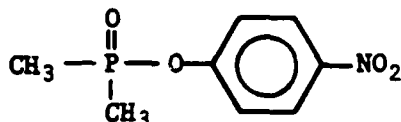
CHART NO. 5

4-NITROPHENYL 4-CHLOROPHENYL (METHYL) PHOSPHINATE



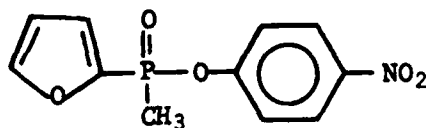
for the current resynthesis. The Grignard reagent, prepared from 4-chlorobromobenzene and magnesium metal, was treated with N,N-diethyl-P-methylphosphonamidic chloride and the resulting phosphinamide was hydrolyzed with hydrochloric acid in situ to give phosphinic acid 1 in 56% yield. Treatment of intermediate 1 with 4-nitrophenol in the presence of DCC gave title compound 2 in 78% yield.

#### 2.6 4-Nitrophenyl Dimethylphosphinate



The title compound was prepared earlier by Ash Stevens Inc. during the first year of the current contract (ref. 1, p. 8). A modified procedure, based on the literature, was developed for the current resynthesis as shown in Chart No. 6. Tetramethylbiphosphine disulfide was oxidized with 30% hydrogen peroxide to dimethylphosphinic acid (1) in 83% yield (refs. 12 and 13). Intermediate 1 was coupled directly with 4-nitrophenol using DCC as an esterification agent to give the title ester 2 in 43% yield.

#### 2.7 4-Nitrophenyl 2-Furyl(methyl)phosphinate

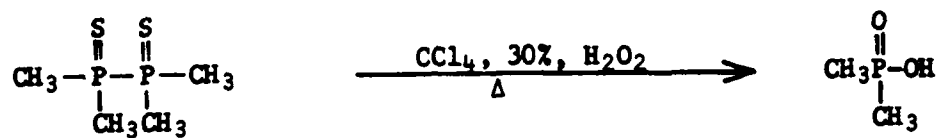


Preparation of the title compound in low overall yield via a four-step reaction sequence was described in an earlier report (ref. 1, p. 8). For the current resynthesis, the improved five-step sequence shown in Chart No. 7 was developed. The first three steps follow a reported literature procedure (ref. 14).

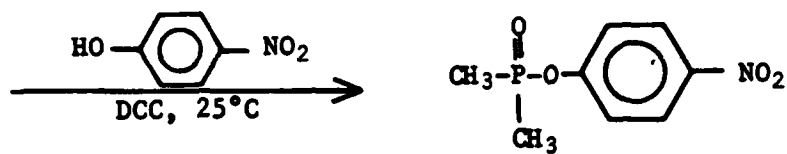
2-Furyllithium, prepared in situ from furan and n-butyllithium, was treated with phosphorus trichloride to give tris(2-furyl)phosphine (1) in 75% yield. Treatment of compound 1 with methyl iodide gave the quaternary phosphonium iodide 2 (89%). Treatment of compound 2 with sodium hydroxide in aq. ethanol for one hour at room temperature gave phosphine oxide 3 (81%). In the new work, compound 3, under more forcing conditions (aqueous hydroxide at reflux), was converted to phosphinic acid 4 (64%). Treatment of the acid 4 with 4-nitrophenol and dicyclohexylcarbodiimide in ethyl acetate at reflux gave the title target ester 5

CHART NO. 6

4-NITROPHENYL DIMETHYLPHOSPHINATE



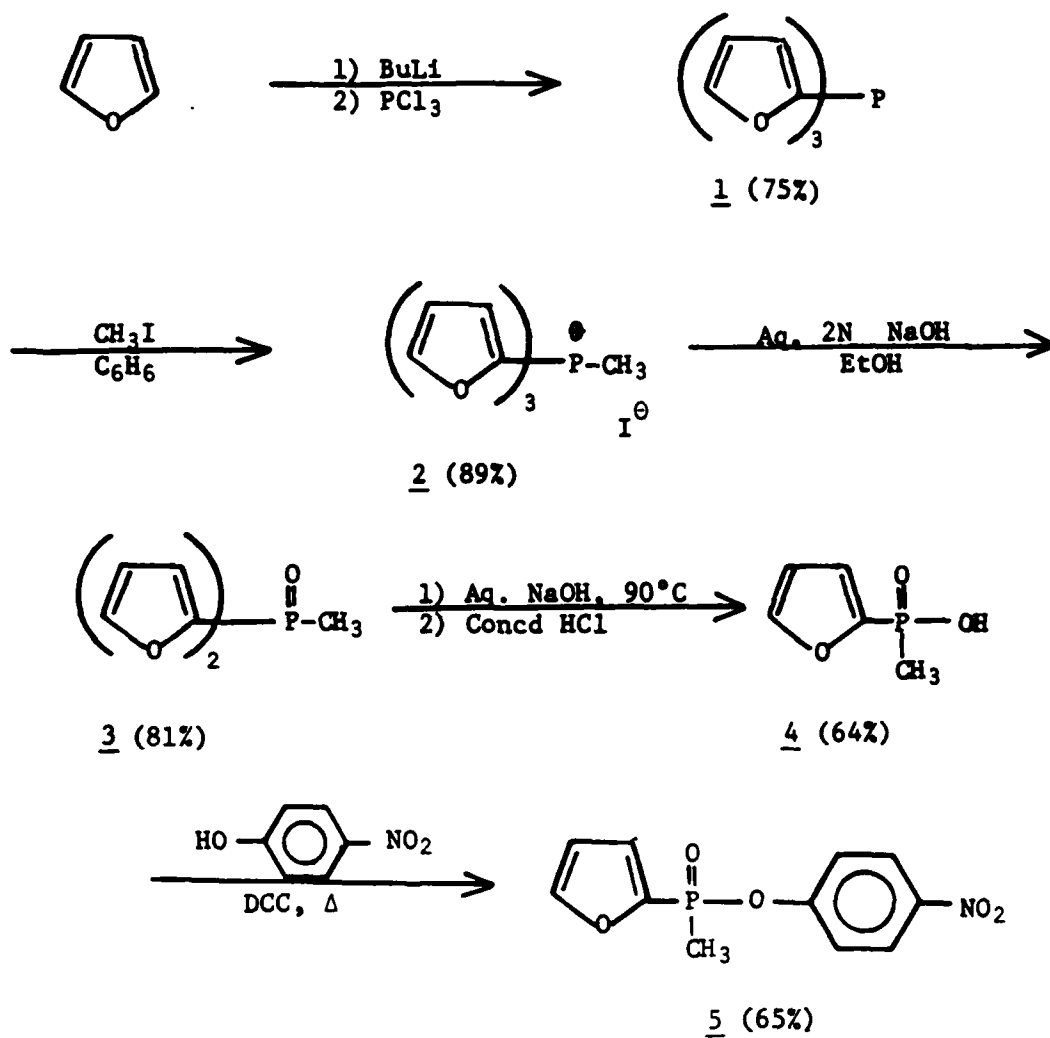
1 (83%)



2 (43%)

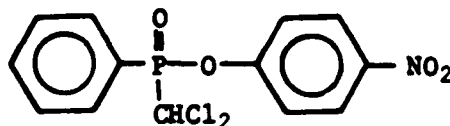
CHART NO. 7

4-NITROPHENYL 2-FURYL(METHYL)PHOSPHINATE



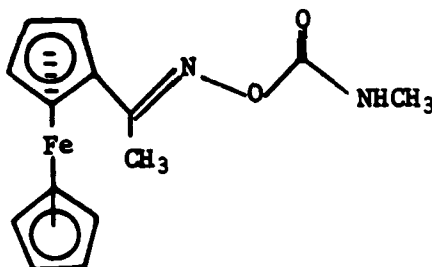
in 65% yield. The overall yield of 22% represents a threefold improvement over that reported previously (ref. 1).

2.8 4-Nitrophenyl Dichloromethyl(phenyl)phosphinate



A sample of the title compound was prepared earlier in this laboratory under a prior contract (ref. 15). The same two-step sequence, outlined in Chart No. 8, utilized for the current resynthesis, followed a general literature procedure (ref. 16). Phenyl dichlorophosphine aluminum chloride complex was treated with chloroform to give the dichloromethyl substituted phosphinic chloride 1 (23% yield) which was allowed to react with 4-nitrophenol in the presence of diisopropylethylamine to give the title compound 2 in 61% yield.

2.9 [1-[[[(Methylamino)carbonyl]oxy]imino]ethyl]ferrocene



The title ferrocene carbamate was prepared by a two-step literature procedure outlined in Chart No. 9 (ref. 17, 18). Acetylferrocene was converted to ferroceneoxime 1 in 44% yield by treatment with hydroxylamine in absolute ethanol. Intermediate 1 was treated with methylisocyanate to give the title ferrocene carbamate 2 in 60% yield.

CHART NO. 8

4-NITROPHENYL DICHLOROMETHYL(PHENYL)PHOSPHINATE

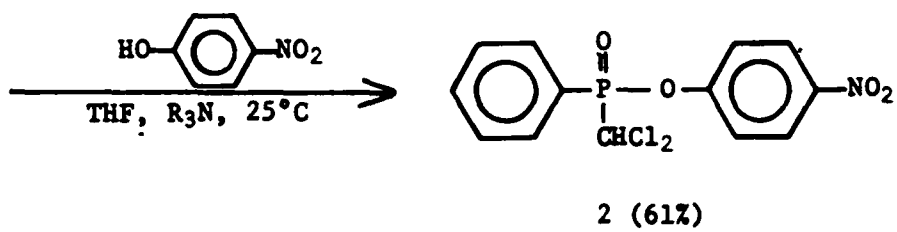
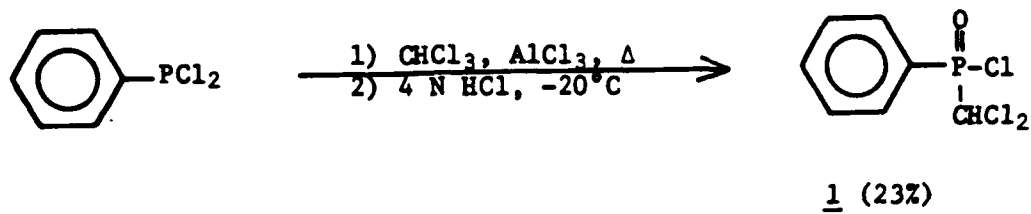
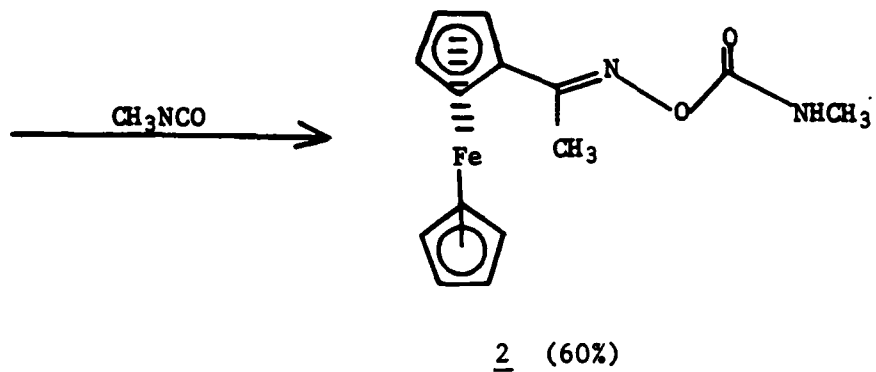
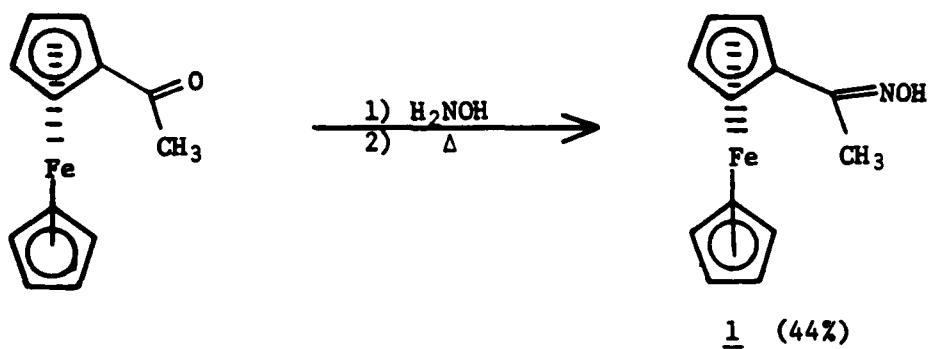
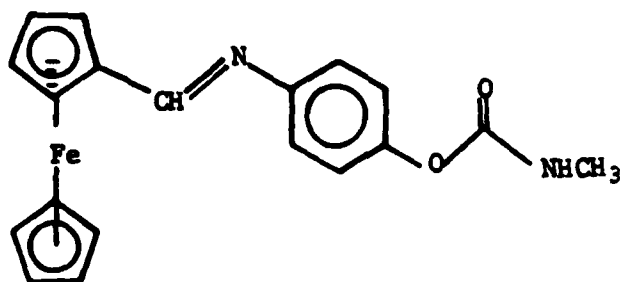


CHART NO. 9

[1-[[[(METHYLAMINO) CARBONYL] OXY] IMINO] ETHYL] FERROCENE

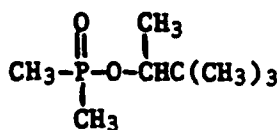


2.10 [[[4-[[[(Methylamino)carbonyl]oxy]phenyl]imino]methyl]ferrocene



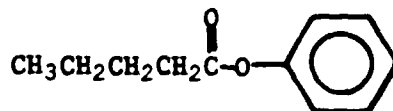
The title ferrocene carbamate was prepared by the two-step synthesis sequence outlined in Chart No. 10 (ref. 18, 19). Ferrocenecarboxaldehyde was condensed with 4-aminophenol to give ferrocene imine 1 in 77% yield. Treatment of intermediate 1 with methylisocyanate gave the title ferrocene carbamate 2 in 63% yield.

2.11 3,3-Dimethyl-2-butyl Dimethylphosphinate



The title compound is a new structure not reported in the chemical literature. The synthetic route to this ester is shown in Chart No. 11. Dimethylphosphinic chloride (2) was prepared in 73% yield from tetramethyldiphosphine disulfide following a two-step literature procedure (ref.12). Esterification of intermediate 2 was accomplished by treatment with pinacol in the presence of tertiary amine base to give the title compound in 62% yield.

2.12 Phenyl Valerate



The title compound was prepared following a one-step literature procedure (ref 20). Thus, commercially available valeryl chloride was treated with phenol in the presence of amine base to give the title ester (1) in 83% yield as shown below.

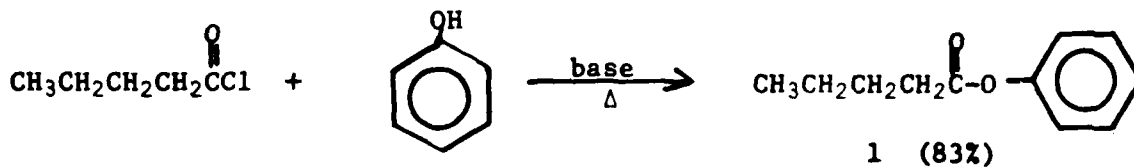




CHART NO. 10

[[[4-[[ (METHYLAMINO) CARBONYL] OXY] PHENYL] IMINO] METHYL] FERROCENE

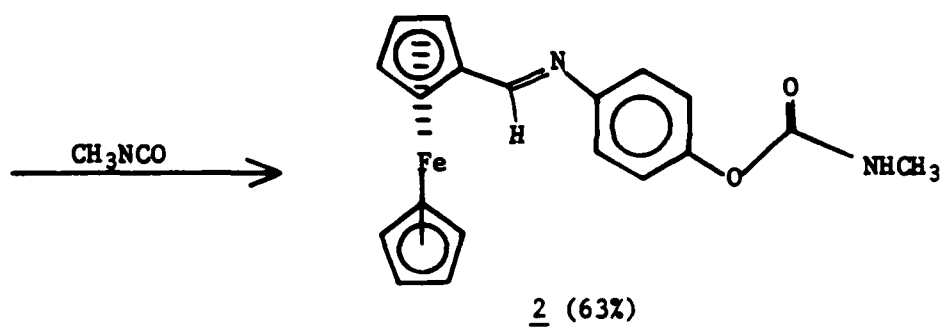
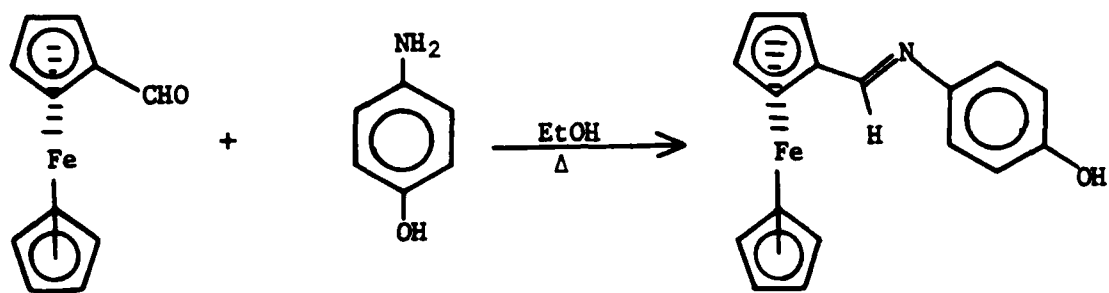
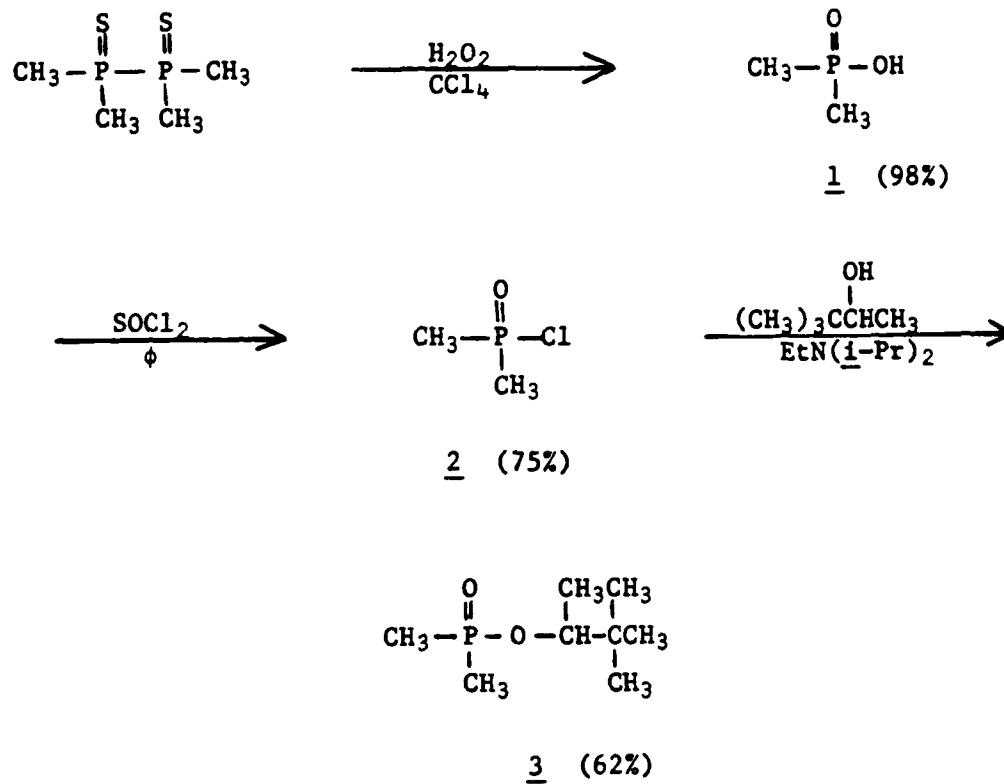
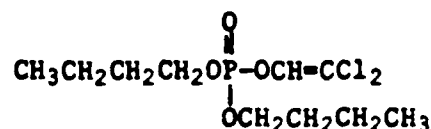


CHART NO. 11

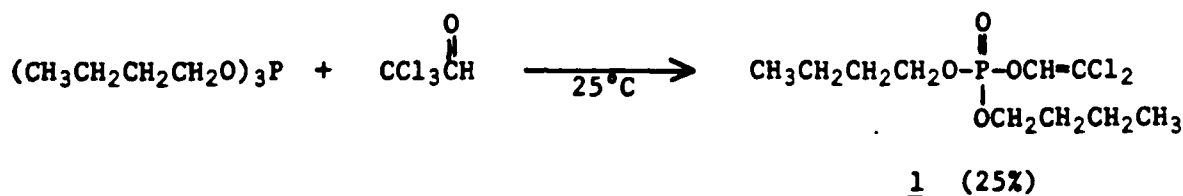
3,3-DIMETHYL-2-BUTYL DIMETHYLPHOSPHINATE



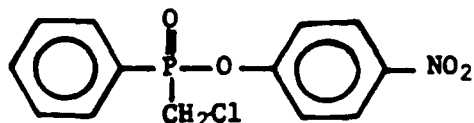
2.13 Di-1-butyl 2,2-Dichlorovinyl Phosphate



The title phosphate ester was prepared by a one-step literature procedure (ref.21) as shown below. Thus tributylphosphite was treated neat with one equivalent of chloral with cooling. Careful fractional distillation gave the title compound in 25% yield, free from a minor close-boiling byproduct.



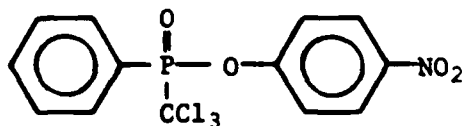
2.14 4-Nitrophenyl Chloromethyl(phenyl)phosphinate



A total of 102 g of the title compound was prepared by Ash Stevens Inc. in the first two years of the current contract. The same procedure, shown in Chart No.12 was used for the current resynthesis.

Thus, phenyldichlorophosphine was treated with paraformaldehyde to give the phosphinic chloride 1 (ref. 22,23). Chloride 1 was esterified with 4-nitrophenol in the presence of ethyl diisopropylamine to give the title phosphinate ester 2.

2.15 4-Nitrophenyl Phenyl(trichloromethyl)phosphinate



A 10 g sample of the title compound was prepared by Ash Stevens Inc. under a previous contract (ref.15). For the current resynthesis the same procedure outlined in Chart No.13 was used. Thus, diethyl phenylphosphonite was heated with carbon tetrachloride to give ethyl ester 1 in 61% yield (ref. 24). Intermediate 1 was converted to phosphinic chloride 2 by treatment with phosphorus pentachloride (ref. 4). Intermediate 2 was treated with 4-nitrophenol and amine base to give the title compound 3 in 10% yield.

CHART NO. 12

4-NITROPHENYL CHLOROMETHYL(PHENYL)PHOSPHINATE

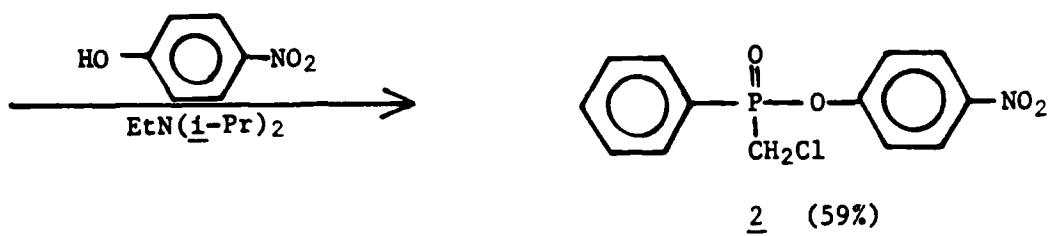
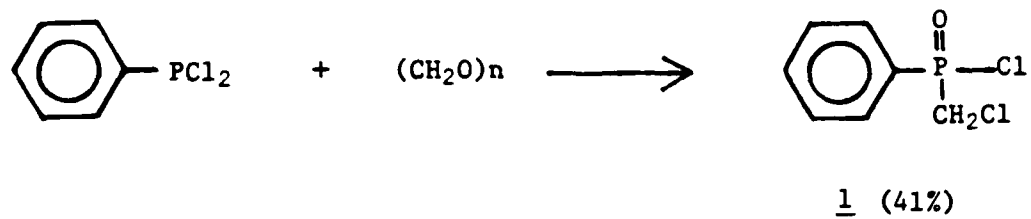
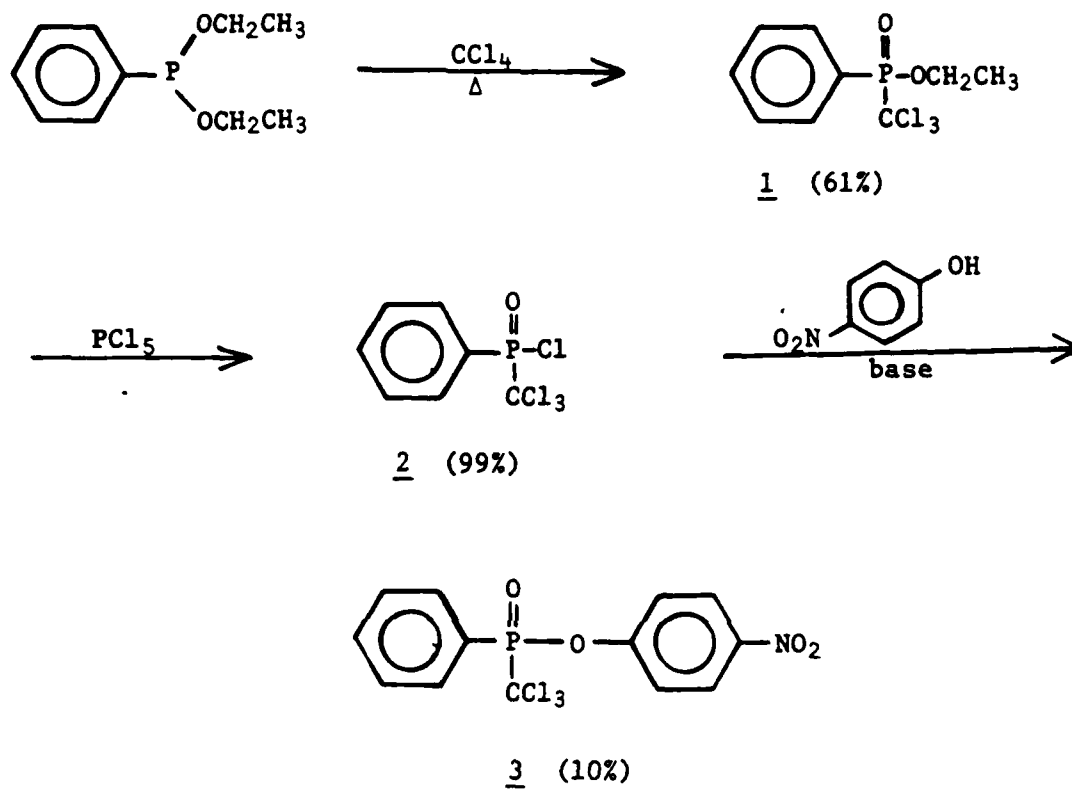
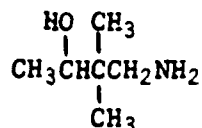


CHART NO. 13

4-NITROPHENYL PHENYL(TRICHLOROMETHYL)PHOSPHINATE

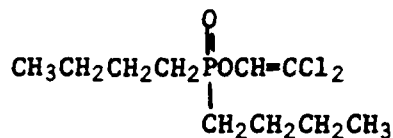


2.16 2,2-Dimethyl-3-hydroxybutylamine



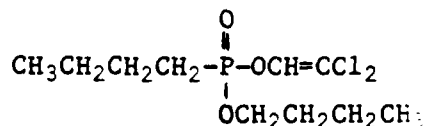
The title compound is a new structure not reported in the chemical literature. A two-step preparative route, outlined in Chart No. 14, was developed for this synthesis. Thus, following a literature procedure (ref. 25) isobutyronitrile was treated with lithiodiisopropylamine followed by acetaldehyde to give  $\beta$ -hydroxynitrile 1 in 70% yield. Reduction of the nitrile to the amino alcohol 2 was accomplished with lithium aluminum hydride in tetrahydrofuran in 84% yield.

2.17 2,2-Dichlorovinyl Di(1-butyl)phosphinate



The title compound was prepared by a four-step synthetic sequence outlined in Chart No. 15 following literature procedures (ref. 26-28). Thus, diethylaminodichlorophosphine was treated with two equivalents of butyl Grignard reagent to give phosphinous amide 1 in 63% yield. Conversion of amide 2 to phosphinous chloride was accomplished with dry hydrogen chloride in 87% yield. The reaction of intermediate 2 with 1-butanol gave butyl phosphosphinite 3 in 66% yield. The title phosphinate ester 4 was obtained by treatment of intermediate 3 with one equivalent of anhydrous chloral.

2.18 1-Butyl 2,2-Dichlorovinyl 1-Butylphosphonate



The title compound was prepared by a four-step synthetic sequence shown in Chart No. 16. The diamide 1 was prepared in 73% yield by treatment of commercially available bis(diethylamino)chlorophosphine with one equivalent of butylmagnesium chloride (ref. 29). The conversion of intermediate 1 to the dichlorophosphine 2 with dry hydrogen chloride in ether followed a literature procedure (ref. 30). Esterification with 1-butanol gave phosphonite ester 3 (ref. 31) in 85% yield. The title compound 4 was prepared by the reaction of one equivalent of chloral

CHART NO. 14

2,2-DIMETHYL-3-HYDROXYBUTYLAMINE

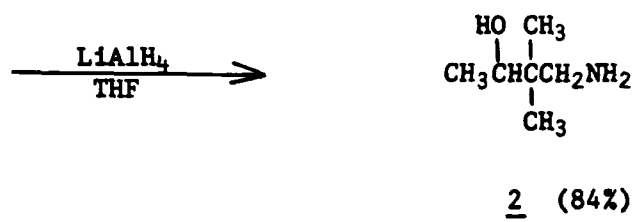
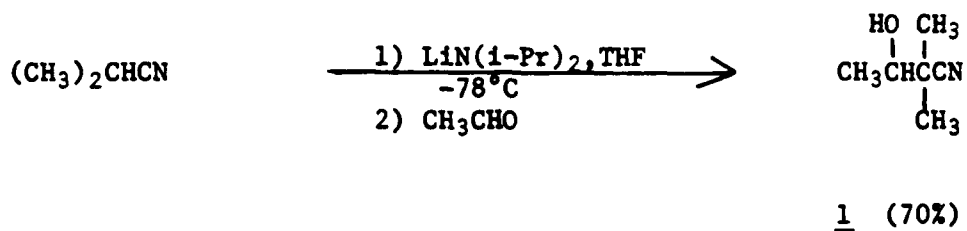


CHART NO. 15

2,2-DICHLOROVINYL DI(1-BUTYL)PHOSPHINATE

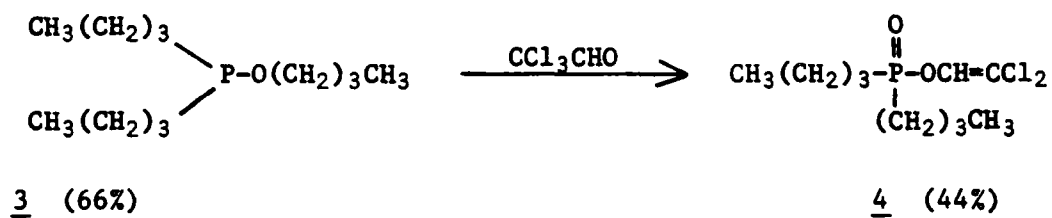
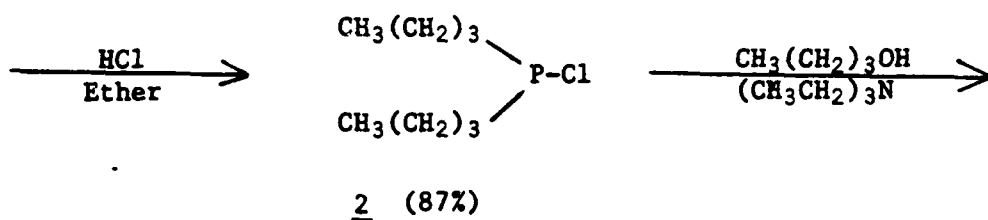
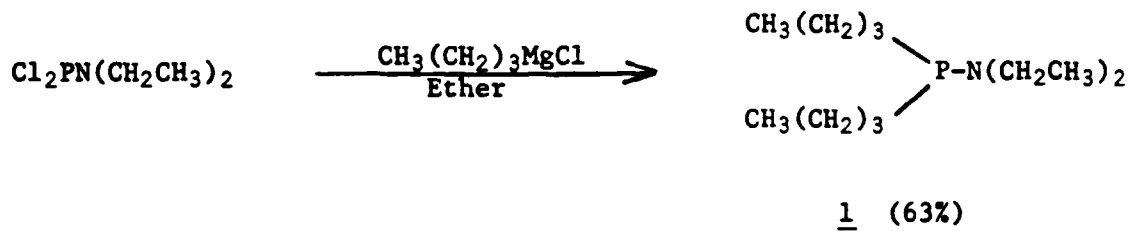
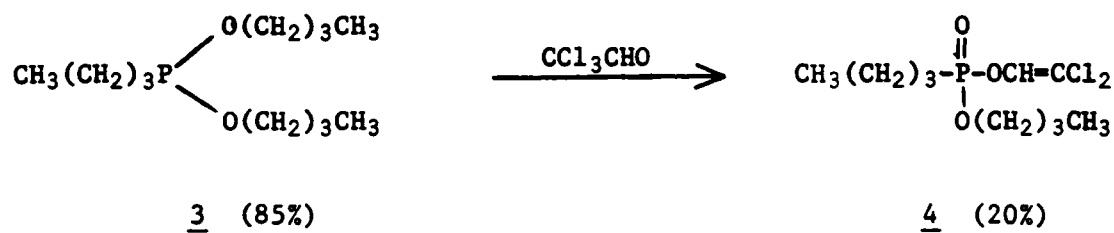
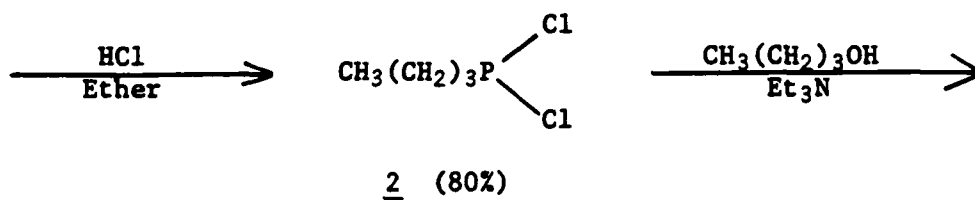
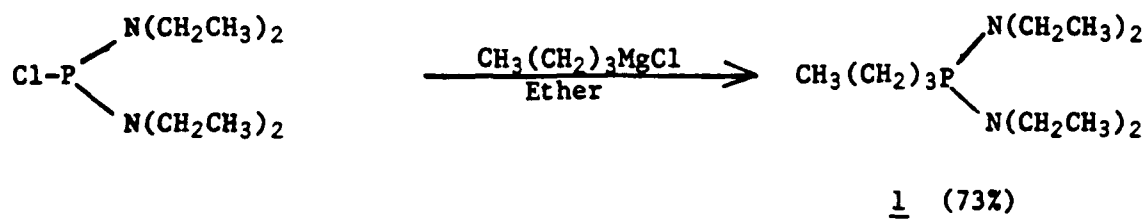




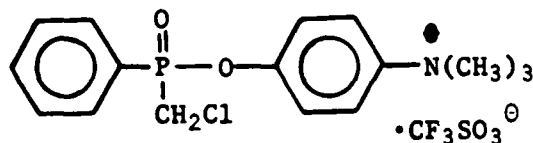
CHART NO. 16

1-BUTYL 2,2-DICHLOROVINYL 1-BUTYLPHOSPHONATE



with intermediate 3 (ref. 32). Fractional distillation to remove two close-boiling impurities gave analytical title compound in 20% yield.

2.19 4-Trimethylammoniohenyl Chloromethyl(phenyl)phosphinate  
Trifluoromethylsulfonate

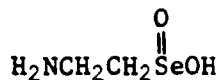


The title compound represents the first of a series of phosphinate esters currently under development which contain a water solubilizing functionality, in this case a quaternary ammonium moiety located on the leaving group. This compound, a new structure not reported in the chemical literature, was prepared by a three-step synthetic sequence as shown in Chart No. 17.

4-Dimethylaminophenol was prepared from 4-methylaminophenol sulfate by a standard literature method (ref. 33), and chloromethyl(phenyl)-phosphinic acid was resynthesized by a procedure developed by Ash Stevens Inc. and described in an earlier report (ref. 2, p. 5). The phosphinic acid and phenol were coupled with dicyclohexylcarbodiimide in ethyl acetate to give phosphinate 2 in 60% yield. Intermediate 2 could not be quaternized by treatment with methyl iodide, but treatment of ester 2 with methyl trifluoromethylsulfonate in methylene chloride gave the quaternary ester 3 in 61% yield.

The title phosphinate ester is freely soluble in water and has a half-life of 98 min in 0.10 M MOPS buffer at pH 7.60.

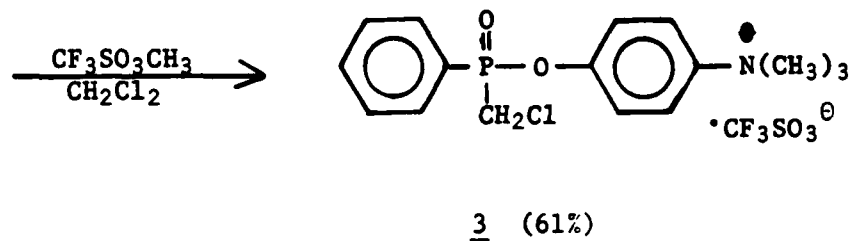
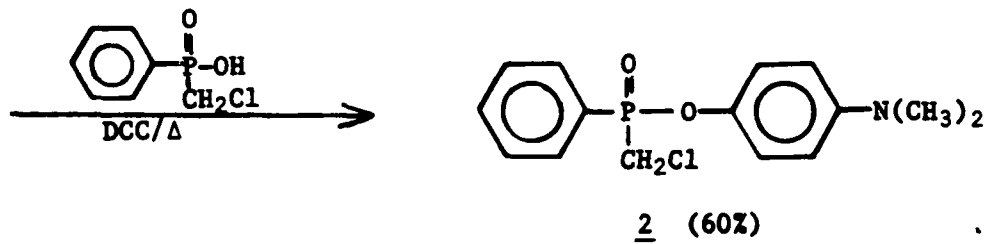
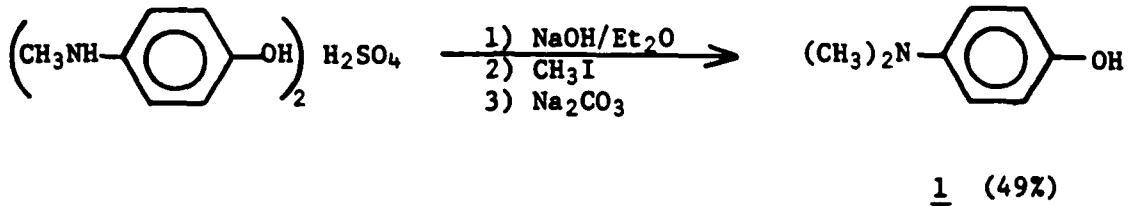
2.20 2-Aminoethylseleninic Acid



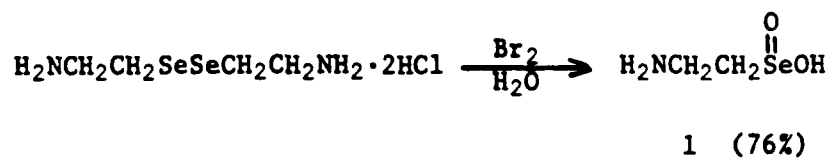
The title compound was prepared by a one-step literature procedure (ref. 34) shown below. Thus, selenocystamine dihydrochloride was carefully oxidized by treatment with three equivalents of bromine in aqueous solution. The crude selenic acid 1 was purified by passing the concentrated reaction mixture through a Dow 50W-X2 (H<sup>+</sup> form) resin column. The product was eluted with dilute aqueous ammonium hydroxide and isolated by lyophilization. The white crystalline title compound

CHART NO. 17

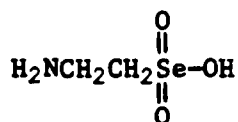
4-TRIMETHYLAMMONIOPHENYL CHLOROMETHYL (PHENYL)-  
PHOSPHINATE TRIFLUOROMETHYL SULFONATE



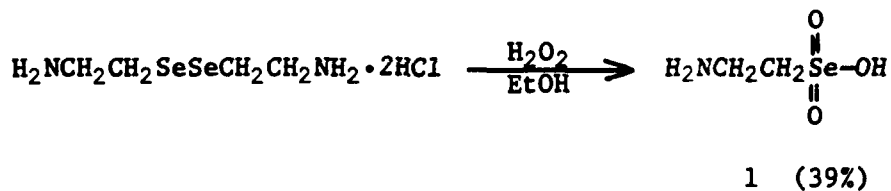
obtained in this manner had analytical and spectral data in agreement with the structure shown.



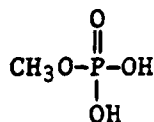
### 2.21 2-Aminoethylselenonic Acid



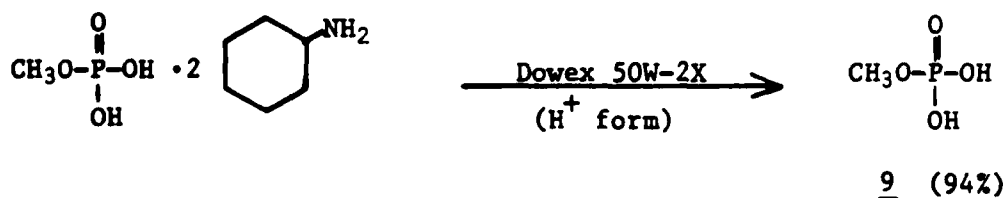
The title compound was prepared by a one-step literature procedure (ref. 34,35) shown below. Thus, selenocystamine dihydrochloride was oxidized with excess hydrogen peroxide in ethanol. The crude selenonic acid obtained in this manner was purified by recrystallization from ethanol. The purified title compound had analytical and spectral data which were in agreement with the structure.



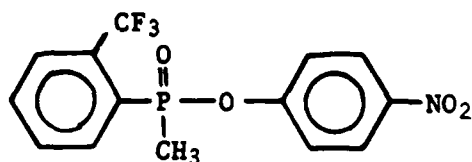
### 2.22 Monomethyl Phosphate



The title compound was prepared by a one-step procedure shown below. Commercially available monomethyl phosphate di(cyclohexylammonium) salt was purified by recrystallization from ethanol and was then converted to the acid by passage through a Dowex 50W-X2 (hydrogen ion form) anion exchange column. The resulting solution was lyophilized to give the title ester 1 in 94% yield as a thick oil.

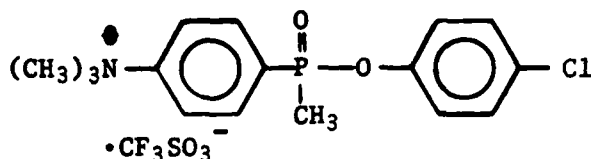


2.23 4-Nitrophenyl Methyl(2-trifluoromethylphenyl)phosphinate



The title compound represents a new structure not reported in the chemical literature. A synthetic scheme, outlined in Chart No. 18, was utilized for the preparation of this compound following a general method developed by Ash Stevens Inc. for the synthesis of substituted aryl methylphosphinates. Thus, the Grignard reagent prepared from 2-bromobenzotrifluoride was treated with N,N-diethyl-P-methylphosphonamidic chloride, prepared as described in an earlier report (ref. 15), to give the phosphinamide 1 in 29% yield. Intermediate 1 was hydrolyzed with aqueous hydrochloric acid in dioxane to the phosphinic acid 2 in 90% yield. Esterification of 2 with 4-nitrophenol and dicyclohexylcarbodiimide gave the title ester 3 in 60% yield.

2.24 4-Chlorophenyl Methyl(4-trimethylammoniohenyl)phosphinate Trifluoromethylsulfonate



The title compound is a new structure not reported in the chemical literature. This phosphinate ester is the second member of a series of water soluble esters which are being developed by Ash Stevens Inc. In this compound water solubility is achieved by the introduction of a quaternary ammonium functionality in the carbon-phosphorus bound aryl group. A six-step synthetic scheme for the preparation of the title compound is outlined in Chart No. 19.

Thus, following a literature procedure (ref. 36) dimethylaniline was treated with phosphorus trichloride and aluminum trichloride in a Friedel-Crafts reaction to give phosphinous chloride 1 in 25% yield. Intermediate 1 was converted to the dimethyl ester 2 with sodium methoxide, then subjected to Michaelis-Arbusov conditions (ref. 37) to give methyl phosphinate ester 3 in 91% yield. Treatment of ester 3 with one equivalent of sodium hydroxide followed by one equivalent of hydrochloric acid gave phosphinic acid 4. Ester 5 was prepared in 71% yield by heating a mixture of acid 4, 4-chlorophenol and DCC in toluene-acetonitrile

CHART NO. 18

4-NITROPHENYL METHYL (2-TRIFLUOROMETHYLPHENYL) PHOSPHINATE

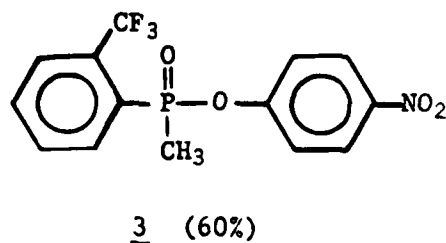
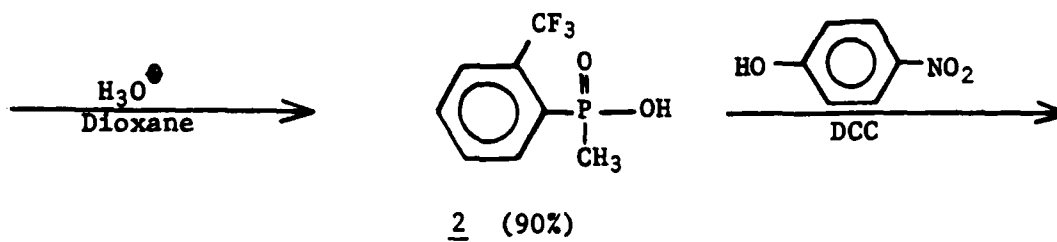
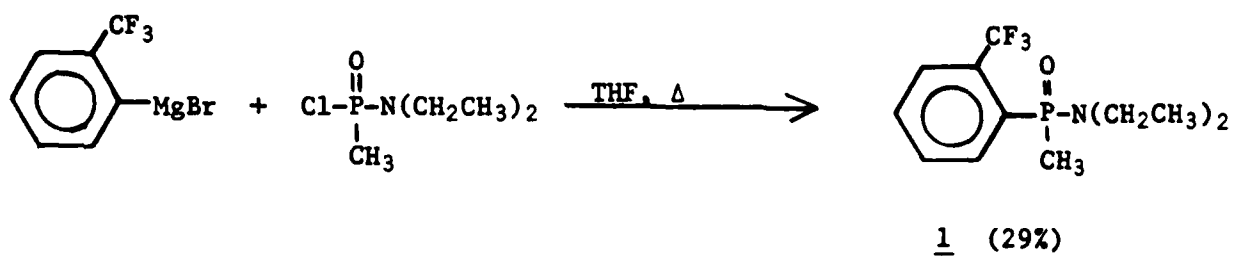
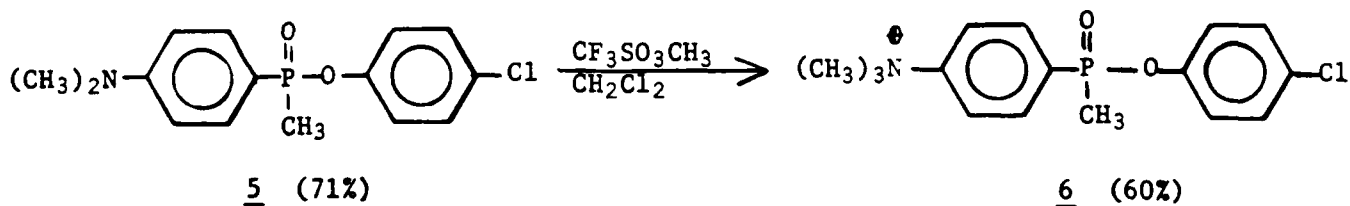
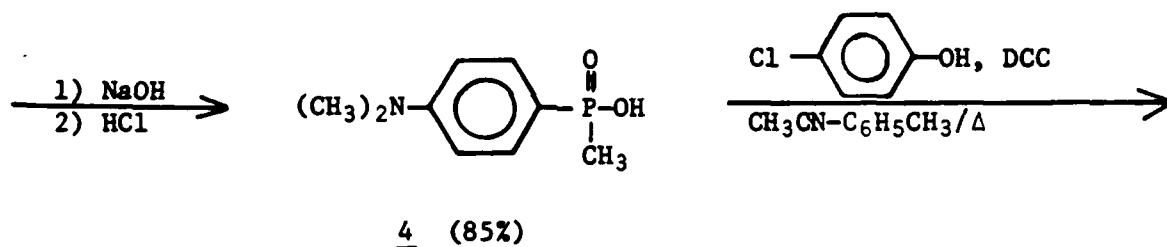
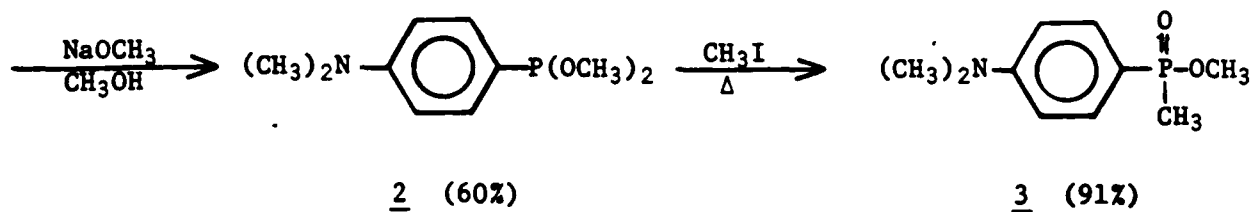
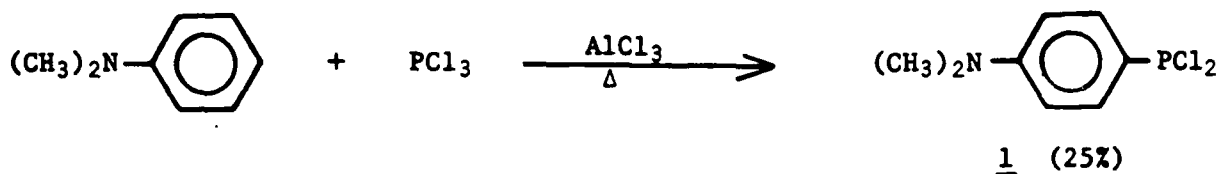


CHART NO. 19

4-CHLOROPHENYL METHYL (4-TRIMETHYLAMMONIOPHENYL)-  
PHOSPHINATE TRIFLUOROMETHYLSULFONATE



at reflux for four days. The dimethylamino group in ester 5 could not be quaternized with methyl iodide, but treatment of 5 with methyl trifluoromethylsulfonate gave the title compound in 60% yield.

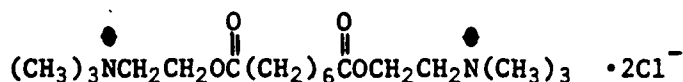
The title phosphinate ester is freely soluble in water and has a half-life of 95.5 min in 0.10 M MOPS buffer at pH 7.60.



### 3. WORK IN PROGRESS AND WORK ABANDONED

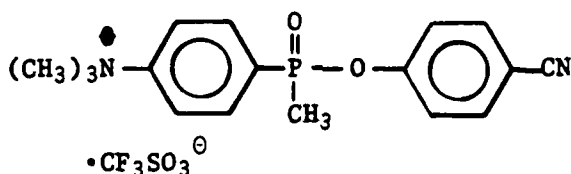
As of 31 August 1984 work was in progress on five assignments and, during the past year, work was abandoned on two assignments. These seven assignments are discussed in detail below. Four compounds were submitted post-report and experimental details for these will be reported under a follow-on contract (ref. 35).

#### 3.1 Suberyldicholine Dichloride



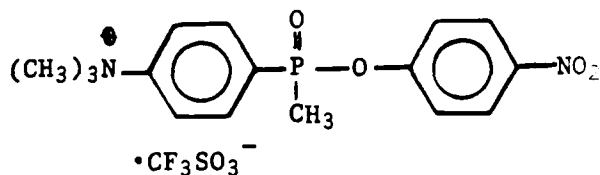
The synthesis of the title compound was completed and a 74 g sample was shipped post-report to Edgewood on 5 October 1984.

#### 3.2 4-Cyanophenyl Methyl(4-trimethylammoniohenyl)phosphinate Trifluoromethylsulfonate



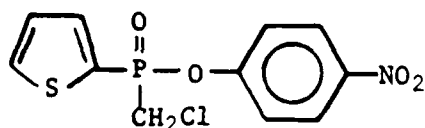
Synthesis of the title phosphinate was completed and a 1.50 g sample was shipped post-report to Edgewood on 12 October 1984.

#### 3.3 4-Nitrophenyl Methyl(4-trimethylammoniohenyl)phosphinate Trifluoromethylsulfonate



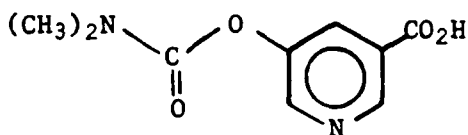
Synthesis of the title compound was completed and a 0.50 g sample was shipped post-report to Edgewood on 12 October 1984.

3.4 4-Nitrophenyl Chloromethyl(2-thienyl)phosphate



Synthesis of the title compound was completed and a 10 g sample was shipped post-report to Edgewood on 25 October 1984.

3.5 5-(N,N-Dimethylcarbamyl)oxynicotinic Acid



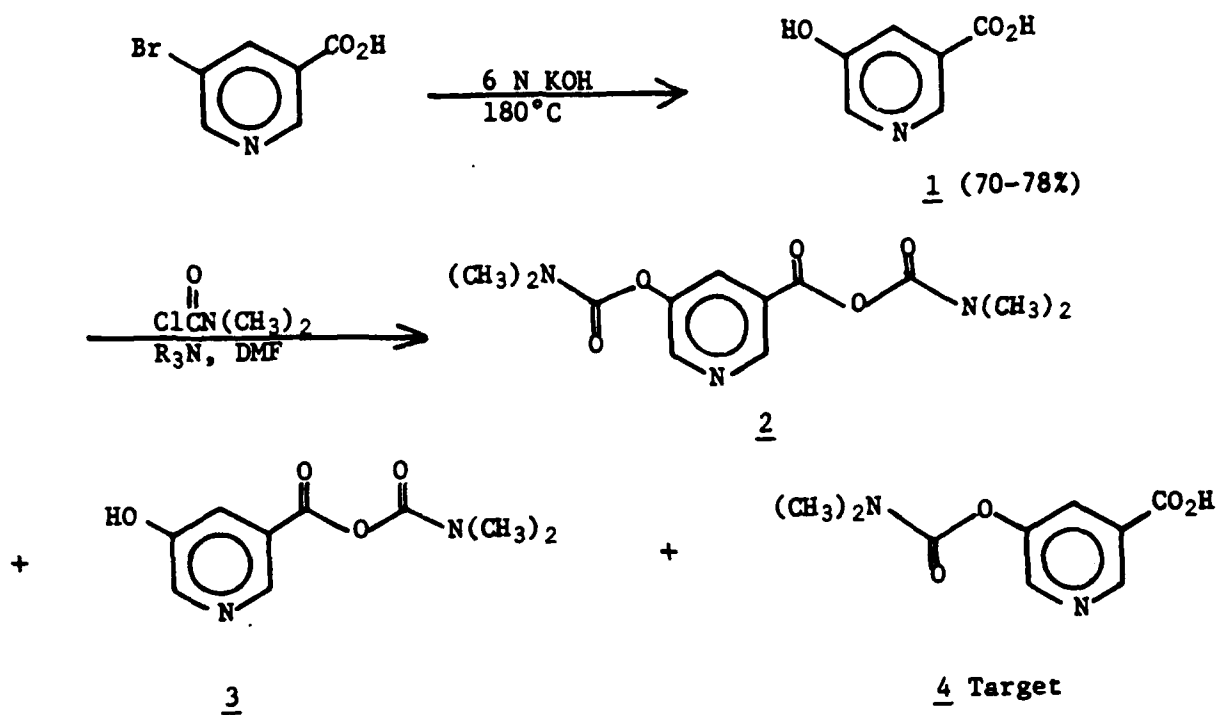
The title compound is a new structure which is not reported in the chemical literature. A preparative scheme for this compound is shown in Chart No. 20. Synthesis of the key intermediate 5-hydroxynicotinic acid (1) by a three-step sequence starting with 5-bromonicotinic acid via 3-aminonicotinic acid has been reported (ref. 39).

In our work, the literature procedure was modified such that the starting 3-bromonicotinic acid was heated in a bomb with 6 N aqueous potassium hydroxide at 170-180°C for 18 h to give 5-hydroxynicotinic acid (1) directly in 74-78% yield. Treatment of compound 1 with one equivalent of dimethylcarbamyl chloride in DMF with an acid acceptor (R<sub>3</sub>N) gave, unfortunately, a mixture of three carbamylated products, 2, 3 and 4, along with unreacted starting compound 1. The use of more than one equivalent of carbamyl chloride decreased the amount of unreacted 1 and favored the formation of dicarbamate 2, but had no apparent effect on the ratios of carbamates 3 and 4.

The reaction was repeated on a preparative scale in an attempt to isolate and characterize the title carbamate 4. The crude reaction mixture was chromatographed on a silica gel column eluting with 20% methanol in chloroform. Three fast-running products (R<sub>f</sub> 0.6 to 0.8) were isolated and identified as dicarbamylated product 2, carbamylanhydride 3 and 5-hydroxy-N,N-dimethylnicotinamide. The latter product we believe is formed from the decomposition of intermediate 3. Exhaustive elution of the column yielded material with an R<sub>f</sub> of 0.0 to 0.10. This fraction consisted of primarily amine hydrochloride salt and traces of what may be the desired product 4. All attempts to isolate a pure sample of 4 from this mixture by fractional crystallization or trituration have been unsuccessful.

CHART NO. 20

5-(N,N-DIMETHYL CARBAMYL) OXYNICOTINIC ACID



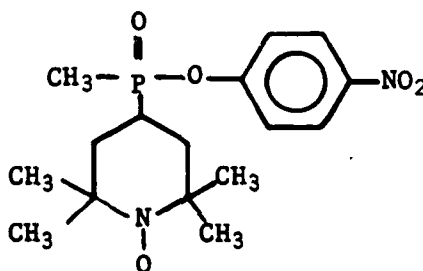
### 3.6 Omagatoxin ( $\omega$ CgTX)

A request for 100 mg of the title compound has been received. According to the literature (ref. 40), the compound is a highly basic twenty two-residue peptide toxin which has been isolated from the marine snail, Conus geographus. Omagatoxin is reported to have a most unusual amino acid composition consisting of Lys<sub>4</sub>, Arg<sub>3</sub>, 1/2 Cys<sub>6</sub>, Asx<sub>2</sub>, Glx<sub>2</sub>, Thr, Ala, plus three residues of trans-4-hydroxyproline. However, to the best of our knowledge, the exact structure of omagatoxin has not been reported. Accordingly, no laboratory work was carried out on this assignment.

### 3.7 Paramagnetic ESR-Labeled Compounds

Synthetic work to date has been directed towards the preparation of two general classes of spin-labeled compounds: 1) spin-label substituted 4-nitrophenyl methylphosphinate esters and 2) spin-label substituted 3-quinuclidinyl phenylglycolate esters.

#### 3.7.1 4-Nitrophenyl Methyl(1-oxy-2,2,6,6-tetramethyl-4-piperidinyl)-phosphinate



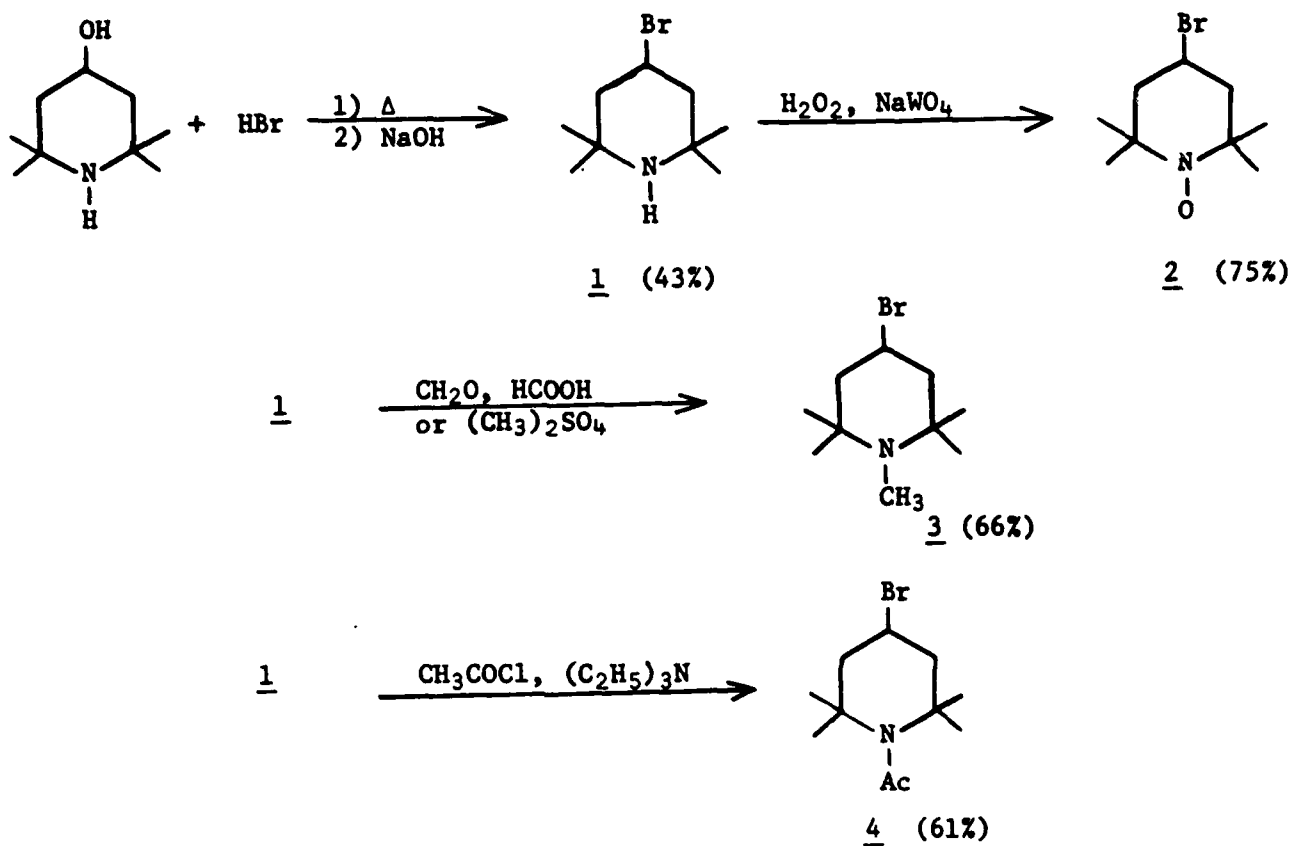
The title structure was proposed for use as an ESR spin-label probe. The key step in the synthesis of this compound is the formation of the bond between phosphorus and the piperidine ring.

One method to form a carbon-phosphorus bond involves the reaction of an organometallic nucleophile, such as a Grignard reagent, with a properly substituted phosphorus moiety. This approach, used successfully in these laboratories to prepare several phosphinic acid structures, was investigated first. The necessary 4-halopiperidine precursors were prepared as shown in Chart No. 21.

Commercially available 4-hydroxy-2,2,6,6-tetramethylpiperidine was treated with hydrobromic acid by a modified literature procedure (ref. 41) to yield the 4-bromopiperidine hydrobromide salt (not shown) which, upon treatment with sodium hydroxide gave the desired free base, compound 1. The overall yield was 43%. Preparation of the piperidinoxy radical 2 followed a general literature procedure (ref. 42). Thus compound 1 was treated with hydrogen peroxide in the presence of sodium tungstate and tetrasodium EDTA to give intermediate 2 in 75% yield. N-Methylation of substituted piperidines with formaldehyde-formic acid has been reported (ref. 43). Treatment of compound 1 in this manner

CHART NO. 21

1-SUBSTITUTED-4-BROMO-2,2,6,6-TETRAMETHYLPIPERIDINES



gave a 22% yield of the N-methyl derivative 3. The same product was isolated in 66% yield from the treatment of compound 1 with dimethyl sulfate. Also, treatment of 1 with acetyl chloride in the presence of triethylamine gave the N-acetyl derivative 4 (61%).

Metallation and coupling reactions studied, using three of the above 4-bromopiperidine structures, shown in Chart No. 21 are summarized in Chart No. 22. Treatment of 4-bromopiperidine 3 with magnesium turnings or activated magnesium (ref. 44) failed to yield the corresponding Grignard reagent. Workup of the reaction mixture led to the recovery of unreacted 3. We are at a loss to explain these results. While steric crowding may be a contributing factor, it probably is not the principal cause for this lack of reactivity.

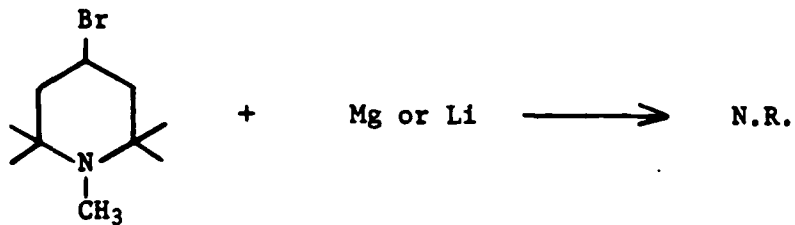
In contrast to compound 3, the nitroxy derivative 2 did undergo a reaction when treated with magnesium metal. Aqueous quench of the reaction mixture failed, however, to give the 4-debrominated compound 5 which would be expected if a Grignard reagent had been formed. Preliminary analysis indicated that the major reaction product still contained a halogen. Accordingly, this approach was abandoned.

In another attempt to form a Grignard reagent, bromopiperidine 1 was converted with butyllithium to the lithium amide 6 which was then treated in situ with activated magnesium metal. TLC analysis of quenched reaction samples showed the disappearance of bromide 1, indicating that a metallation reaction had taken place. Treatment of this reaction product, presumed intermediate 7, with phosphonamide 8 failed to yield the desired phosphinamide 9. The only product isolated and identified (as the p-toluenesulfonic acid salt, ref. 45) was the debrominated piperidine 10. Similarly, reaction of intermediate 7 with methylphosphonodichloridate followed by aqueous quench failed to yield phosphinic acid 11. In view of these negative results, other routes were explored as shown in Chart No. 23.

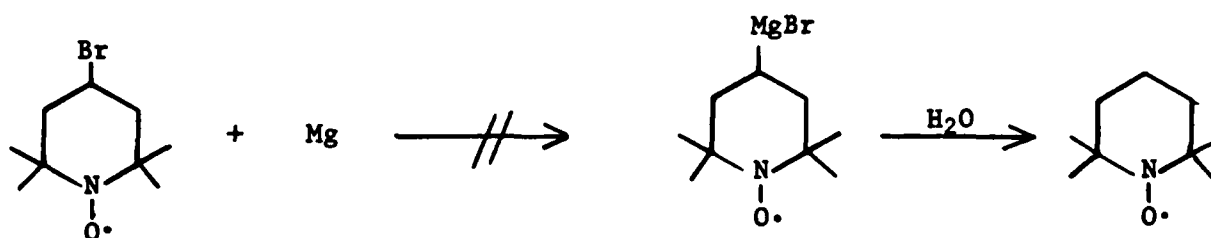
Aluminum chloride catalyzed condensation of alkyl and aryl halides with phosphorus trichloride has been reported in the literature (ref. 46). An attempt was made to apply this coupling reaction to the synthesis of a 4-piperidylphosphinic acid. Treatment of the N-acetylpiperidine 4 with aluminum chloride and methylphosphonous dichloride gave nonacidic material as the major reaction product. A small, acidic fraction was isolated which, by TLC, was shown to consist of three products. Efforts to separate and identify the three components failed. In a slightly modified approach, N-methylpiperidine 3 was treated with aluminum chloride and phosphorus trichloride, then quenched with ethanol. Major products isolated were unreacted starting material and diethyl phosphite. The latter undoubtedly arose from the reaction of phosphorus trichloride with ethanol followed by partial hydrolysis during workup. Treatment of nitroxide 2 with aluminum chloride and methylphosphonous dichloride gave similarly unpromising results. While a reaction appeared to take place, attempts to purify the product(s) by ion exchange chromatography and preparative TLC failed; the material could not be extracted from the silica gel plate.

CHART NO. 22

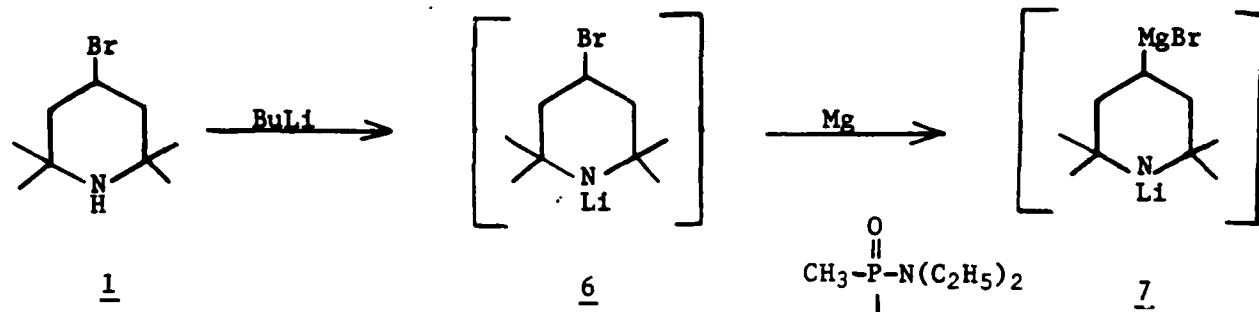
ATTEMPTED CONVERSIONS OF THE 4-BROMOPIPERIDENE  
STRUCTURES FROM CHART NO. 21



3



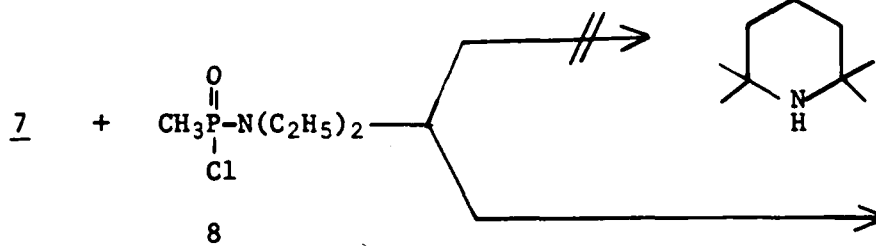
2



1

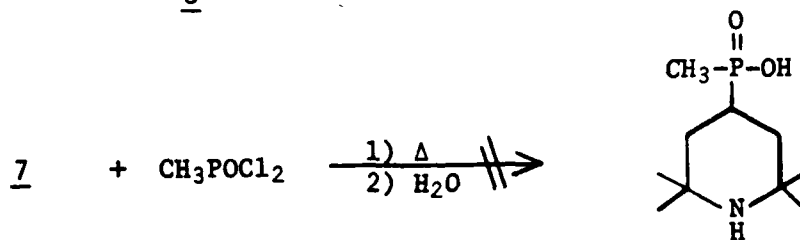
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7

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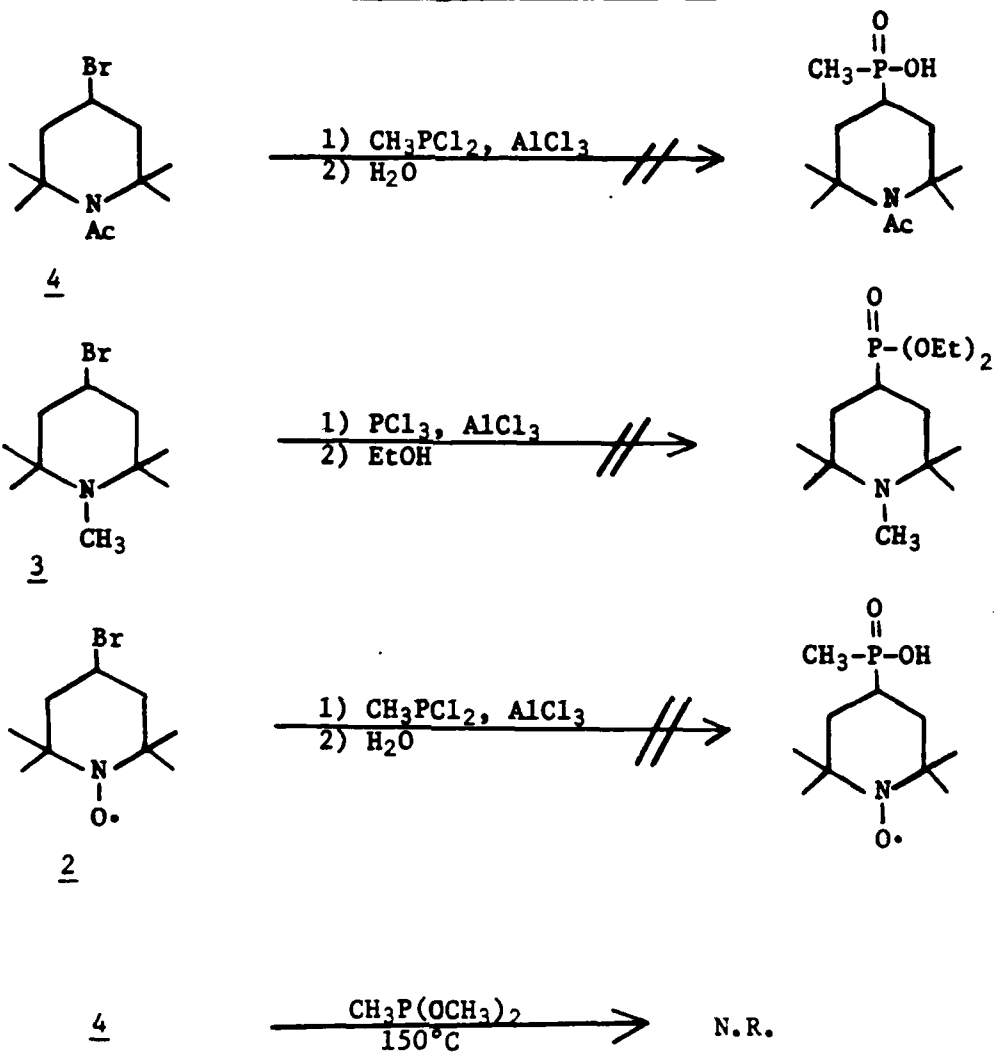


11

CHART NO. 23

OTHER ATTEMPTED CONVERSIONS OF THE 4-BROMOPIPERIDINE

STRUCTURES OF CHART NO. 21

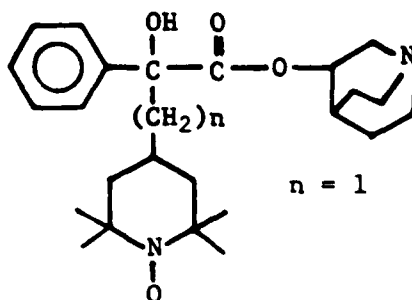




An attempt was made also to effect the Arbusov rearrangement with bromopiperidine 4 and dimethyl methylphosphonite. No reaction was observed at 150°C and compound 4 was recovered unchanged. Due to the volatility of the phosphonite, higher temperatures were not investigated.

In view of all of the negative results, work on this assignment was discontinued.

3.7.2 3-Quinuclidinyl  $\alpha$ -[[4-(1-oxo-2,2,6,6-tetramethylpiperidinyl)]-methyl]- $\alpha$ -phenylglycolate



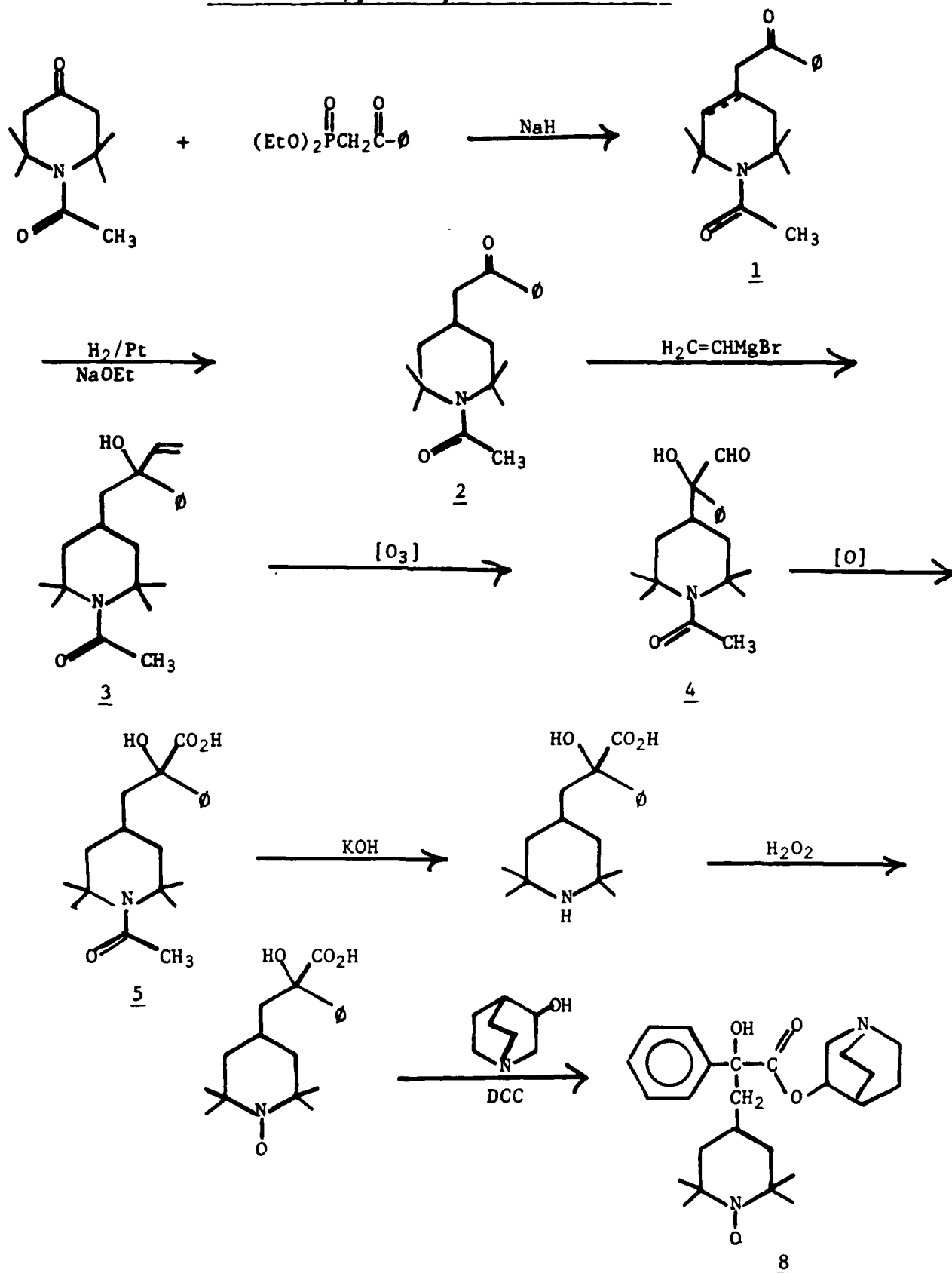
Synthesis of the title compound (n=1) was initiated after attempts to prepare the originally proposed analog (n=0) were unsuccessful. This is attributed to steric hindrance on both the 4-position of the piperidine moiety and on the  $\alpha$ -carbon of the glycolate moiety which defeated all attempts to form a C-C bond between them.

A synthetic scheme outlined in Chart No. 24 was devised for the title compound (n=1). 1-Acetyl-2,2,6,6-tetramethyl-4-piperidone was condensed with diethyl  $\alpha$ -benzoylmethylphosphonate in a Wittig reaction to give intermediate 1, a mixture of  $\alpha,\beta$  and  $\beta,\gamma$  unsaturated ketones. The mixture of unsaturated ketones was catalytically reduced (Pt/H<sub>2</sub>) in basic media to afford phenyl ketone 2. Attempts to effect a reaction of ketone 2 with sodium acetylide were unsuccessful. However, reaction of ketone 2 with vinyl magnesium bromide gave intermediate 3 and the small scale ozonolysis of intermediate 3 gave low yields of aldehyde 4.

Only a very limited amount of work was done on this assignment during the past year. Synthetic efforts have been directed toward preparing a sufficient quantity of intermediate 4 to explore the remainder of the synthesis sequence. The work continues.

CHART NO. 24

3-QUINUCLIDINYL  $\alpha$ -[[-(1-OXO-2,2,6,6-TETRAMETHYL-PIPERIDINYL)METHYL]- $\alpha$ -PHENYLGLYCOLATE



#### 4. EXPERIMENTAL

All melting points and boiling points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 237B Spectrometer. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Indiana. Vapor phase chromatography was performed using an F and M Model 810 with a flame ionization detector. NMR spectra, when required, were determined on a Varian Model T60 Spectrometer. All thin layer chromatography was carried out using Analtech Uniplate silica gel GF 250 $\mu$  plates with fluorescent indicator.

##### 4.1 Phenyl(trichloromethyl)phosphinic Acid

The route to the title compound is shown in Chart No. 1.

Methyl Phenyl(trichloromethyl)phosphinate (1): -- To a 50 mL flask, under a nitrogen atmosphere were added carbon tetrachloride (4.08 g, 0.026 mol distilled from phosphorus pentoxide) and dimethyl phenylphosphonite (4.51 g, 0.026 mol). A vigorous exothermic reaction occurred. The light-brown solution was refluxed for 1 h at which time additional carbon tetrachloride (0.82 g, 0.0053 mol) was added. After heating for 2 h the reaction mixture was distilled to give 3.62 g of crude product, bp 114-150°C/0.2 mmHg. Further purification by column chromatography (petr. ether/ether-7:3, silica gel) gave pure title compound, 1.65 g (23%), mp 107.5-110°C, white crystalline solid (lit. mp 108°C, ref. 3). An additional 1.01 g of the title compound was prepared by this procedure.

Phenyl(trichloromethyl)phosphinic Chloride (2): -- Phosphorus pentachloride (5.52 g, 0.027 mol) and methyl phenyl(trichloromethyl)phosphinate (2.42 g, 0.0089 mol) were heated at 110-120°C for 2 h, then at 160°C for one additional hour. The mixture was cooled to 0°C and poured onto ice (14 g). The solid was collected by filtration, dissolved in dichloromethane (25 mL), the solution was dried over magnesium sulfate and concentrated to give the title compound, 2.14 g (87%), mp 83-84°C, waxy tan solid (lit. mp 87°C, ref. 4).

Phenyl(trichloromethyl)phosphinic Acid (3): -- A slurry of phenyl-(trichloromethyl)phosphinic chloride (2.06 g, 0.0074 mol) and 1 N nitric acid (50 mL) was stirred and warmed at 90°C on a steam bath for 1 h. After cooling to 0°C the tan solid was collected by filtration, washed with petroleum ether (10 mL) and dried at 23°C/0.4 mmHg to give crude product, 1.52 g. The crude product was dissolved in a mixture of ether (20 mL) and tetrahydrofuran (1 mL) at reflux. The solution was treated with charcoal and filtered. The filtrate was concentrated to a volume of 10 mL and petroleum ether (5 mL) was added at reflux until crystallization began. The crystalline product was collected, washed with petroleum ether (5 mL), and dried at 78°C/0.10 mmHg for 16 h to yield anhydrous title compound, 1.07 g (52%), mp 163-163.5°C, white powder (lit. mp 164.5°C, ref. 5);

NMR (DMSO- $d_6$ )  $\delta$  7.40-8.20 (m, 5, ArH) and 11.4 (s, 1, OH).

Anal. Calcd for  $C_7H_6Cl_3O_2P$  (259.46): C, 32.40; H, 2.33; Cl, 41.00; P, 11.94. Found: C, 32.42; H, 2.39; Cl, 41.05; P, 11.93.

#### Thin Layer Chromatography

	<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
	Methylene chloride-methanol (19:1)	0.42	homogeneous
4.2	<u><math>\gamma</math>-Methyladenosine 5'-Triphosphate</u>		

The route (ref. 6) to the title compound is shown in Chart No. 2.

A solution of adenosine 5'-triphosphate, disodium salt trihydrate (1.81 g, 3 mmol), in water (10 mL) was percolated onto a Dowex 50W-X2 (pyridinium form) column (1.2 x 45 cm). The column was eluted with water (100 mL) and the eluate was lyophilized to give a gummy solid. The solid was dissolved in a mixture of methanol (300 mL) and tri-*n*-butylamine (2.22 g, 12 mmol). The solution was treated with dicyclohexylcarbodiimide (3.09 g, 15 mmol) and allowed to stand at room temperature (30°C) for 7 h, then stored at -5°C overnight. The solution was allowed to warm to room temperature over a period of 5 h and water (27 mL) was added. After 1 h the mixture was concentrated (aspirator) to dryness and the residue was partitioned between ether (100 mL) and water (50 mL). The water layer was separated and lyophilized to give a colorless hygroscopic solid.

This solid was dissolved in water (6 mL) and the solution was percolated onto a DEAE cellulose (bicarbonate form) column (1.5 x 20 cm). The column was eluted with a linear gradient (3 L) of aqueous ammonium bicarbonate (0.005 M to 0.3 M). The fractions containing product (UV monitor, TLC) were combined and lyophilized to give a solid. The solid was freed from residual ammonium bicarbonate by repeated lyophilization from water (4 x 20 mL) to give 1.65 g of product as the ammonium salt. A portion of this material (1.50 g) was dissolved in water (10 mL) and the solution was percolated onto a cold (ice-jacketed) Dowex 50W-X2 (hydrogen form) column (1.2 x 45 cm). The column was eluted with ice cold water (100 mL) and the eluate was adjusted to pH 6 with calcium hydroxide. The solution was then adjusted to pH 5.2 by treatment with carbon dioxide (dry ice), and lyophilized to give a fluffy white solid. The solid was dissolved in water (10 mL) and filtered (celite). The solution was lyophilized to give 1.38 g of product contaminated with a small amount of calcium carbonate. The solid was dissolved in water (10 mL) and filtered. The solution was percolated onto a Sephadex G-15 column (2.5 x 95 cm). The column was eluted with water and the fractions containing product were combined and lyophilized to give 1.2 g (61.5%) of pure product as a colorless solid, decomp. 240-250°C with browning at ca. 220°C.

Anal. Calcd for  $C_{11}H_{15}N_5O_{13}P_3Ca_{1.5} \cdot 4H_2O$  (650.36): C, 20.31; H, 3.56; N, 10.77; P, 14.29. Found: C, 20.13; H, 3.48; N, 10.84; P, 14.36.

### Thin Layer Chromatography:

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
<u>n-Propanol-methanol-water-ammonium hydroxide (4:3:2:1)</u>	0.42	homogeneous

### Ultraviolet Spectrum:

$\lambda_{\max}$  (H<sub>2</sub>O) = 260 nm  $\epsilon_{\max}$  = 15,600 (4H<sub>2</sub>O)

### 4.3 4-Nitrophenyl Ethyl(phenyl)phosphinate

The route to the title compound is shown in Chart No. 3.

Ethyl(phenyl)phosphinic Acid (1): — Diphenyl(ethyl)phosphine oxide (47.0 g, 0.204 mol) and sodium hydroxide (16.3 g, 0.408 mol) were ground with a mortar and pestle to a homogeneous powder. This mixture was fused at 260°C for 1 h. After cooling the solidified mass was dissolved in water (200 mL) and washed with methylene chloride (3 x 50 mL). The aqueous phase was taken to pH 1 with concd hydrochloric acid (70 mL). An oil separated which, on cooling, solidified to a white crystalline solid. The solid was collected and dried at 50°C/1 mmHg to give 24.0 g (69%) of the title compound, mp 78–81°C, white prisms (lit. mp 80–81°C, ref. 7).

Ethyl(phenyl)phosphinic Chloride (2): — Phosphorous pentachloride (27.1 g, 0.120 mol) was added in portions to a solution of ethyl(phenyl)phosphinic acid (20.5 g, 0.120 mol) in benzene (125 mL) and the mixture was heated at reflux for 2 h. The solution was concentrated (aspirator) and the residual brown oil was distilled to give 20.7 g (91%) of product, bp 95–96°C/0.16 mmHg, colorless oil (lit. bp 148–150°C/4 mmHg, ref. 21).

4-Nitrophenyl Ethyl(phenyl)phosphinate (3): -- To a solution of 4-nitrophenol (15.1 g, 0.108 mol) and triethylamine (11.2 g, 0.111 mol) in dry tetrahydrofuran (170 mL) was added ethyl(phenyl)phosphinic chloride (20.7 g, 0.109 mol) in tetrahydrofuran (60 mL). The reaction mixture was stirred for 1 h at ambient temperature, filtered and concentrated (aspirator) to a yellow oil. The oil was dissolved in methylene chloride (100 mL) and washed with cold 5% aq. sodium bicarbonate (50 mL), water (50 mL) and cold 1 N hydrochloric acid. The organic phase was dried over sodium sulfate, filtered and concentrated to give crude lt yellow product (31.0 g). Recrystallization from a mixture of ether (250 mL) and cyclohexane (40 mL) gave pure title compound, 22.0 g (70%), mp 80–82°C, white crystals (lit. mp 81°C, ref. 8); NMR (CDCl<sub>3</sub>)  $\delta$  1.10 and 1.42 (dt, 3, CH<sub>3</sub>,  $J_p=20$ Hz and  $J_H=7$ Hz), 2.15 and 2.40 (dq, 2, CH<sub>2</sub>,  $J_p=20$ Hz and  $J_H=7$ Hz), 7.20 (d, 2, ArH), 7.30–8.00 (m, 5, ArH) and 8.10 (d, 2, ArH).

Anal. Calcd for C<sub>14</sub>H<sub>14</sub>NO<sub>4</sub>P (291.24): C, 57.73; H, 4.84; N, 4.81; P, 10.63. Found: C, 57.59; H, 5.00; N, 4.83; P, 10.45.

## Thin Layer Chromatography

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
Ethyl acetate	0.44	homogeneous

4.4 4-Nitrophenyl Di-1-butylphosphinothioate

The route to the title compound is shown in Chart No. 4.

Di-1-butylphosphinothioic Acid (1): — Diethyl phosphite (55.2 g, 0.040 mol) was added dropwise to a 3 L flask containing a 2 M ethereal solution of 1-butyilmagnesium bromide (650 mL, 1.30 mol) over a 1 h period with external cooling. The reaction mixture was heated at reflux for 1 h and cooled to 5°C. Finely powdered sulfur (16.0 g, 0.50 mol) was added in small portions and then the resulting mixture was refluxed for 1 h. The reaction mixture was cooled and 4 N hydrochloric acid (350 mL) was added. The ether layer was separated, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated (aspirator) to a yellow oil. The concentrate was dissolved in 5% aq. sodium bicarbonate solution and the solution was washed with ether (3 x 50 mL). The aqueous layer was taken to pH 1 by the addition of concd hydrochloric acid and extracted with benzene (2 x 100 mL). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated (aspirator) to a thick, light yellow oil, 59.4 g (73%). Distillation resulted in decomposition and so this material was utilized in the next step without further purification.

Di-1-butylphosphinothioic Chloride (2): — To a 500 mL flask which contained dry benzene (220 mL) and slightly crude di-1-butylphosphinothioic acid (56.8 g, 0.292 mol) was added phosphorous pentachloride (64.5 g, 0.310 mol) in small portions over 30 min. The reaction mixture was heated at reflux for 1 h, cooled and poured onto ice (60 g). The organic phase was separated, washed with cold water (3 x 30 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was removed (aspirator) and the residual oil was distilled to yield pure product, 28.4 g (46%), bp 107-108°C/0.65 mmHg (lit. bp 84-85°C/2 mmHg, ref. 9).

Anal. Calcd for C<sub>8</sub>H<sub>18</sub>ClPS (212.72): C, 45.17; H, 8.53; Cl, 16.66; P, 14.56; S, 15.07. Found: C, 45.38; H, 8.72; Cl, 16.41; P, 14.58; S, 15.00.

4-Nitrophenyl Di-1-butylphosphinothioate (3): — To a 500 mL flask containing 4-nitrophenol (17.9 g, 0.129 mol), dry tetrahydrofuran (25.0 mL) and triethylamine (13.4 g, 0.132 mol) was added a solution of di-1-butylphosphinothioic chloride (28.0 g, 0.131 mol) in dry tetrahydrofuran (60 mL) over a 10 min period. The reaction mixture was heated at reflux for 1 h, cooled and filtered. The filtrate was concentrated. The residue was taken into methylene chloride (100 mL) and washed successively with 5% aq. sodium bicarbonate solution (50 mL), water (50 mL) and 1 N hydrochloric acid (50 mL). The organic phase was concentrated to a thick brown oil (39.0 g). Crystallization from ethanol (100 mL) gave pure title compound 28.0 g (67%), mp 42.5-44.5°C, white crystals (lit. mp 44°C, ref. 10); NMR (CDCl<sub>3</sub>) δ 0.96 (t, 6, CH<sub>3</sub>), 1.10-2.45 (m, 12, CH<sub>2</sub>), 7.30 (d, 2, ArH) and 8.20 (d, 2, ArH).

Anal. Calcd for  $C_{14}H_{22}NO_3PS$  (315.36): C, 53.31; H, 7.03; N, 4.44; P, 9.82; S, 10.16. Found: C, 53.16; H, 7.20; N, 4.46; P, 9.81; S, 10.08.

Thin Layer Chromatography

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
Ether	0.71	homogeneous

4.5 4-Nitrophenyl 4-Chlorophenyl(methyl)phosphinate

The route to the title compound is shown in Chart No. 5.

4-Chlorophenyl(methyl)phosphinic Acid (1): -- To a 1 L flask were added magnesium turnings (7.10 g, 0.295 mol) anhydrous ether (20 mL) followed by the dropwise addition of a solution of 4-bromochlorobenzene (43.5 g, 0.227 mol) in ether (130 mL). After the formation of the Grignard reagent was complete (2 h), tetrahydrofuran (200 mL) was added and the mixture was cooled to 5°C. A solution of N,N-diethyl-P-methylphosphonamidic chloride (33.5 g, 0.197 mol) in tetrahydrofuran (200 mL) was added over a 10 min period and the mixture was stirred at 25°C for 3 h. Water (10 mL) was added and the solution was concentrated (aspirator). The residue was dissolved in a solution of dioxane (300 mL) and 4 N hydrochloric acid (200 mL) and stirred at ambient temperature overnight. Conc'd hydrochloric acid (50 mL) was added and the solution was extracted with chloroform (2 x 100 mL). The combined organic fractions were washed with 2 N sodium hydroxide solution (2 x 150 mL). The combined basic wash was taken to pH 1 by the addition of conc'd hydrochloric acid (70 mL) and the oily precipitate was extracted into chloroform (2 x 100 mL). The combined organic phase was dried ( $Na_2SO_4$ ), filtered and concentrated (aspirator) to give the title compound 21.1 g (56%), mp 104-105°C, white powder.

Anal. Calcd for  $C_7H_8ClO_2P$  (190.56): C, 44.11; H, 4.23; Cl, 18.60; P, 16.24. Found: C, 44.12; H, 4.47; Cl, 18.49; P, 16.09.

4-Nitrophenyl 4-Chlorophenyl(methyl)phosphinate (2): -- To a solution of 4-chlorophenyl(methyl)phosphinic acid (18.3 g, 0.096 mol) and 4-nitrophenol (13.1 g, 0.094 mol) in ethyl acetate (100 mL) was added a solution of dicyclohexylcarbodiimide (20.6 g, 0.100 mol) in ethyl acetate (60 mL). The reaction mixture was heated at reflux for 2 h, cooled to 5°C and filtered. The filtrate was concentrated to a thick yellow oil and triturated with ether to give crude ester 2, 28 g, as a tan solid. Recrystallization from a mixture of ethyl acetate (50 mL) and ether (125 mL) gave pure title compound 2, 19.8 g (78%), mp 92-93°C, white crystals (lit. mp 90-92°C, ref. 11); NMR ( $CDCl_3$ )  $\delta$  1.92 (d, 3,  $CH_3$ ,  $J_p=14Hz$ ), 7.20 (d, 2, ArH), 7.24-7.95 (m, 4, ArH) and 8.10 (d, 2, ArH).

Anal. Calcd for  $C_{13}H_{11}ClNO_4P$  (311.65): C, 50.09; H, 3.56; Cl, 11.37; N, 4.49; P, 9.94. Found: C, 50.15; H, 3.60; Cl, 11.56; N, 4.51; P, 9.99.

### Thin Layer Chromatography

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
Ethyl acetate	0.37	homogeneous

#### 4.6 4-Nitrophenyl Dimethylphosphinate

The route to the title compound is shown in Chart No. 6.

Dimethylphosphinic Acid (1): -- To a refluxing slurry of tetramethylbiphosphine disulfide (50.3 g, 0.27 mol) in carbon tetrachloride (170 mL) was carefully added dropwise a 30% hydrogen peroxide solution over a 1 h period. The mixture was refluxed for 2 h and allowed to stand at ambient temperature overnight. Precipitated elemental sulfur was removed by filtration. The aqueous layer was separated from the two-phase filtrate and concentrated (aspirator) to a thick oil which was dried under high vacuum to give white crystalline product (42 g) mp 85-86°C. Recrystallization from tetrahydrofuran-ether gave pure title compound, 42.1 g (83%), mp 86-89°C, white needles (lit. mp 88-90°C, ref. 12).

4-Nitrophenyl Dimethylphosphinate (2): -- To a solution of dimethylphosphinic acid (25.0 g, 0.266 mol) ethyl acetate (300 mL) and 4-nitrophenol (36.2 g, 0.260 mol) was added dicyclohexylcarbodiimide (58.7 g, 0.284 mol). The mixture was stirred at room temperature for 2 h. The resulting solution was treated with charcoal, filtered and concentrated (aspirator) to a crude solid, 33 g. Recrystallization from ethyl acetate-ether gave pure title compound, 23.8 g (43%), mp 97-100°C, white needles (lit. mp 99-100°C, ref. 13); NMR (CDCl<sub>3</sub>) δ 1.78 (d, 6, CH<sub>3</sub>, J<sub>p</sub>=14Hz), 7.30 (d, 2, ArH) and 8.10 (d, 2, ArH).

Anal. Calcd for C<sub>8</sub>H<sub>10</sub>NO<sub>4</sub>P (215.14): C, 44.66; H, 4.69; N, 6.51; P, 14.40. Found: C, 44.58; H, 4.81; N, 6.45; P, 14.17.

### Thin Layer Chromatography

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
Acetonitrile	0.28	homogeneous

#### 4.7 4-Nitrophenyl 2-Furyl(methyl)phosphinate

The route to the title compound is shown in Chart No. 7.

tris(2-Furyl)phosphine (1): -- Furan (192 g, 2.84 mol) in ether (850 mL) was treated with a 2.7 M hexane solution of 1-butyllithium (750 mL, 2.02 mol) added dropwise over a 1 h period. The mixture was cooled and a solution of phosphorus trichloride in benzene (400 mL) was added over a 1 h period. After standing at 25°C overnight, a 10% aq. ammonium chloride solution (800 mL) was added carefully. The organic phase was separated, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated (aspirator) to give a crude solid, 95 g.



This material was distilled to give the title compound, 77.5 g (75%), bp 112°C/0.03 mmHg, colorless oil which solidified on standing, mp 60-63°C (lit. bp 114°C/0.60 mmHg, ref. 14).

tris(2-Furyl)methylphosphonium Iodide (2): -- Methyl iodide (93 g, 0.66 mol) was added to a solution of tris(2-furyl)phosphine (76.0 g, 0.327 mol) in benzene (160 mL). The reaction mixture was heated at reflux for 3 h then cooled and stoppered. After 2 days the precipitated solid was collected to give the title compound, 109.3 g (89%), mp 127-130°C, white crystals (lit. mp 112-113°C, ref. 14).

bis(2-Furyl)methylphosphine Oxide (3): -- An aq. 2 N sodium hydroxide solution (151 mL, 0.303 mol) was added over a 10 min period to a solution of tris(2-furyl)methylphosphonium iodide (108 g, 0.289 mol) in water (200 mL) and ethanol (300 mL). The reaction mixture was stirred at 25°C for 30 min and concentrated (aspirator) to about 400 mL in volume. The solution was extracted with chloroform (2 x 150 mL). The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to give a solid, mp 78-80°C. Recrystallization from tetrahydrofuran (80 mL) and ether (120 mL) gave pure title compound, 46.0 g (81%), mp 79-81°C, white solid (lit. mp 78-80°C, ref. 14).

2-Furyl(methyl)phosphinic Acid (4): -- A mixture of bis(2-furyl)-methylphosphine oxide (50.7 g, 0.258 mol), water (500 mL) and sodium hydroxide (20.6 g, 0.517 mol) was heated at 90°C for 13 h. The aqueous solution was washed with chloroform (150 mL) and taken to pH 1 by the addition of concd hydrochloric acid. The aqueous solution was concentrated to a paste and the residue was partially dissolved in chloroform. The mixture was filtered and the filtrate was concentrated to give crude product (37.1 g). This material was purified by recrystallization from a mixture of THF (45 mL) and ether (80 mL) to give pure title compound, 24.0 g (64%), mp 70-72°C, white crystals (lit. mp 67-68°C, ref. 1).

4-Nitrophenyl 2-Furyl(methyl)phosphinate (5): -- A solution of 2-furyl(methyl)phosphinic acid (23.1 g, 0.158 mol), 4-nitrophenol (21.4 g, 0.154 mol), ethyl acetate (200 mL) and dicyclohexylcarbodiimide (34.2 g, 0.166 mol) was heated at reflux for 1 h, cooled and filtered. The solution was concentrated to give a crude pink solid (40 g). Recrystallization from tetrahydrofuran (75 mL) and ether (150 mL) gave the title compound, 26.9 g (65%), mp 105-106°C, white crystals (lit. mp 105-106°C, ref. 1); NMR (CDCl<sub>3</sub>) δ 1.95 (d, 3, CH<sub>3</sub>J<sub>p</sub>=18Hz), 6.45 (m, 1, ArH), 7.25 (m, 3, ArH), 7.65 (m, 1, ArH) and 8.15 (d, 2, ArH).

Anal. Calcd for C<sub>11</sub>H<sub>10</sub>NO<sub>5</sub>P (267.17): C, 49.45; H, 3.77; N, 5.24; P, 11.59. Found: C, 49.46; H, 3.77; N, 5.24; P, 11.76.

#### Thin Layer Chromatography

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
Ethyl acetate	0.35	homogeneous

#### 4.8 4-Nitrophenyl Dichloromethyl(phenyl)phosphinate

The route to the title compound is shown in Chart No. 8.

Dichloromethyl(phenyl)phosphinic Chloride (1): -- To a 2 L flask containing a solution of phenyldichlorophosphine (89.2 g, 0.498 mol) in chloroform (118.4 g, 0.997 mol) was added aluminum chloride (132 g, 0.990 mol). The mixture was heated at reflux for 1 h, cooled to  $-20^{\circ}\text{C}$  and 4 N hydrochloric acid (200 mL) was added dropwise over 30 min. The mixture was filtered. The filtrate was dried ( $\text{MgSO}_4$ ) and concentrated (aspirator) to an oil (54.5 g). Distillation gave the title compound, 28.0 g (23%), bp  $130-170^{\circ}\text{C}/0.4$  mmHg, colorless oil which solidified on standing, mp  $48-53^{\circ}\text{C}$  (lit. bp  $130-150^{\circ}\text{C}/0.5$  mmHg, lit. mp  $47-55^{\circ}\text{C}$ , ref. 15).

4-Nitrophenyl Dichloromethyl(phenyl)phosphinate (2): -- To a 500 mL flask which contained 4-nitrophenol (13.9 g, 0.100 mol), tetrahydrofuran (150 mL), and ethyldisopropylamine (14.0 g, 0.108 mol) was added a solution of dichloromethyl(phenyl)phosphinic acid (25.0 g, 0.103 mol) in tetrahydrofuran (50 mL) over a 5 min period. The mixture was stirred at ambient temperature for 2 h, filtered and concentrated to a yellow oil. The oil was dissolved in chloroform (200 mL) and washed successively with cold 1 N hydrochloric acid (100 mL), water (100 mL) and 5% aq. sodium bicarbonate (100 mL). The organic layer was dried ( $\text{MgSO}_4$ ), filtered and concentrated to an off-white solid, 33.5 g, mp  $100-106^{\circ}\text{C}$ . Two recrystallizations from ethyl acetate-ether gave pure title compound, 21.2 g (61%), mp  $114-116^{\circ}\text{C}$ , white powder (lit. mp  $114-116^{\circ}\text{C}$ , ref. 15); NMR ( $\text{CDCl}_3$ )  $\delta$  6.00 (s, 1, CH), 7.44 (d, 2, ArH), 7.50-8.20 (m, 5, ArH) and 8.25 (d, 2, ArH).

Anal. Calcd for  $\text{C}_{13}\text{H}_{10}\text{Cl}_2\text{NO}_4\text{P}$  (346.11): C, 45.11; H, 2.91; Cl, 20.49; N, 4.05; P, 8.95. Found: C, 45.04; H, 2.82; Cl, 20.59; N, 4.24; P, 8.88.

#### Thin Layer Chromatography

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
Ethyl acetate	0.85	homogeneous

#### 4.9 [1-[[[(Methylamino)carbonyl]oxy]imino]ethyl]ferrocene

The route to the title compound is shown in Chart No. 9.

1-(Hydroxyimino)ethylferrocene (1): -- To a solution of acetylferrocene (99.6 g, 0.44 mol) and hydroxylamine hydrochloride (80.2 g, 1.15 mol) in ethanol (3.6 L) was added a solution of potassium hydroxide (98.1 g, 1.75 mol) in ethanol (900 mL). The solution was heated at reflux for 3.5 h, cooled and concentrated (aspirator) to 400 mL. Ether (400 mL) was added and the insolubles were removed by filtration. The filtrate was dried over magnesium sulfate and concentrated to a dark oil (132.6 g) which was dissolved in hot ethyl acetate (700 mL). The solution was cooled and the product crystallized to give a first crop of 37.8 g, mp  $169-172^{\circ}\text{C}$ .

A second crop was obtained by concentrating the mother liquors to 75 mL and diluting with hexanes (150 mL) to give 21.2 g, mp 161-167°C. The combined crops (59 g) were recrystallized from ethyl acetate to give the title compound, 46.4 g (44%), mp 172-175°C (lit. mp 174-175°C, ref. 17).

[1-[[[(Methylamino)carbonyl]oxy]imino]ethyl]ferrocene (2): -- To a solution of ferrocene oxime (44.4 g, 0.183 mol), ether (440 mL) and dry tetrahydrofuran (355 mL) at 25°C was added methyl isocyanate (11.5 g, 0.201 mol). The flask was stoppered and allowed to stand at room temperature overnight. The solution was concentrated (aspirator) to give the title compound as a crude solid, 52.2 g, mp 121-122°C. Two recrystallizations from ethyl acetate-hexanes (5:3) gave pure title compound, 33.0 g (60%), mp 125-126°C (lit. mp 126-128°C, ref. 18); NMR (CDCl<sub>3</sub>) δ 2.28 (s, 3, CH<sub>3</sub>), 2.92 (d, 3, NCH<sub>3</sub>, J=5Hz), 4.20 (s, 5, ArH), 4.40 (m, 2, ArH), 4.60 (m, 2, ArH) and 6.40 (bs, 1, NH).

Anal. Calcd for C<sub>14</sub>H<sub>16</sub>FeN<sub>2</sub>O<sub>2</sub> (300.14): C, 56.02; H, 5.37; N, 9.33.  
Found: C, 55.97; H, 5.18; N, 9.10.

#### Thin Layer Chromatography

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
Hexane-ethyl acetate (5:2)	0.18	homogeneous

4.10 [[[4-[[[(Methylamino)carbonyl]oxy]phenyl]imino]methyl]ferrocene

The route to the title compound is shown in Chart No. 10.

[[4-Hydroxyphenyl]imino]methyl]ferrocene (1): -- To a solution of 4-aminophenol (38.3 g, 0.35 mol) in ethanol (550 mL) at 40°C was added ferrocenecarboxaldehyde (75.2 g, 0.35 mol). The solution was heated at reflux for 40 min, concentrated to 300 mL, cooled at 0°C for 2 h, and the resulting mixture was filtered. The collected solid was triturated with cold ethanol (50 mL) and dried to give a dark red granular solid, 99.4 g, mp 189-190°C. This solid was recrystallized from ethanol to give pure title compound, 82.4 g (77%), mp 189-190°C, purple flakes (lit. mp > 250°C, ref. 19).

Anal. Calcd for C<sub>17</sub>H<sub>15</sub>FeNO (305.16): C, 66.91; H, 4.95; N, 4.59.  
Found: C, 67.09; H, 4.79; N, 4.69.

[[[4-[[[(Methylamino)carbonyl]oxy]phenyl]imino]methyl]ferrocene (2): -- To a solution of [[4-hydroxyphenyl]imino]methyl]ferrocene (75.1 g, 0.25 mol) in tetrahydrofuran (1.35 L) was added methyl isocyanate (48.4 g, 0.85 mol). The reaction flask was stoppered and allowed to stand at 25°C for 26 h. The solution was concentrated (aspirator) to a dark oil which was dissolved in ethyl acetate (225 mL). The solution was charcoaled, filtered and diluted with hexanes (245 mL). The crystallized product was isolated by filtration to give a red powder, 63.6 g, mp 129-131°C. This

material was recrystallized from acetate-hexanes (1:1) to give pure title compound, 55.6 g (63%), mp 131-133°C, red crystalline powder (lit. mp 119-121°C, ref. 18); NMR (acetone-d<sub>6</sub>) δ 2.83 (d, 3, NCH<sub>3</sub>, J=5Hz), 4.28 (s, 5, ArH), 4.50 (m, 2, ArH), 4.85 (m, 2, ArH), 6.60 (bs, 1, NH), 7.20 (s, 4, ArH) and 8.42 (s, 1, =CH).

Anal. Calcd for C<sub>19</sub>H<sub>18</sub>FeN<sub>2</sub>O (360.19): C, 63.35; H, 4.48; N, 7.78. Found: C, 63.61; H, 4.67; N, 7.63.

#### Thin Layer Chromatography

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
Ethyl acetate	0.20	homogeneous

#### 4.11 3,3-Dimethyl-2-butyl Dimethylphosphinate

The three-step synthetic route to the title compound is shown in Chart No. 11.

Dimethylphosphinic Acid (1): -- To a 1 L three-necked flask were added tetramethyldiphosphinedisulfide (50 g, 0.269 mol) and carbon tetrachloride (170 mL). The resulting slurry was heated at reflux while 30% aqueous hydrogen peroxide (79 mL, 0.697 mol) was added dropwise over a 1.5 h period to avoid excess foaming. The reaction mixture was heated at reflux for an additional 1.5 h and was allowed to stand at 25°C overnight. Precipitated elemental sulfur was removed by filtration and the filtrate was concentrated to a light yellow oil which solidified on standing. This solid was slurried in ether-tetrahydrofuran and isolated by filtration to give the title compound, 26.6 g, mp 86-89°C, white needles (lit. mp 89-91°C, ref. 12). A crude second crop was obtained by concentration of the mother liquors, 23.0 g, mp 78-84°C, for a total yield of 49.6 g (98%).

Dimethylphosphinic Chloride (2): -- A mixture of dimethylphosphinic acid (26.5 g, 0.282 mol), benzene (110 mL) and thionyl chloride (110 mL) was heated at a gentle reflux for 1.5 h. The reaction mixture was concentrated (aspirator) to a crude solid. Distillation of this material gave the title compound, 23.8 g (75%), bp 110-140°C/5.4 mmHg, solidifies, mp 68-71°C, white crystals (lit. bp 204-205°C, ref. 12).

3,3-Dimethyl-2-butyl Dimethylphosphinate (3): -- To a 500 mL flask were added pinacol (21.6 g, 0.211 mol), dry tetrahydrofuran (140 mL) and ethyldiisopropylamine (30 g, 0.232 mol). A solution of dimethylphosphinic chloride (23.7 g, 0.211 mol) in tetrahydrofuran (60 mL) was added dropwise over a 5 min period. The reaction mixture was stirred at 25°C for 2 h, cooled and the precipitated salts were removed by filtration. The filtrate was concentrated (aspirator) to a dark oil, which was dissolved in chloroform and washed with 1 N hydrochloric acid (80 mL). The organic fraction was

dried over magnesium sulfate, filtered and reconcentrated to a dark oil. This material was distilled to give 27.3 g, bp 56-60°C/0.25 mmHg. This slightly turbid, colorless oil was redistilled to give pure title compound, 23.1 g (62%), bp 58-59°C/0.30 mmHg, colorless oil; NMR (CDCl<sub>3</sub>) δ 0.92 (s, 9, CH<sub>3</sub>), 1.30 (d, 3, CH<sub>3</sub>, J=7Hz), 1.50 (d, 6, PCH<sub>3</sub>, J=14Hz), 4.20 (dq, 1, CH, J<sub>P</sub>=11Hz, J<sub>H</sub>=7Hz).

Anal. Calcd for C<sub>8</sub>H<sub>13</sub>O<sub>2</sub>P (178.21): C, 53.92; H, 10.75; P, 17.38. Found: C, 53.70; H, 10.71; P, 17.30.

#### Thin Layer Chromatography

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
Ethyl acetate	0.85	homogeneous

#### 4.12 Phenyl Valerate

To an ice-cooled solution of phenol (128.8 g, 1.368 mol), ether (2 L) and triethylamine (146.9 g, 1.450 mol) in a 5 L flask was added dropwise with stirring a solution of valeryl chloride (165 g, 1.368 mol) in ether (300 mL) over a 45 min period. The reaction mixture was stirred at room temperature for 2 h. Water (1 L) was added followed by 1 N hydrochloric acid (500 mL). The organic phase was separated and washed with 1 N sodium hydroxide solution (500 mL). The ethereal solution was dried over magnesium sulfate, filtered and concentrated to a light yellow oil (239 g). This material was combined with crude product (47.9 g) obtained from a small scale probe run and distilled to give pure title compound, 245 g (83%), bp 73-75°C/0.25 mmHg, colorless oil (lit. bp 160°C/14 mmHg, ref. 20); NMR (CDCl<sub>3</sub>) δ 0.96 (t, 3, CH<sub>3</sub>), 1.20-2.00 (m, 6, CH<sub>2</sub>) 2.60 (t, 2, CH<sub>2</sub>), 6.90-7.40 (m, 5, ArH).

Anal. Calcd for C<sub>11</sub>H<sub>15</sub>O<sub>2</sub> (178.23): C, 74.13; H, 7.92. Found: C, 73.96; H, 7.92.

#### Thin Layer Chromatography

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
Ether	0.85	homogeneous

#### 4.13 Di-1-butyl 2,2-Dichlorovinyl Phosphate

To a 2 L flask containing tributylphosphite (125 g, 0.499 mol) under a nitrogen atmosphere was added chloral (73.6 g, 0.499 mol) dropwise over a 1.5 h period with moderate cooling. The reaction mixture was stirred at ambient temperature for 1 h. Bump distillation gave crude product, 119 g, bp 114-134°C/0.30 mmHg containing about 10% of a close-boiling contaminant. The crude product was fractionally distilled through a 32 cm 5 bubble plate column to yield pure title compound, 38.6 g (25%), bp 95-96°C/0.06 colorless oil (lit. bp 125-128°C/0.35 mmHg, ref. 21); NMR (CDCl<sub>3</sub>) δ 0.98

(t,6,CH<sub>3</sub>), 1.20-1.90 (m,8,CH<sub>2</sub>), 4.16 (q,5,CH<sub>2</sub>,J=6Hz), 7.00 (d,1,CH=,J=6Hz).

Anal. Calcd for C<sub>10</sub>H<sub>13</sub>Cl<sub>2</sub>O<sub>4</sub>P (305.14): C, 39.36; H, 6.28; Cl, 23.24; P, 10.15. Found: C, 39.27; H, 6.54; Cl, 23.27; P, 10.01.

#### Gas Liquid Phase Chromatography

3 ft. 10% Carbowax on Chromosorb WHP at 200°C, retention time 34 sec. > 99% purity.

#### 4.14 4-Nitrophenyl Chloromethyl(phenyl)phosphinate

The synthetic route to the title compound is shown in Chart No. 12.

Chloromethyl(phenyl)phosphinic Chloride (1): -- Dichlorophenylphosphine (250 g, 1.40 mol) was added to a 500 mL flask containing paraformaldehyde (63.1 g, 2.10 mol) under an inert atmosphere. After a short induction period (3 min), the reaction mixture exothermed to reflux temperature. The solution was then heated at reflux for 2 h. The reaction mixture was distilled and a forerun of unreacted dichlorophenylphosphine, 57.7 g, bp 40-120°C/.2 mmHg was collected. Crude product, 165 g, bp 124-170°C/.2 mmHg was then collected. This crude material was redistilled to yield purified title compound, 121 g (41%), bp 102-104°C/0.08 mmHg, colorless oil, solidifies on standing, (lit. bp 105°C/0.009 mmHg, ref. 23).

4-Nitrophenyl Chloromethyl(phenyl)phosphinate (2): -- To a 500 mL three-necked flask containing 4-nitrophenol (31.6 g, 0.239 mol), dry tetrahydrofuran (200 mL) and ethyldiisopropylamine (35.5 g, 0.275 mol) was added a solution of chloromethyl(phenyl)phosphinic chloride (50 g, 0.239 mol) in tetrahydrofuran (100 mL) over 5 min. The reaction mixture was stirred at 25°C for 1 h and concentrated (aspirator). The residue was dissolved in methylene chloride (250 mL) and washed successively with cold 1 N hydrochloric acid (200 mL), water (200 mL) and cold 1 N sodium bicarbonate solution (200 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated to a thick yellow oil. This crude product was dissolved in ether (80 mL). After standing for 18 h crystalline product was collected by filtration, 44.1 g (59%), mp 73-76°C. This material was combined with similar quality product from previous runs (7.80 g) and recrystallized from ethyl acetate-ether mixture to give pure title compound, 44.2 g, mp 77-79°C, white rhombs; NMR (CDCl<sub>3</sub>) δ 3.85 (d,2,CH<sub>2</sub>,J=14Hz), 7.30 (d,2,ArH) 7.35-8.00 (m,5,ArH), 8.15 (d,2,ArH).

Anal. Calcd for C<sub>13</sub>H<sub>11</sub>ClNO<sub>4</sub>P (311.66): C, 50.10; H, 3.56; Cl, 11.38; N, 4.49; P, 9.94. Found: C, 49.96; H, 3.61; Cl, 11.24; N, 4.36; P, 9.80.

#### Thin Layer Chromatography

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
Ether	0.70	homogeneous

4.15 4-Nitrophenyl Phenyl(trichloromethyl)phosphinate

The synthetic route to the title compound is shown in Chart No. 13.

Ethyl Phenyl(trichloromethyl)phosphinate (1): -- Diethyl phenylphosphonite (146.4 g, 0.74 mol) was added dropwise to dry carbon tetrachloride (1.2 L) at reflux under nitrogen atmosphere over a 0.5 h period. The reaction mixture was refluxed for 22 h. The orange solution was concentrated (aspirator) and distilled to give crude product, 154.3 g, bp 151-157°C/0.8 mmHg. This product was dissolved in hot cyclohexane (300 mL), the solution was diluted with hexanes (800 mL) and cooled (25°C/16 h, 5°C/2 h). The crystalline product was collected by filtration and washed with ether (2 x 50 ml) to give pure title compound, 130.3 g (61%), mp 82-84°C, pale yellow granular crystals (lit. mp 79°C, ref. 24).

Phenyl(trichloromethyl)phosphinic Chloride (2): -- Phosphorus pentachloride (283.0 g, 1.36 mol) and ethyl phenyl(trichloromethyl)phosphinate (130.3 g, 0.45 mol) were heated at 83°C (steam bath) for 8 h. The reaction mixture was cooled, broken up, and was poured on ice (750 g). This mixture was cooled to 10°C and the solid was collected. The crude product was washed with water (100 mL) and dissolved in dichloromethane (500 mL). The organic phase was separated from some water, dried over magnesium sulfate and concd to give pure title compound, 125.3 g (99%), mp 82-84°C, white amorphous powder (lit. mp 87°C, ref. 4).

4-Nitrophenyl Phenyl(trichloromethyl)phosphinate (3): -- To a rapidly stirred solution of 4-nitrophenol (19.5 g, 0.14 mol) ethyldiisopropylamine (distilled from calcium hydride, 18.1 g, 0.14 mol) and dry tetrahydrofuran (39 mL) at 5°C was added rapidly a solution of phenyl(trichloromethyl)phosphinic chloride (39.0 g, 0.14 mol) in dry tetrahydrofuran (78 mL). After 2 h at ambient temperature, the mixture was concentrated, the residue was dissolved in dichloromethane (200 mL) and washed with cold 1 N hydrochloric acid (3 x 50 mL), followed by cold saturated aqueous sodium bicarbonate (3 x 50 mL). The organic phase was dried over sodium sulfate and concentrated to give a crude oil (49.6 g) which contained a mixture of two compounds by TLC (4:1, CH<sub>2</sub>Cl<sub>2</sub>-hexanes). This oil was purified by column chromatography over silica gel (petr. ether-ether, 4:1 then 3:1) to give slightly crude product, 12.8 g, mp 119-124°C. This solid was dissolved in acetone (65 mL), charcoaled, filtered, concentrated to 25 mL volume and diluted with ether (128 mL). After cooling (2 h/25°C, 16 h/3°C) the product was collected and washed with ether (2 x 10 mL) to give 4.9 g, mp 124-127°C. The mother liquors were concd to ca. 10 mL and diluted with ether (64 mL) to afford a second crop (3.2 g), mp 124-127°C. By this procedure a total of 147.8 g of phosphinic chloride 2 was converted to 25.0 g (12%) of product, mp 124-127°C. The combined product (25 g) was recrystallized from acetone-ether to give pure title compound, 21 g (10%), mp 124.5-127°C, white granular crystals (lit. mp 124-127°C, ref. 15); NMR (CDCl<sub>3</sub>) δ 7.30-7.80 (m, 5, ArH), 7.85-8.35 (m, 4, ArH).

Anal. Calcd for  $C_{13}H_{19}Cl_3NO_4P$  (380.6): C, 41.03; H, 2.38; Cl, 27.95; N, 3.68; P, 8.14. Found: C, 41.29; H, 2.36; Cl, 27.87; N, 3.56; P, 8.09.

Thin Layer Chromatography

	<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
	Methylene chloride	0.30	homogeneous
4.16	<u>2,2-Dimethyl-3-hydroxybutyl Amine</u>		

The two-step synthetic route to the title compound is presented in Chart No. 14.

2,2-Dimethyl-3-hydroxybutyronitrile (1): — A 2.4 M solution of *n*-butyllithium in hexane (525 mL, 1.26 mol) was added over 20 min to a solution of dry diisopropylamine (127 g, 1.25 mol) in dry tetrahydrofuran (500 mL) at  $-74^{\circ}\text{C}$  and under a nitrogen atmosphere. The reaction mixture was stirred for 20 min and a solution of isobutyronitrile (78.9 g, 1.14 mol) in tetrahydrofuran (50 mL) was added over a 20 min period. After 35 min, acetaldehyde (75 g, 1.70 mol) was added dropwise over a 10 min period (exotherm to  $-30^{\circ}\text{C}$ ). The mixture was stirred at  $-62^{\circ}\text{C}$  for one additional hour, then warmed to ambient temperature over a period of 1 h. The mixture was cooled to  $10^{\circ}\text{C}$  and acidified to pH 1 by the addition of 1.3 M hydrochloric acid (900 mL), followed by concd hydrochloric acid (100 mL) while maintaining the temperature below  $10^{\circ}\text{C}$ . The organic phase was separated and the aqueous layer was extracted with ether (2 x 1 L). The combined organic fractions were washed with a saturated sodium chloride solution (500 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated (aspirator) to an orange oil (130 g). Distillation of the oil gave 94.3 g of product, bp  $52-53^{\circ}\text{C}/0.3$  mmHg as a light yellow oil. This material was redistilled through a 20 cm Vigreux column to give pure title compound, 90.6 g (70%), bp  $43-45^{\circ}\text{C}/0.10$  mmHg, pale yellow oil; NMR ( $\text{CDCl}_3$ )  $\delta$  1.35 (d, 3,  $\text{CH}_3$ , J=6Hz), 1.37 (s, 6,  $\text{CH}_3$ ), 3.07 (s, 1, OH) and 3.60 (q, 1,  $\text{CH}$ , J=6Hz).

Anal. Calcd for  $C_6H_{11}NO$  (113.16): C, 63.68; H, 9.80; N, 12.38. Found: C, 63.43; H, 10.03; N, 12.38.

2,2-Dimethyl-3-hydroxybutylamine (2): — A solution of 2,2-dimethyl-3-hydroxybutyronitrile (57 g, 0.5 mol) in dry tetrahydrofuran (200 mL) was added dropwise over a 40 min period to a suspension of lithium aluminum hydride (28.5 g, 0.75 mol) in dry tetrahydrofuran (750 mL) at  $40^{\circ}\text{C}$  (exotherm to  $48^{\circ}\text{C}$  during addition). After the addition was completed, the mixture was stirred for 90 min at  $45^{\circ}\text{C}-50^{\circ}\text{C}$  (water bath). Water (30 mL) was added slowly with cooling followed by 30% aq. sodium hydroxide (60 mL) and water (30 mL) while maintaining the temperature at  $10^{\circ}\text{C}$  to give an off-white granular precipitate. Ether (1 L) was added and the mixture was stirred at room temperature for 20 min and filtered through celite. The filter cake was reslurried with ether (1 L) and filtered. The combined filtrates were concentrated (aspirator),



maintaining the temperature between 45 to 55°C) to give a light yellow oil (60 g). Distillation gave 53.3 g of product, bp 42-44°C/0.10 mmHg. This material was redistilled through a 20 cm Vigreux column to give pure title compound, 49.6 g (84%), bp 31-33°C/0.05 mmHg, colorless oil; NMR (CDCl<sub>3</sub>) δ 0.82 (d, 6, CH<sub>3</sub>, J=3.5Hz), 1.10 (d, 3, CH, J=8Hz), 2.75 (q, 2, CH<sub>2</sub>), 3.05 (bs, 3, OH, NH<sub>2</sub>) 3.68 (q, 1, CH, J=8Hz).

Anal. Calcd for C<sub>6</sub>H<sub>15</sub>NO (117.19): C, 61.49; H, 12.90; N, 11.95.  
Found: C, 61.25; H, 13.05; N, 11.76.

#### Thin Layer Chromatography

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
Methanol-water-acetic acid-chloroform (8:1:1:30)	0.27	homogeneous (ninhydrin)

#### Vapor Phase Chromatography

6 ft 10% carbowax column at 150°C; retention time 3 min, homogeneous.

#### 4.17 2,2-Dichlorovinyl Di(1-butyl)phosphinate

The four-step preparative route to the title compound is shown in Chart No. 15.

P,P-Di(1-butyl)-N,N-diethylphosphinous Amide (1): -- A 2.27 M tetrahydrofuran solution of 1-butylmagnesium chloride (506 mL, 1.15 mol) was added dropwise to a solution of diethylaminodichlorophosphine (100 g, 0.57 mol) in ether (700 mL) at -20°C. The mixture was maintained at -20°C to -10°C during the addition (dry ice bath), then was allowed to warm to room temperature and stirred for 2 h. The mixture was filtered under a nitrogen atmosphere (glove bag) and the collected solid was washed with ether (200 mL). The combined filtrate and washings were concentrated (aspirator). The residual liquid was distilled to give the title compound, 78 g (63%), bp 108-110°C/4 mmHg, colorless oil (lit. bp 121°C/16 mmHg, ref. 26).

Di(1-butyl)phosphinous Chloride (2): -- P,P-Di(1-butyl)-N,N-diethylphosphinous amide (77 g, 0.35 mol) was added dropwise to a solution of anhydrous hydrogen chloride (28 g, 0.76 mol) in ether (500 mL). The temperature was maintained near -40°C during the addition (dry ice bath). The reaction mixture was allowed to warm to room temperature and filtered under a nitrogen atmosphere (glove bag). The collected solid was washed with ether (150 mL) and the combined filtrate and washings were concentrated (aspirator) to an oil. The oil was distilled to give pure title compound, 56 g (87%), bp 82-88°C/3 mmHg, colorless oil; (lit. bp 91-92°C/12 mmHg, ref. 26).

1-Butyl Di(1-butyl)phosphinite (3): — A mixture of 1-butanol (23 g, 0.31 mol) and triethylamine (31 g, 0.31 mol) was added dropwise to a solution of di(1-butyl)phosphinous chloride (55 g, 0.30 mol) in ether (500 mL), while maintaining the temperature at 20°C (ice bath). The reaction mixture was stirred for 30 min and filtered under a nitrogen atmosphere (glove bag). The residual solid was washed with ether (200 mL). The combined filtrate and washings were concentrated (aspirator). The residual oil was distilled to give pure title compound, 45 g (66%), bp 100–105°C/1.2 mmHg, colorless, air-sensitive liquid, (lit. bp 78–83°C/0.5 mmHg, ref. 27).

2,2-Dichlorovinyl Di(1-butyl)phosphinate (4):— Freshly distilled chloral (30 g, 0.20 mol) was added dropwise to 1-butyl di(1-butyl)phosphinite (40 g, 0.18 mol) while maintaining the temperature at 20–30°C. The reaction mixture was concentrated (aspirator) and the residual liquid was flash-distilled to give 52 g of crude product, bp 150–155°C/1.5 mmHg. This material was redistilled to give 41 g of partially purified product, bp 139–143°C/1.2 mmHg. This product was redistilled through a 15 cm Vigreux column to give a forerun of 16 g, bp 136–139°C/1.0 mmHg, followed by pure title compound, 22 g (44%), bp 139–141°C/1.0 mmHg, pale yellow oil (lit. bp 143–144°C/6 mmHg, ref. 28); NMR (CDCl<sub>3</sub>) δ 0.75–1.10 (m, 6, CH<sub>3</sub>), 1.15–2.20 (m, 12, CH<sub>2</sub>), 7.10 (d, 1=CH, J=8Hz).

Anal. Calcd for C<sub>10</sub>H<sub>19</sub>Cl<sub>2</sub>O<sub>2</sub>P (273.13): C, 43.97; H, 7.01; Cl, 25.96; P, 11.34. Found: C, 43.99; H, 7.10; Cl, 25.71; P, 11.48.

Vapor Phase Chromatography (6 ft. 1% OV-17 on Chromasorb W-HP)

<u>Temperature</u>	<u>Retention Time</u>	<u>Comment</u>
160°C	2.0 min	~ 1% faster impurity

4.18 1-Butyl 2,2-Dichlorovinyl 1-Butylphosphonate

The four-step preparative route to the title compound is shown in Chart No. 16.

P-(1-Butyl)-N,N,N',N'-tetraethylphosphonous Diamide (1): -- A 2 N ethereal solution of 1-butyilmagnesium chloride (475 mL, 0.95 mol) was added dropwise to a cold (-20°C) solution of bis(diethylamino)chlorophosphine (200 g, 0.95 mol) in ether (800 mL). The temperature was maintained between -10°C and -20°C during the addition (dry ice bath). The solution was allowed to warm to room temperature and was stirred for 1 h. The mixture was filtered under a nitrogen atmosphere (glove bag) and the collected solid was washed with ether (400 mL). The combined filtrate and washings were concentrated (aspirator). The residual liquid was distilled to give pure title compound, 160 g (73%), bp 106–110°C/0.5 mmHg (lit. bp 124°C/0.5 mmHg ref. 29). An additional 108 g of the title compound was prepared by the same procedure.

1-Butylphosphonous Dichloride (2): -- P-(1-butyl)-N,N,N',N'-tetraethylphosphonous diamide (135 g, 0.58 mol) was added dropwise to a solution of anhydrous hydrogen chloride (90 g, 2.47 mol) in ether (1200 mL). The temperature was maintained near  $-40^{\circ}\text{C}$  (dry ice bath) during the addition. The reaction mixture was allowed to warm to room temperature and was filtered under a nitrogen atmosphere (glove bag). The residual solid was washed with ether (300 mL), and the combined filtrate and washings were concentrated (aspirator, water bath, internal temp.  $< 35^{\circ}\text{C}$ ). The residual liquid was distilled to give pure title compound, 73 g (80%), bp  $53-57^{\circ}\text{C}/10$  mmHg, colorless oil (lit. bp  $62-64^{\circ}\text{C}/23$  mmHg, ref. 30). An additional 68 g of the title compound was prepared by this procedure.

Di(1-butyl) 1-Butylphosphonite (3) -- A mixture of 1-butanol (78 g, 1.05 mol) and triethylamine (106 g, 1.05 mol) was added dropwise to a solution of 1-butylphosphonous dichloride (75 g, 0.47 mol) in ether (1.2 L) while maintaining the temperature below  $20^{\circ}\text{C}$  (ice bath). The reaction mixture was stirred for 30 min and filtered under a nitrogen atmosphere (glove bag). The residual solid was washed with ether (200 mL) and the combined filtrate and washings were concentrated (aspirator). The residual liquid was distilled to give the title compound, 94 g (85%), bp  $93-97^{\circ}\text{C}/0.60$  mmHg, colorless oil (lit. bp  $109-112^{\circ}\text{C}/13$  mmHg, ref. 31). An additional 68 g of the title compound was prepared by this procedure.

1-Butyl 2,2-Dichlorovinyl 1-Butylphosphonate (4): -- Freshly distilled chloral (69 g, 0.47 mol) was added dropwise to di(1-butyl) 1-butylphosphonite (100 g, 0.43 mol) while maintaining the temperature at  $20-35^{\circ}\text{C}$  (ice bath). The reaction mixture was concentrated (aspirator) and the residual liquid was flash-distilled to give crude product (117 g), bp  $135-140^{\circ}\text{C}/1.2$  mmHg. This material was redistilled through a 60 cm Vigreux column and a center cut was collected to give pure title compound, 25 g (20%), bp  $128-129^{\circ}\text{C}/0.80$  mmHg (lit. bp  $148-149^{\circ}\text{C}/6$  mmHg, ref. 32); NMR ( $\text{CDCl}_3$ )  $\delta$  0.70-1.15 (m, 6,  $\text{CH}_3$ ), 1.20-2.25 (m, 10,  $\text{CH}_2$ ), 4.20 (q, 2,  $\text{OCH}_2$ ,  $J=7\text{Hz}$ ), 7.10 (d, 1,  $=\text{CH}$ ,  $J=8\text{Hz}$ ).

Anal. Calcd for  $\text{C}_{10}\text{H}_{19}\text{Cl}_2\text{O}_3\text{P}$  (289.14): C, 41.54; H, 6.62; Cl, 24.52; P, 10.71. Found: C, 41.39; H, 6.84; Cl, 24.66; P, 10.58.

Vapor Phase Chromatography (6 ft. 1% OV-17 on Chromasorb W-HP)

	<u>Temperature</u>	<u>Retention Time</u>	<u>Comment</u>
	150°C	2.1 min	trace faster and slower impurities

4.19 4-Trimethylammoniohenyl Chloromethyl(phenyl)phosphinate Trifluoromethylsulfonate

The three-step route to the title compound is shown in Chart No. 17.

4-Dimethylaminophenol (1): -- A mixture of 4-methylaminophenol sulfate (35.0 g, 0.102 mol), sodium hydroxide (8.16 g, 0.204 mol) and water

(300 mL) was extracted with ether (2 x 400 mL). The combined ether extracts were concentrated (aspirator) to give 4-methylaminophenol, 23.5 g, mp 86-87°C, light brown solid. This material was heated at reflux in methyl iodide (142 g) for 5 h and the mixture was allowed to stand at room temperature overnight. The crude solid product was isolated by filtration and air-dried. This material was finely powdered with a mortar and pestle and added to a suspension of sodium carbonate (13 g, 0.15 mol) in isoamyl alcohol (300 mL). The resulting slurry was heated at reflux for 5 h, cooled to 70°C and filtered. The filtrate was washed with brine (100 mL), dried (MgSO<sub>4</sub>) and concentrated (aspirator) to a black tar. Distillation gave the title compound, 13.0 g (49%), bp 156-160°C/30 mmHg, mp 72-75°C, light yellow solid (lit. mp 75-77°C. ref. 33).

4-Dimethylaminophenyl Chloromethyl(phenyl)phosphinate (2): -- A mixture of chloromethyl(phenyl)phosphinic acid (2.00 g, 0.0105 mol), ethyl acetate (15 mL), 4-dimethylaminophenol (1.44 g, 0.0105 mol) and dicyclohexylcarbodiimide (2.27 g, 0.011 mol) was stored at 25°C for 18 h. The mixture was filtered and the filtrate was concentrated to a light yellow oil. The oil was chromatographed (silica gel-ether) to give a product fraction as an oil (2.86 g). Crystallization from ether gave pure title compound, 1.96 g (60%), mp 74-76°C, white prisms.

Anal. Calcd for C<sub>15</sub>H<sub>17</sub>ClNO<sub>2</sub>P (309.73): C, 58.17; H, 5.53; Cl, 11.45; N, 4.52; P, 10.00. Found: C, 58.14; H, 5.60; Cl, 11.22; N, 4.68; P, 9.83.

Thin Layer Chromatography

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
Ether	0.65	homogeneous

4-Trimethylammoniofenyl Chloromethyl(phenyl)phosphinate (3): -- A mixture of 4-dimethylaminophenyl chloromethyl(phenyl)phosphinate (1.20 g, 0.0039 mol), methylene chloride (25 mL) and methyl trifluoromethylsulfonate (0.65 g, 0.0039 mol) was stirred at 25°C for 2 h and concentrated (aspirator) to a white solid. The solid was triturated with ethyl acetate to give a white powder, 1.68 g, mp 152-155°C. This material was recrystallized twice from acetonitrile-ethyl acetate to give pure title compound, 1.11 g (61%), mp 158-163°C, fine white needles; NMR (d<sub>6</sub>-DMSO) δ 3.61 (s, 9, NCH<sub>3</sub>) 4.42 (d, 2, CH<sub>2</sub>, J<sub>p</sub>=7.5 Hz), 7.30-8.20 (m, 9, ArH).

Anal. Calcd for C<sub>17</sub>H<sub>20</sub>ClF<sub>3</sub>NO<sub>5</sub>PS (473.83): C, 43.09; H, 4.25; Cl, 7.48; F, 12.03; N, 2.96; P, 6.54; S, 6.77. Found: C, 43.09; H, 4.37; Cl, 7.34; F, 12.11; N, 3.11; P, 6.36; S, 6.94.

Thin Layer Chromatography

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
Ethyl acetate	0.0	homogeneous

#### 4.20 2-Aminoethylseleninic Acid

A solution of selenocystamine dihydrochloride (8 g, 0.25 mol) in water (50 mL) was cooled to 5°C (ice bath) and a cold solution of bromine (12 g, 0.75 mol) in water (450 mL) was added dropwise over a 10 min period. The solution was stirred at 5°C for 2 h, then passed through a Dowex 50W-X2 (H<sup>+</sup> form) column. The column was eluted with water (200 mL) and the eluant was discarded. The column was then eluted with aqueous ammonium hydroxide (2 N, 200 mL) and the eluant was lyophilized. The resultant solid (7.6 g) was slurried in anhydrous ethanol (160 mL) for 3 h at room temperature. The resulting fine white solid was isolated by filtration with the exclusion of moisture, washed with abs. ethanol (2 x 10 mL) and dried at room temperature under a nitrogen atmosphere to give the title compound, 5.95 g (76%), mp 132-133°C (dec), white powder (lit. mp 150-152°C with slow dec at 130°C, ref. 34); NMR (D<sub>2</sub>O)  $\delta$  2.80 (t, 2, CH<sub>2</sub>, J=7Hz), 3.60 (t, 2, CH<sub>2</sub>, J=7Hz).

Anal. Calcd for C<sub>2</sub>H<sub>7</sub>NO<sub>2</sub>Se (156.05): C, 15.39; H, 4.52; N, 8.98; O, 20.51. Found: C, 15.57; H, 4.59; N, 8.72; O, 20.78.

#### Paper Chromatography (Whatman No. 1, descending)

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
1-Butanol-formic acid-water (75:15:10)	0.11	homogeneous
Ethanol-22% ammonium hydroxide (90:10)	0.09	homogeneous

#### 4.21 2-Aminoethylselenonic Acid

To a 100 mL flask containing a solution of selenocystamine dihydrochloride (10 g, 0.031 mol) in water (20 mL) was added 4 N sodium hydroxide (20 mL). The mixture was extracted with chloroform (3 x 50 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated to a light yellow oil. The selenocystamine, free-base, thus obtained was dissolved in water (15 mL). The solution was cooled (ice bath) while 30% aq. hydrogen peroxide (15.5 mL) was added dropwise over a 1 h period. One hour later the reaction mixture was diluted with 2-propanol until turbid and stored at -10°C overnight. The product was isolated by filtration and air-dried to give 7.40 g, mp 155-156°C (dec), dk at 140°C. Three recrystallizations from ethanol-water (3:1), gave pure title compound, 3.80 g (39%), mp 156°C (dec), dk at 145°C, large white crystals (lit. mp 150°C, dks at 130-135°C, ref. 34); NMR (D<sub>2</sub>O)  $\delta$  3.78 (t, 2, CH<sub>2</sub>) 3.82 (t, 2, CH<sub>2</sub>).

Anal. Calcd for C<sub>2</sub>H<sub>7</sub>NO<sub>3</sub>Se (172.04): C, 13.96; H, 4.10; N, 8.14; O, 27.90. Found: C, 14.16; H, 4.36; N, 7.98; O, 28.18.

Paper Chromatography (Whatman No. 1, descending)

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
1-Butanol-formic acid-water (75:15:10)	0.03	homogeneous
Ethanol-22% ammonium hydroxide	0.15	homogeneous

4.22 Monomethyl Phosphate

Commercial monomethyl phosphate di(cyclohexylammonium) salt (50 g) was dissolved in hot absolute ethanol (1.25 L) and the solution was filtered. The volume was reduced to 700 mL and the solution was cooled in an ice bath for 1 h. The white solid was collected by filtration, washed with hexanes (125 mL) and dried (25°C/0.3 mmHg) for 18 h to give purified salt, 39.6 g (79%), mp 202-204°C (eff) shrinkage between 196-198°C (lit. mp 195-198°C dec, ref. 47).

Anal. Calcd for C<sub>13</sub>H<sub>31</sub>N<sub>2</sub>O<sub>4</sub>P (310.39): C, 50.30; H, 10.07; N, 9.03; P, 9.98. Found: C, 49.24; H, 10.13; N, 8.84; P, 10.12.

Purified monomethyl phosphate di(cyclohexylammonium) salt (39.6 g, 0.28 mol) was dissolved in deionized water (170 mL), the solution was passed through a Dowex 50W-2X resin column (hydrogen ion form) and the column was washed with deionized water (3 L). The acidic eluate (1.6 L) was lyophilized to give a thick oil (14 g). This oil was dissolved in 25 mL of deionized water, the solution was filtered (Whatman No. 3 filter paper) and the filtrate was lyophilized to give pure title compound, 13.5 g (94%), thick colorless oil; NMR (D<sub>2</sub>O) δ 3.80 (d, 3, CH<sub>3</sub>, J=13Hz).

Anal. Calcd for CH<sub>5</sub>O<sub>4</sub>P (112.03): C, 10.72; H, 4.50; P, 27.65. Found: C, 10.50; H, 4.71; P, 27.55.

Neutralization Equivalent (titration with 0.01 N sodium hydroxide, phenolphthalein indicator)

Found: 55.80

Theory: 56.01

4.23 4-Nitrophenyl Methyl(2-trifluoromethylphenyl)phosphinate

The three-step route to the title compound is shown in Chart No. 18.

N,N-Diethyl-P-methyl-P-(2-trifluoromethylphenyl)phosphinic amide (1):--  
To a 3 L flask were added magnesium turnings (10.82 g, 0.445 mol) and sufficient dry ether to cover the turnings. A solution of 2-bromobenzo-trifluoride (83.5 g, 0.371 mol) in ether (450 mL) was added dropwise at a rate sufficient to maintain a gentle reflux. The reaction mixture was stirred for 2 h at 25°C after the addition was complete. A solution of

N,N-diethyl-P-methylphosphonamidic chloride (62.9 g, 0.371 mol) in dry tetrahydrofuran (500 mL) was added and the mixture was stirred at ambient temperature for 18 h. Water (10 mL) was added, the mixture was filtered and the filtrate was concentrated (aspirator). The residual brown oil was dissolved in methylene chloride (500 mL) and the solution was washed with 1 N hydrochloric acid (200 mL) and concentrated sodium bicarbonate solution (200 mL). The organic phase was concentrated and the residual liquid was distilled to give the title compound, 39.5 g (29%), bp 126-130°C/0.18 mmHg, light yellow oil.

Methyl(2-trifluoromethylphenyl)phosphinic Acid (2): -- A mixture of N,N-diethyl-P-methyl-P-(2-trifluoromethylphenyl)phosphinic amide (39.5 g, 0.141 mol), dioxane (200 mL) and 3 N hydrochloric acid (200 mL) was stirred at 25°C for 18 h. The reaction mixture was concentrated to a volume of 50 mL and added to a mixture of chloroform (200 mL) and 3 N sodium hydroxide (200 mL). The basic aqueous layer was acidified to pH 1 with concentrated hydrochloric acid and extracted with chloroform (2 x 200 mL). The combined chloroform extract was dried over magnesium sulphate and concentrated to an off-white solid, 28.5 g (90%), mp 88-90°C. The slightly crude title compound was used without further purification, in the next step.

4-Nitrophenyl Methyl(2-trifluoromethylphenyl)phosphinate (3): -- To a solution of methyl(2-trifluoromethylphenyl)phosphinic acid (26.0 g, 0.116 mol) and 4-nitrophenol (16.1 g, 0.116 mol) in methylene chloride (100 mL) was added a solution of dicyclohexylcarbodiimide (23.9 g, 0.116 mol) in methylene chloride (200 mL). After the initial exothermic reaction subsided, the mixture was stirred at 25°C for 18 h. The mixture was filtered and the filtrate was concentrated to a yellow oil (37.8 g). The oil was chromatographed twice over silica gel, eluting with ether to give the title compound 23.9 g (60%), light yellow syrup; NMR (CDCl<sub>3</sub>) δ 2.04 (d, 3, CH<sub>3</sub>, J=16Hz), 7.35 (d, 2, ArH), 7.75 (m, 4, ArH), 8.20 (d, 2, ArH).

Anal. Calcd for C<sub>14</sub>H<sub>11</sub>F<sub>3</sub>NO<sub>4</sub>P (345.22): C, 48.71; H, 3.21; F, 16.51; N, 4.06; P, 8.97. Found: C, 48.57; H, 3.19; F, 16.24; N, 3.90; P, 8.84.

#### Thin Layer Chromatography

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
Ether	0.60	traces of 4-nitrophenol at R <sub>f</sub> 0.85

#### 4.24 4-Chlorophenyl Methyl(4-trimethylammoniohenyl)phosphinate Trifluoromethylsulfonate

The six-step synthetic route to the title compound is shown in Chart No. 19.

4-Dimethylaminophenylphosphonous Dichloride (1): -- Dimethylaniline (270 g, 2.23 mol) and phosphorus trichloride (386 g, 2.81 mol) were added to a 5 L flask under a nitrogen atmosphere. The mixture was cooled (ice bath)

and anhydrous aluminum chloride (74 g, 0.557 mol) was added in small portions over a 1 h period. The reaction mixture was heated at reflux for 18 h. The resulting yellow oil was extracted with warm cyclohexane (3 x 700 mL). The combined cyclohexane extracts were concentrated by distillation under nitrogen to give a thick yellow oil which solidified on cooling. The solid product was mostly dissolved in ether (1 L) and separated from a flocculent white solid by decanting the solution through a cotton plug. The ethereal solution was concentrated by distillation under nitrogen to give the title compound, 126 g (25%), mp 56-62°C, large yellow crystals (lit. mp 66°C, ref. 36).

Dimethyl 4-Dimethylaminophenylphosphonite (2): -- To a 2 L flask containing methanol (486 mL) was added sodium metal (24.85 g, 1.08 mol) in small portions over a 1 h period. When the reaction was complete the solution was cooled to 0°C and a solution of 4-dimethylaminophenylphosphonous dichloride (120 g, 0.540 mol) in dry benzene (245 mL) was added over a 30 min period. The reaction mixture was stirred for one additional hour at 0-20°C, filtered and the filtrate was concentrated by distillation under nitrogen to a light yellow oil (103 g). The oil was distilled twice to give the title compound, 68.8 g (60%), bp 108-112°C/0.10 mmHg colorless oil (lit. bp 112-114°C/0.35 mmHg, ref. 37).

Methyl 4-Dimethylaminophenyl(methyl)phosphinate (3): -- A mixture of dimethyl 4-dimethylaminophenylphosphonite (68.5 g, 0.321 mol), dry benzene (200 mL) and methyl iodide (1 mL) was slowly heated to reflux on a steam bath. Refluxing was continued for 1.5 h, the solution was cooled, filtered and concentrated (aspirator) to give crude product as a white crystalline solid. This material was recrystallized from ethyl acetate-ether (1:4) to give the title compound, 62.5 g (91%), mp 78-81°C, white crystalline solid (lit. mp 81-82°C, ref. 37).

4-Dimethylaminophenyl(methyl)phosphinic Acid (4): -- To a 500 mL flask were added methyl 4-dimethylaminophenyl(methyl)phosphinate (20 g, 0.0938 mol), tetrahydrofuran (100 mL), methanol (100 mL) and 1 N sodium hydroxide solution (103 mL, 0.103 mol) and the resulting solution was heated at reflux for 8 h. After standing at ambient temperature overnight, concd. hydrochloric acid (8.5 mL, 0.103 mol) was added and the solution was concentrated to a volume of 125 mL. The precipitated white solid was isolated by filtration and dried (110°C/1 mmHg) to give slightly crude title compound, 15.90 g (85%), mp 193-195°C, white flakes. This material was used without further purification in the next step of the reaction sequence.

4-Chlorophenyl 4-Dimethylaminophenyl(methyl)phosphinate (5): -- A mixture of 4-dimethylaminophenyl(methyl)phosphinic acid (15.65 g, 0.0785 mol), 4-chlorophenol (10.1 g, 0.0785 mol), toluene (300 mL), acetonitrile (300 mL) and dicyclohexylcarbodiimide (16.2 g, 0.082 mol) was heated at reflux for 3 days. The reaction mixture was cooled, filtered and the filtrate was concentrated (aspirator) to a light yellow oil. The oil was dissolved in ether (30 mL) and after standing overnight the crystalline solid was collected



to yield 21.8 g of crude product, mp 72-78°C. The crude material was recrystallized from a minimum volume of ether to give pure title compound, 17.2 g (71%), mp 84-86°C, white crystals.

Anal. Calcd for  $C_{15}H_{17}ClNO_2P$  (309.73): C, 58.17; H, 5.53; Cl, 11.45; N, 4.52; P, 10.00. Found: C, 57.88; H, 5.50; Cl, 11.20; N, 4.67; P, 9.94.

#### Thin Layer Chromatography

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
Ethyl acetate	0.55	homogeneous

4-Chlorophenyl Methyl(4-trimethylammonio-phenyl)phosphinate Trifluoromethylsulfonate (6): — A mixture of methyl trifluoromethylsulfonate (9.00 g, 0.0549 mol), methylene chloride (150 mL) and 4-chlorophenyl 4-dimethylaminophenyl(methyl)phosphinate (17.0 g, 0.549 mol) was heated at a gentle reflux for 3 h. The reaction mixture was concentrated (aspirator) to a white solid which was triturated with ethyl acetate to give crude product, 20.1 g, mp 150-152°C. Two recrystallizations by dissolving in a minimum volume of hot acetonitrile and diluting with ethyl acetate gave pure title compound, 15.7 g (60%), mp 156-158°C, white needles; NMR ( $d_6$ -DMSO)  $\delta$  1.96 (d, 3,  $PCH_3$ ,  $J=15$  Hz), 3.64 (s, 9,  $NCH_3$ ), 7.10-7.50 (m, 4,  $ArH$ ), 8.00-8.30 (m, 4,  $ArH$ ).

Anal. Calcd for  $C_{16}H_{20}ClNO_2P \cdot CF_3SO_3$  (473.83): C, 43.09; H, 4.25; Cl, 7.48; F, 12.03; N, 2.96; P, 6.54; S, 6.77. Found: C, 43.19; H, 4.38; Cl, 7.50; F, 12.30; N, 3.16; P, 6.50; S, 6.88.

#### Thin Layer Chromatography

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
Ethyl acetate	0.0	homogeneous

#### 4.25 1-Substituted-4-bromo-2,2,6,6-tetramethylpiperidine

The synthesis of the title piperidines is shown in Chart No. 21 as part of Work in Progress, Section 3.7.

4-Bromo-2,2,6,6-tetramethylpiperidine (1): — 4-Hydroxy-2,2,6,6-tetramethylpiperidine (15 g, 0.095 mol) was added to 47% hydrobromic acid (100 mL). Dry hydrogen bromide gas was bubbled through the suspension for 30 min. The mixture was then heated at reflux for 20 h, cooled and filtered. The solid was dried at 60°C/1 mmHg for 3 h to give title compound hydrobromide salt, 10.3 g as a white solid, mp > 300°C. The filtrate was resaturated with hydrogen bromide and heated at reflux for an additional 18 h. The mixture was cooled and filtered. The solid was dried at 60°C/1 mmHg for 2 h to give an additional 4.8 g of the hydrobromide salt. The first crop of the hydrobromide salt (10.3 g) was stirred in ether (60 mL) and 1 N sodium hydroxide solution was added until the pH of the aqueous phase reached 12.

The phases were separated and the aqueous phase was extracted with ether (2 x 35 mL). The organic phases were combined, dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was removed. The residue was distilled to give the title compound, 5.8 g (28%), bp 75-80°C/3 mmHg; mp 40-41°C.

Anal. Calcd for  $\text{C}_9\text{H}_{18}\text{BrN}$  (220.15): C, 49.10; H, 8.24; N, 6.36. Found: C, 49.23; H, 8.36; N, 6.47.

The second crop of hydrobromide salt (4.8 g) was treated with 1 N sodium hydroxide solution in a similar manner to give additional title compound, 3.2 g (15%), bp 85-90°C/6 mmHg, mp 40-41°C. The combined yield was 9.0 g (43%).

#### Thin Layer Chromatography

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
Chloroform-methanol-ammonium hydroxide (18:2:1)	0.41	homogeneous

4-Bromo-2,2,6,6-tetramethylpiperidin-1-oxyl (2): — A solution of tetrasodium ethylenediaminetetraacetate (1.0 g, 0.002 mol) and sodium tungstate dihydrate (1.0 g, 0.003 mol) in water (10 mL) was added to a solution of 4-bromo-2,2,6,6-tetramethylpiperidine (10 g, 0.043 mol) in methanol (110 mL). Hydrogen peroxide (30%, 17 g, 0.15 mol) was added. The solution was stirred for 2 days. The volume was reduced to 50 mL (aspirator) and the mixture was partitioned between water (50 mL) and methylene chloride (50 mL). The aqueous phase was extracted with methylene chloride (2 x 50 mL). The organic phases were combined, dried ( $\text{MgSO}_4$ ) and the solvent was removed (aspirator). The residual solid was recrystallized from cyclohexane (50 mL) to give the title compound, 7.5 g (70%), mp 128-129°C (lit. mp 129°C, ref. 42). The volume was reduced to 25 mL to obtain a second crop of the title compound, 0.5 g (5%), mp 125-127°C.

#### Thin Layer Chromatography

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
Petr. ether-ether (3:1)	0.69	homogeneous

#### 4-Bromo-1,2,2,6,6-pentamethylpiperidine (3)

##### Method A. Eshweiler Methylation

Formic acid (2.1 g, 0.046 mol) was added dropwise to a suspension of 4-bromo-2,2,6,6-tetramethylpiperidine (10 g, 0.045 mol) in 37% formaldehyde solution (10 mL, 0.133 mol). The mixture was heated at reflux for 3 h. The reaction mixture was partitioned between 10% sodium carbonate solution (100 mL) and ether (100 mL). The aqueous phase was extracted with ether (100 mL). The ether phases were combined and dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was removed. The residual oil was distilled to give the title

compound, 2.3 g (22%), bp 100-105°C/15 mmHg.

Anal. Calcd for  $C_{10}H_{20}BrN$  (234.18): C, 51.29; H, 8.61; Br, 34.12; N, 5.98. Found: C, 51.32; H, 8.91; Br, 34.18; N, 6.08.

#### Method B. Dimethyl Sulfate

Dimethyl sulfate (20 g, 0.16 mol) was added to a solution of 4-bromo-2,2,6,6-tetramethylpiperidine (20 g, 0.091 mol) in tetrahydrofuran (100 mL). The solution was stirred at ambient temperature overnight, then partitioned between 20% sodium carbonate solution (200 mL) and ether (200 mL). The ether phase was dried ( $K_2CO_3$ ), treated with additional dimethyl sulfate (5.0 g, 0.04 mol) and allowed to stir overnight. The solution was washed with 20% aq. sodium carbonate (50 mL), dried ( $K_2CO_3$ ) and the solvent was removed. The residue was purified by column chromatography over silica gel (300 g) eluting with ethyl acetate. The product containing fractions were combined and distilled to give the title compound, 14 g (66%), bp 100-105°C/15 mmHg.

#### Thin Layer Chromatography

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
Chloroform-methanol-ammonium hydroxide (15:4:1)	0.41	homogeneous

1-Acetyl-4-bromo-2,2,6,6-tetramethylpiperidine (4): -- Acetyl chloride (2.0 g, 0.025 mol) was added dropwise to a solution of 4-bromo-2,2,6,6-tetramethylpiperidine (5.0 g, 0.023 mol) and triethylamine (2.5 g, 0.025 mol) in chloroform (40 mL) with cooling. The reaction mixture was stirred for 1 h and additional triethylamine (0.72 g, 0.007 mol) and acetyl chloride (0.56 g, 0.007 mol) were added. The reaction mixture was stirred for one additional hour and poured into water (40 mL). The phases were separated and the chloroform phase was washed with cold 1 N hydrochloric acid (40 mL) and dried ( $MgSO_4$ ). The solvent was removed (aspirator) and the residual oil was distilled to give the title compound, 3.65 g (61%), bp 100-110°C/0.2 mmHg, mp 48-50°C.

Anal. Calcd for  $C_{11}H_{20}BrNO$  (262.19): C, 50.39; H, 7.69; Br, 30.48; N, 5.34. Found: C, 50.49; H, 7.40; Br, 30.21; N, 5.29.

#### Thin Layer Chromatography

<u>Eluent</u>	<u>R<sub>f</sub></u>	<u>Comment</u>
Ethyl acetate	0.60	homogeneous

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